

UC Irvine

UC Irvine Previously Published Works

Title

The fetal programming of telomere biology hypothesis: an update.

Permalink

<https://escholarship.org/uc/item/1j1242xv>

Journal

Philosophical transactions of the Royal Society of London. Series B, Biological sciences, 373(1741)

ISSN

0962-8436

Authors

Entringer, Sonja
de Punder, Karin
Buss, Claudia
et al.

Publication Date

2018-03-01

DOI

10.1098/rstb.2017.0151

Peer reviewed

Review



Cite this article: Entringer S, de Punder K, Buss C, Wadhwa PD. 2018 The fetal programming of telomere biology hypothesis: an update. *Phil. Trans. R. Soc. B* **373**: 20170151.
<http://dx.doi.org/10.1098/rstb.2017.0151>

Accepted: 26 September 2017

One contribution of 19 to a theme issue 'Understanding diversity in telomere dynamics'.

Subject Areas:

cellular biology, developmental biology, health and disease and epidemiology

Keywords:

telomere, telomerase, development, fetal programming, health and disease risk

Authors for correspondence:

Sonja Entringer
e-mail: sonja.entringer@charite.de
Pathik D. Wadhwa
e-mail: pwadhwa@uci.edu

The fetal programming of telomere biology hypothesis: an update

Sonja Entringer^{1,4,6}, Karin de Punder¹, Claudia Buss^{1,4,6}
and Pathik D. Wadhwa^{2,3,4,5,6}

¹Charité—Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health (BIH), Institute of Medical Psychology, Berlin, Germany
²Department of Psychiatry and Human Behavior, ³Department of Obstetrics and Gynecology, ⁴Department of Pediatrics, ⁵Department of Epidemiology, and ⁶Development, Health and Disease Research Program, University of California, School of Medicine, Irvine, CA, USA

KdP, 0000-0003-0510-9147

Research on mechanisms underlying fetal programming of health and disease risk has focused primarily on processes that are specific to cell types, organs or phenotypes of interest. However, the observation that developmental conditions concomitantly influence a diverse set of phenotypes, the majority of which are implicated in age-related disorders, raises the possibility that such developmental conditions may additionally exert effects via a common underlying mechanism that involves cellular/molecular ageing-related processes. In this context, we submit that telomere biology represents a process of particular interest in humans because, firstly, this system represents among the most salient antecedent cellular phenotypes for common age-related disorders; secondly, its initial (newborn) setting appears to be particularly important for its long-term effects; and thirdly, its initial setting appears to be plastic and under developmental regulation. We propose that the effects of suboptimal intrauterine conditions on the initial setting of telomere length and telomerase expression/activity capacity may be mediated by the programming actions of stress-related maternal–placental–fetal oxidative, immune, endocrine and metabolic pathways in a manner that may ultimately accelerate cellular dysfunction, ageing and disease susceptibility over the lifespan. This perspectives paper provides an overview of each of the elements underlying this hypothesis, with an emphasis on recent developments, findings and future directions.

This article is part of the theme issue 'Understanding diversity in telomere dynamics'.

1. Overview

This perspectives paper articulates a transdisciplinary framework that underlies the fetal programming of telomere biology hypothesis primarily in the context of humans. Our model, depicted in figure 1, proposes that (a) intrauterine life represents a particularly sensitive time period when the effects of maternal states and conditions around conception and across pregnancy may be transmitted to the developing embryo/fetus; (b) transmission occurs primarily via the effects of various maternal biophysical, clinical, psychological and behavioural states and conditions on stress-related maternal–placental–fetal (MPF) oxidative, immune/inflammatory, endocrine and metabolic pathways that participate in the process of fetal programming of health and disease risk; and (c) the initial setting and function of the offspring telomere biology system—telomere length and telomerase expression and activity capacity—exhibits developmental plasticity and represents a key cellular target of such programming, with important implications for long-term health and susceptibility for common age-related disorders.

We begin this paper with brief overviews of the concept of fetal programming of health and disease risk and the role of telomere dynamics in humans. We then proceed to discuss the importance of the initial setting of the telomere biology

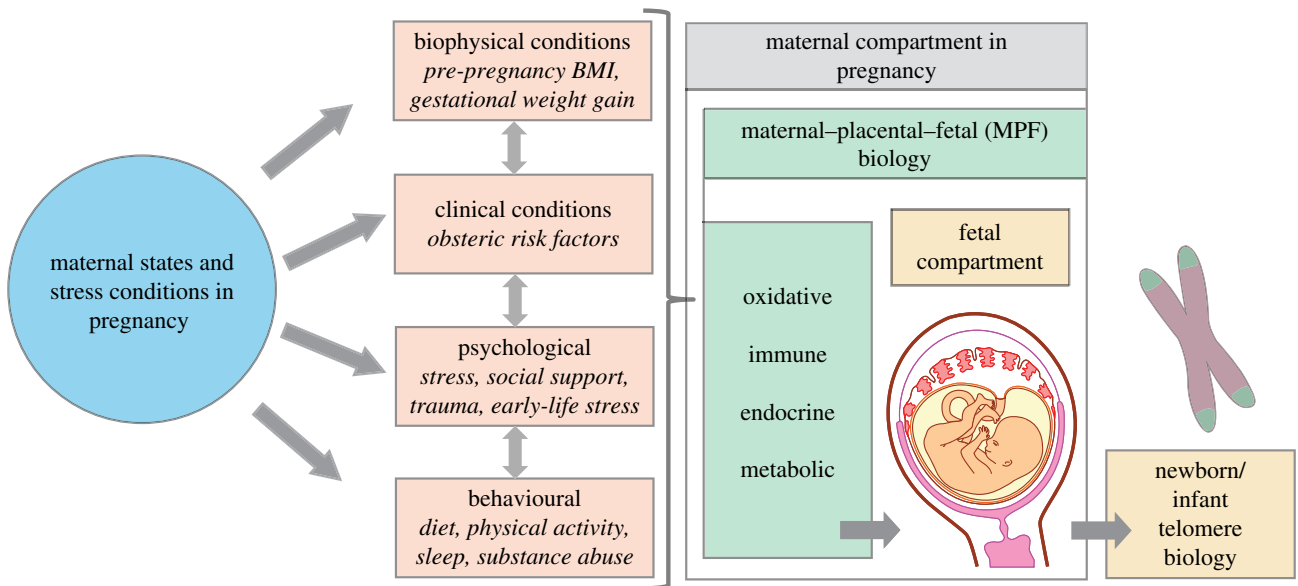


Figure 1. The fetal programming of telomere biology hypothesis: a conceptual framework.

system. Next, we discuss the concept of fetal programming specifically in reference to the telomere biology system. In the context of inter-generational transmission, we identify stress-related MPF gestational biology as a leading candidate pathway of interest, and we describe how variation in stress-related MPF gestational biology may impact fetal developmental trajectories. While this perspectives paper is focused on humans, we note that there are related studies on a wide range of taxa, including non-primate mammals, birds, reptiles and fish, that may not have the same telomere dynamics across the lifespan as humans, but nevertheless make important contributions towards understanding the role of the telomere system in linking developmental conditions in early life with life-history trajectories, health and longevity [1–3]. We conclude by articulating current knowledge gaps and future research directions. We have described various aspects of this formulation in previous papers [4–7], and the present perspective updates our framework, with an emphasis on a discussion of recent findings in the literature and implications for future research directions.

2. The concept of fetal/developmental programming

The origins of many, if not all, complex common age-related disorders that confer the major societal burden of disease can be traced back to developmental processes in embryonic, fetal and early postnatal life. At the individual level, the likelihood of developing a complex common disorder is a joint function of cumulative risk exposures (e.g. excess caloric intake, infection, stressful life events) and susceptibility to these exposures (e.g. as reflected in the wide inter-individual variation in biological responses to the particular risk exposure(s) in question) [5,8,9]. Development is a plastic, context-dependent process, wherein a range of different phenotypes can be expressed from a given genotype. Thus, contrary to the conventional paradigm that asserts individual susceptibility is determined primarily by DNA sequence variation, it is apparent that susceptibility for complex common disorders is more profoundly determined by the dynamic interplay between genetic make-up and environmental conditions, particularly during the earlier periods of life

[10,11]. The embryo/fetus seeks, receives and responds to, or is acted upon by, its environment during sensitive periods, resulting in structural and functional changes in cells, tissues and organ systems. These changes may, either independently or through interactions with subsequent developmental processes and environments, have major consequences for health and disease susceptibility over the individual's lifespan [10,12,13]. These concepts have variously been referred to as the fetal or developmental origins of health and disease risk. The process is adaptive from an evolutionary perspective, but may in some instances confer increased susceptibility at the individual level, particularly when there is a discrepancy between the nature of environmental conditions during development and those during later stages of life. Also, except in extreme cases, fetal programming does not, *per se*, 'cause' disease, but, instead, may influence an individual's susceptibility or propensity for disease(s) in later life, for instance, by shaping responsivity to subsequent endogenous and exogenous conditions.

The majority of studies on mechanisms underlying fetal/developmental programming effects have focused primarily on processes that are specific to cells, organs or phenotypes of interest (e.g. mechanisms within the adipocyte, haematopoietic cell, brain, pancreas, liver, etc.). However, the observation that exposure to adverse intrauterine conditions concomitantly influences a diverse set of phenotypes, coupled with the fact that the majority of these phenotypes are implicated in common age-related disorders, raises the possibility that prenatal and early postnatal conditions may also additionally (not instead) exert effects via a common underlying mechanism, and that such a mechanism may involve cellular ageing-related molecular processes. In this context, we submit that the telomere biology system represents a candidate mechanism of particular interest [4].

3. The importance of the telomere biology system: a brief overview

Telomere biology is a highly evolutionarily conserved system that plays a central role in maintaining the integrity of the genome and cell [14]. Telomere biology refers to the structure and function of two entities—*telomeres*, non-coding double-

stranded repeats of guanine-rich tandem DNA sequences and shelterin protein structures that cap the ends of linear chromosomes, and *telomerase*, the reverse transcriptase enzyme that adds telomeric DNA to telomeres.

(a) Telomeres

Telomeres protect chromosomes from mistaken recognition by the DNA damage-repair system as DNA breaks. Because DNA polymerase is unable to fully replicate the 3' end of the DNA strand, telomeres lose approximately 30–150 base pairs (bp) with each cell division [15]. Eventually, telomeres reach a critical short length, resulting in decreased recruitment of shelterin proteins to form the protective internal nucleotide loops, which, in turn, leads to cellular senescence or apoptosis. Once cells become senescent, they exhibit a variety of genetic and morphological changes, such as chromosomal fusion, activation of DNA damage checkpoint responses and genome instability, that result in loss of tissue function. Senescent cells also produce inflammatory mediators that affect neighbouring cells, leading to further damage within tissues and organs that accumulates over time. Thus, as individuals age, they acquire more senescent cells, accompanied by various age-related pathologies [14]. Moreover, recent important discoveries suggest that the integrity of telomeres affects not only the replicative capacity of the cell, but also underlies other changes that enforce a self-perpetuating pathway of global epigenetic changes to affect the integrity of overall chromatin structure (DNA folding) that protects against senescence and cellular ageing [16–18]. Thus, this is how a reduction in telomere length and a steeper telomere attrition rate relate not only to longevity, but also to earlier onset and more rapid progression of common age-related disorders.

(b) Telomerase

Telomerase is a ribonucleoprotein enzyme consisting of an RNA component (TR or TERC) and a catalytic protein domain (TERT). Conventional DNA polymerase machinery is unable to fully replicate the ends of linear chromosomes. Telomerase uses its own template to add short TG-rich repeats to chromosome ends, thus attenuating their gradual erosion at each round of replication [19]. Typically, telomerase activity is diminished or absent in most adult somatic cells, with the exception of cells with a strong potential for division, such as stem cells and active lymphocytes [20]. The selective reduction of telomerase expression makes senescence inevitable by placing an upper bound on cellular lifespan [21]. Moreover, telomerase not only regulates telomere length but also preserves healthy cell function. Loss of telomerase affects chromatin configuration and impairs the DNA damage response. Telomerase also promotes proliferation of resting stem cells and directly modulates crucial developmental signalling pathways [22]. Through telomere capping and maintenance, telomerase plays a particularly important role in cellular proliferation capacity and survival under conditions of cellular stress. Finally, telomerase also performs an extra-nuclear role to co-localize with mitochondria to protect mitochondrial DNA, decrease oxidative stress, and improve energy production and cellular function [23–25]. Thus, a diminished capacity to express telomerase leads to more rapid telomere attrition over time, impaired DNA damage responses and impaired cellular energetic function.

If telomere shortening represents the clock ticking forwards on cells' limited lifespan, telomerase can reverse or

slow this clock, making the two an intricately inter-dependent, dynamic system.

(c) Telomerase maximal expression/activity capacity

The majority of human studies of telomere biology have focused largely on the telomere length component of the system; relatively few studies have considered the role of telomerase. The importance of including measures of telomerase derives from the understanding that its expression and activity constitutes a *critical* and *complementary* (i.e. non-redundant) component of the functional integrity of the telomere biology system [26–28]. For example, in a yeast single-cell model system, Blackburn and colleagues showed that well before critical telomere shortening occurs, telomerase is continuously required to respond to transient DNA replication stress, and that a lack of telomerase accelerates otherwise normal ageing [29]. The few studies that have included measures of telomerase have typically measured telomerase expression or activity under basal conditions or in terms of its acute (short-term) response to systemic challenges (see, e.g. [30]). However, given the limitations in the quantification and interpretation of basal telomerase data (because telomerase is typically not expressed, or expressed only at very low levels, in most resting cells [20]; telomerase levels may vary as a function of cell-cycle stage and other factors [31]; and differences or changes in telomerase may reflect either the direct effects of states or conditions that stimulate telomerase expression, or the secondary (compensatory/counter-regulatory) adaptations to states or conditions that reduce telomere length [32]), we have recently proposed the use of an *in vitro* measure of *maximal telomerase activity capacity* of human leucocytes in response to mitogen challenge (*mTAC*). We have determined that this measure empirically meets the key criteria to represent a potentially useful individual difference construct in this context (i.e. adequate within-subject stability and across-subject variability; see de Punder K *et al.* [33]).

