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Telomere Length and Health Outcomes: A Two-Sample Genetic Instrumental Variables Analysis

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Abstract

Objective—Previous studies linking telomere length (TL) and health have been largely associational. We apply genetic instrumental variables (IV) analysis, also known as Mendelian randomization, to test the hypothesis that shorter TL leads to poorer health. This method reduces bias from reverse causation or confounding.

Methods—We used two approaches in this study that rely on two separate data sources: (1) individual-level data from the Health and Retirement Study (HRS) (N=3,734), and (2) coefficients from genome-wide association studies (GWAS). We employed two-sample genetic IV analyses, constructing a polygenic risk score (PRS) of TL-associated single nucleotide polymorphisms. The first approach examined the association of the PRS with nine individual health outcomes in HRS. The second approach took advantage of estimates available in GWAS databases to estimate the impact of TL on five health outcomes using an inverse variance-weighted meta-analytic technique.

Results—Using individual-level data, shorter TL was marginally statistically significantly associated with decreased risk of stroke and increased risk of heart disease. Using the meta-analytic approach, shorter TL was associated with increased risk of coronary artery disease (OR 1.02 per 100 base pairs, 95%CI: 1.00, 1.03).

Discussion—With the exception of a small contribution to heart disease, our findings suggest that TL may be a marker of disease rather than a cause. They also demonstrate the utility of the inverse variance-weighted meta-analytic approach when examining small effect sizes.

Keywords

Telomere length; cardiovascular disease; genetic instrumental variables; aging; Mendelian randomization

1. INTRODUCTION

Telomeres are DNA-protein structures that include a repeated nucleotide sequence at the ends of eukaryotic chromosomes, acting to protect the degradation of functional DNA

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sequences during cellular replication (Olovnikov 1973). Shortening of telomeres in human cells *in vitro* has been shown to lead to cellular dysfunction, senescence, and death (Allsopp and Harley 1995; Blackburn 2000). Shorter mean telomere length (TL) is associated with increased risk of mortality (Cawthon and others 2003; Kim and others 2012b; Rehkopf and others 2013), and a growing number of observational and longitudinal studies have also demonstrated links between shorter TL and human illnesses. For example, researchers have found associations between shorter TL and higher prevalence of coronary artery disease, Type 2 diabetes, Alzheimer's, and Parkinson's disease, and an association between shorter TL and vulnerability to acute infections (Brouilette and others 2007; Cohen and others 2013; Zhu and others 2011). Almost without exception, however, these studies have been conducted on small samples using observational methods, leaving researchers unable to determine whether TL is in fact a cause of illness or simply a marker of the disease process.

There are a number of reasons why observational studies of TL and chronic disease may not have accurately estimated the relationship. A growing literature suggests that lower socioeconomic status is associated with shorter telomeres (Cherkas and others 2006; Needham and others 2013; Robertson and others 2013). While this may suggest that TL is a pathway through which adverse social conditions get "under the skin," translating into vulnerability to disease and "host susceptibility" (Cassel 1976), it may also be an indication that the relationship between TL and health is confounded by environmental and social exposures. For example, many lifestyle factors – including smoking, exercise, and diet – have been associated with TL (Lin and others 2012; Mirabello and others 2009; Shammas 2011; Valdes and others). It may be the case that these factors or other physiological attributes of disease itself actually cause shortened TL rather than the reverse. An additional source of potential bias in observational studies of TL obtained from blood and buccal cells is that these samples are composed of different cell types, each of which have different mean TL (Lin and others 2010). Therefore differences in cell type composition due to differences in immune function or infection could confound findings in observational studies.

Given the limitations of observational studies, one promising avenue is genetic instrumental variables (IV) analysis, also known as Mendelian randomization. Genetic IV analyses are increasingly used in the field of epidemiology, enabling researchers to estimate causal relationships when randomization of the exposure is not feasible (Lawlor and others 2008). In the case of telomeres, prior research has identified numerous genetic markers – or single nucleotide polymorphisms (SNPs) – that are associated with longer telomeres. These SNPs undergo random assortment from parents to offspring, creating a "randomization" of the exposure, i.e., TL. Thus, while the effect of TL on health outcomes cannot be directly measured due to an inability on the part of researchers to randomly assign TL, investigators use a quasi-randomly assigned third variable that influences health through its effect on TL – i.e., the presence of SNPs that predict TL – to estimate the relationship between TL and health. This method has become increasingly applied to estimate the effects on health outcomes of risk factors that otherwise are not amenable to randomization (Klerk and others 2002; Theodoratou and others 2012; Wehby and others 2011).

