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Childhood adversities are associated with shorter leukocyte telomere length at adult age in a population-based study

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ABSTRACT

Telomeres are repeat sequences and an associated protein complex located at the end of the chromosomes. They shorten with every cell division and are regarded markers for cellular aging. Shorter leukocyte telomere length (LTL) has been observed in many complex diseases, including psychiatric disorders. However, analyses focusing on psychiatric disorders are mainly based on clinical samples and the significance of shorter LTL on the population level remains uncertain. We addressed this question in a population-based sample from Finland (N = 7142). The survey was performed and the blood samples were collected in 2000–2001 to assess major public health problems and their determinants. DSM-IV diagnoses of major psychiatric illnesses were obtained by interview using the Composite International Diagnostic Interview. Information regarding their risk factors, including the number of self-reported childhood adversities, recent psychological distress, and sleep difficulties was collected by questionnaires. LTL was measured by qPCR. None of the studied psychiatric illnesses, sleep difficulties, or recent psychological distress associated with LTL. However, individuals with three or more childhood adversities had shorter LTL at adult age ($\beta = -0.006$, $P = 0.005$). Also, current occupational status was associated with LTL ($\beta = -0.03$, $P = 0.04$). These effects remained significant after adjusting for known LTL-associated lifestyle or sociodemographic factors. In conclusion, relatively common childhood adversities were associated with shorter LTL at adult age in a nationally representative population-based cohort, implying that childhood adversities may cause accelerated telomere shortening. Our finding has potentially important implications as it supports the view that childhood adversities have an impact on psychological and somatic well-being later in life.

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1. Introduction

Telomere length is considered a marker for biological age of a cell (Blasco, 2005). Telomeres are nucleoprotein complexes consisting of TTAGGG DNA repeats at the extreme ends of chromosomes. Their function is to maintain chromosomal integrity. Telomeres progressively shorten with each cell division in proliferative cells, leading ultimately to chromosomal fusion and programmed cell death. Cells can counteract telomere shortening with telomerase, a telomere synthesizing enzyme, but it is expressed at a low level in somatic cells (von Zglinicki, 2002). In non-proliferative cells, telomere shortening is associated with cytotoxic factors, such as reactive oxygen species (ROS) that damage telomere DNA. Therefore, telomere length also informs about ROS levels and function of cells (Blasco, 2005). Leukocyte telomere length (LTL) has been suggested as an indicator of current and prospective risk for medical illnesses based on its assumed capacity to function as a cumulative index of oxidative stress and inflammation (Demissie et al., 2006). Both genetic and environmental factors affect telomere length, and several genetic variants have been associated with LTL (Codd et al., 2013). Environmental factors associated with LTL include smoking, poor sleep, physical inactivity, and psychological distress (Tempaku et al., 2015; Mathur et al., 2016; Arsenis et al., 2017; Zhan and Hägg, 2019). Shorter LTL predicts all-cause mortality in the general population, and it is associated with many chronic diseases, including cardiovascular diseases, cancer, and psychiatric illness (Epel et al., 2004; Lindqvist et al., 2015; Cleal et al., 2018).

In case-control studies or clinical samples of psychiatric illnesses, all common psychotic disorders and bipolar disorder have been associated with shorter LTL (Huang et al., 2018; Russo et al., 2018). Also, patients with major depressive disorder and anxiety disorders have shorter LTL (Verhoeven et al., 2016; Vance et al., 2018; Verhoeven et al., 2018) compared to controls. For alcohol consumption, results are mixed, but the largest studies have failed to associate the amount of alcohol consumed with telomere length or LTL attrition rate (Monroy-Jaramillo et al., 2018; Dixit et al., 2019). Studies using population-based cohorts are rarer. Anxiety disorders, but not major depression, associated with shorter LTL in a population ascertained from the city of Groningen (Hoen et al., 2013). In population-based studies of current depressive disorder (Shaffer et al., 2012), internalizing problems (Shalev et al., 2014), and alcohol consumption (Wang et al., 2017) LTL was similar to controls. However, post traumatic disorder (PTSD) (Ladwig et al., 2013) and insomnia disorder were associated with shorter LTL in population-based cohorts (Tempaku et al., 2018). Thus, further large population-based studies are needed to replicate the earlier findings and to assess the importance of LTL in psychiatric disorders in general.

Risk factors for psychiatric disorders have also been associated with shorter LTL. The original observation of Epel et al. (2004) that self-perceived psychological stress is associated with shorter LTL has been widely extended to childhood adversities. Childhood adversities may impact childhood health in multiple ways, including effects on cognitive development, weight gain, and sleep (Li et al., 2017). Childhood adversities have also been linked to all-cause mortality (Martikainen et al., 2020) and shorter LTL in meta-analyses (Ridout et al., 2018; Bürgin et al., 2019). Some reviews on the topic, however, point out the heterogeneity of the studies, excess of clinical and small sample studies (Ridout et al., 2019), and that also longer LTL has been associated with childhood adversities (Mayer et al., 2019). The effect of cumulative stress may thus be more important for the LTL than a single episode of stress. Cumulative stress has indeed been linked with shorter LTL and a faster LTL attrition rate. For example, in children, repeated exposure to violence has been associated with shorter LTL and telomere attrition at a 5-year follow up (Shalev et al., 2013). Many studies have investigated severe stressful events, e.g., repeated violence or severe abuse, and relatively little is known about more subtle and more common stressors that affect people widely in the general population. Given these inconsistencies, additional studies are needed to understand the

significance of short LTL as a marker for childhood adversities and well-being later in life.

To determine the significance of major psychiatric disorders and their risk factors on LTL at the population level, we measured LTL in the epidemiological Health 2000 Cohort that represents the adult Finnish population, aged 30 years or older. The investigated risk factors included childhood adversities, recent perceived psychosocial stress, and sleep phenotypes, while carefully controlling for lifestyle and sociodemographic factors.

