

# Is childhood stress associated with shorter telomeres?

**BACKGROUND** It has been shown that severe stress in childhood is harmful to later health. New research aims to ascertain whether – and if so, how – the telomeres, the protective caps at the end of our chromosomes, may be one of the links between this type of experience and later morbidity. Here we present an overview of studies which have examined the association between childhood stress and telomere length.

**METHOD** The review encompasses 26 original studies found through a literature search in PubMed. We included studies of the relationship between telomere length and various stress-inducing factors from conception throughout childhood and adolescence.

**RESULTS** The studies were grouped into four topics. The empirical research base for *maternal stress in pregnancy* and *parents' ability to care for their children* is too small to draw any conclusions. Childhood *psychosocial stress* was associated with shorter telomere length in 12 of 14 studies. *Socioeconomic status* in childhood was not unequivocally associated with telomere length.

**INTERPRETATION** Shorter telomeres are possibly associated with childhood psychosocial stress. This field of research is still new, and more longitudinal studies are needed with an emphasis on childhood experiences and coordination of measurement variables and outcome measures in order to confirm this association.

Adverse childhood experiences, such as abuse, neglect or poverty, are associated with increased morbidity and mortality in adulthood (1–3). Low socioeconomic status, either as a child or as an adult, has long been recognised as such a risk factor (4, 5). In children, severe stress has been linked to changes in brain structure, stress responsivity and immunity (5), as well as to increased risk-taking behaviours such as smoking and substance abuse in adulthood (6).

In recent years, research has examined whether – and if so how – telomeres might be one of the links between adverse childhood experiences and later health. Telomeres are made up of repetitive DNA sequences (7, 8). They form protective caps on the ends of chromosomes and shorten with each cell division (8). When the telomeres reach a critical length, the cell goes into apoptosis or senescence, a state in which it can no longer divide (8). The enzyme telomerase maintains the length of the telomeres in stem cells, but is unable to counteract the shortening of telomeres over time in somatic cells (8). Based on average telomere loss with aging, it is possible to estimate how many years «older» the cells of one group are compared to another.

Shorter telomeres have been linked to increased morbidity and mortality (8), although the relationship is not conclusive (9). In addition to genetic variation, telomere length is strongly associated with age, race and gender, and to a lesser degree with body mass index (BMI), lifestyle and socioeco-

omic status (10). A number of studies have linked shorter telomeres with psychosocial stress in adults (11). This review summarises the research on the relationship between childhood stress and telomere length.

## Method

A PubMed search using the search string «telomere AND ('psychological stress' OR 'social environment' OR socioeconomic OR abuse OR neglect OR 'early life stress')» generated 221 articles. Original studies published prior to 14 March 2015 in English or Scandinavian languages that referred to both childhood stress and measurement of telomere length were included. Studies were included on the basis of the title, but if it was unclear whether a study fulfilled the criteria, the abstract was also read. A total of 26 studies met the inclusion criteria for the review.

## Results

The results are presented briefly in Table 1 (12–37), and are divided into four themes:

- Studies that measured maternal stress in pregnancy
- Studies that measured parental caregiving ability
- The theme 'childhood psychosocial stress' included all studies that referred to various types of adverse experiences, such as physical and psychological abuse and neglect, or events such as divorce or loss of parents during childhood
- Studies that mainly measured childhood socioeconomic status

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## MAIN POINTS

An association is seen in many studies between adverse childhood conditions and shorter telomeres, although the evidence base is not conclusive.

The robust association between childhood adversity and impaired adult health may be mediated by reduced telomere length, among other factors.

There was a certain degree of overlap between the groups, which has been shown in the text and in Table 1.

#### *Maternal stress in pregnancy*

In the two studies identified (12, 13), stress – measured in terms either of adverse experiences (12) or of anxiety related to pregnancy and childbirth (13) – was associated with cells that were 3.5 years «older» in the children as adults in the one study (12), and was responsible for 25 % of the variance in telomere length in newborns in the other (13).