In this study, we construct a polygenic risk score that incorporates seven TL-associated SNPs identified in a recent meta-analysis of genome-wide association studies (GWAS). We

then employ a two-sample genetic IV analysis to determine the causal effect of TL on a variety of health outcomes previously associated with TL. We first use data on individual-level outcomes, testing the hypothesis that differences in TL contribute to the development of human disease. This is a typical genetic IV approach that is often underpowered when effect sizes are small. Consequently, we also take advantage of coefficients from several GWAS databases, highlighting the utility of publicly available GWAS data to reach sufficient sample sizes to query phenotype-outcome relationships of potentially small magnitude in a meaningful way.

2. METHODS

2.1. Individual-Level Data Set

We used data from the U.S. Health and Retirement Study (HRS), a longitudinal panel study that has collected data biennially since 1992 among a representative sample of over 26,000 men and women over 50 years of age, with an over-sampling of older individuals. The survey also includes data on respondents' spouses, which includes individuals under 50 years of age. A description of the HRS, including survey design, can be found in previous studies (Juster and Suzman 1995). We restricted our analyses to individuals for whom we have data on both genotype and TL (N = 5,225). Because the samples in which the TL-associated SNPs were identified include only those of European descent, as described below, we further restricted our sample to include only HRS participants who self-reported as non-Hispanic white (N = 3,734).

Our primary predictor variable was mean TL, which was obtained in 2008 from HRS participants who consented to provide a salivary sample. Samples were analyzed by Telome Health using a standard quantitative polymerase chain reaction assay. TL was measured in standard fashion, using the telomere-to-single copy gene (T/S) ratio. This ratio is determined by comparing the telomere sequence copy number (T) with a single-copy gene copy number (S). The equation for conversion of the T/S ratio to TL varies by lab, and for this study was: base pairs = (T/S) * 2,400.

Genetic data were also collected from respondents during the 2008 study wave. Subjects provided DNA samples using a mouthwash technique. Genotyping was conducted by the National Institutes of Health Center for Inherited Disease Research using the Illumina Human Omni-2.5 Quad beadchip, which includes roughly 2.5 million SNPs.

Outcome variables included measures of multiple health outcomes. In each survey wave, respondents self-reported whether they had ever been diagnosed with the following health conditions: diabetes, hypertension, heart disease, lung disease, stroke, arthritis, psychiatric disease, and cancer. For each of these conditions, we constructed a binary variable indicating whether the individual ever reported being diagnosed in any survey wave (1992–2010). Respondents also self-reported their height and weight, allowing us to calculate their body mass index (BMI) for each survey wave. We created a binary variable indicating whether an individual ever met criteria for obesity (BMI greater than 30).

Covariates included age, gender, and educational attainment. We measured age at collection of the telomere assay in 2008. Educational attainment was constructed as a categorical variable with four levels: less than high school education (reference group), high school or GED completed, some college, and college completed. We also account for residual population stratification by including the first four genetic principal components-derived eigenvectors, a technique used in prior work (Chang and others 2014; Walter and others 2015).

2.2. GWAS Databases

The polygenic risk score we constructed, described below, was derived from a genome-wide meta-analysis that identified SNPs associated with TL (Codd and others 2013). It included 37,684 individuals, with replication of selected variants in 10,739 controls. Additionally, we used coefficients drawn from five GWAS databases that examine health outcomes similar to those included in HRS (Locke and others 2015; Ripke and others 2013; Schunkert and others 2011; Soranzo and others 2010; Stahl and others 2010). These are summarized in Table 1. Of note, several of these outcomes represent different constructs than those in HRS. For example, in HRS, respondents self-report a diagnosis of “heart disease,” while actual cases of coronary artery disease have been identified in the CARDIoGRAM study. These should therefore not be interpreted as identical to the outcomes from the HRS analyses, but rather complementary.