2. Materials and methods

2.1. The Health 2000 sample

We have earlier found an association between a larger number of childhood adversities and shorter leukocyte telomere length (LTL) in a subsample of the Health 2000 cohort, consisting of 321 individuals with DSM-IV anxiety disorder or subthreshold diagnosis and 653 matched controls (Kananen et al., 2010). In the present study, we assessed LTL in the entire cohort (N = 8028), with unbiased representation of the whole Finnish population of age 30 or over. Number of subjects varied from variable to variable, and detailed information about each variable is presented in the Supplement Table 1. The National Public Health Institute (currently National Institute for Health and Welfare) collected the Health 2000 cohort during 2000 and 2001 to assess the major public

Table 1

Current diagnosis of a DSM-IV psychiatric disorder, current stress, sleep disturbances, lifestyle factors, or adulthood socioeconomic status do not associate with leukocyte telomere length. Results from 16 different independent linear regression models are shown, each including PCR plate, age, and sex as covariates. GHQ= General health questionnaire, BMI=body mass index, LTL=leukocyte telomere length.

	Unstandardized coefficients	Standardized coefficients	P-value	95.0% confidence interval for β	
	β	β		Lower Bound	Upper Bound
Sex	0.045	0.104	1.0 10^{-6}	0.034	0.056
Age	-0.005	-0.322	4.2 10^{-6}	-0.005	-0.004
PCR plate	0.001	0.105	2.6 10^{-25}	0.001	0.001
Any anxiety disorder	-0.006	-0.006	0.618	-0.029	0.017
Depression or dysthymia	-0.011	-0.012	0.356	-0.036	0.013
Any psychotic disorder	-0.001	0.000	0.997	-0.031	0.031
Any substance abuse	-0.005	-0.020	0.125	-0.012	0.001
GHQ total score	-0.001	-0.013	0.326	-0.021	0.034
Difficulties falling asleep	-0.006	-0.021	0.110	-0.012	0.001
Early morning awakenings	-0.002	-0.009	0.482	-0.009	0.004
Tiredness	0.005	0.017	0.176	-0.002	0.013
Sleep length	0.000	-0.001	0.945	-0.014	0.013
BMI	-0.001	-0.017	0.163	-0.002	0.000
Physical activity	0.001	0.003	0.805	-0.005	0.007
Smoking	0.003	0.017	0.168	-0.001	0.008
Marital status	0.000	0.003	0.836	-0.003	0.004
Education	0.001	0.003	0.535	-0.001	0.002
Hospital district	0.001	0.015	0.202	-0.005	0.001
Occupational status	-0.006	-0.029	0.045	-0.013	-0.001

a Dependent Variable: LTL

health problems, functional capacity and their determinants representatively of the Finnish mainland population (Aromaa, 2004). The sample was recruited as a two-stage stratified cluster sample, with the five university hospital districts, each serving about one million inhabitants, as strata. First, the 15 largest towns in Finland were included with a probability of one. Next, within each of the five districts, 65 other areas were sampled applying the probability proportional to population size (PPS) method. Finally, from each of these 80 areas, a random sample of individuals was drawn from the National Population Register, the total number of people drawn from each stratum being proportional to the population size of the area in question (Pirkola et al., 2005). The study protocol was approved by the Helsingin and Uudenmaan Hospital District ethics committee and National Public Health Institute (nowadays National Institute for Health and Welfare) ethics committee. All participants received written information about the study and all subjects gave their written consent to participate in the study.

2.2. Psychiatric diagnoses

Current mental illness, including psychoses, alcohol dependence or abuse, major depression or dysthymia, and anxiety disorders were assessed in a structured psychiatric interview (Munich Composite International Diagnostic Interview, M-CIDI) using DSM-IV criteria (Assouline, 2000). The diagnosed anxiety disorders included panic disorder, generalized anxiety disorder, social phobia, agoraphobia, and phobia not otherwise specified.

2.3. Childhood psychosocial stress

Childhood psychosocial stress was assessed with various measures. First, parental death of one or both parents under age of 16 years was examined. Second, we studied childhood socioeconomic status based on the subject-informed educational status of the father and the mother. The education level was classified into three categories: basic, secondary, and higher. If the father and mother had different education levels, the higher level was taken to represent the entire family.

Third, childhood adversities were assessed with a questionnaire containing a series of 11 questions regarding the childhood social environment before age of 16 (Pirkola et al., 2005; Heistaro, 2008). The questionnaire was given to the subjects during the home interview. The subjects were instructed to choose “no”, “yes”, or “cannot say” when asked the following: “When you think about your growth years, i.e., before you were age 16.”

1. Did your family have long-term financial difficulties?
2. Were your father or mother often unemployed although they wanted to work?
3. Did your father or mother suffer from some serious disease or disability?
4. Did your father have alcohol problems?
5. Did your mother have alcohol problems?
6. Did your father have any mental health problem, e.g., schizophrenia, other psychosis, or depression?
7. Did your mother have any mental health problem, e.g., schizophrenia, other psychosis, or depression?
8. Were there any serious conflicts within your family?
9. Did your parents divorce?
10. Were you yourself seriously or chronically ill?
11. Were you bullied at school?

Only “yes” answers were coded positive, and the total number of reported adversities per subject was recorded from 0 to 11, and was categorized into four groups: 0 (N = 2695), 1 (N = 1656), 2 (N = 983), or 3–11 (N = 1021) adversities. This categorization was based on the distribution of the number of adversities and follows quartiles to obtain approximate same sized categories. In the original sample, 48.7% of

responders reported 0 adversities, 15.7% reported one, 12.6% reported two, and 23.2% reported three or more adversities.