#### *Parental caregiving ability*

Poor parental caregiving ability was linked to shorter telomere length in children (14) and African American adolescents (15), but only when conditions around the children were worse than those of the control group. Children at high risk of abuse, determined by whether their parents were in contact with the child protection services, had shorter telomeres than children who were not at risk (14). In the high-risk group alone, good parental caregiving was associated with longer telomeres in the children. Brody et al. found that adolescents with non-supportive parents had shorter telomere lengths than those with supportive parents, but that this only applied to the group that had not participated in a behaviour modification programme for parents and adolescents (15).

#### *Childhood psychosocial stress*

A total of 14 studies examined the relationship between various types of childhood stress and telomere length either in children (16–19) or adults (20–29). The studies were mainly cross-sectional with retrospective reporting of childhood events. Adverse childhood experiences were recorded longitudinally in four studies (16, 17, 19, 26), and one of these also measured telomere length over time (17). Two studies found no relationship between childhood experiences and telomere length (20, 26), one of which measured life stress longitudinally in a birth cohort (26). The remaining 12 studies found an association between shorter telomere length and some or all of their measures of childhood psychosocial stress.

Three studies estimated the proportion of the variance in telomere length that could be attributed to psychosocial stress (16, 19, 27). The proportions were found to be 0.4–1.2 % (27), 12.2 % (16) and 40 % (19). A dose-response relationship between the number of stressors and telomere length as an adult was reported in three studies (21, 24, 25). One of these found that each «additional» stressor was associated with three «additio-

nal» years of ageing (25); the others did not present their results in this form.

All four studies that measured telomere length in children (16–19) found that psychosocial stress was associated with shorter telomere length. A larger proportion of life spent in an orphanage was associated with shorter telomeres in Romanian children who were followed longitudinally (16). Children who were exposed to two or more types of violence between the ages of 5 and 10 years showed significantly faster telomere shortening during this period than other children (17). Growing up in a family with difficulties such as parents in an unstable relationship or in prison, or family violence, was also associated with shorter telomere length in children (18, 19).

#### *Childhood socioeconomic status*

Twelve studies examined the relationship between childhood socioeconomic status and telomere length (19, 21, 25, 29–37), four of which are also mentioned above (19, 21, 25, 29). In several of these studies, large cohorts were followed with measuring of socioeconomic status in childhood and adulthood (Table 1). A multiethnic American study found that having a father with a low educational level was linked to greater telomere length (0.7 % of the variance), but only in Hispanics (35). Four of the studies (25, 29–31) found no relationship between selected measures of childhood socioeconomic status and telomere length as an adult. Three studies found that only some of their selected measures of socioeconomic status were associated with shorter telomeres as an adult (21, 32, 34). In a Scottish birth cohort from the 1970s, for example, growing up in a family from a low social class or without a car was linked to having cells that were almost 20 years and 8.5 years «older» respectively (34). However, the same study did not observe this association for other measures of childhood socioeconomic status, nor for cohorts born in the 1930s and 1950s (34).

Three studies measured socioeconomic status and telomere length in children (19, 33, 37). Children of parents with low educational levels had shorter telomeres, equivalent to six years of «additional» ageing, than children with at least one parent with higher education (33). Family financial status did not affect telomere length in this study. However, another study found that a doubling of family income was associated with 5 % longer telomeres, and that children of poorly educated mothers had telomeres that were around 30 % shorter than those of other children (19). In the third study, children from neighbourhoods with a high degree of disorder and poverty had below-average telomere lengths (37).

## **Discussion**

### *Childhood conditions and telomere length*

Studies of the association between maternal stress in pregnancy and parents' caregiving ability and telomere length in the children have been too small and limited to enable definite conclusions to be drawn. The results are most consistent for psychosocial stress and telomere length. Twelve of fourteen studies show that different measures of such stress correlate with shorter telomere length in both adults and children. This is consistent with the conclusions in a review study of the subject from 2013 (38). Whether socioeconomic status in childhood is associated with shorter telomere length is more uncertain. Various measures of socioeconomic status have been investigated in the studies, and conflicting results have been arrived at.