(d) Role of telomere biology in ageing, disease susceptibility and longevity

A substantial and largely convergent body of human and animal research has linked shortened telomeres and/or reduced telomerase expression to several age-related risk factors, diseases [34–43] and longevity [44–48]. For example, relatively recent papers have reported associations in humans between telomere length and increased mortality risk [49,50], cardiovascular disease [51,52], diabetes and the metabolic syndrome [53,54], suboptimal brain anatomy [55], impaired cognitive function [56], psychiatric disorders [57] including depression [58–61] and PTSD [62], toxicity of chemotherapy [63] and the robustness of the immune system [64,65]. Shorter telomere length also has been associated in embryonic stem cells with unstable differentiation [66], and in haematopoietic progenitor cells with reduced proliferative reserve [67]. Lastly, a *causal* role for the telomere biology system in human health and disease risk is suggested by findings from several organ transplantation studies that report recipient survival time and disease progression-related outcomes are a function of donor and not recipient telomere length [68–71]. Despite the evidence linking short telomeres with increased disease risk in humans, the above-mentioned association studies do not prove causality, and the involvement of short telomeres

in ageing-related processes has been questioned in some non-human model systems [72,73]. Further experimental and mechanistic studies are clearly warranted.

Nevertheless, to summarize, it appears that telomere homeostasis in various cell types, including the germ line, stem cells and proliferating as well as post-mitotic tissue, may serve as a fundamental integrator and regulator of processes underlying cell genomic integrity, function, ageing and senescence, which, in turn, may have major implications for health and disease susceptibility for complex common disorders.

(e) Determinants of variation in the telomere biology system

In humans, telomere length and telomerase expression and activity is associated with a host of socio-demographic, biophysical, clinical, biological, behavioural and psychosocial states and conditions, including age, sex, socio-economic status, race/ethnicity, body mass index, infection, diet/nutrition, physical activity, sleep, stress and social relationships. A detailed description is outside the purview of the current paper, but see [74–85] for recent studies and reviews.

(i) Role of stress and stress biology

Most of the above-mentioned states and conditions associated with unfavourable alterations in telomere dynamics reflect forms of social disadvantage or adversity characterized by high levels of stress. Epel, Blackburn and co-workers were the first to propose and demonstrate a link between chronic psychosocial stress burden and telomere biology [86]. This relationship has since been replicated in several [77,87–89] but not all studies [90,91]. Exposure to severe psychological trauma or other psychopathological conditions also has been linked to telomere biology [92–96]. A recently published meta-analysis on one specific component of psychosocial stress—perceived stress—suggests there is a significant association across studies, but of relatively modest magnitude [77]. Furthermore, some studies have suggested that lifestyle interventions that attenuate stress may increase telomerase activity and slow down cellular ageing [82,97,98].

A substantial body of animal and human research has elucidated the role of stress-related biological processes in mediating the effects of stress and unhealthy behaviours on the regulation of telomere dynamics, including oxidative stress, inflammation, stress hormones and metabolic processes, as discussed below.

Oxidative stress: Telomeres have a high content of guanine residues, and these are particularly sensitive to oxidative damage. Thus, oxidative stress potently accelerates telomere shortening, decreases telomerase activity and induces senescence or apoptosis via DNA damage-induced activation of the *p53* pathway [96,99–104]. Oxidative stress also can induce the nuclear export of TERT to the cytosol and into the mitochondria, thereby decreasing nuclear and total telomerase activity [100]. The effects and mechanisms by which oxidative stress at the cellular and organismal level impacts telomeres are discussed in greater detail by Monaghan & Ozanne [28].

Inflammatory mediators: Biological mediators of inflammation such as C-Reactive Protein, Interleukin (*IL*)-6 and tumour necrosis factor (TNF)- α have been linked to telomere shortening [105–107] and T-cell senescence [108]. Activated immune cells such as T-cells express high telomerase levels. The upregulation of telomerase prevents immune cell senescence and facilitates a

rapid and profound clonal cell expansion. However, the level of telomerase expression is not sufficient to indefinitely prevent telomere shortening and senescence [109]. For instance, continuous antigen challenge has been shown to produce accelerated telomere shortening and premature senescence in human cytotoxic T-cells [109]. In human lymphocytes, TNF- α administration *in vitro* induced the nuclear translocation of TERT and increased telomerase activity via the nuclear factor kappa B (NF- κ B) signalling pathway [110]. Conversely, TERT regulates the expression of a subset of NF- κ B-dependent genes [111,112]. The observation that TERT binds to the NF- κ B p65 subunit and is recruited to a subset of NF- κ B target gene promoters such as those of IL-6 and TNF- α suggests that telomerase can provide a feed-forward loop for the immune system by stimulating NF- κ B-dependent gene expression [112].

Stress hormones: In humans, several measures of the activity of the hypothalamic–pituitary–adrenal stress axis and its adrenal end product, cortisol, including higher production (overnight urinary free cortisol levels), dysregulation of feedback sensitivity (disruption of the diurnal cortisol rhythm) and greater reactivity (higher acute stress-induced cortisol responses) have been linked to shorter telomeres [113–115]. We recently reported that immune cells from individuals who exhibit greater cortisol responses to stress have a lower capacity to induce telomerase activity (mTAC) (see de Punder K *et al.* [33]). Consistent with this finding, exogenous cortisol exposure has been shown to inhibit telomerase production in mitogen-stimulated human T-cells [116]. Long-term stress exposure also is known to induce oxidative stress and inflammation [117], both of which accelerate telomere shortening (as discussed above).

Metabolic processes: Metabolic processes related particularly to lipid and glucose–insulin physiology have been shown to regulate telomere dynamics. Evidence across several studies has linked the intake of total fat or specific fatty acids with leucocyte telomere length (LTL; summarized in [118]). A recent and large cross-sectional study demonstrated an association between key metabolic biomarkers (high-density lipoprotein (HDL) cholesterol and triglycerides) and LTL after controlling for the effects of socio-demographic factors, health-related behaviours and immune cell-type composition [119]. Another recent study of metabolomic profiling in a large group of females reported that specific alterations in lipid metabolism that indicate changes in cell membrane composition were associated with LTL, and also with higher blood pressure, HDL cholesterol levels, and poorer lung, liver and kidney function [104]. In terms of glucose–insulin physiology, insulin resistance is associated with shorter LTL [34,37], and a more recent longitudinal study indicated that individuals with shorter LTL are more likely to develop insulin resistance later in life [120]. A study in rodents demonstrated a regulatory role for telomerase in glucose metabolism; telomerase-deficient mice exhibited impaired glucose metabolism and insulin secretion [39]. In addition, *in vitro* studies revealed an extra-nuclear function of TERT in glucose uptake in mouse skeletal muscle cells [121].

4. The importance of the initial setting of the telomere system

Telomere length, at any given age, is a joint function of the initial (newborn) setting of TL and the magnitude of TL attrition over time, which, in turn, is a function of the number of cell divisions (reflected by growth, age), exposure to oxidative

and other forms of biological stress that reduce TL, and the counter-regulatory effect of telomerase expression and activity that attenuates TL reduction [4]. Studies in animals and humans converge to provide a strong rationale for the importance of newborn and infant telomere biology in long-term health and disease risk, as discussed below.

(a) Animal studies

Animal models of telomere dynamics *over the lifespan and across generations* suggest that *initial TL* and the *TL attrition rate in early life* is (a) a better predictor of realized lifespan than TL and the TL attrition rate in later life [122–124], and (b) the effects of early-life TL persist over and beyond those of risk exposures in later life [122–124]. For example, a recent study on telomere dynamics in birds reported that early-life TL predicted lifespan, and its effect persisted and was substantially unchanged even after accounting for the effect of subsequent life course exposures such as chronic infection [124]. Another study of life-long (birth to death) patterns of LTL variation in sheep reported that LTL variation was significantly associated with longevity, and particularly that it was longer LTL *specifically during the first 2 years of life, but not later in life (during adulthood)*, that drove this observed association [125].

(b) Human studies

We are not aware of any human studies that have prospectively tracked TL from birth until old age (with characterization of common age-related disorders) or death. However, findings from cohorts that have longitudinally tracked TL over time, and others that have estimated the heritability of age-related TL attrition, have collectively suggested that *it is the initial (early life) setting of the system that accounts for the largest proportion of its attributable effects on health and disease risk-related outcomes*. For example, a recent study of 4 longitudinal cohorts ($N = 1156$) with mean ages of 30, 31, 58 and 78 years at baseline and an average 12-year follow-up concluded that most of the inter-individual variation in adult LTL originated early in life, because the overwhelming majority of individuals maintained their LTL ranking and it remained unchanged over 6 decades of adult life [126]. A study of the age-related heritability of LTL dynamics using the same-sex twin model (355 MZ and 297 DZ twins aged 19–64 years at baseline with an average follow-up of 12 years) reported that the *early-life* environment was the main determinant of LTL variation throughout the life course (72%), an approximately 2.5-fold greater effect than that of heritability (28%) [127]. Another recent human study in newborns demonstrated that compared to newborns with normal TL, newborns with reduced TL at birth exhibited greater DNA damage at baseline and also upon exposure to a genotoxic challenge [128]. Lastly, although TL is known to differ across tissue types, the rate of age-dependent TL shortening in humans appears to be similar across different somatic tissues (leucocyte, skeletal muscle, skin and fat), suggesting that the observed TL differences between tissues are established in early life [129].

(c) Conceptual considerations

Several recent papers have considered some of the implications of the above-described findings. Broadly, it appears that selection may have favoured short telomeres as a mechanism to protect against cancer, and may have favoured long

telomeres as a protective mechanism against DNA damage and replicative senescence [130,131].

Firstly, as discussed in their paper on telomere dynamics and ageing-related diseases in humans, Aviv and Shay have questioned the commonly held premise that adult telomere length may be an active determinant in adult-onset disease [131]. They submit that the view of adult telomere length as a 'clock' or maker of risk for age-related disorders, whose pace is modified by the cumulative burden of stress-related biological exposures such as oxidative stress and inflammation, may be overlooking the facts that telomere length is not uniformly calibrated at 'zero time' across newborns (on the contrary, the *magnitude* of TL variation in newborns is similar to that observed in adults), and that telomere length at birth is the principal determinant of telomere length throughout the life course. They also point out that longitudinal studies indicate that adults characterized by intermediate phenotypes underlying common age-related disorders (e.g. more atherosclerotic burden and insulin resistance) have shorter LTL but do not exhibit any evidence of a higher rate of age-dependent LTL shortening. They suggest that the overall influence of telomere length dynamics during adulthood may be smaller than that of TL at birth and its dynamics prior to adulthood, and they highlight the importance of expanding telomere research to newborns and children to better understand the role of telomere biology in age-related disorders and the causes of its variation.

Secondly, Monaghan & Ozanne [28] have highlighted the significance particularly of telomere length loss rate in early life. They argue that if short telomeres have a causal role in suboptimal health, the same loss rate may have different consequences, depending on the initial telomere length setting. They underscore the need to obtain repeated measures from the same individual, particularly during the early-life period, because telomere dynamics might be differentially related to individual state at different life stages, and because differential mortality with respect to telomere length may alter variation in telomere length in different age categories.

Thirdly, as reviewed in §3e above, a range of health-related behaviours such as diet/nutrition, physical activity and sleep have been associated in adults with telomere length and telomerase expression and activity, leading to the premise that one mechanism by which such behaviours influence health and disease risk is via their effects on telomere dynamics. However, Bateson & Nettle [132] have recently proposed a provocative alternative. They argue it is plausible that individuals with short telomeres may be more likely to adopt specific health-related behavioural patterns (i.e. the selective adoption hypothesis), and they suggest selective adoption could occur either because telomere length directly affects behaviour, or because behaviour and telomere length may both be affected by a third variable, such as exposure to early-life adversity. Thus, this formulation, again, but for a different set of reasons, highlights the potential importance of the initial setting of the telomere system in health and disease risk.

5. Fetal programming of the telomere biology system

It appears that the initial setting and regulation of telomere homeostasis, including chromosomal telomere length and both the telomeric and extra-telomeric activities of telomerase,

may be plastic and receptive to the influence of conditions during intrauterine or early postnatal life. The assumption that the initial setting of telomere length is largely under genetic (DNA base pair sequence variation) control has been challenged for the following reasons: First, although the heritability of TL is high, known genetic variants (across all candidate gene and GWAS studies to date) collectively account for only a small proportion of variation in TL (e.g. [133,134]). Second, the mother–offspring correlation in TL appears to be larger than the father–offspring correlation, regardless of the sex of the offspring [135]. Third, a recent study that examined the association of the weighted genetic scores of TL-related variants with telomere length in over 400 maternal and newborn (cord) blood samples found that the maternal genetic score was significantly associated with maternal TL, but that there was no significant association of the newborn genetic score (or any of its individual variants) with newborn TL. This finding suggests that currently identified genetic loci do not appear to influence the initial (newborn) setting of telomere length, but that they may play a role in telomere length modification during the life course [136]. Collectively, these observations, in conjunction with the understanding that heritability may overestimate genetic effects (because it includes maternal intrauterine effects), emphasize a major role for maternal and intrauterine effects in the initial setting of TL. In fact, as underscored recently by Dugdale & Richardson [137], accurate and meaningful measures of the heritability of telomere length can be derived only after fully understanding and accounting for the nature and timing of environmental effects. Furthermore, experimental and observational studies in animals and humans (discussed below in §§5b and 5c) suggest adverse intrauterine conditions such as stress, poor diet/nutrition and obstetric complications are associated with shorter offspring TL or reduced telomerase activity at birth and/or in childhood and adult life [4,138], thereby providing biological plausibility for the fetal/developmental programming hypothesis.