2.4. Recent psychosocial stress

Self-perceived recent psychosocial distress was assessed with the 12-item General Health Questionnaire (GHQ) (Goldberg and Williams, 1988).

2.5. Sleep

Sleep difficulties were assessed by questionnaire-based self-reports. Four questions were used to screen for self-reported sleep difficulties: 1. difficulties initiating sleep, 2. difficulties maintaining sleep (awakenings during the night or very early in the morning), 3. fatigue, and 4. tiredness (Kronholm et al., 2009). Each question had answer alternatives in a four-point Likert scale from “not at all” to “every night or nearly every night”, except for tiredness. The tiredness question was “Are you usually more tired during daytime than other people of your age?”, and the subjects were asked to answer “yes, almost every time”, “yes”, “often”, “no I am not”, and “I don't know”. Secondly, total sleep time was asked and dichotomized into short sleep (<6 hrs) or normal sleep (6–9 hrs). Those who slept 10 or more hours were omitted from the analysis (N = 189) because very long sleep associates with several health adversities, and thus may affect LTL.

2.6. Sociodemographic factors

We studied the following sociodemographic factors: age, sex, university hospital district (five in the entire country, representing Northern, Eastern, Western, Southwestern, and Southern Finland, each with approximately 1 million inhabitants), marital status (1. married or living as married, 2. divorced, 3. widow, 4. unmarried), education (divided into three categories based on general education and on higher and vocational education), and current employment status (1. full or part-time employed, 2. unemployed or laid off, 3. retired, 4. other).

2.7. Lifestyle factors

Other studied variables previously associated with LTL included body mass index (kg/m²), smoking (yes/no), and physical activity (1. ideal = at least 30 min leisure time physical activity at least 4 days a week and at least 30 min walking or bicycling to work, 2. adequate = at least 30 min leisure time physical activity at least 4 days a week or at least 30 min walking or bicycling to work, 3. uncertain, 4. inadequate).

2.8. Telomere length measurement

LTL was determined by a quantitative real-time PCR-based method from genomic DNA extracted from peripheral blood (Kananen et al., 2010). Relative LTL was determined by dividing the value from absolute quantification of telomere DNA amount by a single copy reference gene, β -hemoglobin, amount (T/S ratio). To analyze 7364 DNA samples in 80 plates (i.e. batches), we used the same high through-put method as before (Kananen et al., 2010), except that the standard curve was modified for this sample. It consisted of a series of genomic DNA dilutions: 0.5, 1.0, 2.5, 5.0, 7.5, 10.0, and 15.0 ng, and was present on each 384-well plate. The correlation coefficient of the standard curve was on average 0.997 for the telomere reaction (range 0.994–0.999) and 0.997 for β -hemoglobin reaction (range 0.993–0.999). The corresponding PCR reaction efficiencies were 88.4% for the telomere reaction (range 77.8–97.1%) and 92.7% for β -hemoglobin reaction (range 85.9–100.4%).

Following qPCR, quality control was performed. Samples with triplicate standard deviation exceeding 0.5 were excluded. Also, samples with no amplification or outside of the standard curve, and outliers that

deviated more than 3 standard deviations from the mean were removed leaving a total of 7142 samples. Plate effect was taken into account by normalizing the telomere signal and the reference gene signal to the corresponding average of five control samples analyzed on every qPCR plate. These control samples were also used to calculate the inter-assay correlation of coefficient (CV) % based on their mean and standard deviation values on the 80 plates. The CV% was 6.96% for the telomere, 5.48% for the β -hemoglobin reaction, and 8.06% for their ratio (T/S).

2.9. Statistical analysis

Statistical analysis was carried out using SPSS v.26. Multiple linear regression modelling was carried out with LTL as the dependent variable to assess the influence of a psychiatric diagnosis, sleep, or risk factors on LTL. Age, sex, and PCR plate were adjusted in the regression modelling. Population weight coefficient adjusting for sampling effects were also included in the analysis. The significance P value threshold was set to 0.05, uncorrected for multiple testing.

3. Results

3.1. LTL associates with age and sex

One of the most consistent findings in epidemiological studies of telomere length is the inverse association of LTL with age. We also found that LTL was significantly affected by age ($\beta = -0.322$, $P = 4.23 \times 10^{-6}$) and sex ($\beta = 0.104$, $P = 1.0 \times 10^{-6}$; Fig. 1), with younger individuals and females having longer LTL than older individuals and males, as expected. Also, the qPCR plate (batch) had a significant effect on LTL ($\beta = 0.105$, $P = 2.6 \times 10^{-25}$), despite careful measures to avoid variation between batches.

3.1.1. No association of current diagnosis of mental illness, recent psychological distress, or subjective sleep traits with LTL

We first investigated if current diagnosis of mental illness, or their risk factors, including psychological distress or sleep difficulties affect LTL. The DSM-IV diagnoses available for this study included psychoses, major depression or dysthymia, anxiety disorders, and alcohol use disorder. We tested their effect on LTL in individual linear regression models. None of them significantly associated with LTL (Table 1). Recent psychological distress, as measured by the 12-item version of the General Health Questionnaire did not significantly affect LTL either. Current sleep difficulties, measured with questions concerning sleep length, difficulties falling asleep, early morning awakenings, and tiredness did not influence LTL either. All sleep variables correlated with each other modestly or highly significantly (correlation coefficients

varying between 0.24 and 0.58, $P < 1 \times 10^{-4}$).

3.1.2. Shorter LTL in individuals with more childhood adversities

We next examined the effect of childhood psychosocial stress on LTL. The categorized childhood adverse life events score predicted shorter LTL at adult age ($\beta = -0.006$, $P = 0.005$); adjusted by age, sex and PCR plate; (Table 2 and Fig. 2). Of the individual adversities none had a significant effect alone (Table 3).