2.3. Polygenic Risk Score

We constructed a polygenic risk score (PRS) based on seven SNPs found to be significantly associated with TL in the largest genome-wide meta-analysis to date (Codd and others 2013). We used information on these seven SNPs from each individual in HRS to create the PRS. Weights were assigned for each SNP using the number of base pairs of decrease in TL associated with each allele, as reported in the meta-analysis (Codd and others 2013). Importantly, a higher value of the PRS means that an individual is genetically predisposed to shorter telomeres. Prior research has suggested that analyses using a PRS may be more successful in predicting disease risk than use of individual genetic markers (Dudbridge 2013).

2.4. Data Analysis

2.4.1. Individual-level Data—We first examined the association between the PRS and the health outcomes of interest using individual-level HRS data, employing a two-sample instrumental variables approach. This technique is valuable in cases where there are concerns of weak instrument bias and insufficient power in the first stage of a typical IV analysis (Evans and Davey Smith 2015; Pierce and Burgess 2013). We conducted the first stage of the IV analysis in the HRS sample, regressing TL on the PRS and the covariates above, to evaluate the validity of the PRS in this sample. As expected, this F-statistic was small (Table 3), confirming the importance of the two-sample IV approach, although the coefficient was in the expected direction, with higher levels of the PRS associated with shorter TL.

Given that the first stage using individual-level data was likely underpowered, we next regressed each of the individual-level health outcomes on the PRS itself in separate logistic regressions, controlling for the covariates described above, and no longer relying on the first-stage estimates of predicted TL. In this case, the coefficient on the PRS is interpreted as the increased odds of each of the health outcomes of interest for each 100 base pair decrease in mean TL. Standard errors were clustered at the household level and robust to an unknown form of heteroscedasticity. This approach rests on the assumption that the separate samples employed in the first and second stages are drawn from the same population, leading us to restrict the HRS sample to individuals of self-identified non-Hispanic white race to match the samples of European ancestry included in the genome-wide meta-analysis from which the PRS coefficients were obtained. Another important assumption is that the first and second stage samples are independent. This assumption is met, as HRS data were not included in the GWAS samples.

2.4.2. GWAS Disease Data—Given the small effect sizes, using individual-level data is likely to be underpowered even with a two-sample IV approach. We therefore next employed an inverse-variance weighted meta-analytic approach to estimate the effect of TL on a subset of these health outcomes that were available from the GWAS databases described above in order to leverage the greater statistical power available in these larger samples. This approach has been described previously (Burgess and others 2013), and is increasingly employed in two-sample genetic IV analyses in the absence of individual-level data (Mukherjee and others ; Østergaard and others 2015). In this case, it allowed for the estimation of the effect of TL on the odds of a given binary health outcome given a difference of 100 base pairs in TL; or for continuous outcomes (hemoglobin A1c and BMI), this method gives the change in the outcome measure per 100 base pairs. As shown previously (Burgess and others 2015), the coefficient and standard error can be calculated as follows:

$$\hat{\beta} = \frac{\sum_{k=1}^{K} X_k Y_k \sigma_{Y_k}^{-2}}{\sum_{k=1}^{K} X_k^2 \sigma_{Y_k}^{-2}}$$

$$se(\hat{\beta}) = \sqrt{\frac{1}{\sum_{k=1}^{K} X_k^2 \sigma_{Y_k}^{-2}}}$$

Here, X_k is the GWAS-derived estimate of the association between each SNP k with TL, while Y_k is the GWAS-derived estimate of the association between each SNP and the outcome of interest with standard error σ_{Y_k}.

As above, this approach assumes that the first and second stage samples are independent. In this case, while it is possible that a given individual was recruited for multiple GWAS samples, this is unlikely. At worst, this would be limited to a handful of individuals, and would not present a serious violation of this assumption.

Data analysis was conducted using Stata 14 (College Station, Texas) and R 3.2.1. Analytic code to conduct the inverse-variance weighted analysis has been provided in prior publications (Pierce and Burgess 2013).