(a) Developmental ontogeny of the telomere biology system

Telomerase is especially active in germ cells, presumably to ensure the maintenance and transmission of full-length chromosomes to offspring [139–141]. After fertilization, telomerase remains abundant in the blastocyst and during early embryonic stages, and then decreases with increasing gestational age and cellular differentiation [142,143]. In children and adults, telomerase is largely inactive in most tissues except rapidly proliferating tissues such as certain types of stem cells and active lymphocytes [20]. However, when stimulated to divide, many stem or stem-like cells in adults exhibit telomerase activity. This activity is sufficient to slow, but not prevent, telomere shortening [20].

Consistent with their high levels of telomerase activity, germ cells have significantly longer telomeres than somatic cells, possibly because of telomere elongation during maturation [144,145]. It appears from studies in animals that telomeres may first be elongated during early embryonic development [141,146]. Later, during the fetal period, human studies of tissue samples from abortuses and newborns suggest that telomere length remains stable (does not decline) across gestation, and also that it is comparable across most fetal tissues [147]. In newborns, TL is highly synchronized between white blood cells, umbilical artery and foreskin tissues, but

there is high variability between individuals [148]. Among cord blood haematopoietic cells, correlations in TL between the different cell types also are very high [149]. After birth, infants show a rapid decrease in TL [150,151], corresponding with rapid growth and high turnover of immune cells in the process of developing acquired immunity [152]. We are aware of only one prospective study that quantified telomere shortening during the first few years of life. In this study of a relatively small number of subjects, LTL was assessed serially from birth until 3 years of age [150]. Collectively, the findings from cross-sectional and longitudinal studies suggest that telomere shortening is accelerated during the first years of life (approx. 270 base pairs per year), compared to early adulthood (approx. 60 bp year⁻¹ at 20 years of age) and old age (approx. 26 bp year⁻¹) [152]. Furthermore, there is considerable variation in the rate of telomere shortening among young children [150].

(b) Determinants of the initial setting of the telomere biology system

Human and animal studies support the concept that the initial setting of the telomere system exhibits developmental plasticity and is influenced by various physiological, social, environmental and clinical conditions in early life. We have advanced the hypothesis that context- and time-inappropriate exposures to *physiological* stress mediators during the conceptional, embryonic, fetal and early postnatal periods of development may alter or programme the telomere biology system in a manner that accelerates cellular dysfunction, ageing and disease susceptibility over the lifespan [4,5]. We have proposed that the same stress-related biological processes that mediate the effects of a range of unfavourable conditions on telomere biology during adult life (reviewed above in §3e(i)) may also impact fetal programming of the telomere system during the development. These stress-related MPF oxidative, immune endocrine and metabolic processes represent a plausible mechanism in this context because (a) they are sensitive to an array of adverse physiological, social, environmental and clinical exposures (summarized in [9]); (b) they constitute some of the key signalling molecules between the fetal and maternal compartments during intrauterine development [153]; and (c) they may exert stable, long-term effects via epigenetic and other processes on the developing telomere biology system [4,11]. Moreover, it is possible that the effects of these stress-related biological processes on telomere biology during development may be stronger than those during adulthood, because the system is undergoing particularly rapid changes during this period (e.g. faster TL attrition rate) [131].

We note that compared to many other phenotypes and outcomes that have been examined in the context of the process of fetal programming of health and disease risk, there are a relatively small number of studies to date that have addressed telomere biology-related phenotypes. Moreover, these studies vary considerably in terms of their study populations, research designs, measures and other methodological considerations.

(i) Role of prenatal conditions

Animal studies: Several experimental studies suggest a link between exposure to suboptimal intrauterine conditions such as cortisol, stress or poor diet and shortened offspring

telomeres in cells across different tissues [154–158]. For example, a recent study in rodents reported that maternal stress exposure during pregnancy was associated with shorter telomeres in the brain of the adult offspring [158]. In birds, mothers with infection produced offspring with shorter post-hatching TL than non-infected mothers, and there was no effect of paternal infection status, together suggesting a maternally mediated environmental effect [124].

Human studies: Several studies in humans have described the effects of prenatal exposures and maternal states and conditions such as obstetric complications, obesity, over- or undernutrition, stress and low socio-economic status during pregnancy, and adverse birth outcomes on offspring telomere biology [159–174]. We have previously reviewed the literature on the role of maternal stress [4,7] and maternal obstetric complications and nutrition during pregnancy [6] in programming offspring telomere biology. Consistent with our framework, many of these obstetric conditions that are related to various aspects of placental or newborn/offspring telomere biology produce perturbations in stress-related oxidative, endocrine, metabolic and immune biological mediators [9]. The majority of these studies have assessed TL or telomerase activity in placenta or cord blood, and only a few studies have examined effects on child or adult telomere dynamics. One of the first studies that examined the long-term effects of adverse intrauterine exposures on later-life telomere length found an association between low birth weight and shorter telomere length in peripheral blood mononuclear cells in preschool aged children [173]. In a study that followed individuals from birth through adulthood, exposure to maternal or perinatal complications was linked to shorter LTL at 38 years of age [138]. In survivors of the siege of Leningrad, exposure to famine during the intrauterine period or childhood was associated with shorter telomere length 70 years after the siege [175]. With reference to prenatal stress, we published the first human study on the long-term effects of maternal psychosocial stress exposure during pregnancy on offspring TL and reported a significant association with LTL in young adult offspring [165]. We and others have since replicated this association between maternal stress during pregnancy and shorter offspring telomere length in several independent cohorts [167,176–178].

(c) Biological pathways and mechanisms underlying fetal programming of telomere biology

There are no direct neural or vascular connections between the maternal and fetal compartments, and our model proposes that the proximate pathway by which maternal states and conditions during gestation impact embryonic and fetal development is ultimately biological in nature. These biological pathways collectively constitute a process that begins before and around conception and extends through gestation into the postnatal period of life. We propose that the same biological processes that mediate the effects of a range of suboptimal conditions on telomere biology during adult life (reviewed in §3e(i)) also impact fetal programming of the telomere system. Thus, our model focuses particularly on the role of stress-related MPF gestational biology as the key pathways by which maternal states and conditions during pregnancy may programme the offspring telomere biology system. Moreover, we postulate that the mechanisms underlying such programming may be mediated, in part, by the production of stable

epigenetic alterations in embryonic and fetal tissues [11]. We also discuss two additional avenues that may be implicated here: trans-generational epigenetic transmission via the germ line, and oocyte biology.

(i) Maternal–placental–fetal gestational biology

A substantial body of literature in humans and animals has implicated various maternal–placental–fetal oxidative, immune/inflammatory, endocrine and metabolic pathways in the process of fetal programming of various outcomes [4,8]. However, only a relatively small number of studies to date have examined these pathways in the context of telomere biology-related phenotypes.

Animal studies: Animal models have been particularly useful in elucidating the tissue-specific consequences of various experimental manipulations during pregnancy on the offspring's telomere biology system. For example, manipulation of cortisol concentration in the egg yolk of chicken resulted in a higher proportion of short telomeres (and increased levels of reactive oxygen metabolites and prolongation of acute stress response) in the offspring compared to a non-treated control group [154]. In a rodent model, protein restriction *in utero* combined with rapid postnatal catch-up growth (recuperated phenotype) was associated with increased oxidative stress, decreased antioxidant defence mechanisms and accelerated telomere shortening across different tissues in the offspring [155–157,179], and some of these effects persisted in tissues of the reproductive tracts of even second-generation offspring [180]. Post-weaning supplementation with coenzyme Q10, a key component of the electron transport chain and a potent antioxidant, attenuated telomere shortening in leucocytes and aortic cells of recuperated animals [181,182]. Another rodent study of programmed cardiovascular dysfunction indicated that aged offspring of hypoxic pregnancies with maternal antioxidant treatment displayed fewer numbers of short telomeres in vascular tissue compared to offspring of untreated hypoxic pregnancies [183], indicating that therapeutic interventions can be effective in counteracting the detrimental effects of suboptimal intrauterine conditions on cellular ageing.

Human studies: Maternal diabetes during pregnancy is an obstetric complication of increasing prevalence and concern. Pregnancies complicated by diabetes exhibit higher oxidative stress in maternal and cord plasma and placental tissue [184]. Gestational diabetes has been associated in a higher percentage of trophoblasts with shortened telomeres [185], shorter newborn LTL [186] and an upregulation of mitochondrial telomerase (TERT) in newborn leucocytes [187]. Another study found that although cord blood TL was not different between offspring from mothers with pre-gestational or gestational diabetes and controls, maternal and newborn glucose concentrations were associated with newborn LTL [188]. Maternal hypertension and its more serious form, pre-eclampsia, represent obstetric complications that confer serious health risks for mother and baby and are related to higher levels of oxidative stress in the mother and child [189]. Hypertensive disorders of pregnancy have been linked to increased expression of placental telomerase mRNA [190] and signs of telomere dysfunction in the placenta and cord blood cells [174,191]. A more recent study reported an association between cord blood levels of dehydroepiandrosterone sulfate (DHEAS), reactive oxygen species and newborn LTL [192]. Finally, yet other studies have reported associations between

maternal oestrogen levels [193], folate [166] and vitamin D status during pregnancy [194] with newborn LTL.

(ii) Epigenetic alterations in embryonic/fetal tissues

We and others have highlighted the role of epigenetic modifications in the context of intergenerational transmission of maternal effects and fetal programming [11,13,195]. The telomere biology system is under tight epigenetic regulation. Chromatin modifications are key regulators of mammalian telomeres. Sub-telomeric regions are enriched in epigenetic marks that are characteristic of heterochromatin, and the abrogation of master epigenetic regulators such as histone methyltransferases and DNA methyltransferases correlate with loss of TL control (reviewed in [196]). Specifically, the regulation of TL is dependent on the level of methylation in sub-telomeric regions of the histones H3 and H4. The methylation of these histones decreases access to telomere sequences and thus reduces telomerase activity [196]. Hence, proteins such as DNA methyltransferase (that play a role in regulation of methylation) have an impact on TL. Also, DNA methyltransferase is a key candidate mechanism by which early-life conditions such as prenatal nutrition [197] and stress [198] may produce stable, long-term epigenetic alternations. In addition, several studies have suggested that epigenetic modulation of the core promoter region of the TERT gene that regulates telomerase is involved in regulation the telomere maintenance (see [199]). Thus, determining whether these epigenetic mechanisms can potentially be modified by stress-related states and conditions in early life is a future research priority.

(iii) Trans-generational epigenetic transmission

Epigenetic alterations in the maternal germ line may provide an avenue for the intergenerational transmission of maternal effects via two possible routes: (a) inheritance of maternally derived epigenetic alterations and (b) *de novo* production of epigenetic marks in the offspring via exposure to intrauterine conditions [195,200]. With respect to *true* trans-generational epigenetic inheritance, there is currently limited evidence (and only in some animal models) to suggest that epigenetic marks can survive the erasure and re-establishment of epigenetic characteristics that occurs shortly after fertilization [201–204]. Animal models of early-life stress have demonstrated that epigenetic inheritance may be possible through the paternal germ line [205,206], but, to the best of our knowledge, there are yet no studies that have demonstrated such effects through the maternal germ line. However, as discussed in the previous section, it remains highly plausible that *de novo* production of epigenetic alterations in the developing embryo/fetus, via the sequelae of maternal states and conditions, may contribute to the process of fetal/developmental programming

(iv) Oocyte cytoplasm and mitochondrial function

The constituents of the oocyte cytoplasm represent the first environmental exposure for a fertilized egg, and variation in oocyte quality significantly affects early embryonic survival, establishment and maintenance of pregnancy, fetal development and even adult disease risk [207–209]. The structure and function of mitochondria, cellular proteins and RNA molecules (e.g. miRNAs) contained in the oocyte cytoplasm are central to these processes [210]. Each of these may, in turn, be impacted by preconception states and conditions at the time of oocyte growth and maturation. For example, maternal

obesity prior to conception is associated with altered oocyte endoplasmic reticulum stress signalling [211] and consequently reduced mitochondrial membrane potential and increased autophagy [212]. Empirical evidence from studies of women undergoing *in vitro* fertilization also indicates a significant effect of psychosocial stress [213,214] and physiological stress vulnerability [215] on reduced oocyte competence and failure to conceive. Although alterations in oocyte cytoplasm have not yet been studied in relation to the development of the telomere biology system, it is plausible that the adverse lifelong sequelae of maternal adversity could affect oocyte quality and mitochondrial function across all stages of oocyte development and maturation, contributing to the process of fetal programming of the telomere biology system.

A model integrating telomere biology and mitochondrial function has been suggested by several studies. In fact, a telomere p53–mitochondrion axis may account for many processes that have been implicated in pathophysiological ageing [22]. According to this model, telomere shortening is the driving force that generates mitochondrial dysfunction via activation of the transcription factor p53. Then, mitochondrial dysfunction leads to impaired metabolic as well as energetic homeostasis and increased oxidative stress, which sustains a feed-forward cycle of further DNA damage and mitochondrial dysfunction.

As discussed in a recent review paper [216], the effects of parental stress exposure on offspring telomere length could be directly mediated by parental germ-line telomere length prior to fertilization and its subsequent consequence on the telomere length inherited by the offspring. By contrast, and as described above, indirect effects of parental stress exposure may induce telomere shortening in offspring tissues through increases in maternally derived biological stress mediators during intrauterine life, or through alterations in parental behaviour or care, which then affects offspring stress regulation and thereby induces changes in telomere biology [216].