Our childhood adversities questionnaire detects relatively mild adversities which are rather common in the Finnish population. As a more traumatic childhood adversity, we investigated the effect of paternal or maternal death before age of 16 ($N = 735$), but it did not affect LTL ($\beta = 0.009$, $P = 0.43$, Table 2). We also examined whether childhood family's socioeconomic status could weaken the association between adversities and LTL, but this was not the case ($\beta = -0.016$, $P = 0.216$; Table 2).

The effect of childhood adversities on LTL at adult age remained significant after adjusting for past 12-month psychosis, alcohol use disorder, depression or dysthymia, and anxiety disorder diagnoses ($\beta = -0.030$, $P = 0.02$).

The effect of the childhood adversities on shorter LTL at adult age remained significant also after adjusting for known LTL-affecting lifestyle factors body mass index, smoking, and physical activity ($\beta = -0.030$, $P = 0.013$) and sociodemographic factors including marital status, education, employment status, and hospital district ($\beta = -0.03$, $P = 0.01$). In this analysis, the current employment status significantly associated with LTL ($\beta = -0.033$, $P = 0.006$).

4. Discussion

We used the nationwide population-based Health 2000 Study to investigate the influence of major mental disorders and their risk factors on LTL. Current mental health diagnoses, symptoms of disturbed sleep, or recent psychological distress did not associate with LTL. However, we observed a negative association between childhood adversities and LTL. Thus, we confirm the previous results of negative association between childhood adversities and LTL, and extend them to show that this effect can be detected in a large, nationally representative population-based sample with a wide age range (30–98 years). Our results support earlier findings that childhood stress may lead to accelerated telomere shortening observable at the adult age (Ridout et al., 2019).

Stress is not a monolith, but a process that involves constant interactions with the surrounding environment, promoting various types of emotional and behavioral responses, which in turn further shape the interaction with the stressor. Stress can be conceptualized based on its characteristics, e.g., acute, event-based vs daily-appearing, chronic type (Epel and Prather, 2018). In our sample, most studied stressors were of chronic, daily-affecting type. None of the single stressors had a significant effect on LTL alone, which is in line with the study of Puterman et al. (2016). They reported that multiple stressors had a cumulative effect on buccal cell TL, unlike any single stressor alone. The type of stress can have profound effects on the biological outcomes of a stress exposure. In a meta-analysis of > 116,000 subjects stressors related to threat (e.g., violence) were associated with LTL and DNA methylation age, whereas stressors related to neglect, such as deprivation and socioeconomic status (SES), were not (Colich et al., 2020). Threat-related stressors were also associated with accelerated pubertal development and cortical thinning in the ventromedial prefrontal cortex. The questions we used did not directly ask exposure to violence or threat because the aim of our questionnaire was to assess more common childhood adversities. Also, timing of a stressor regarding child's age and developmental stage can have a profound effect on its physiological effects. In our sample, stressors were timed to childhood and puberty, up to 16 years of age. Thus, acute, severe stressors may affect LTL differently than chronic mild stress, and these effects may also depend on their timing with respect to specific developmental windows.

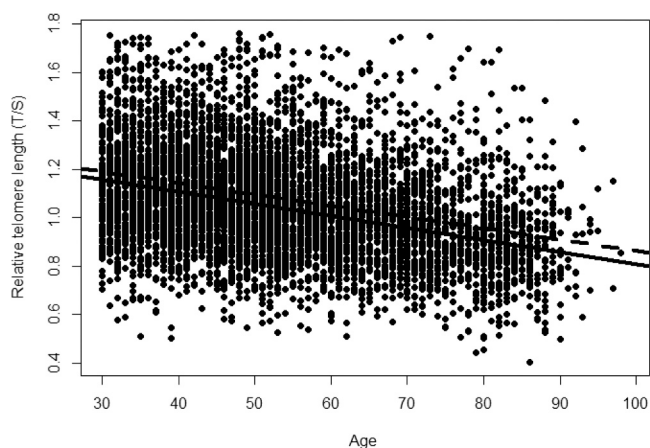


Fig. 1. Telomere length as a function of age and sex. Regression lines for males are shown as a dashed line and for females as a solid line.

Table 2

The number of childhood adversities associates with leukocyte telomere length at adult age, whereas parental death nor childhood socioeconomic status do not. Results from three different independent models are shown, each including age, sex, and PCR-plate as covariates. Childhood adversities were categorized into four groups (0, 1, 2, or 3–11), LTL=leucocyte telomere length. SES= socioeconomic status.

	Unstandardized coefficients		Standardized coefficients	Sig.	95.0% Confidence interval for β	
	β	β	β		Lower bound	Upper bound
Sex	0.045		0.104	1.0 10 ⁻⁶	0.034	0.056
Age	-0.005		-0.322	1.0 10 ⁻⁶	-0.005	-0.004
PCR plate	0.001		0.105	2.6 10 ⁻²⁵	0.001	0.001
Childhood adversities	-0.006		-0.033	0.005	-0.010	-0.002
Parental death	0.007		0.009	0.430	-0.010	0.023
Childhood SES	-0.006		-0.016	0.216	-0.016	0.004