2.5. Ethics Approval

Ethics approval for the HRS was provided by the University of Michigan Health Services Institutional Review Board. Approval for this study was provided by Stanford University Institutional Review Board (protocol 25818).

3. RESULTS

3.1. Characteristics of HRS Sample

Almost 60% of study subjects were female, with an average age of 69.5 in 2008 (Table 2). Participants were diverse with respect to educational attainment. The prevalence for the health conditions under investigation ranged from 10.6% for stroke to 67.8% for arthritis.

3.2. Two-Sample IV Analysis: Individual-level Data

Using individual-level data in HRS, the first stage of the IV analysis demonstrated that a higher PRS is associated with a decrease in TL, as expected, although this was not statistically significant likely due to the smaller size of this sample relative to the GWAS ($\beta = -43.0$ base pairs per unit of PRS, 95%CI: −96.9, 10.9) (Table 3). As described above, this supports our use of the two-sample IV analysis. In the second stage, the PRS was not statistically significantly associated with any of the health outcomes under study (Table 4). The majority of the odds ratios were close to one. This suggests that TL does not have a causal effect on these measures of disease. An increase in TL of 100 base pairs was marginally associated with a decreased odds of stroke (OR 0.92, 95%CI: 0.83, 1.01) and an increased odds of heart disease (OR 1.06, 95%CI: 0.99, 1.13).

3.3. Two-Sample IV Analysis: GWAS Data

Using the inverse variance-weighted approach with coefficients from GWAS databases (Table 5), we found that a decrease in TL of 100 base pairs was associated with an increased odds of heart disease (OR 1.02, 95%CI: 1.003, 1.03). There were no other associations of a meaningful magnitude or that attained traditional statistical significance levels for the other health outcomes we examined.

4. DISCUSSION

Our study employs two-sample genetic IV analyses to examine the effect of TL on health using both individual-level data and meta-analytic approaches. Using a weighted polygenic risk score of TL-associated genetic markers as an instrument for TL, we find that shorter telomeres lead to a marginally significantly decreased odds or stroke and increased odds of heart disease in individual-level data. Given the small sample size of HRS, however, and the low F-statistic on the first stage of the IV analysis in this sample, it is likely that this type of analysis is underpowered in the setting of small effect sizes. This increases the chances of Type II error, i.e., failing to reject the null when it is not true. We therefore carried out

parallel analyses using an inverse variance-weighted meta-analytic approach with GWAS data, in which the finding for heart disease was confirmed. This speaks to the potential significance of TL as an actual determinant for heart disease, rather than only as a marker of disease process. Our novel methodological approach to the question provides a critical piece of evidence for the literature on understanding the potential impacts of TL on health. Our findings for heart disease were of a small magnitude, and our null results (with narrow confidence intervals) for other outcomes suggest that TL should primarily be viewed as a marker of disease processes, rather than a cause in itself.

Our findings on heart disease are consistent with a large body of observational studies in the extant literature, in which shortened telomeres have been extensively implicated in the development of heart disease (Brouilette and others 2007; Farzaneh-Far and others 2010; Fitzpatrick and others 2007; Fyhrquist and others 2013; Nilsson and others 2013; Samani and others 2001; Starr and others 2007). This finding has been replicated in studies using a variety of designs – including cross-sectional, longitudinal, and case-control – and in diverse populations, although prior studies employ largely correlational methodologies. A recent systematic review of observational studies also found a consistent relationship between shorter TL and higher risk of coronary heart disease (Haycock and others 2014). One prior study also documented an association between TL-associated SNPs and coronary artery disease (Codd and others 2013), although the authors did not conduct a two-stage analysis as we do here, to determine the effect of the SNPs that acts through TL itself. The two-sample IV technique we employ here suggests that this relationship may in fact be causal, although the meta-analysis approach precludes the ability to test the assumptions behind the IV model. It is not straightforward to compare this effect size with those of prior studies given the differences in analytic strategies and measurement of outcomes, but the magnitude of the association in the present study is among the smallest of those previously documented. Of note, we report odds ratios per 100 base pairs. To put this difference in TL in context, population-based studies have shown that TL differs by approximately 14 base pairs with each year of age (Needham and others 2015). This suggests that prior associations are biased in part by unobserved confounding or reverse causation, and may indicate that TL should be viewed as a marker rather than a determinant of disease.