(d) Role of postnatal conditions

The influence of postnatal conditions on the characteristics of the telomere biology system has been described in a growing number of studies. For example, several human studies have found that exposure to adverse experiences in infancy and childhood such as abuse and maltreatment, exposure to violence, family disruption and institutionalized care is associated with child TL or TL attrition rate [106,217–225] and leukocyte resting telomerase activity [224]; but see [226–228] for recent reviews and a meta-analysis [229] on this topic. In animals, induction of stress during the early postnatal period (handling and cortisol exposure [230] as well as manipulation of nutrition and begging effort [231] in avian models and maternal separation in a rhesus monkey model [232]) has been shown to produce higher age-related decline of TL during early life [230] and shorter TL in adult life [232].

Our model recognizes that the effects of prenatal and postnatal states and conditions may not be mutually exclusive, and that in many instances the effects of postnatal exposures may, in part, be conditioned upon the effects of prenatal exposures. For example, a recent study reported that early exclusive breastfeeding is associated with longer child telomere length [233]. Prenatal stress exposure is a determinant of breastfeeding behaviour/success [234] as well as of newborn telomere dynamics (as discussed above in §5b(i)). Thus, the likelihood

of exposure to certain postnatal conditions, such as reduced breastfeeding, as well as its consequences, such as shorter child telomere length, may be particularly pronounced among individuals exposed to prenatal conditions such as excess stress. It also is possible that the effects of prenatal conditions may be attenuated by other kinds of postnatal experiences such as high maternal and paternal sensitivity and secure attachment patterns.

6. Future research directions and conclusion

Based on the conceptual framework and empirical findings presented here, we suggest it is important to consider the potential role of developmental conditions during intrauterine and early postnatal life to arrive at a better understanding of the determinants of the initial setting and function of the telomere biology system and, beyond this, the cellular processes underlying ageing and risk of age-related disorders. Questions and knowledge gaps remain regarding (a) the magnitude and duration of the long-term effects of developmental conditions on the initial (newborn) setting of telomere length and telomerase expression and activity; (b) the clinical significance of these observed effects on health and disease risk over the lifespan; and (c) the precise molecular mechanism(s) underlying the fetal/developmental programming effects on telomere homeostasis. Thus, longitudinal studies are warranted that track the effects of early-life conditions on the telomere biology system from prenatal life and birth onwards through childhood until adulthood and beyond, in order to systematically elucidate their implications in terms of susceptibility for common age-related disorders and longevity.

Given the limitations in humans for performing experimental manipulations of the intrauterine and early postnatal environment and for access to many of the target tissues of interest, appropriate animal models and *in vitro* mechanistic studies are warranted, including studies of stem cells and placental and fetal tissue culture systems and organoids to examine the effects of stress-related oxidative, endocrine, immune and biological processes on telomere biology at various stages of cellular replication and differentiation, as well as their downstream consequences on gene regulatory processes (such as epigenetic characteristics) and cellular energetics (such as mitochondrial function). Moreover, with respect to the putative role of female and male germ cells in the initial

setting of offspring telomere dynamics, an intriguing question has recently emerged concerning the relative contribution of factors contained within germ cells as they differentiate, versus the effects of the local micro-environment on germ cells (for example, as established in males by Sertoli cells of the seminiferous epithelium, and in females by Granulosa cells in the primordial follicle) [235].

Methodological barriers to progress in the field of fetal programming of telomere biology include issues related to the reliability of various telomere length measurement approaches [236,237]. The comparability of different methods (e.g. quantitative polymerase chain reaction-based methods, southern blot, fluorescence *in situ* hybridization-based techniques) remains to be established for samples collected from cord blood, placenta and young infants. Furthermore, protocols should be established and harmonized across different laboratories for DNA extraction methods and sample storage conditions. This is particularly important in studies with longitudinal follow-up of the same individuals over time, to reduce possible artefacts such as the observed phenomenon of telomere lengthening that has been attributed to measurement error and short follow-up periods [238].

To conclude, the concepts and findings discussed in this perspectives paper add to the growing appreciation and evidence that the foundations of common, age-related disorders that confer the major societal burden of disease may originate very early in life, and secondly, point to potentially modifiable factors as intervention targets with important implications for primary prevention. The process of fetal programming of the telomere system may represent an important avenue by which population health disparities are propagated across generations to influence the health and well-being of individuals and their offspring across the entire lifespan.

Data accessibility. This article has no additional data.

Authors' contributions. S.E. and P.D.W. developed the concepts, reviewed the literature, the manuscript and provided final editorial oversight. C.B. and K.d.P. assisted with the literature review and provided editorial assistance.

Competing interests. We declare we have no competing interests.

Funding. The preparation of this paper was supported, in part, by U.S. Public Health Service (National Institutes of Health) grants R01 AG-050455, R01 HD-060628, R01 HD-065825, UG3 OD-023349 to P.D.W. and S.E., and by ESR 678073 to S.E. K.d.P.'s effort was supported by the German Federal Ministry of Education and Research (01KR1301A).

References

- Hausmann MF, Marchetto NM. 2010 Telomeres: linking stress and survival, ecology and evolution. *Curr. Zool.* **56**, 714–727.
- Monaghan P. 2014 Organismal stress, telomeres and life histories. *J. Exp. Biol.* **217**, 57–66. (doi:10.1242/jeb.090043)
- Monaghan P, Hausmann MF. 2015 The positive and negative consequences of stressors during early life. *Early Hum. Dev.* **91**, 643–647. (doi:10.1016/j.earlhumdev.2015.08.008)
- Entringer S, Buss C, Wadhwa PD. 2012 Prenatal stress, telomere biology, and fetal programming of health and disease risk. *Sci. Signal.* **5**, pt12. (doi:10.1126/scisignal.2003580)
- Entringer S, Buss C, Wadhwa PD. 2015 Prenatal stress, development, health and disease risk: a psychobiological perspective-2015 Curt Richter Award Paper. *Psychoneuroendocrinology* **62**, 366–375. (doi:10.1016/j.psyneuen.2015.08.019)
- Entringer S, de Punder K, Verner G, Wadhwa PD. 2017 Fetal programming of telomere biology: role of maternal nutrition, obstetric risk factors and suboptimal birth outcomes. In *Diet, nutrition, and fetal programming* (eds R Rajendram, VR Preedy, VB Patel), pp. 569–593. New York, NY: Humana Press.
- Entringer S, Wadhwa PD. 2014 Developmental programming of telomere biology: role of stress and stress biology. In *Stress and developmental programming of health and disease: beyond phenomenology* (eds L Zhang, DL Longo), pp. 633–650. New York, NY: Nova Science Publishers.
- Buss C, Entringer S, Wadhwa PD. 2012 Fetal programming of brain development: intrauterine stress and susceptibility to psychopathology. *Sci. Signal.* **5**, pt7. (doi:10.1126/scisignal.2003406)
- Entringer S, Buss C, Wadhwa PD. 2010 Prenatal stress and developmental programming of human health and disease risk: concepts and integration of empirical findings. *Curr. Opin. Endocrinol. Diabetes Obes.* **17**, 507–516. (doi:10.1097/MED.0b013e3283405921)
- Gluckman PD, Hanson MA. 2004 Living with the past: evolution, development, and patterns of

- disease. *Science* **305**, 1733–1736. (doi:10.1126/science.1095292)
11. Wadhwa PD, Buss C, Entringer S, Swanson JM. 2009 Developmental origins of health and disease: brief history of the approach and current focus on epigenetic mechanisms. *Semin. Reprod. Med.* **27**, 358–368. (doi:10.1055/s-0029-1237424)
 12. Gluckman PD, Low FM, Buklijas T, Hanson MA, Beedle AS. 2011 How evolutionary principles improve the understanding of human health and disease. *Evol. Appl.* **4**, 249–263. (doi:10.1111/j.1752-4571.2010.00164.x)
 13. Hanson M, Godfrey KM, Lillycrop KA, Burdge GC, Gluckman PD. 2011 Developmental plasticity and developmental origins of non-communicable disease: theoretical considerations and epigenetic mechanisms. *Prog. Biophys. Mol. Biol.* **106**, 272–280. (doi:10.1016/j.pbiomolbio.2010.12.008)
 14. Blackburn EH, Epel ES, Lin J. 2015 Human telomere biology: a contributory and interactive factor in aging, disease risks, and protection. *Science* **350**, 1193–1198. (doi:10.1126/science.aab3389)
 15. Harley CB, Futcher AB, Greider CW. 1990 Telomeres shorten during ageing of human fibroblasts. *Nature* **345**, 458–460. (doi:10.1038/345458a0)
 16. Karlseder J. 2009 Chromosome end protection becomes even more complex. *Nat. Struct. Mol. Biol.* **16**, 1205–1206. (doi:10.1038/nsmb1209-1205)
 17. O'Sullivan RJ, Kubicek S, Schreiber SL, Karlseder J. 2010 Reduced histone biosynthesis and chromatin changes arising from a damage signal at telomeres. *Nat. Struct. Mol. Biol.* **17**, 1218–1225. (doi:10.1038/nsmb.1897)
 18. Harrington L, Pucci F. 2018 *In medio stat virtus*: unanticipated consequences of telomere dysequilibrium. *Phil. Trans. R. Soc. B* **373**, 20160444. (doi:10.1098/rstb.2016.0444)
 19. Shore D, Bianchi A. 2009 Telomere length regulation: coupling DNA end processing to feedback regulation of telomerase. *EMBO J.* **28**, 2309–2322. (doi:10.1038/emboj.2009.195)
 20. Forsyth NR, Wright WE, Shay JW. 2002 Telomerase and differentiation in multicellular organisms: turn it off, turn it on, and turn it off again. *Differentiation* **69**, 188–197. (doi:10.1046/j.1432-0436.2002.690412.x)
 21. Aubert G, Lansdorp PM. 2008 Telomeres and aging. *Physiol. Rev.* **88**, 557–579. (doi:10.1152/physrev.00026.2007)
 22. Sahin E, Depinho RA. 2010 Linking functional decline of telomeres, mitochondria and stem cells during ageing. *Nature* **464**, 520–528. (doi:10.1038/nature08982)
 23. Ahmed S, Passos JF, Birket MJ, Beckmann T, Brings S, Peters H, Birch-Machin MA, von Zglinicki T, Saretzki G. 2008 Telomerase does not counteract telomere shortening but protects mitochondrial function under oxidative stress. *J. Cell Sci.* **121**, 1046–1053. (doi:10.1242/jcs.019372)
 24. Jaskieloff M *et al.* 2011 Telomerase reactivation reverses tissue degeneration in aged telomerase-deficient mice. *Nature* **469**, 102–106. (doi:10.1038/nature09603)
 25. Sahin E *et al.* 2011 Telomere dysfunction induces metabolic and mitochondrial compromise. *Nature* **470**, 359–365. (doi:10.1038/nature09787)
 26. Blasco MA. 2002 Telomerase beyond telomeres. *Nat. Rev. Cancer* **2**, 627–633. (doi:10.1038/nrc862)
 27. Criscuolo F, Smith S, Zahn S, Heidinger BJ, Haussmann MF. 2018 Experimental manipulation of telomere length: does it reveal a corner-stone role for telomerase in the natural variability of individual fitness? *Phil. Trans. R. Soc. B* **373**, 20160440. (doi:10.1098/rstb.2016.0440)
 28. Monaghan P, Ozanne SE. 2018 Somatic growth and telomere dynamics in vertebrates: relationships, mechanisms and consequences. *Phil. Trans. R. Soc. B* **373**, 20160446. (doi:10.1098/rstb.2016.0446)
 29. Xie Z, Jay KA, Smith DL, Zhang Y, Liu Z, Zheng J, Tian R, Li H, Blackburn EH. 2015 Early telomerase inactivation accelerates aging independently of telomere length. *Cell* **160**, 928–939. (doi:10.1016/j.cell.2015.02.002)
 30. Epel ES, Lin J, Dhabhar FS, Wolkowitz OM, Puterman E, Karan L, Blackburn EH. 2010 Dynamics of telomerase activity in response to acute psychological stress. *Brain Behav. Immun.* **24**, 531–539. (doi:10.1016/j.bbi.2009.11.018)
 31. Buchkovich KJ, Greider CW. 1996 Telomerase regulation during entry into the cell cycle in normal human T cells. *Mol. Biol. Cell* **7**, 1443–1454. (doi:10.1091/mbc.7.9.1443)
 32. Zalli A, Carvalho LA, Lin J, Hamer M, Erusalimsky JD, Blackburn EH, Steptoe A. 2014 Shorter telomeres with high telomerase activity are associated with raised allostatic load and impoverished psychosocial resources. *Proc. Natl Acad. Sci. USA* **111**, 4519–4524. (doi:10.1073/pnas.1322145111)
 33. de Punder K, Heim C, Przesdzin I, Wadhwa PD, Entringer S. 2018 Characterization in humans of *in vitro* leucocyte maximal telomerase activity capacity and association with stress. *Phil. Trans. R. Soc. B* **373**, 20160441. (doi:10.1098/rstb.2016.0441)
 34. Aviv A, Valdes A, Gardner JP, Swaminathan R, Kimura M, Spector TD. 2006 Menopause modifies the association of leukocyte telomere length with insulin resistance and inflammation. *J. Clin. Endocrinol. Metab.* **91**, 635–640. (doi:10.1210/jc.2005-1814)
 35. Benetos A, Okuda K, Lajemi M, Kimura M, Thomas F, Skurnick J, Labat C, Bean K, Aviv A. 2001 Telomere length as an indicator of biological aging: the gender effect and relation with pulse pressure and pulse wave velocity. *Hypertension* **37**, 381–385. (doi:10.1161/01.HYP.37.2.381)
 36. Brouillette S, Singh RK, Thompson JR, Goodall AH, Samani NJ. 2003 White cell telomere length and risk of premature myocardial infarction. *Arterioscler. Thromb. Vasc. Biol.* **23**, 842–846. (doi:10.1161/01.ATV.0000067426.96344.32)
 37. Gardner JP, Li S, Srinivasan SR, Chen W, Kimura M, Lu X, Berenson GS, Aviv A. 2005 Rise in insulin resistance is associated with escalated telomere attrition. *Circulation* **111**, 2171–2177. (doi:10.1161/01.CIR.0000163550.70487.0B)
 38. Jeanclos E, Schork NJ, Kyvik KO, Kimura M, Skurnick JH, Aviv A. 2000 Telomere length inversely correlates with pulse pressure and is highly familial. *Hypertension* **36**, 195–200. (doi:10.1161/01.HYP.36.2.195)
 39. Kuhlow D *et al.* 2010 Telomerase deficiency impairs glucose metabolism and insulin secretion. *Aging* **2**, 650–658. (doi:10.18632/aging.100200)
 40. Samani NJ, Boulby R, Butler R, Thompson JR, Goodall AH. 2001 Telomere shortening in atherosclerosis. *Lancet* **358**, 472–473. (doi:10.1016/S0140-6736(01)05633-1)
 41. Sampson MJ, Winterbone MS, Hughes JC, Dozio N, Hughes DA. 2006 Monocyte telomere shortening and oxidative DNA damage in type 2 diabetes. *Diabetes Care* **29**, 283–289. (doi:10.2337/diacare.29.02.06.dc05-1715)
 42. Valdes AM, Andrew T, Gardner JP, Kimura M, Oelsner E, Cherkas LF, Aviv A, Spector TD. 2005 Obesity, cigarette smoking, and telomere length in women. *Lancet* **366**, 662–664. (doi:10.1016/S0140-6736(05)66630-5)
 43. Zhu H, Belcher M, van der Harst P. 2011 Healthy aging and disease: role for telomere biology? *Clin. Sci.* **120**, 427–440. (doi:10.1042/CS20100385)
 44. Bakaysa SL, Mucci LA, Slagboom PE, Boomsma DI, McClearn GE, Johansson B, Pedersen NL. 2007 Telomere length predicts survival independent of genetic influences. *Aging Cell* **6**, 769–774. (doi:10.1111/j.1474-9726.2007.00340.x)
 45. Cawthon RM, Smith KR, O'Brien E, Sivatchenko A, Kerber RA. 2003 Association between telomere length in blood and mortality in people aged 60 years or older. *Lancet* **361**, 393–395. (doi:10.1016/S0140-6736(03)12384-7)
 46. Honig LS, Schupf N, Lee JH, Tang MX, Mayeux R. 2006 Shorter telomeres are associated with mortality in those with APOE epsilon4 and dementia. *Ann. Neurol.* **60**, 181–187. (doi:10.1002/ana.20894)
 47. Kimura M *et al.* 2008 Telomere length and mortality: a study of leukocytes in elderly Danish twins. *Am. J. Epidemiol.* **167**, 799–806. (doi:10.1093/aje/kwm380)
 48. Martin-Ruiz C, Dickinson HO, Keys B, Rowan E, Kenny RA, Von Zglinicki T. 2006 Telomere length predicts poststroke mortality, dementia, and cognitive decline. *Ann. Neurol.* **60**, 174–180. (doi:10.1002/ana.20869)
 49. Mons U *et al.* 2017 Leukocyte telomere length and all-cause, cardiovascular disease, and cancer mortality: results from individual-participant-data meta-analysis of 2 large prospective cohort studies. *Am. J. Epidemiol.* **185**, 1317–1326. (doi:10.1093/aje/kww210)
 50. Rode L, Nordestgaard BG, Bojesen SE. 2015 Peripheral blood leukocyte telomere length and mortality among 64 637 individuals from the general population. *J. Natl. Cancer Inst.* **107**, djv074. (doi:10.1093/jnci/djv074)
 51. Haycock PC, Heydon EE, Kaptoge S, Butterworth AS, Thompson A, Willeit P. 2014 Leukocyte telomere length and risk of cardiovascular disease: systematic