### *Methodological problems*

The studies in the review reveal a heterogeneity of measurement variables that extends beyond what our table presents. This makes it difficult to draw conclusions based on the studies viewed as a whole. The heterogeneity may be due to the fact that there is still no conceptual apparatus for defining which types of experience are definitively adverse. Any such apparatus would be problematic in itself, as experience is subjective and context-dependent. The study authors also report very different outcome measures for telomere length. This makes it difficult to compare the results of the studies, and impossible to conduct a meta-analysis.

The studies in the review have controlled for a number of factors found to be associated with telomere length, such as gender and age. However, one weakness is that the studies did not always control for the same factors.

In order to determine whether adverse childhood experiences lead to telomere attrition, more longitudinal studies are needed in which telomere length is measured over time. So far only one such study exists (17). As telomere shortening takes place slowly, it is recommended that change should be measured over several decades in longitudinal studies in order to achieve more reliable results (10). Moreover, experiences are by their very nature subjective phenomena. As such they are not quantifiable in the way that an objectively defined event is. At the same time, it is the subjects' interpretation of their own experiences that presumably determines how these experiences affect their health subsequently. How to include these aspects in further research presents a challenge.

Telomere length is measured in different ways in some of the studies. Most have used cells from peripheral blood (leukocytes) and

**Table 1** Overview of 26 original studies that examined the relationship between telomere length and various stressors from conception and throughout childhood and adolescence. In all studies, telomere length was measured at a single time point in adult men and women unless otherwise specified. PB = peripheral blood, PCR = polymerase chain reaction, UCB = umbilical cord blood, BM = buccal mucosa (mouth swab), SB = Southern blotting

First author	Year and country	Measure of stress	Design/ participants	Tissue type/ telomere measurement	Controlled for	Main findings
Entringer [12]	2011 Germany	Severe stress in pregnancy	Case control, N = 94; mother with stress (n = 45) and without stress (n = 49)	PB PCR	Age, gender, BMI, socioeconomic status, birth weight, childhood stress, disease, smoking, risk during pregnancy	Severe stress was significantly associated with shorter telomere length in the children as young adults
Entringer [13]	2013 USA	Pregnancy-specific stress during pregnancy	Cross-section, N = 27, mother-newborn dyads	UCB PCR	Gestational age at birth, pregnancy complications, birth weight, gender	Shorter telomere length in newborns was significantly associated with pregnancy-specific stress
Asok [14]	2013 USA	Parental caregiving ability and responsiveness	Case control, N = 89 children at risk of abuse (n = 51) and not at risk (n = 38)	BM PCR	Socioeconomic status, birth weight, gender, minority background	High-risk children had significantly shorter telomeres. Responsive parents moderated the association between telomere length and risk
Brody [15]	2015 USA	Parental caregiving ability (supportive/non-supportive)	Case control, N = 216 adolescents; Intervention (n = 114)/no intervention (n = 102)	PB PCR	Gender, socioeconomic status, current stress, smoking, alcohol consumption, BMI, blood pressure	Shorter telomere length at the age of 22 years was significantly associated with non-supportive parenting style at the age of 17, but only in the control group
Tyrka [22]	2010 USA	5 types of adverse childhood experience	Cross-section, N = 31	PB PCR	Age, smoking, BMI, hormonal contraception, minority background, socioeconomic status, current stress	Adverse childhood experience was significantly associated with shorter telomere length
Glass [20]	2010 England	3 types of adverse childhood experience	Cohort, N = 1 871	PB SB	Age, gender, smoking, BMI	No relationship found between adverse childhood experiences and telomere length
Kananen <sup>1</sup> [21]	2010 Finland	11 types of adverse childhood experience	Case control, N = 974; with anxiety (n = 321)/control (n = 653)	PB PCR	Age, gender	Adverse childhood experiences were significantly associated in a dose-response relationship with shorter telomere length in both groups
Surtees <sup>1</sup> [25]	2011 England	8 types of adverse childhood experience	Cross-section, N = 4 441 women	PB PCR	Health, socioeconomic status, overweight, smoking	Shorter telomere length was significantly associated with increasing numbers of adverse childhood experiences
O'Donovan [24]	2011 USA	5 types of adverse childhood experience	Case control, N = 90; PTSD (n = 43)/control (n = 47)	PB PCR	Age	Shorter telomere length was significantly associated with adverse childhood experiences in persons with post-traumatic stress disorder
Kiecolt-Glaser [23]	2011 USA	11 types of adverse childhood experience	Case control (subgroup), N = 86; care of individuals with dementia/controls	PB SB	Age, gender, BMI, caregiving responsibility	Shorter telomere length was significantly associated with adverse events in childhood, but not with abuse, in both groups
Savolainen [27]	2014 Finland	1 type of adverse childhood experience	Cross section, N = 1 486	PB PCR	Age, gender, sample quality (DNA), health, BMI, socioeconomic status (adult and childhood), smoking, physical activity, alcohol consumption, mother's age	Shorter telomere length was significantly associated with adverse childhood experiences (evacuation as children) in persons with later traumatic experience in addition.
Zalli [28]	2014 England	5 types of adverse childhood experience	Cross section, N = 333	PB PCR	Age, gender, socioeconomic status, BMI	Shorter telomere length was significantly associated with loss of mother as a child, but not with other types of adverse childhood experience
Jodczyk [26]	2014 New Zealand	4 types of adverse childhood experience	Birth cohort, N = 677	PB PCR	Gender, minority, socioeconomic status at birth	There was no association between telomere length and adverse childhood experience