While other studies have found that shorter telomeres are associated with other health outcomes that we examine here – including obesity, diabetes, hypertension, cancer, and arthritis – we are not able to confirm that there exists a causal relationship for these conditions (Codd and others 2013; Demissie and others 2006; Nai-chieh and others 2012; Pellatt and others 2013; Valdes and others ; Zhai and others 2006). Prior observational studies may suffer from confounding and reverse causation (i.e., the impacts of disease on TL), and thus a true causal link may not exist. Alternately, our null findings for these conditions may be a result of measurement error, in that HRS participants self-reported whether they had been diagnosed with each disease, or insufficient power in the individual-level analysis. Nevertheless, we replicated several of the null results using the meta-analytic approach, which is ideal for detecting small effect sizes. Unfortunately, GWAS databases are not available for the full range of health outcomes in HRS, so we are not able to confirm all of the findings using the meta-analytic approach.

Our results also suggest that there is no association between TL and psychiatric disease using individual-level data, with no association for depression specifically using the meta-analytic approach. Preliminary randomized studies have shown that meditation and stress reduction techniques may lead to increased telomerase activity – which is thought to promote telomere maintenance – and longer telomeres (Lavretsky and others 2013; Ornish and others 2013). This would suggest that improved mental health may bring about longer TL, while our study suggests that the reverse may not be true. Nevertheless, the primary limitation of the IV approach is that results represent a "local average treatment effect." In other words, our findings are that differences in TL *brought about by differences in genetic markers* do not lead to large differences in health outcomes. Our results therefore do not rule out the possibility that changes in TL brought about by changes in behaviors, social conditions, or other non-genetic factors may affect disease.

There are a few studies that have examined the relationship between TL-associated SNPs and health, rather than the association of telomeres with health. One study found no association between a TL-associated SNP – SIRT1 – and a variety of health outcomes, although this study was limited to a few hundred participants and only included a single SNP (Kim and others 2012a). Another study examined seven SNPs associated with TL, finding that several were associated with higher rates of cancer and autoimmune disease (Codd and others 2013). This analysis did not include other potential covariates to rule out confounding by genetic ancestry or socioeconomic position. For example, some sub-populations have different allele frequencies due to population stratification or disparities in social and environmental exposures, which would result in confounding because of different rates of disease (Hamad and others under review). Another study found that a single TL-associated SNP was associated with higher risks of heart disease and diabetes, but also failed to control for confounding by race or SEP (Maubaret and others 2013). None of these studies included a measure of TL, thus representing a reduced form estimate of the impact of the observed SNPs rather than a two-staged least-squares analysis of the impact of TL itself; in other words, these estimates provide only the association between the SNPs and the health outcomes, rather than the causal effect that acts through TL itself. Moreover, the effect size cannot be put into context with observational evidence obtained from studies relating TL to health. A fourth study involved a genetic IV analysis using nine TL-associated SNPs, and found no significant association with risk of diabetes (Nai-chieh and others 2012). This study did not consider other disease outcomes.

We were unable to conduct analyses to explore the relationship between TL and health among non-white participants, given that the overwhelming majority of GWAS databases are conducted among individuals of European ancestry. This highlights the need for further research to identify TL-associated SNPs among minority groups, and speaks to the larger gap in the literature on genetic studies among non-white populations (Bustamante and others 2011).

There are several avenues for future research to elaborate upon these findings. As additional TL-associated SNPs are identified and replicated in large samples, a more comprehensive PRS could be constructed that may result in a stronger genetic instrument. Further studies are also needed on the mechanisms through which social conditions may impact TL, and on

the biological mechanisms through which shortened telomeres may play a role in coronary artery disease.