- review and meta-analysis. *BMJ* **349**, g4227. (doi:10.1136/bmj.g4227)
52. D'Mello MJ, Ross SA, Briel M, Anand SS, Gerstein H, Pare G. 2015 Association between shortened leukocyte telomere length and cardiometabolic outcomes: systematic review and meta-analysis. *Circ. Cardiovasc. Genet.* **8**, 82–90. (doi:10.1161/CIRCGENETICS.113.000485)
 53. Revesz D, Milaneschi Y, Verhoeven JE, Penninx BW. 2014 Telomere length as a marker of cellular aging is associated with prevalence and progression of metabolic syndrome. *J. Clin. Endocrinol. Metab.* **99**, 4607–4615. (doi:10.1210/jc.2014-1851)
 54. Tamura Y, Takubo K, Aida J, Araki A, Ito H. 2016 Telomere attrition and diabetes mellitus. *Geriatr. Gerontol. Int.* **16**(Suppl. 1), 66–74. (doi:10.1111/ggi.12738)
 55. King KS, Kozlitina J, Rosenberg RN, Peshock RM, McColl RW, Garcia CK. 2014 Effect of leukocyte telomere length on total and regional brain volumes in a large population-based cohort. *JAMA Neurol.* **71**, 1247–1254. (doi:10.1001/jamaneurol.2014.1926)
 56. Hagg S *et al.* 2017 Short telomere length is associated with impaired cognitive performance in European ancestry cohorts. *Transl. Psychiatry* **7**, e1100. (doi:10.1038/tp.2017.73)
 57. Lindqvist D *et al.* 2015 Psychiatric disorders and leukocyte telomere length: underlying mechanisms linking mental illness with cellular aging. *Neurosci. Biobehav. Rev.* **55**, 333–364. (doi:10.1016/j.neubiorev.2015.05.007)
 58. Schutte NS, Malouff JM. 2015 The association between depression and leukocyte telomere length: a meta-analysis. *Depress Anxiety* **32**, 229–238. (doi:10.1002/da.22351)
 59. Needham BL, Mezuk B, Bareis N, Lin J, Blackburn EH, Epel ES. 2015 Depression, anxiety and telomere length in young adults: evidence from the national health and nutrition examination survey. *Mol. Psychiatry* **20**, 520–528. (doi:10.1038/mp.2014.89)
 60. Karabatsiakos A, Kolassa IT, Kolassa S, Rudolph KL, Dietrich DE. 2014 Telomere shortening in leukocyte subpopulations in depression. *BMC Psychiatry* **14**, 192. (doi:10.1186/1471-244X-14-192)
 61. Verhoeven JE, Revesz D, Picard M, Epel EE, Wolkowitz OM, Matthews KA, Penninx BW, Puterman E. 2017 Depression, telomeres and mitochondrial DNA: between- and within-person associations from a 10-year longitudinal study. *Mol. Psychiatry*. (doi:10.1038/mp.2017.48)
 62. Roberts AL *et al.* 2017 Posttraumatic stress disorder and accelerated aging: PTSD and leukocyte telomere length in a sample of civilian women. *Depress Anxiety* **34**, 391–400. (doi:10.1002/da.22620)
 63. Quintela-Fandino M *et al.* 2017 Critically short telomeres and toxicity of chemotherapy in early breast cancer. *Oncotarget* **8**, 21 472–21 482. (doi:10.18632/oncotarget.15592)
 64. Najjaro K *et al.* 2015 Telomere length as an indicator of the robustness of B- and T-Cell response to influenza in older adults. *J. Infect. Dis.* **212**, 1261–1269. (doi:10.1093/infdis/jiv202)
 65. Helby J, Nordestgaard BG, Benfield T, Bojesen SE. 2017 Shorter leukocyte telomere length is associated with higher risk of infections: a prospective study of 75 309 individuals from the general population. *Haematologica* **102**, 1457–1465. (doi:10.3324/haematol.2016.161943)
 66. Pucci F, Gardano L, Harrington L. 2013 Short telomeres in ESCs lead to unstable differentiation. *Cell Stem Cell* **12**, 479–486. (doi:10.1016/j.stem.2013.01.018)
 67. Mazidi M, Penson P, Banach M. 2017 Association between telomere length and complete blood count in US adults. *Arch. Med. Sci.* **13**, 601–605. (doi:10.5114/aoms.2017.67281)
 68. Faust HE *et al.* 2017 Short lung transplant donor telomere length is associated with decreased CLAD-free survival. *Thorax* **72**, 1052–1054. (doi:10.1136/thoraxjnl-2016-209897)
 69. Gadalla SM *et al.* 2016 Effect of recipient age and stem cell source on the association between donor telomere length and survival after allogeneic unrelated hematopoietic cell transplantation for severe aplastic anemia. *Biol. Blood Marrow Transplant.* **22**, 2276–2282. (doi:10.1016/j.bbmt.2016.09.012)
 70. Gadalla SM, Wang T, Haagenson M, Spellman SR, Lee SJ, Williams KM, Wong JY, De Vivo I, Savage SA. 2015 Association between donor leukocyte telomere length and survival after unrelated allogeneic hematopoietic cell transplantation for severe aplastic anemia. *JAMA* **313**, 594–602. (doi:10.1001/jama.2015.7)
 71. Wang Y *et al.* 2017 Relative telomere length before hematopoietic cell transplantation and outcome after unrelated donor hematopoietic cell transplantation for acute leukemia. *Biol. Blood Marrow Transplant.* **23**, 1054–1058. (doi:10.1016/j.bbmt.2017.03.032)
 72. Bauch C, Becker PH, Verhulst S. 2014 Within the genome, long telomeres are more informative than short telomeres with respect to fitness components in a long-lived seabird. *Mol. Ecol.* **23**, 300–310. (doi:10.1111/mec.12602)
 73. Simons MJ. 2015 Questioning causal involvement of telomeres in aging. *Ageing Res. Rev.* **24**, 191–196. (doi:10.1016/j.arr.2015.08.002)
 74. Arsenis NC, You T, Ogawa EF, Tinsley GM, Zuo L. 2017 Physical activity and telomere length: impact of aging and potential mechanisms of action. *Oncotarget* **8**, 45 008–45 019. (doi:10.18632/oncotarget.16726)
 75. Gardner M *et al.* 2014 Gender and telomere length: systematic review and meta-analysis. *Exp. Gerontol.* **51**, 15–27. (doi:10.1016/j.exger.2013.12.004)
 76. Kordinas V, Ioannidis A, Chatzipanagiotou S. 2016 The telomere/telomerase system in chronic inflammatory diseases. Cause or effect? *Genes* **7**, 60. (doi:10.3390/genes7090060)
 77. Mathur MB, Epel E, Kind S, Desai M, Parks CG, Sandler DP, 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. (doi:10.1016/j.bbi.2016.02.002)
 78. Prather AA *et al.* 2015 Tired telomeres: Poor global sleep quality, perceived stress, and telomere length in immune cell subsets in obese men and women. *Brain Behav. Immun.* **47**, 155–162. (doi:10.1016/j.bbi.2014.12.011)
 79. Rafie N, Golpour Hamedani S, Barak F, Safavi SM, Miraghajani M. 2017 Dietary patterns, food groups and telomere length: a systematic review of current studies. *Eur. J. Clin. Nutr.* **71**, 151–158. (doi:10.1038/ejcn.2016.149)
 80. Revesz D, Milaneschi Y, Terpstra EM, Penninx BW. 2016 Baseline biopsychosocial determinants of telomere length and 6-year attrition rate. *Psychoneuroendocrinology* **67**, 153–162. (doi:10.1016/j.psyneuen.2016.02.007)
 81. Schrock JM, Adler NE, Epel ES, Nuru-Jeter AM, Lin J, Blackburn EH, Taylor RJ, Chae DH. 2017 Socioeconomic status, financial strain, and leukocyte telomere length in a sample of african american midlife men. *J. Racial Ethn Health Disparities* (doi:10.1007/s40615-017-0388-3)
 82. Tolahunase M, Sagar R, Dada R. 2017 Impact of yoga and meditation on cellular aging in apparently healthy individuals: a prospective, open-label single-arm exploratory study. *Oxid. Med. Cell. Longev.* **2017**, 7928981. (doi:10.1155/2017/7928981)
 83. Tucker LA. 2017 Physical activity and telomere length in U.S. men and women: an NHANES investigation. *Prev. Med.* **100**, 145–151. (doi:10.1016/j.ypmed.2017.04.027)
 84. Tucker LA. 2017 Consumption of nuts and seeds and telomere length in 5,582 men and women of the national health and nutrition examination survey (NHANES). *J. Nutr. Health Aging* **21**, 233–240. (doi:10.1007/s12603-017-0876-5)
 85. Wulaningsih W, Watkins J, Matsuguchi T, Hardy R. 2016 Investigating the associations between adiposity, life course overweight trajectories, and telomere length. *Ageing* **8**, 2689–2701. (doi:10.18632/aging.101036)
 86. Epel ES, Blackburn EH, Lin J, Dhabhar FS, Adler NE, Morrow JD, Cawthon RM. 2004 Accelerated telomere shortening in response to life stress. *Proc. Natl Acad. Sci. USA* **101**, 17312–17315. (doi:10.1073/pnas.0407162101)
 87. Cherkas LF, Aviv A, Valdes AM, Hunkin JL, Gardner JP, Surdulescu GL, Kimura M, Spector TD. 2006 The effects of social status on biological aging as measured by white-blood-cell telomere length. *Ageing Cell* **5**, 361–365. (doi:10.1111/j.1474-9726.2006.00222.x)
 88. Damjanovic AK, Yang Y, Glaser R, Kiecolt-Glaser JK, Nguyen H, Laskowski B, Zou Y, Beversdorf DQ, Weng NP. 2007 Accelerated telomere erosion is associated with a declining immune function of caregivers of Alzheimer's disease patients. *J. Immunol.* **179**, 4249–4254. (doi:10.4049/jimmunol.179.6.4249)
 89. Steptoe A, Hamer M, Butcher L, Lin J, Brydon L, Kivimaki M, Marmot M, Blackburn E, Erusalimsky JD. 2011 Educational attainment but not measures