Tyrka <sup>1</sup> [29]	2015 USA	6 types of adverse childhood experience	Cross section, N = 290	PB PCR	Age, gender, socioeconomic status (adult and childhood), BMI	Adverse childhood experience was significantly associated with shorter telomere length
Drury [16]	2012 Romania	1 type of adverse childhood experience	Randomised, controlled, N = 136 children; children's home (n = 68)/foster home (n = 68)	BM PCR	Intervention, gender, birth weight, age	Shorter telomere length at the age of 6–10 years was significantly correlated with adverse childhood experience (time spent in orphanage before the age of four)
Shalev [17]	2013 England	3 types of adverse childhood experience	Cohort, N = 236 children	BM PCR	Telomere length at the age of 5 years, gender, socioeconomic status in childhood, BMI	Significantly increased loss of telomere length at the age of 5–10 years was demonstrated in connection with experience of two or more adverse childhood experiences (various types of violence)
Mitchell <sup>1</sup> [19]	2014 USA	5 types of adverse childhood experience	Cohort (sub-group), N = 40 children	BM PCR	Age, minority, gender, BMI	Shorter telomere lengths were significantly associated with adverse childhood experiences and low socioeconomic status
Drury [18]	2014 USA	3 types of adverse childhood experience	Cross section, N = 80	BM PCR	Gender, age, mother's and father's age at conception, minority, socioeconomic status as child	Shorter telomere length was significantly associated with adverse childhood experience, but only in girls in a dose-response relationship
Adams [30]	2006 England	Socioeconomic status – occupational class of the head of the household	Birth cohort, N = 318	PB PCR	Smoking, alcohol consumption, BMI, diet, gender, father's age	There was no association between socioeconomic status at birth (sole measurement) and telomere length as an adult
Batty [31]	2009 Scotland	Socioeconomic status – height as adult	Case control, N = 1 542 men with coronary disease (n = 484)/without coronary disease (n = 1 058)	PB PCR	Age, smoking, BMI, alcohol intake, disease, statins	No association between socioeconomic status as a child and telomere length
Carroll [35]	2013 USA	Socioeconomic status – parents' educational level	Cross section, N = 963	PB PCR	Gender, age, minority, BMI, health, physical activity, smoking, diet.	Longer telomere length was significantly associated in Latin-Americans with a father with a low education, not associated with mother's education.
Kajantie [32]	2012 Finland	Socioeconomic status – father's occupation (A, B), parents' educational level (C)	Cohort, N = 2 376; 3 cohorts (A, B and C)	PB PCR	Age, gender, mother's age, socioeconomic status, smoking	Socioeconomic status as a child was associated with a shorter telomere length in A and B (n = 2 142), not in C (n = 334).
Robertson [34]	2012 Scotland	Socioeconomic status – parents' occupational class, insecure family economy, own car, subjective socioeconomic status	Cohort, N = 2 185; born in the 1930s (A), 1950s (B) and 1970s (C)	PB PCR	Gender	Shorter telomere length was associated with low socioeconomic status (parents' occupational class, own car) in childhood in C (n = 755), but not in A and B
Cohen [36]	2013 USA	Socioeconomic status – parents owned home	Cross section, N = 135	PB PCR	Age, gender, minority, BMI, neuroticism	Shorter telomere length was significantly associated with fewer childhood years (5–18) where parents did not own their own home
Needham [33]	2012 USA	Socioeconomic status – parents' educational level and income	Cross section, N = 70 children	PB PCR	Gender, age, minority, diet, physical activity, BMI	Shorter telomere length significantly associated with parents with low education, not with income
Theall [37]	2013 USA	Socioeconomic status – poverty and neighbourhood disorder	Cross section, N = 99	BM PCR	Gender, age, number of children in the family, socioeconomic status, number of years lived in neighbourhood	Shorter telomere length was significantly associated with living in a neighbourhood with a high level of disorder and poverty