a Dependent Variable: LTL

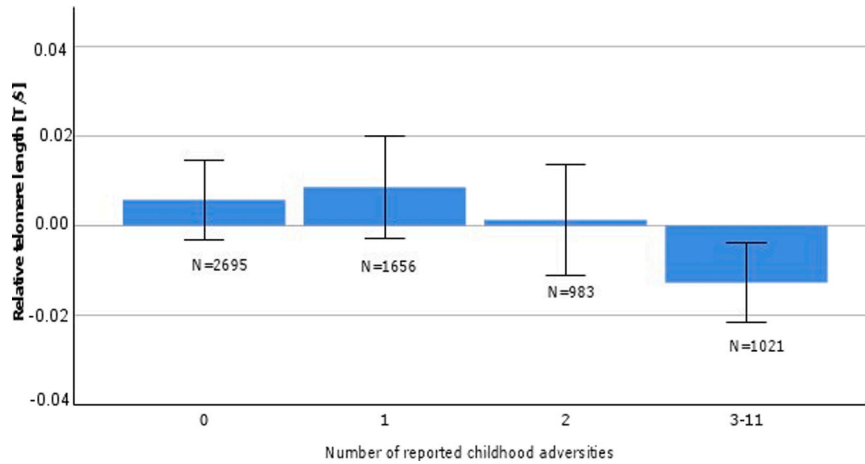


Fig. 2. The number of childhood adversities significantly affects leukocyte telomere length at adult age. Relative telomere length was adjusted for age, sex, and PCR plate. Childhood adversities were categorized into four groups (0, 1, 2, or 3–11) and the number of individuals in each category is shown. LTL=leucocyte telomere length, error bars: 95% CI.

Table 3

Leukocyte telomere length at adult age is not affected by individual adversities. Results from 11 independent regression models, each including PCR-plate, age, and sex as covariates.

	Unstandardized coefficients		Standardized coefficients	P-value	95.0% Confidence interval for β	
	β	β	β		Lower bound	Upper bound
Childhood adversity						
1. Financial difficulties	-0.003	-0.010		0.420	-0.010	0.004
2. Parental unemployment	-0.007	-0.017		0.180	-0.016	0.003
3. Parental medical illness or injury	0.000	0.000		0.981	-0.009	0.009
4. Paternal alcohol problems	-0.007	-0.018		0.141	-0.015	0.002
5. Maternal alcohol problems	-0.013	-0.018		0.153	-0.031	0.005
6. Paternal mental health problems	-0.009	-0.020		0.113	-0.020	0.002
7. Maternal mental health problems	0.009	-0.018		0.136	-0.022	0.003
8. Family discord	-0.006	-0.020		0.111	-0.014	0.001
9. Parental divorce	-0.015	-0.023		0.065	-0.030	0.001
10. Own serious or chronic illness	-0.004	-0.007		0.573	-0.020	0.011
11. Bullied at school	0.000	0.001		0.962	-0.010	0.011

The relationship between childhood adversities and mental health problems is well-characterized (Hughes et al., 2017). In our sample, childhood adversities correlated significantly with having a current psychiatric disorder (p-values ranging from 2.32×10^{-15} to 0.04). However, correlation coefficients were modest, between 0.10 and 0.03. It was thus interesting to note, that having a psychiatric disorder did not associate with LTL. A moderate dose-response relationship exists between the total number of experienced adversities and mental health problems, in addition to a strong sex specific effect between the type of adversity and the type of mental health problem (Pirkola et al., 2005). Another association we found was between LTL and occupational status, with employed individuals having longer LTL than non-employed. As expected, having a psychiatric diagnosis also correlated with the

occupational status, creating a possible issue of collinearity with multiple contributing factors (Sackett, 1979). The previous literature on the topic seems mixed. One study reported that women who currently work full-time have shorter LTL than non-employed women with moderate or substantial work history (Parks et al., 2011). In men, one study found that being out of work associated with shorter LTL compared to being employed (Batty et al., 2009), while another study found no effect of occupational status and LTL (Fujishiro et al., 2013). The association between occupational status and LTL might be moderated by several factors, e.g., work-related exhaustion which we previously showed in our sample (Ahola et al., 2012). Additional studies are needed to assess whether there is a true association between employment status and LTL or whether this finding reflects other associated factors, such as

work-related exhaustion.

Our study has some limitations. The childhood adversity questionnaire we used is not validated against other similar instruments, but the questions are convergent with those widely used in the previous research (Ahola et al., 2006; Hanssen et al., 2017). In addition, several studies using the same questionnaire has been published, for example investigating sex-specific role of traumatic childhood experiences and adverse experiences in developing adulthood mental disorders (Pirkola et al., 2005) and especially first episode psychosis (Lindgren et al., 2017; Morales-Muñoz et al., 2018). These studies demonstrate the useability of this questionnaire to predict various outcomes. The questionnaire did not include severe childhood adversities, such as maltreatment or sexual abuse. On the other hand, these stressors have been largely covered in other studies. We investigated parental death as a single, more severe stressor, and it did not associate with LTL on a population level. Regarding adulthood stressors, we were limited to recent psychological distress and did not have an instrument to measure cumulative stress. Our study is cross-sectional and therefore we were unable to address telomere dynamics and rate of LTL shortening. Studies conducting a follow up have reported LTL attrition in relation to childhood adversities during a five-year period in childhood (Shalev et al., 2013). Moreover, cross-sectional studies may be affected by the recall bias. However, a previous study found no difference in telomere length associations when information from records or information collected from self-reported questionnaires were used (Hanssen et al., 2017).

In conclusion, we found that having a current psychiatric disorder is not associated with LTL on a population level. This result is in line with previous population-based studies. The previously observed associations of shorter LTL and psychiatric disorders are more prevalent in patient cohorts and in other high-risk groups that likely represent more severe forms of mental illness. Our main finding was that relatively common childhood adversities were associated with shorter LTL at adult age, and this effect could be detected in a nationally representative population-based cohort. Our results extend the previous findings on the relationship of childhood adversities and shorter LTL observed in smaller cohorts and patient groups into general population. Our results imply that childhood adversities may cause accelerated telomere shortening. Our finding has potentially important implications as it supports the view that childhood adversities may have a considerable impact on psychological and somatic well-being later in life.

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Author contributions

Study design: AJÄ, TP, IH. Obtained funding: IH. Data acquisition: JS, JL, SR and SP (the Health 2000 Sample) and LK and IH (LTL measurement). Data analysis and interpretation AJÄ (statistical analysis) and LK (LTL data). Drafting of the work AJÄ and IH. Revising paper critically for important intellectual content: JS, LK, JL, SR, SP, TP. All authors provided the final approval to the submitted version and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declarations of interest

None.