- of current socioeconomic circumstances are associated with leukocyte telomere length in healthy older men and women. *Brain Behav. Immun.* **25**, 1292–1298. (doi:10.1016/j.bbi.2011.04.010)
90. Jodczyk S, Fergusson DM, Horwood LJ, Pearson JF, Kennedy MA. 2014 No association between mean telomere length and life stress observed in a 30 year birth cohort. *PLoS ONE* **9**, e97102. (doi:10.1371/journal.pone.0097102)
91. Savolainen K, Eriksson JG, Kananen L, Kajantie E, Pesonen AK, Heinonen K, Raikkonen K. 2014 Associations between early life stress, self-reported traumatic experiences across the lifespan and leukocyte telomere length in elderly adults. *Biol. Psychol.* **97**, 35–42. (doi:10.1016/j.biopsycho.2014.02.002)
92. Hartmann N, Boehner M, Groenen F, Kalb R. 2010 Telomere length of patients with major depression is shortened but independent from therapy and severity of the disease. *Depress Anxiety* **27**, 1111–1116. (doi:10.1002/da.20749)
93. Humphreys J, Epel ES, Cooper BA, Lin J, Blackburn EH, Lee KA. 2012 Telomere shortening in formerly abused and never abused women. *Biol. Res. Nurs.* **14**, 115–123. (doi:10.1177/1099800411398479)
94. Simon NM, Smoller JW, McNamara KL, Maser RS, Zalta AK, Pollack MH, Nierenberg AA, Fava M, Wong KK. 2006 Telomere shortening and mood disorders: preliminary support for a chronic stress model of accelerated aging. *Biol. Psychiatry* **60**, 432–435. (doi:10.1016/j.biopsych.2006.02.004)
95. Starnino L, Busque L, Tardif JC, D'Antonio B. 2016 Psychological profiles in the prediction of leukocyte telomere length in healthy individuals. *PLoS ONE* **11**, e0165482. (doi:10.1371/journal.pone.0165482)
96. Wolkowitz OM *et al.* 2011 Leukocyte telomere length in major depression: correlations with chronicity, inflammation and oxidative stress—preliminary findings. *PLoS ONE* **6**, e17837. (doi:10.1371/journal.pone.0017837)
97. Daubenmier J *et al.* 2012 Changes in stress, eating, and metabolic factors are related to changes in telomerase activity in a randomized mindfulness intervention pilot study. *Psychoneuroendocrinology* **37**, 917–928. (doi:10.1016/j.psyneuen.2011.10.008)
98. Jacobs TL *et al.* 2011 Intensive meditation training, immune cell telomerase activity, and psychological mediators. *Psychoneuroendocrinology* **36**, 664–681. (doi:10.1016/j.psyneuen.2010.09.010)
99. Gonzalez-Guardia L *et al.* 2014 Influence of endothelial dysfunction on telomere length in subjects with metabolic syndrome: LIPGENE study. *Age* **36**, 9681. (doi:10.1007/s11357-014-9681-9)
100. Haendeler J, Hoffmann J, Diehl JF, Vasa M, Spyridopoulos I, Zeiher AM, Dimmeler S. 2004 Antioxidants inhibit nuclear export of telomerase reverse transcriptase and delay replicative senescence of endothelial cells. *Circ. Res.* **94**, 768–775. (doi:10.1161/01.RES.0000121104.05977.F3)
101. Ma D, Zhu W, Hu S, Yu X, Yang Y. 2013 Association between oxidative stress and telomere length in Type 1 and Type 2 diabetic patients. *J. Endocrinol. Invest.* **36**, 1032–1037.
102. Saretzki G. 2009 Telomerase, mitochondria and oxidative stress. *Exp. Gerontol.* **44**, 485–492. (doi:10.1016/j.exger.2009.05.004)
103. von Zglinicki T. 2002 Oxidative stress shortens telomeres. *Trends Biochem. Sci.* **27**, 339–344. (doi:10.1016/S0968-0004(02)02110-2)
104. Zierer J *et al.* 2016 Metabolomics profiling reveals novel markers for leukocyte telomere length. *Aging* **8**, 77–94. (doi:10.18632/aging.100874)
105. Bekaert S *et al.* 2007 Telomere length and cardiovascular risk factors in a middle-aged population free of overt cardiovascular disease. *Aging Cell* **6**, 639–647. (doi:10.1111/j.1474-9726.2007.00321.x)
106. Kiecolt-Glaser JK, Gouin JP, Weng NP, Malarkey WB, Beversdorf DQ, Glaser R. 2011 Childhood adversity heightens the impact of later-life caregiving stress on telomere length and inflammation. *Psychosom. Med.* **73**, 16–22. (doi:10.1097/PSY.0b013e31820573b6)
107. Osler M, Bendix L, Rask L, Rod NH. 2016 Stressful life events and leucocyte telomere length: Do lifestyle factors, somatic and mental health, or low grade inflammation mediate this relationship? Results from a cohort of Danish men born in 1953. *Brain Behav. Immun.* **58**, 248–253. (doi:10.1016/j.bbi.2016.07.154)
108. Effros RB. 2009 Kleemeier award lecture 2008—the canary in the coal mine: telomeres and human healthspan. *J. Gerontol. A Biol. Sci. Med. Sci.* **64**, 511–515. (doi:10.1093/gerona/glp001)
109. Akbar AN, Vukmanovic-Stejić M. 2007 Telomerase in T lymphocytes: use it and lose it? *J. Immunol.* **178**, 6689–6694. (doi:10.4049/jimmunol.178.11.6689)
110. Akiyama M, Yamada O, Hideshima T, Yanagisawa T, Yokoi K, Fujisawa K, Eto Y, Yamada H, Anderson KC. 2004 TNF α induces rapid activation and nuclear translocation of telomerase in human lymphocytes. *Biochem. Biophys. Res. Commun.* **316**, 528–532. (doi:10.1016/j.bbrc.2004.02.080)
111. Ding D, Xi P, Zhou J, Wang M, Cong YS. 2013 Human telomerase reverse transcriptase regulates MMP expression independently of telomerase activity via NF- κ B-dependent transcription. *FASEB J.* **27**, 4375–4383. (doi:10.1096/fj.13-230904)
112. Ghosh A *et al.* 2012 Telomerase directly regulates NF- κ B-dependent transcription. *Nat. Cell Biol.* **14**, 1270–1281. (doi:10.1038/ncb2621)
113. Epel ES, Lin J, Wilhelm FH, Wolkowitz OM, Cawthon R, Adler NE, Dolbier C, Mendes WB, Blackburn EH. 2006 Cell aging in relation to stress arousal and cardiovascular disease risk factors. *Psychoneuroendocrinology* **31**, 277–287. (doi:10.1016/j.psyneuen.2005.08.011)
114. Parks CG, Miller DB, McCanlies EC, Cawthon RM, Andrew ME, DeRoo LA, Sandler DP. 2009 Telomere length, current perceived stress, and urinary stress hormones in women. *Cancer Epidemiol. Biomarkers Prev.* **18**, 551–560. (doi:10.1158/1055-9965.EPI-08-0614)
115. Tomiyama AJ *et al.* 2012 Does cellular aging relate to patterns of allostasis? An examination of basal and stress reactive HPA axis activity and telomere length. *Physiol. Behav.* **106**, 40–45. (doi:10.1016/j.physbeh.2011.11.016)
116. Choi J, Fauce SR, Effros RB. 2008 Reduced telomerase activity in human T lymphocytes exposed to cortisol. *Brain Behav. Immun.* **22**, 600–605. (doi:10.1016/j.bbi.2007.12.004)
117. Epel ES. 2009 Psychological and metabolic stress: a recipe for accelerated cellular aging? *Hormones* **8**, 7–22. (doi:10.14310/horm.2002.1217)
118. Freitas-Simoes TM, Ros E, Sala-Vila A. 2016 Nutrients, foods, dietary patterns and telomere length: update of epidemiological studies and randomized trials. *Metabolism* **65**, 406–415. (doi:10.1016/j.metabol.2015.11.004)
119. Rehkopf DH, Needham BL, Lin J, Blackburn EH, Zota AR, Wojcicki JM, Epel ES. 2016 Leukocyte telomere length in relation to 17 biomarkers of cardiovascular disease risk: a cross-sectional study of US adults. *PLoS Med.* **13**, e1002188. (doi:10.1371/journal.pmed.1002188)
120. Verhulst S *et al.* 2016 A short leucocyte telomere length is associated with development of insulin resistance. *Diabetologia* **59**, 1258–1265. (doi:10.1007/s00125-016-3915-6)
121. Shaheen F, Grammatopoulos DK, Muller J, Zammit WA, Lehnert H. 2014 Extra-nuclear telomerase reverse transcriptase (TERT) regulates glucose transport in skeletal muscle cells. *Biochim. Biophys. Acta* **1842**, 1762–1769. (doi:10.1016/j.bbdis.2014.06.018)
122. Heidinger BJ, Blount JD, Boner W, Griffiths K, Metcalfe NB, Monaghan P. 2012 Telomere length in early life predicts lifespan. *Proc. Natl Acad. Sci. USA* **109**, 1743–1748. (doi:10.1073/pnas.1113306109)
123. Bateson M, Brilot BO, Gillespie R, Monaghan P, Nettle D. 2015 Developmental telomere attrition predicts impulsive decision-making in adult starlings. *Proc. R. Soc. B* **282**, 20142140. (doi:10.1098/rspb.2014.2140)
124. Asghar M, Hasselquist D, Hansson B, Zehndindjev P, Westerdaal H, Bensch S. 2015 Chronic infection. Hidden costs of infection: chronic malaria accelerates telomere degradation and senescence in wild birds. *Science* **347**, 436–438. (doi:10.1126/science.1261121)
125. Fairlie J, Holland R, Pilkington JG, Pemberton JM, Harrington L, Nussey DH. 2016 Lifelong leukocyte telomere dynamics and survival in a free-living mammal. *Aging Cell* **15**, 140–148. (doi:10.1111/accel.12417)
126. Benetos A *et al.* 2013 Tracking and fixed ranking of leukocyte telomere length across the adult life course. *Aging Cell* **12**, 615–621. (doi:10.1111/accel.12086)
127. Hjelmborg JB, Dalgard C, Moller S, Steenstrup T, Kimura M, Christensen K, Kyvik KO, Aviv A. 2015 The heritability of leucocyte telomere length dynamics. *J. Med. Genet.* **52**, 297–302. (doi:10.1136/jmedgenet-2014-102736)
128. Moreno-Palomo J, Creus A, Marcos R, Hernandez A. 2014 Genomic instability in newborn with short telomeres. *PLoS ONE* **9**, e91753. (doi:10.1371/journal.pone.0091753)