<sup>1</sup> Socioeconomic status has also been considered in these studies, but not primarily; see article text

polymerase chain reaction tests (PCR), while a few have used Southern blotting (SB) (Table 1). Acceptable consistency has been found between the methods, but larger measurement error is associated with PCR. Cells from the buccal mucosa were used in a few studies (16), but there is still disagreement as to whether telomere length in different tissues can be compared (9, 40).

#### Possible mechanisms

There are several hypotheses about the effects of childhood stress on both telomeres and subsequent morbidity. There are probably many mechanisms involved. Behavioural changes due to growing up in a threatening and stressful environment, such as excessive threat vigilance, mistrust, poor social relationships and unhealthy lifestyles (41) may lead to an increased risk of morbidity. Smoking, overweight and limited physical activity are also associated with shorter telomere length (42), but not always conclusively.

Severe psychological stress in childhood leads to altered stress responsivity, both physiological and psychological (41). Psychological stress has been shown to correlate with higher cortisol levels, increased inflammation and increased oxidative stress (43). All of these factors are associated in their turn with shorter telomere length (43). Psychological stress can also accelerate ageing of the immune system through increased reactivation of latent viruses, and thereby increase wear and tear on T-cells (7). When telomeres in T-cells approach a critical length, the cells are no longer able to replicate, and *in vitro* these cells have been shown to secrete pro-inflammatory cytokines (7). A vicious circle may be created, where psychological stress causes increased cortisol production and oxidative stress, accelerated ageing of the immune system, shorter telomeres, increased inflammation and again shorter telomeres.

#### Conclusion

It may be possible to link severe stress in childhood with shorter telomeres. The evidence base is still too limited, recent and methodologically heterogeneous for it to be possible to assert this conclusively. More longitudinal studies are needed in which the participants are monitored closely, plus agreement as to what types of adversity should or can be measured, and how differences in telomere length can best be presented statistically. Having said that, a robust correlation has already been demonstrated between a tough childhood, poor parental ability to give care and low socioeconomic status on the one hand, and subsequent poor health on the other. The findings up to the present, including those from telomere

research, give every reason to increase efforts in all health-related professions and society at large to prevent serious stress in children.

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