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References

- Ahola, K., Honkonen, T., Pirkola, S., Isometsä, E., Kalimo, R., Nykyri, E., Aromaa, A., Lönnqvist, J., 2006. Alcohol dependence in relation to burnout among the Finnish working population. *Addiction* 101 (10), 1438–1443.
- Ahola, K., Sirén, I., Kivimäki, M., Ripatti, S., Aromaa, A., Lönnqvist, J., Hovatta, I., 2012. Work-related exhaustion and telomere length: a population-based study. *PLoS One* 7 (7), 40186.
- Aromaa, A., 2004. Health and Functional Capacity in Finland: Baseline Results of the Health 2000 Health Examination Survey in Kansanterveyslaitoksen Julkaisuja B. National Institute of Health and Welfare (THL), Helsinki.
- Arsenis, N.C., You, T., Ogawa, E.F., Tinsley, G.M., Zuo, L., 2017. Physical activity and telomere length: Impact of aging and potential mechanisms of action. *Oncotarget* 8 (27), 45008–45019.
- Association, A.P., 2000. Diagnostic and statistical manual of mental disorders (4th ed., text rev.). Washington, DC.
- Batty, G.D., Wang, Y., Brouillette, S.W., Shiels, P., Packard, C., Moore, J., Samani, N.J., Ford, I., 2009. Socioeconomic status and telomere length: the west of Scotland coronary prevention study. *J. Epidemiol. Community Health* 63 (10), 839–841.
- Blasco, M.A., 2005. Telomeres and human disease: ageing, cancer and beyond. *Nat. Rev. Genet.* 6 (8), 611–622.
- Bürgin, D., O'Donovan, A., d'Huurt, D., di Gallo, A., Eckert, A., Fegert, J., Schmeck, K., Schmid, M., Boonmann, C., 2019. Adverse childhood experiences and telomere length a look into the heterogeneity of findings—a narrative review. *Front. Neurosci.* 13, 490.
- Cleal, K., Norris, K., Baird, D., 2018. Telomere length dynamics and the evolution of cancer genome architecture. *Int. J. Mol. Sci.* 19, 2.
- Codd, V., Nelson, C.P., Albrecht, E., Mangino, M., Deelen, J., Buxton, J.L., Hottenga, J.J., Fischer, K., Esko, T., Surakka, I., Broer, L., Nyholt, D.R., Mateo Leach, I., Salo, P., Hägg, S., Matthews, M.K., Palmen, J., Norata, G.D., O'Reilly, P.F., Saleheen, D., Amin, N., Balmforth, A.J., Beekman, M., de Boer, R.A., Böhringer, S., Braund, P.S., Burton, P.R., de Craen, A.J., Denniff, M., Dong, Y., Douroudis, K., Dubinina, E., Eriksson, J.G., Garlaschelli, K., Guo, D., Hartikainen, A.L., Henders, A.K., Houwing-Duistermaat, J.J., Kananen, L., Karssen, L.C., Kettunen, J., Klopp, N., Lagou, V., van Leeuwen, E.M., Madden, P.A., Mägi, R., Magnusson, P.K., Männistö, S., McCarthy, M.I., Medland, S.E., Mihailov, E., Montgomery, G.W., Oostra, B.A., Palotie, A., Peters, A., Pollard, H., Pouta, A., Prokopenko, I., Ripatti, S., Salomaa, V., Suchiman, H.E., Valdes, A.M., Verweij, N., Viñuela, A., Wang, X., Wichmann, H.E., Widen, S., Willemssen, G., Wright, M.J., Xia, K., Xiao, X., van Veldhuisen, D.J., Catapano, A.L., Tobin, M.D., Hall, A.S., Blakemore, A.I., van Gilst, W.H., Zhu, H., CARDIoGRAM, c, Erdmann, J., Reilly, M.P., Kathiresan, S., Schunkert, H., Talmud, P. J., Pedersen, N.L., Perola, M., Ouwehand, W., Kaprio, J., Martin, N.G., van Duijn, C. M., Hovatta, I., Gieger, C., Metspalu, A., Boomsma, D.I., Jarvelin, M.R., Slagboom, P. E., Thompson, J.R., Spector, T.D., van der Harst, P., Samani, N.J., 2013. Identification of seven loci affecting mean telomere length and their association with disease. *Nat. Genet.* 45 (4), 422–427, 427e1–2.
- Colich, N.L., Rosen, M.L., Williams, E.S., McLaughlin, K.A., 2020. Biological aging in childhood and adolescence following experiences of threat and deprivation: a systematic review and meta-analysis. *Psychol. Bull.* 146 (9), 721–764.
- Demissie, S., Levy, D., Benjamin, E.J., Cupples, L.A., Gardner, J.P., Herberg, A., Kimura, M., Larson, M.G., Meigs, J.B., Keaney, J.F., Aviv, A., 2006. Insulin resistance, oxidative stress, hypertension, and leukocyte telomere length in men from the Framingham heart study. *Aging Cell* 5 (4), 325–330.
- Dixit, S., Whooley, M.A., Vittinghoff, E., Roberts, J.D., Heckbert, S.R., Fitzpatrick, A.L., Lin, J., Leung, C., Mukamal, K.J., Marcus, G.M., 2019. Alcohol consumption and leukocyte telomere length. *Sci. Rep.* 9 (1), 1404.
- Epel, E.S., Prather, A.A., 2018. Stress, telomeres, and psychopathology: toward a deeper understanding of a triad of early aging. *Annu. Rev. Clin. Psychol.* 14, 371–397.
- Epel, E.S., Blackburn, E.H., Lin, J., Dhabhar, F.S., Adler, N.E., Morrow, J.D., Cawthon, R. M., 2004. Accelerated telomere shortening in response to life stress. *Proc. Natl. Acad. Sci. U.S.A.* 101 (49), 17312–17315.
- Fujishiro, K., Diez-Roux, A.V., Landsbergis, P.A., Jenny, N.S., Seeman, T., 2013. Current employment status, occupational category, occupational hazard exposure and job stress in relation to telomere length: the Multiethnic Study of Atherosclerosis (MESA). *Occup. Environ. Med.* 70 (8), 552–560.
- Goldberg, D., Williams, P., 1988. A User's Guide to the General Health Questionnaire. Windsor. NFER.
- Hanssen, L.M., Schutte, N.S., Malouff, J.M., Epel, E.S., 2017. The relationship between childhood psychosocial stressor level and telomere length: a meta-analysis. *Health Psychol. Res.* 5 (1), 6378.
- Heistaro, S., 2008. Methodology Report: Health 2000 Survey in Kansanterveyslaitoksen Julkaisuja B. National Institute of Health and Welfare (THL), Helsinki.
- Hoer, P.W., Rosmalen, J.G., Schoevers, R.A., Huzen, J., van der Harst, P., de Jonge, P., 2013. Association between anxiety but not depressive disorders and leukocyte telomere length after 2 years of follow-up in a population-based sample. *Psychol. Med.* 43 (4), 689–697.
- Huang, Y.C., Wang, L.J., Tseng, P.T., Hung, C.F., Lin, P.Y., 2018. Leukocyte telomere length in patients with bipolar disorder: an updated meta-analysis and subgroup analysis by mood status. *Psychiatry Res.* 270, 41–49.