129. Daniali L, Benetos A, Susser E, Kark JD, Labat C, Kimura M, Desai K, Granick M, Aviv A. 2013 Telomeres shorten at equivalent rates in somatic tissues of adults. *Nat. Commun.* **4**, 1597. (doi:10.1038/ncomms2602)
130. Risques RA, Promislow DEL. 2018 All's well that ends well: why large species have short telomeres. *Phil. Trans. R. Soc. B* **373**, 20160448. (doi:10.1098/rstb.2016.0448)
131. Aviv A, Shay JW. 2018 Reflections on telomere dynamics and ageing-related diseases in humans. *Phil. Trans. R. Soc. B* **373**, 20160436. (doi:10.1098/rstb.2016.0436)
132. Bateson M, Nettle D. 2018 Why are there associations between telomere length and behaviour? *Phil. Trans. R. Soc. B* **373**, 20160438. (doi:10.1098/rstb.2016.0438)
133. Prescott J *et al.* 2011 Genome-wide association study of relative telomere length. *PLoS ONE* **6**, e19635. (doi:10.1371/journal.pone.0019635)
134. Codd V *et al.* 2013 Identification of seven loci affecting mean telomere length and their association with disease. *Nat. Genet.* **45**, 422–427, 427e421–422. (doi:10.1038/ng.2528)
135. Factor-Litvak P, Susser E, Kezios K, McKeague I, Kark JD, Hoffman M, Kimura M, Wapner R, Aviv A. 2016 Leukocyte telomere length in newborns: implications for the role of telomeres in human disease. *Pediatrics* **137**, e20153927. (doi:10.1542/peds.2015-3927)
136. Weng Q *et al.* 2016 The known genetic loci for telomere length may be involved in the modification of telomeres length after birth. *Sci. Rep.* **6**, 38729. (doi:10.1038/srep38729)
137. Dugdale HL, Richardson DS. 2018 Heritability of telomere variation: it is all about the environment! *Phil. Trans. R. Soc. B* **373**, 20160450. (doi:10.1098/rstb.2016.0450)
138. Shalev I *et al.* 2014 Perinatal complications and aging indicators by midlife. *Pediatrics* **134**, e1315–e1323. (doi:10.1542/peds.2014-1669)
139. Hiyama K, Hirai Y, Kyoizumi S, Akiyama M, Hiyama E, Piatyszek MA, Shay JW, Ishioka S, Yamakido M. 1995 Activation of telomerase in human lymphocytes and hematopoietic progenitor cells. *J. Immunol.* **155**, 3711–3715.
140. Kim NW *et al.* 1994 Specific association of human telomerase activity with immortal cells and cancer. *Science* **266**, 2011–2015. (doi:10.1126/science.7605428)
141. Schaeetzlein S, Lucas-Hahn A, Lemme E, Kues WA, Dorsch M, Manns MP, Niemann H, Rudolph KL. 2004 Telomere length is reset during early mammalian embryogenesis. *Proc. Natl Acad. Sci. USA* **101**, 8034–8038. (doi:10.1073/pnas.0402400101)
142. Ulaner GA, Hu JF, Vu TH, Giudice LC, Hoffman AR. 1998 Telomerase activity in human development is regulated by human telomerase reverse transcriptase (hTERT) transcription and by alternate splicing of hTERT transcripts. *Cancer Res.* **58**, 4168–4172.
143. Wright WE, Piatyszek MA, Rainey WE, Byrd W, Shay JW. 1996 Telomerase activity in human germline and embryonic tissues and cells. *Dev. Genet.* **18**, 173–179. (doi:10.1002/(SICI)1520-6408(1996)18:2<173::AID-DVG10>3.0.CO;2-3)
144. Achi MV, Ravindranath N, Dym M. 2000 Telomere length in male germ cells is inversely correlated with telomerase activity. *Biol. Reprod.* **63**, 591–598. (doi:10.1095/biolreprod63.2.591)
145. Ozturk S, Sozen B, Demir N. 2014 Telomere length and telomerase activity during oocyte maturation and early embryo development in mammalian species. *Mol. Hum. Reprod.* **20**, 15–30. (doi:10.1093/molehr/gat055)
146. Liu L *et al.* 2007 Telomere lengthening early in development. *Nat. Cell Biol.* **9**, 1436–1441. (doi:10.1038/ncb1664)
147. Youngren K, Jeancos E, Aviv H, Kimura M, Stock J, Hanna M, Skurnick J, Bardeguet A, Aviv A. 1998 Synchrony in telomere length of the human fetus. *Hum. Genet.* **102**, 640–643. (doi:10.1007/s004390050755)
148. Okuda K, Bardeguet A, Gardner JP, Rodriguez P, Ganesh V, Kimura M, Skurnick J, Awad G, Aviv A. 2002 Telomere length in the newborn. *Pediatr. Res.* **52**, 377–381. (doi:10.1203/00006450-200209000-00012)
149. Kimura M, Gazitt Y, Cao X, Zhao X, Lansdorp PM, Aviv A. 2010 Synchrony of telomere length among hematopoietic cells. *Exp. Hematol.* **38**, 854–859. (doi:10.1016/j.exphem.2010.06.010)
150. Zeichner SL, Palumbo P, Feng Y, Xiao X, Gee D, Sleasman J, Goodenow M, Biggar R, Dimitrov D. 1999 Rapid telomere shortening in children. *Blood* **93**, 2824–2830.
151. Frencz Jr RW, Blackburn EH, Shannon KM. 1998 The rate of telomere sequence loss in human leukocytes varies with age. *Proc. Natl Acad. Sci. USA* **95**, 5607–5610. (doi:10.1073/pnas.95.10.5607)
152. Eisenberg DT. 2010 An evolutionary review of human telomere biology: the thrifty telomere hypothesis and notes on potential adaptive paternal effects. *Am. J. Hum. Biol.* **23**, 149–167. (doi:10.1002/ajhb.21127)
153. Wadhwa PD. 2005 Psychoneuroendocrine processes in human pregnancy influence fetal development and health. *Psychoneuroendocrinology* **30**, 724–743. (doi:10.1016/j.psychuen.2005.02.004)
154. Haussmann MF, Longenecker AS, Marchetto NM, Juliano SA, Bowden RM. 2011 Embryonic exposure to corticosterone modifies the juvenile stress response, oxidative stress and telomere length. *Proc. R. Soc. B* **279**, 1447–1456. (doi:10.1098/rspb.2011.1913)
155. Tarry-Adkins JL, Martin-Gronert MS, Chen JH, Cripps RL, Ozanne SE. 2008 Maternal diet influences DNA damage, aortic telomere length, oxidative stress, and antioxidant defense capacity in rats. *FASEB J.* **22**, 2037–2044. (doi:10.1096/fj.07-099523)
156. Tarry-Adkins JL, Chen JH, Smith NS, Jones RH, Cherif H, Ozanne SE. 2009 Poor maternal nutrition followed by accelerated postnatal growth leads to telomere shortening and increased markers of cell senescence in rat islets. *FASEB J.* **23**, 1521–1528. (doi:10.1096/fj.08-122796)
157. Jennings BJ, Ozanne SE, Dorling MW, Hales CN. 1999 Early growth determines longevity in male rats and may be related to telomere shortening in the kidney. *FEBS Lett.* **448**, 4–8. (doi:10.1016/S0014-5793(99)00336-1)
158. Blaze J, Asok A, Borrelli K, Tulbert C, Bollinger J, Ronca AE, Roth TL. 2017 Intrauterine exposure to maternal stress alters Bdnf IV DNA methylation and telomere length in the brain of adult rat offspring. *Int. J. Dev. Neurosci.* **62**, 56–62. (doi:10.1016/j.ijdevneu.2017.03.007)
159. Akkad A, Hastings R, Konje JC, Bell SC, Thurston H, Williams B. 2006 Telomere length in small-for-gestational-age babies. *BJOG* **113**, 318–323. (doi:10.1111/j.1471-0528.2005.00839.x)
160. Biron-Shental T, Kidron D, Sukenik-Halevy R, Goldberg-Bittman L, Sharony R, Fejgin MD, Amiel A. 2011 TERC telomerase subunit gene copy number in placentas from pregnancies complicated with intrauterine growth restriction. *Early Hum. Dev.* **87**, 73–75. (doi:10.1016/j.earlhumdev.2010.08.024)
161. Biron-Shental T, Sukenik Halevy R, Goldberg-Bittman L, Kidron D, Fejgin MD, Amiel A. 2010 Telomeres are shorter in placental trophoblasts of pregnancies complicated with intrauterine growth restriction (IUGR). *Early Hum. Dev.* **86**, 451–456. (doi:10.1016/j.earlhumdev.2010.06.002)
162. Cross JA *et al.* 2009 Absence of telomere shortening and oxidative DNA damage in the young adult offspring of women with pre-gestational type 1 diabetes. *Diabetologia* **52**, 226–234. (doi:10.1007/s00125-008-1207-5)
163. Cross JA *et al.* 2010 Cord blood telomere length, telomerase activity and inflammatory markers in pregnancies in women with diabetes or gestational diabetes. *Diabet. Med.* **27**, 1264–1270. (doi:10.1111/j.1464-5491.2010.03099.x)
164. Davy P, Nagata M, Bullard P, Fogelson NS, Allsopp R. 2009 Fetal growth restriction is associated with accelerated telomere shortening and increased expression of cell senescence markers in the placenta. *Placenta* **30**, 539–542. (doi:10.1016/j.placenta.2009.03.005)
165. Entringer S, Epel ES, Kumsta R, Lin J, Hellhammer DH, Blackburn EH, Wust S, Wadhwa PD. 2011 Stress exposure in intrauterine life is associated with shorter telomere length in young adulthood. *Proc. Natl Acad. Sci. USA* **108**, E513–E518. (doi:10.1073/pnas.1107759108)
166. Entringer S *et al.* 2015 Maternal folate concentration in early pregnancy and newborn telomere length. *Ann. Nutr. Metab.* **66**, 202–208. (doi:10.1159/000381925)
167. Entringer S, Epel ES, Lin J, Buss C, Shahbaba B, Blackburn EH, Simhan HN, Wadhwa PD. 2013 Maternal psychosocial stress during pregnancy is associated with newborn leukocyte telomere length. *Am. J. Obstet. Gynecol.* **208**, 134.e1–134.e7. (doi:10.1016/j.ajog.2012.11.033)
168. Fragkiadaki P, Tsoukalas D, Fragkiadoulaki I, Psycharakis C, Nikitovic D, Spandidos DA, Tsatsakis

- AM. 2016 Telomerase activity in pregnancy complications (Review). *Mol. Med. Rep.* **14**, 16–21. (doi:10.3892/mmr.2016.5231)
169. Friedrich U, Schwab M, Griese EU, Fritz P, Klotz U. 2001 Telomeres in neonates: new insights in fetal hematopoiesis. *Pediatr. Res.* **49**, 252–256. (doi:10.1203/00006450-200102000-00020)
170. Gielen M, Hageman G, Pachen D, Derom C, Vlietinck R, Zeegers MP. 2014 Placental telomere length decreases with gestational age and is influenced by parity: a study of third trimester live-born twins. *Placenta* **35**, 791–796. (doi:10.1016/j.placenta.2014.05.010)
171. Izutsu T, Kudo T, Sato T, Nishiya I, Ohyashiki K, Mori M, Nakagawara K. 1998 Telomerase activity in human chorionic villi and placenta determined by TRAP and *in situ* TRAP assay. *Placenta* **19**, 613–618. (doi:10.1016/S0143-4004(98)90022-4)
172. Martens DS, Plusquin M, Gyselaers W, De Vivo I, Nawrot TS. 2016 Maternal pre-pregnancy body mass index and newborn telomere length. *BMC Med.* **14**, 148. (doi:10.1186/s12916-016-0689-0)
173. Raqib R, Alam DS, Sarker P, Ahmad SM, Ara G, Yunus M, Moore SE, Fuchs G. 2007 Low birth weight is associated with altered immune function in rural Bangladeshi children: a birth cohort study. *Am. J. Clin. Nutr.* **85**, 845–852.
174. Sukenik-Halevy R, Fejgin M, Kidron D, Goldberg-Bittman L, Sharony R, Biron-Shental T, Kitay-Cohen Y, Amiel A. 2009 Telomere aggregate formation in placenta specimens of pregnancies complicated with pre-eclampsia. *Cancer Genet. Cytogenet.* **195**, 27–30. (doi:10.1016/j.cancergencyto.2009.03.015)
175. Rotar O *et al.* 2015 Seventy years after the siege of Leningrad: does early life famine still affect cardiovascular risk and aging? *J. Hypertens.* **33**, 1772–1779; discussion 1779. (doi:10.1097/HJH.0000000000000640)
176. Marchetto NM, Glynn RA, Ferry ML, Ostojic M, Wolff SM, Yao R, Haussmann MF. 2016 Prenatal stress and newborn telomere length. *Am. J. Obstet. Gynecol.* **215**, 94.e1–94.e8. (doi:10.1016/j.ajog.2016.01.177)
177. Send TS *et al.* 2017 Telomere length in newborns is related to maternal stress during pregnancy. *Neuropsychopharmacology* **42**, 2407–2413. (doi:10.1038/npp.2017.73)
178. Salihu HM, King LM, Nwoga C, Paothong A, Pradhan A, Marty PJ, Daas R, Whiteman VE. 2016 Association between maternal-perceived psychological stress and fetal telomere length. *South Med. J.* **109**, 767–772. (doi:10.14423/SMJ.0000000000000567)
179. Aiken CE, Tarry-Adkins JL, Ozanne SE. 2013 Suboptimal nutrition in utero causes DNA damage and accelerated aging of the female reproductive tract. *FASEB J.* **27**, 3959–3965. (doi:10.1096/fj.13-234484)
180. Aiken CE, Tarry-Adkins JL, Ozanne SE. 2015 Transgenerational developmental programming of ovarian reserve. *Sci. Rep.* **5**, 16175. (doi:10.1038/srep16175)
181. Tarry-Adkins JL, Blackmore HL, Martin-Gronert MS, Fernandez-Twinn DS, McConnell JM, Hargreaves IP, Giussani DA, Ozanne SE. 2013 Coenzyme Q10 prevents accelerated cardiac aging in a rat model of poor maternal nutrition and accelerated postnatal growth. *Mol. Metab.* **2**, 480–490. (doi:10.1016/j.molmet.2013.09.004)
182. Tarry-Adkins JL, Fernandez-Twinn DS, Chen JH, Hargreaves IP, Martin-Gronert MS, McConnell JM, Ozanne SE. 2014 Nutritional programming of coenzyme Q: potential for prevention and intervention? *FASEB J.* **28**, 5398–5405. (doi:10.1096/fj.14-259473)
183. Allison BJ *et al.* 2016 Divergence of mechanistic pathways mediating cardiovascular aging and developmental programming of cardiovascular disease. *FASEB J.* **30**, 1968–1975. (doi:10.1096/fj.201500057)
184. Biri A, Onan A, Devrim E, Babacan F, Kavutcu M, Durak I. 2006 Oxidant status in maternal and cord plasma and placental tissue in gestational diabetes. *Placenta* **27**, 327–332. (doi:10.1016/j.placenta.2005.01.002)
185. Biron-Shental T, Sukenik-Halevy R, Naboani H, Liberman M, Kats R, Amiel A. 2015 Telomeres are shorter in placentas from pregnancies with uncontrolled diabetes. *Placenta* **36**, 199–203. (doi:10.1016/j.placenta.2014.11.011)
186. Xu J *et al.* 2014 Reduced fetal telomere length in gestational diabetes. *PLoS ONE* **9**, e86161. (doi:10.1371/journal.pone.0086161)
187. Li P, Tong Y, Yang H, Zhou S, Xiong F, Huo T, Mao M. 2014 Mitochondrial translocation of human telomerase reverse transcriptase in cord blood mononuclear cells of newborns with gestational diabetes mellitus mothers. *Diabetes Res. Clin. Pract.* **103**, 310–318. (doi:10.1016/j.diabetes.2013.12.024)
188. Gilfillan C, Naidu P, Gunawan F, Hassan F, Tian P, Elwood N. 2016 Leukocyte telomere length in the neonatal offspring of mothers with gestational and pre-gestational diabetes. *PLoS ONE* **11**, e0163824. (doi:10.1371/journal.pone.0163824)
189. Bharadwaj S, Bhat VB, Vickneswaran V, Adhisivam B, Zachariah B, Habeebullah S. 2017 Oxidative stress in preeclamptic mother – newborn dyads and its correlation with early neonatal outcome – a case control study. *J. Matern. Fetal. Neonatal. Med.* **1–6**. (doi:10.1080/14767058.2017.1319933)
190. Geifman-Holtzman O, Xiong Y, Holtzman EJ, Hoffman B, Gaughan J, Liebermann DA. 2010 Increased placental telomerase mRNA in hypertensive disorders of pregnancy. *Hypertens. Pregnancy* **29**, 434–445. (doi:10.3109/10641950903214625)
191. Sukenik-Halevy R, Amiel A, Kidron D, Liberman M, Ganor-Paz Y, Biron-Shental T. 2016 Telomere homeostasis in trophoblasts and in cord blood cells from pregnancies complicated with preeclampsia. *Am. J. Obstet. Gynecol.* **214**, 283.e1–283.e7. (doi:10.1016/j.ajog.2015.08.050)
192. Liu H, Zhou G, Chen Q, Ouyang F, Little J, Zhang J, Chen D. 2017 Impact of dehydroepiandrosterone sulfate on newborn leukocyte telomere length. *Clin. Rep.* **7**, 42160. (doi:10.1038/srep42160)
193. Entringer S, Epel ES, Lin J, Blackburn EH, Buss C, Simhan HN, Wadhwa PD. 2015 Maternal estriol concentrations in early gestation predict infant telomere length. *J. Clin. Endocrinol. Metab.* **100**, 267–273. (doi:10.1210/jc.2014-2744)
194. Kim JH, Kim GJ, Lee D, Ko JH, Lim I, Bang H, Koes BW, Seong B, Lee DC. 2017 Higher maternal vitamin D concentrations are associated with longer leukocyte telomeres in newborns. *Matern. Child Nutr.* (doi:10.1111/mcn.12475)
195. Buss C, Entringer S, Moog NK, Toepfer P, Fair DA, Simhan HN, Heim CM, Wadhwa PD. 2017 Intergenerational transmission of maternal childhood maltreatment exposure: implications for fetal brain development. *J. Am. Acad. Child Adolesc. Psychiatry* **56**, 373–382. (doi:10.1016/j.jaac.2017.03.001)
196. Blasco MA. 2007 The epigenetic regulation of mammalian telomeres. *Nat. Rev. Genet.* **8**, 299–309. (doi:10.1038/nrg2047)
197. Burdge GC, Lillycrop KA. 2011 Nutrition, epigenetics, and developmental plasticity: implications for understanding human disease. *Annu. Rev. Nutr.* **30**, 315–339. (doi:10.1146/annurev.nutr.012809.104751)
198. Weaver IC, Cervoni N, Champagne FA, D'Alessio AC, Sharma S, Seckl JR, Dymov S, Szyf M, Meaney MJ. 2004 Epigenetic programming by maternal behavior. *Nat. Neurosci.* **7**, 847–854. (doi:10.1038/nn1276)
199. Daniel M, Peek GW, Tollefsbol TO. 2012 Regulation of the human catalytic subunit of telomerase (hTERT). *Gene* **498**, 135–146. (doi:10.1016/j.gene.2012.01.095)
200. Lappalainen T, Grealley JM. 2017 Associating cellular epigenetic models with human phenotypes. *Nat. Rev. Genet.* **18**, 441–451. (doi:10.1038/nrg.2017.32)
201. Branco MR *et al.* 2016 Maternal DNA methylation regulates early trophoblast development. *Dev. Cell* **36**, 152–163. (doi:10.1016/j.devcel.2015.12.027)
202. Sanchez-Delgado M *et al.* 2016 Human oocyte-derived methylation differences persist in the placenta revealing widespread transient imprinting. *PLoS Genet.* **12**, e1006427. (doi:10.1371/journal.pgen.1006427)
203. Smallwood SA *et al.* 2011 Dynamic CpG island methylation landscape in oocytes and preimplantation embryos. *Nat. Genet.* **43**, 811–814. (doi:10.1038/ng.864)
204. Smith ZD, Chan MM, Mikkelsen TS, Gu H, Gnirke A, Regev A, Meissner A. 2012 A unique regulatory phase of DNA methylation in the early mammalian embryo. *Nature* **484**, 339–344. (doi:10.1038/nature10960)
205. Franklin TB, Russig H, Weiss IC, Graff J, Linder N, Michalon A, Vizi S, Mansuy IM. 2010 Epigenetic transmission of the impact of early stress across generations. *Biol. Psychiatry* **68**, 408–415. (doi:10.1016/j.biopsych.2010.05.036)
206. Gapp K, Jawaid A, Sarkies P, Bohacek J, Pelczar P, Prados J, Farinelli L, Miska E, Mansuy IM. 2014 Implication of sperm RNAs in transgenerational inheritance of the effects of early trauma in mice. *Nat. Neurosci.* **17**, 667–669. (doi:10.1038/nn.3695)