This study has several limitations. First, the individual-level analyses may suffer from measurement error, in that health outcomes were self-reported by participants. It is unlikely to bias the results, but may contribute to the null findings in the HRS sample. Also, while HRS includes a representative and diverse sample of older adults, it is likely limited by survivorship bias and may not reflect the experiences of younger individuals. In other words, those with longer telomeres and a genetic propensity for longevity are over-represented. This form of censorship may result in collider bias, as participation in this study is conditional upon survival to age 50 (Boef and others 2015). Importantly, the meta-analytic approach does not suffer from survivorship bias to the same degree, as the GWAS samples are not limited to older individuals. Nevertheless, future individual-level studies should attempt to replicate these results in younger samples. The limited sample size in HRS also limits our ability to detect small effect sizes in this sample, increasing the chances of Type II error, although a primary strength of this study is the use of the meta-analytic approach that overcomes these limitations of the individual-level data.

Our study employs a two-sample genetic IV analysis to examine whether TL is causally related to human health. It improves upon findings from prior observational studies in its implementation of an IV approach that limits confounding by unobserved factors and precludes reverse causation. Our results are among the first to suggest that TL makes a small causal contribution to heart disease, but not other chronic disease outcomes. This represents a major advance in understanding the role of TL in human health.

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ABBREVIATIONS

BMI	body mass index
GWAS	genome-wide association studies
HRS	Health and Retirement Study
IV	instrumental variable
PRS	polygenic risk score
SNP	single nucleotide polymorphism
TL	telomere length

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HIGHLIGHTS

- Telomere length is associated with illness and mortality in observational studies.
- We apply Mendelian randomization to address confounding and reverse causation.
- Shorter telomeres raise the risk of heart disease with no effect for other diseases.
- Telomere length may be a marker of disease rather than a cause.

Table 1

Genome-wide Association Studies Included in Two-Sample Instrumental Variables Analyses

Study	Cases (N)	Controls (N)	Outcome of Interest	Data Repository Website
MAGIC	N/A	46,368	Hemoglobin A1c	http://www.magicinvestigators.org/
Stahl et al. (2010)	5,500	20,000	Rheumatoid arthritis	http://www.broadinstitute.org/ftp/pub/rheumatoid_arthritis/Stahl_etal_2010NG/
CARDIoGRAMplusC4D	22,233	64,762	Coronary artery disease	http://www.cardiogramplusc4d.org/
Psychiatric Genomics Consortium	18,478	17,558	Depression	http://www.med.unc.edu/pgc/downloads
GIANT Consortium	N/A	339,224	Body mass index	http://www.broadinstitute.org/collaboration/giant/index.php/GIANT_consortium_data_files

Table 2

Sample Characteristics, Health and Retirement Study

Demographics	
Female (%)	58.2
Education (%)	
Less than high school	13.3
High school / GED	38.3
Some college	23.8
College or more	24.6
Age in 2008	
Mean ± SD	69.5 ± 10.2
Median (IQR)	70 (62, 77)
Disease Diagnoses (%)	
Diabetes	20.5
Hypertension	61.4
Stroke	10.6
Arthritis	67.8
Heart disease	31.9
Lung disease	13.7
Psychiatric Illness	19.0
Cancer	19.7
Obesity	39.2
Genetic Characteristics	
Weighted polygenic risk score	
Mean ± SD	4.61 ± 1.08
Median (IQR)	4.66 (3.92, 5.33)
Telomere length in base pairs	
Mean ± SD	3166 ± 1248
Median (IQR)	3020 (2658, 3482)

N = 3,734. Only non-Hispanic white study participants with genetic and telomere data are included. For obesity, an individual is counted as a case if she ever had a body mass index greater than 30 based on self-reported height and weight. For other disease outcomes, an individual is counted as a case if she ever self-reported being diagnosed with that disease by a doctor.

Table 3

Association between Polygenic Risk Score and Telomere Length, First Stage of Instrumental Variable Analysis.

	β Coefficient [95% CI]
Polygenic risk score	−43.00 [−96.94, 10.93]
Sex (ref Male)	
Female	23.79 [−71.02, 118.61]
Education (ref <HS)	
High school	125.34* [9.40, 241.28]
Some college	135.63* [31.39, 239.88]
College	106.13* [9.64, 202.62]
Age	−7.08** [−11.70, −2.47]
Constant	3,766** [3,338, 4,194]
F-statistic	0.48

Note:

* $p < 0.05$,

** $p < 0.01$.

N = 3,734. Analyses conducted using individual-level data from the Health and Retirement Study. Standard errors are clustered by household. Additional covariates include four principal components-derived measures of genetic ancestry.