- Hughes, K., Bellis, M.A., Hardcastle, K.A., Sethi, D., Butchart, A., Mikton, C., Jones, L., Dunne, M.P., 2017. The effect of multiple adverse childhood experiences on health: a systematic review and meta-analysis. *Lancet Public Health* 2 (8), e356–e366.
- Kananen, L., Surakka, I., Pirkola, S., Suvisaari, J., Lönnqvist, J., Peltonen, L., Ripatti, S., Hovatta, I., 2010. Childhood adversities are associated with shorter telomere length at adult age both in individuals with an anxiety disorder and controls. *PLoS One* 5 (5), 10826.
- Kronholm, E., Sallinen, M., Suutama, T., Sulkava, R., Era, P., Partonen, T., 2009. Self-reported sleep duration and cognitive functioning in the general population. *J. Sleep Res.* 18 (4), 436–446.
- Ladwig, K.H., Brockhaus, A.C., Baumert, J., Lukaschek, K., Emeny, R.T., Kruse, J., Codd, V., Häfner, S., Albrecht, E., Illig, T., Samani, N.J., Wichmann, H.E., Gieger, C., Peters, A., 2013. Posttraumatic stress disorder and not depression is associated with shorter leukocyte telomere length: findings from 3,000 participants in the population-based KORA F4 study. *PLoS One* 8 (7), 64762.
- Li, Z., He, Y., Wang, D., Tang, J., Chen, X., 2017. Association between childhood trauma and accelerated telomere erosion in adulthood: a meta-analytic study. *J. Psychiatr. Res.* 93, 64–71.
- Lindgren, M., Mäntylä, T., Rikandi, E., Torniaainen-Holm, M., Morales-Muñoz, I., Kieseppä, T., Mantere, O., Suvisaari, J., 2017. Childhood adversities and clinical symptomatology in first-episode psychosis. *Psychiatry Res.* 258, 374–381.
- Lindqvist, D., Epel, E.S., Mellon, S.H., Penninx, B.W., Révész, D., Verhoeven, J.E., Reus, V.I., Lin, J., Mahan, L., Hough, C.M., Rosser, R., Bersani, F.S., Blackburn, E.H., Wolkowitz, O.M., 2015. Psychiatric disorders and leukocyte telomere length: underlying mechanisms linking mental illness with cellular aging. *Neurosci. Biobehav. Rev.* 55, 333–364.
- Martikainen, P., Elo, I., Tarkkiainen, L., Mikkonen, J., Myrskylä, M., Moustgaard, H., 2020. The changing contribution of childhood social characteristics to mortality: a comparison of Finnish cohorts born in 1936-50 and 1961-75. *Int. J. Epidemiol.* 49 (3), 896–907.
- Mathur, M.B., Epel, E., Kind, S., Desai, M., Parks, C.G., Sandler, D.P., Khazeni, N., 2016. Perceived stress and telomere length: a systematic review, meta-analysis, and methodologic considerations for advancing the field. *Brain Behav. Immun.* 54, 158–169.
- Mayer, S.E., Prather, A.A., Puterman, E., Lin, J., Arenander, J., Coccia, M., Shields, G.S., Slavich, G.M., Epel, E.S., 2019. Cumulative lifetime stress exposure and leukocyte telomere length attrition: the unique role of stressor duration and exposure timing. *Psychoneuroendocrinology* 104, 210–218.
- Monroy-Jaramillo, N., Dyukova, E., Walss-Bass, C., 2018. Telomere length in psychiatric disorders: is it more than an ageing marker? *World J. Biol. Psychiatry* 19 (2), S2–S20.
- Morales-Muñoz, I., Suvisaari, J., Therman, S., Torniaainen-Holm, M., Mäntylä, T., Rikandi, E., Mantere, O., Kieseppä, T., Lindgren, M., 2018. Childhood adversities and cognitive deficits in first-episode psychosis. *Schizophr. Res.* 197, 596–598.
- Parks, C.G., DeRoo, L.A., Miller, D.B., McCanlies, E.C., Cawthon, R.M., Sandler, D.P., 2011. Employment and work schedule are related to telomere length in women. *Occup. Environ. Med.* 68 (8), 582–589.
- Pirkola, S., Isometsä, E., Aro, H., Kestilä, L., Hämäläinen, J., Veijola, J., Kiviruusu, O., Lönnqvist, J., 2005. Childhood adversities as risk factors for adult mental disorders: results from the Health 2000 study. *Soc. Psychiatry Psychiatr. Epidemiol.* 40 (10), 769–777.
- Pirkola, S.P., Isometsä, E., Suvisaari, J., Aro, H., Joukamaa, M., Poikolainen, K., Koskinen, S., Aromaa, A., Lönnqvist, J.K., 2005. DSM-IV mood-, anxiety- and alcohol use disorders and their comorbidity in the Finnish general population—results from the Health 2000 Study. *Soc. Psychiatry Psychiatr. Epidemiol.* 40 (1), 1–10.