207. Dumesic DA, Meldrum DR, Katz-Jaffe MG, Krisher RL, Schoolcraft WB. 2015 Oocyte environment: follicular fluid and cumulus cells are critical for oocyte health. *Fertil. Steril* **103**, 303–316. (doi:10.1016/j.fertnstert.2014.11.015)
208. Krisher RL. 2004 The effect of oocyte quality on development. *J. Anim. Sci.* **82**(Suppl. 13), E14–E23.
209. Shea LD, Woodruff TK, Shikanov A. 2014 Bioengineering the ovarian follicle microenvironment. *Annu. Rev. Biomed. Eng.* **16**, 29–52. (doi:10.1146/annurev-bioeng-071813-105131)
210. Van Blerkom J. 2011 Mitochondrial function in the human oocyte and embryo and their role in developmental competence. *Mitochondrion* **11**, 797–813. (doi:10.1016/j.mito.2010.09.012)
211. Latham KE. 2015 Endoplasmic reticulum stress signaling in mammalian oocytes and embryos: life in balance. *Int. Rev. Cell Mol. Biol.* **316**, 227–265. (doi:10.1016/bs.ircmb.2015.01.005)
212. Wu LL *et al.* 2015 Mitochondrial dysfunction in oocytes of obese mothers: transmission to offspring and reversal by pharmacological endoplasmic reticulum stress inhibitors. *Development* **142**, 681–691. (doi:10.1242/dev.114850)
213. An Y, Sun Z, Li L, Zhang Y, Ji H. 2013 Relationship between psychological stress and reproductive outcome in women undergoing *in vitro* fertilization treatment: psychological and neurohormonal assessment. *J. Assist. Reprod. Genet.* **30**, 35–41. (doi:10.1007/s10815-012-9904-x)
214. Turner K, Reynolds-May MF, Zitek EM, Tisdale RL, Carlisle AB, Westphal LM. 2013 Stress and anxiety scores in first and repeat IVF Cycles: a pilot study. *PLoS ONE* **8**, e63743. (doi:10.1371/journal.pone.0063743)
215. Facchinetti F, Matteo ML, Artini GP, Volpe A, Genazzani AR. 1997 An increased vulnerability to stress is associated with a poor outcome of *in vitro* fertilization-embryo transfer treatment. *Fertil. Steril* **67**, 309–314. (doi:10.1016/S0015-0282(97)81916-4)
216. Haussmann MF, Heidinger BJ. 2015 Telomere dynamics may link stress exposure and ageing across generations. *Biol. Lett.* **11**, 20150396. (doi:10.1098/rsbl.2015.0396)
217. Tyrka AR, Price LH, Kao HT, Porton B, Marsella SA, Carpenter LL. 2010 Childhood maltreatment and telomere shortening: preliminary support for an effect of early stress on cellular aging. *Biol. Psychiatry* **67**, 531–534. (doi:10.1016/j.biopsych.2009.08.014)
218. Drury SS, Theall K, Gleason MM, Smyke AT, De Vivo I, Wong JY, Fox NA, Zeanah CH, Nelson CA. 2012 Telomere length and early severe social deprivation: linking early adversity and cellular aging. *Mol. Psychiatry* **17**, 719–727. (doi:10.1038/mp.2011.53)
219. Drury SS, Mabile E, Brett ZH, Esteves K, Jones E, Shirtcliff EA, Theall KP. 2014 The association of telomere length with family violence and disruption. *Pediatrics* **134**, e128–e137. (doi:10.1542/peds.2013-3415)
220. Kananen L, Surakka I, Pirkola S, Suvisaari J, Lonqvist 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**, e10826. (doi:10.1371/journal.pone.0010826)
221. Surtees PG, Wainwright NW, Pooley KA, Luben RN, Khaw KT, Easton DF, Dunning AM. 2011 Life stress, emotional health, and mean telomere length in the European Prospective Investigation into Cancer (EPIC)-Norfolk population study. *J. Gerontol. A Biol. Sci. Med. Sci.* **66**, 1152–1162. (doi:10.1093/gerona/glr112)
222. Shalev I, Moffitt TE, Sugden K, Williams B, Houts RM, Danese A, Mill J, Arseneault L, Caspi A. 2012 Exposure to violence during childhood is associated with telomere erosion from 5 to 10 years of age: a longitudinal study. *Mol. Psychiatry* **18**, 576–581. (doi:10.1038/mp.2012.32)
223. O'Donovan A *et al.* 2011 Childhood trauma associated with short leukocyte telomere length in posttraumatic stress disorder. *Biol. Psychiatry* **70**, 465–471. (doi:10.1016/j.biopsych.2011.01.035)
224. Chen SH *et al.* 2014 Adverse childhood experiences and leukocyte telomere maintenance in depressed and healthy adults. *J. Affect. Disord.* **169**, 86–90. (doi:10.1016/j.jad.2014.07.035)
225. Mason SM, Prescott J, Tworoger SS, DeVivo I, Rich-Edwards JW. 2015 Childhood physical and sexual abuse history and leukocyte telomere length among women in middle adulthood. *PLoS ONE* **10**, e0124493. (doi:10.1371/journal.pone.0124493)
226. Ridout SJ, Ridout KK, Kao HT, Carpenter LL, Philip NS, Tyrka AR, Price LH. 2015 Telomeres, Early-Life Stress and Mental Illness. In *Clinical challenges in the biopsychosocial interface. Update on psychosomatics for the 21st century. Adv psychosom Med* (eds R Balon, TN Wise), pp. 92–108. Basel, Switzerland: Karger.
227. Coimbra BM, Carvalho CM, Moretti PN, Mello MF, Belangero SI. 2017 Stress-related telomere length in children: a systematic review. *J. Psychiatr. Res.* **92**, 47–54. (doi:10.1016/j.jpsychires.2017.03.023)
228. Blaze J, Asok A, Roth TL. 2015 The long-term impact of adverse caregiving environments on epigenetic modifications and telomeres. *Front. Behav. Neurosci.* **9**, 79. (doi:10.3389/fnbeh.2015.00079)
229. Ridout KK, Levandowski M, Ridout SJ, Gantz L, Goonan K, Palermo D, Price LH, Tyrka AR. 2017 Early life adversity and telomere length: a meta-analysis. *Mol. Psychiatry*. (doi:10.1038/mp.2017.26)
230. Herborn KA, Heidinger BJ, Boner W, Noguera JC, Adam A, Daunt F, Monaghan P. 2014 Stress exposure in early post-natal life reduces telomere length: an experimental demonstration in a long-lived seabird. *Proc. R. Soc. B* **281**, 20133151. (doi:10.1098/rspb.2013.3151)
231. Nettle D, Andrews C, Reichert S, Bedford T, Kolenda C, Parker C, Martin-Ruiz C, Monaghan P, Bateson M. 2017 Early-life adversity accelerates cellular ageing and affects adult inflammation: Experimental evidence from the European starling. *Sci. Rep.* **7**, 40794. (doi:10.1038/srep40794)
232. Schnepfer LM, Brooks-Gunn J, Notterman DA, Suomi SJ. 2016 Early-life experiences and telomere length in adult rhesus monkeys: an exploratory study. *Psychosom. Med.* **78**, 1066–1071. (doi:10.1097/PSY.0000000000000402)
233. Wojcicki JM, Heyman MB, Elwan D, Lin J, Blackburn E, Epel E. 2016 Early exclusive breastfeeding is associated with longer telomeres in Latino preschool children. *Am. J. Clin. Nutr.* **104**, 397–405. (doi:10.3945/ajcn.115.115428)
234. Dozier AM, Nelson A, Brownell E. 2012 The relationship between life stress and breastfeeding outcomes among low-income mothers. *Adv. Prev. Med.* **2012**, 902487. (doi:10.1155/2012/902487)
235. Albertini DF. 2017 Telegraphing your telomere length to the next generation. *J. Assist. Reprod. Genet.* **34**, 829–830. (doi:10.1007/s10815-017-0967-6)
236. Behrens YL, Thomay K, Hagedorn M, Ebersold J, Henrich L, Nustede R, Schlegelberger B, Gohring G. 2017 Comparison of different methods for telomere length measurement in whole blood and blood cell subsets: recommendations for telomere length measurement in hematological diseases. *Genes Chromosomes Cancer* **56**, 700–708. (doi:10.1002/gcc.22475)
237. Lai T-P, Wright WE, Shay JW. 2018 Comparison of telomere length measurement methods. *Phil. Trans. R. Soc. B* **373**, 20160451. (doi:10.1098/rstb.2016.0451)
238. Steenstrup T, Hjelmborg JV, Kark JD, Christensen K, Aviv A. 2013 The telomere lengthening conundrum—artifact or biology? *Nucleic Acids Res.* **41**, e131. (doi:10.1093/nar/gkt370)