Table 4

Two-Sample Instrumental Variables Analyses of Impact of Telomere Length on Health, with Individual-Level Data from Health and Retirement Study

	Odds Ratio [95% CI]								
	Diabetes	**Arthritis**	**Stroke**	**Heart Disease**	**Lung Disease**	**HTN**	**Psychiatric Disease**	**Cancer**	**Obesity**
TL (per 100bp difference)	1.00 [0.93, 1.08]	1.00 [0.93, 1.06]	0.92 [0.83, 1.01]	1.06 [0.99, 1.13]	0.95 [0.87, 1.04]	0.96 [0.89, 1.04]	1.05 [0.97, 1.13]	0.96 [0.90, 1.03]	1.01 [0.95, 1.07]
Sex (ref Male)									
Female	0.58** [0.49, 0.68]	1.71** [1.48, 1.96]	0.63** [0.51, 0.78]	0.58** [0.50, 0.67]	0.95 [0.78, 1.15]	0.83* [0.70, 0.98]	1.70** [1.43, 2.02]	0.94 [0.83, 1.08]	0.85* [0.74, 0.98]
Education (ref <HS)									
High school	0.74* [0.59, 0.94]	0.71** [0.56, 0.91]	0.98 [0.72, 1.34]	0.89 [0.71, 1.11]	0.63** [0.49, 0.82]	1.09 [0.84, 1.41]	0.58** [0.45, 0.74]	0.89 [0.72, 1.11]	0.86 [0.69, 1.07]
Some college	0.65** [0.50, 0.84]	0.72* [0.55, 0.93]	0.73 [0.52, 1.04]	0.83 [0.65, 1.05]	0.51** [0.38, 0.68]	1.04 [0.78, 1.38]	0.51** [0.39, 0.68]	0.87 [0.69, 1.10]	0.83 [0.65, 1.06]
College	0.46** [0.35, 0.60]	0.49** [0.38, 0.63]	0.68* [0.48, 0.97]	0.61** [0.48, 0.78]	0.29** [0.21, 0.41]	1.15 [0.86, 1.52]	0.50** [0.38, 0.67]	0.54** [0.42, 0.68]	0.65** [0.52, 0.83]
Age	1.01 [1.00, 1.01]	1.04** [1.03, 1.05]	1.06** [1.05, 1.07]	1.05** [1.04, 1.05]	1.02** [1.01, 1.03]	1.04** [1.04, 1.05]	0.97** [0.96, 0.98]	0.97** [0.96, 0.98]	1.03** [1.03, 1.04]
Constant	0.43* [0.21, 0.89]	0.15** [0.075, 0.31]	0.0025** [0.00082, 0.0074]	0.022** [0.011, 0.043]	0.092** [0.039, 0.21]	0.0087** [0.0022, 0.034]	1.61 [0.74, 3.50]	6.51** [3.24, 13.0]	0.20** [0.10, 0.40]

Note:

* $p < 0.05$,

** $p < 0.01$.

N = 3,734. TL = telomere length = (T/S) * 2,400. Analyses conducted using logistic regressions, with the weighted polygenic risk score used as an instrument for TL. Standard errors are clustered by household. Additional covariates include four principal components-derived measures of genetic ancestry.

Table 5

Two-Sample Instrumental Variables Analyses of Impact of Telomere Length on Health, using Inverse Variance-Weighted Approach

	Coefficient [95% CI]				
	Hemoglobin A1c	**Rheumatoid Arthritis**	**Heart Disease**	**Depression**	**Body Mass Index**
TL (per 100bp difference)	0.00 [0.00, 0.00]	0.98 [0.95, 1.01]	1.02** [1.00, 1.03]	1.00 [0.97, 1.03]	0.00 [0.00, 0.00]

Note:

* $p < 0.05$.

TL = telomere length = (T/S) * 2,400. Analyses conducted using inverse variance-weighted meta-analytic technique. Coefficients for arthritis, heart disease, and depression represent odds ratios, while values for hemoglobin A1c and BMI represent beta coefficients.