- Puterman, E., Gemmill, A., Karasek, D., Weir, D., Adler, N.E., Prather, A.A., Epel, E.S., 2016. Lifespan adversity and later adulthood telomere length in the nationally representative US Health and Retirement Study. *Proc. Natl. Acad. Sci. U.S.A.* 113 (42), 6335. E6335-e6342.
- Ridout, K.K., Levandowski, M., Ridout, S.J., Gantz, L., Goonan, K., Palermo, D., Price, L.H., Tyrka, A.R., 2018. Early life adversity and telomere length: a meta-analysis. *Mol. Psychiatry* 23 (4), 858–871.
- Ridout, K.K., Parade, S.H., Kao, H.T., Magnan, S., Seifer, R., Porton, B., Price, L.H., Tyrka, A.R., 2019. Childhood maltreatment, behavioral adjustment, and molecular markers of cellular aging in preschool-aged children: a cohort study. *Psychoneuroendocrinology* 107, 261–269.
- Russo, P., Prinzi, G., Proietti, S., Lamonaca, P., Frustaci, A., Boccia, S., Amore, R., Lorenzi, M., Onder, G., Marzetti, E., Valdiglesias, V., Guadagni, F., Valente, M.G., Cascio, G.L., Fraietta, S., Ducchi, G., Bonassi, S., 2018. Shorter telomere length in schizophrenia: evidence from a real-world population and meta-analysis of most recent literature. *Schizophr. Res.* 202, 37–45.
- Sackett, D.L., 1979. Bias in analytic research. *J. Chronic Dis.* 32 (1–2), 51–63.
- Shaffer, J.A., Epel, E., Kang, M.S., Ye, S., Schwartz, J.E., Davidson, K.W., Kirkland, S., Honig, L.S., Shimbo, D., 2012. Depressive symptoms are not associated with leukocyte telomere length: findings from the Nova Scotia Health Survey (NSHS95), a population-based study. *PLoS One* 7 (10), 48318.
- Shalev, I., Moffitt, T.E., Sugden, K., Williams, B., Houts, R.M., Danese, A., Mill, J., Arseneault, L., Caspi, A., 2013. Exposure to violence during childhood is associated with telomere erosion from 5 to 10 years of age: a longitudinal study. *Mol. Psychiatry* 18 (5), 576–581.
- Shalev, I., Moffitt, T.E., Braithwaite, A.W., Danese, A., Fleming, N.I., Goldman-Mellor, S., Harrington, H.L., Houts, R.M., Israel, S., Poulton, R., Robertson, S.P., Sugden, K., Williams, B., Caspi, A., 2014. Internalizing disorders and leukocyte telomere erosion: a prospective study of depression, generalized anxiety disorder and post-traumatic stress disorder. *Mol. Psychiatry* 19 (11), 1163–1170.
- Tempaku, P., Hirotsu, C., Mazzotti, D., Xavier, G., Maurya, P., Brietzke, E., Belangero, S., Poyares, D., Bittencourt, L., Tufik, S., 2018. Long sleep duration, insomnia, and insomnia with short objective sleep duration are independently associated with short telomere length. *J. Clin. Sleep Med.* 14 (12), 2037–2045.
- Tempaku, P.F., Mazzotti, D.R., Tufik, S., 2015. Telomere length as a marker of sleep loss and sleep disturbances: a potential link between sleep and cellular senescence. *Sleep Med.* 16 (5), 559–563.
- Vance, M.C., Bui, E., Hoepfner, S.S., Kovachy, B., Prescott, J., Mischoulon, D., Walton, Z. E., Dong, M., Nadal, M.F., Worthington, J.J., Hoge, E.A., Cassano, P., Orr, E.H., Fava, M., de Vivo, I., Wong, K.K., Simon, N.M., 2018. Prospective association between major depressive disorder and leukocyte telomere length over two years. *Psychoneuroendocrinology* 90, 157–164.
- Verhoeven, J.E., van Oppen, P., Révész, D., Wolkowitz, O.M., Penninx, B.W., 2016. Depressive and anxiety disorders showing robust, but non-dynamic, 6-year longitudinal association with short leukocyte telomere length. *Am. J. Psychiatry* 173 (6), 617–624.
- Verhoeven, J.E., Révész, D., Picard, M., Epel, E.E., Wolkowitz, O.M., Matthews, K.A., Penninx, B., Puterman, E., 2018. Depression, telomeres and mitochondrial DNA: between- and within-person associations from a 10-year longitudinal study. *Mol. Psychiatry* 23 (4), 850–857.
- Wang, H., Kim, H., Baik, I., 2017. Associations of alcohol consumption and alcohol flush reaction with leukocyte telomere length in Korean adults. *Nutr. Res.* 11 (4), 334–339.
- von Zglinicki, T., 2002. Oxidative stress shortens telomeres. *Trends Biochem. Sci.* 27 (7), 339–344.
- Zhan, Y., Hägg, S., 2019. Telomere length and cardiovascular disease risk. *Curr. Opin. Cardiol.* 34 (3), 270–274.