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Basal cortisol, cortisol reactivity, and telomere length: A systematic review and meta-analysis

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ABSTRACT

The objective of the present study is to synthesize the existing empirical literature and perform a meta-analysis of published data on the relationship between cortisol and telomere length. We systematically searched studies that examined the relationship between cortisol and telomere length in humans on electronic databases and screened reference sections of included articles. Fourteen studies were included in the meta-analysis, with effect sizes being extracted for two cortisol measures: basal cortisol levels and cortisol reactivity to acute psychological stress. Results from random effects models showed that basal cortisol levels (13 effect sizes from 12 cross-sectional studies, $N = 3675$ participants) were not significantly correlated with telomere length ($r = -0.05$, 95% CI [−0.11, 0.02]). Further, results stratified by the specimen type for cortisol measurement (i.e., saliva, urine, blood) showed that none of the three basal cortisol level measures were correlated with telomere length. However, we found a statistically significant correlation between salivary cortisol reactivity to acute psychosocial stress (6 cross-sectional studies, $N = 958$ participants) and telomere length ($r = -0.13$, 95% CI [−0.23, −0.03]). Subgroup analyses revealed that correlations between salivary cortisol reactivity and telomere length were more evident in studies conducted among children (vs. adults) and in studies that included female participants only (vs. both genders). However, the small number of available studies limits the conclusions derived from subgroup analyses, and more studies are needed before moderator effects can be properly established. Overall, findings of this study support the existence of a relationship between cortisol reactivity and telomere shortening.

1. Introduction

Psychosocial stress is recognized as an important risk factor for a variety of adverse physical and mental health outcomes, including cancer, cardiovascular diseases, immunological disorders, and mental illness (Backé et al., 2012; Dimsdale, 2008; Esch et al., 2002). Recent studies suggest that stress-related telomere shortening, a cellular marker of aging, might be a crucial mechanism linking psychosocial stress to health problems (Epel et al., 2004; Shalev, 2012).

Telomeres are repeated nucleotide sequences (TTAGG) that act as protective caps at the ends of chromosomes (Witzany, 2008). Telomeres shorten with each cell division, and when telomere length reaches a critical threshold, cells stop dividing or die (Harley et al., 1990). Telomere maintenance is essential for cellular health, and short telomere length has been consistently associated with health risks and diseases (Haycock et al., 2014; Ridout et al., 2016; Zhao et al., 2013). Multiple factors, including environmental stressors and genetic predispositions, influence the process of telomere shortening (Monaghan, 2010). A growing body of empirical research has suggested an association between psychosocial stress and short telomere length (Drury et al., 2012; Epel et al., 2004; O'Donovan et al., 2011 Puterman et al., 2016). For example, evidence from recent meta-analyses shows that both chronic stress exposure and perceived stress are associated with telomere length (Mathur et al., 2016; Ridout et al., 2018; Schutte and Malouff, 2016). As suggested by Mathur et al. (2016), physiological changes in response to stressors and perceived stress might act as the

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proximal mechanism through which stress affects telomere shortening. Thus, examining the effect of physiological stress on telomere length might provide insight on how psychosocial stress modulates cellular aging.

Activity of the hypothalamic-pituitary-adrenal (HPA) axis, the central neuroendocrine axis involved in the stress response, has been linked to telomere length (Epel et al., 2006; Nelson et al., 2018; Savolainen et al., 2015; Tomiyama et al., 2012). The HPA axis encompasses a set of influences and feedback interactions among the hypothalamus, the pituitary gland, and the adrenal glands, which are responsible for the secretion of cortisol, the end product of the HPA axis. Cortisol can be sampled from various body fluids, including saliva, blood, and urine (Klaassens et al., 2012). Cortisol levels follow a circadian rhythm, with a high increase at 30 min after awakening (i.e., cortisol awakening response, CAR; e.g., Stalder et al., 2016), and then decrease over the course of the day (i.e., diurnal cortisol slope; e.g., Adam et al., 2017). Collecting multiple cortisol samples a day is necessary to derive some of these circadian cortisol parameters (e.g., diurnal cortisol slope); however, in many cases cortisol is measured from a single sample collected at a specific time interval to control for hormonal diurnal variation (e.g., Boeck et al., 2017). This single measure of cortisol is often referred to as an indicator of basal cortisol levels. Measurements of area under the curve, which are indicative of total daily cortisol output, are also referred to as basal cortisol levels (e.g., Struja et al., 2017). Laboratory paradigms intended to induce psychological and physiological stress, such as the Trier Social Stress Test (Kirschbaum et al., 1993), are used to assess cortisol reactivity and recovery from stressors. The different cortisol measures (e.g., basal cortisol levels, cortisol circadian rhythm parameters, cortisol reactivity) are not redundant, instead, they can provide distinct information regarding cortisol activity (Ridout et al., 2018).

Recent studies have begun to examine the effect of cortisol on telomere shortening. In vitro studies showed that elevated cortisol exposure accelerated telomere shortening (Choi et al., 2008; Vartak et al., 2014). Correlational evidence from population studies found that elevated basal cortisol levels and heightened cortisol reactivity in response to psychological stress were associated with short telomere length (Epel et al., 2006; Gotlib et al., 2015; Nelson et al., 2018; Tomiyama et al., 2012). However, other studies found no relationship between cortisol and telomere length (e.g., Savolainen et al., 2015; Woody et al., 2017). Inconsistent findings are not surprising given the variability across existing studies in cortisol measurement, sample characteristics, and study designs. Further, many studies in this emergent literature have modest sample sizes, which limit the ability to draw definitive conclusions. To overcome these limitations, there is a need to perform a systematic review and meta-analysis to summarize the increasing evidence from this literature.

The aim of this review is to synthesize existing studies to date and perform a meta-analysis of published data on the relationship between physiological stress (captured by cortisol) and telomere length. Specifically, basal cortisol levels (i.e., salivary and blood cortisol measured at a specific time point during the day or prior to a stressor, urinary cortisol, total daily cortisol output), cortisol reactivity to acute psychosocial stressors, and cortisol circadian rhythm parameters (i.e., CAR, diurnal cortisol slope) were examined if there were adequate data to have meaningful pooled results. A secondary aim of this review is to examine whether the postulated relationship between cortisol and telomere length varies as a function of methodological (e.g., cortisol measurement, study quality) and sample characteristics (e.g., age, gender).

2. Methods

The review was conducted following the guidelines of the PRISMA standards of quality of reporting systematic reviews (Moher et al., 2015).

2.1. Search strategy and inclusion criteria

We systematically searched published studies examining the relationship between cortisol and telomere length in humans in the PubMed, PsycINFO, EMBASE, and Web of Science (latest update February 9, 2018). The search strategy included terms for cortisol (cortisol, hydrocortisone, corticosteroids, dexamethasone, hypothalamic-pituitary adrenal axis, and HPA axis) and telomere length (telomere and telomerase). The search was limited to human studies. Reference lists of included articles in this review were hand-searched to identify additional eligible publications.

Peer-reviewed articles were included if they were written in English and reported estimates for the correlation between basal cortisol secretion (or cortisol reactivity) and telomere length. Articles were excluded for this review if they (1) included interventions (e.g., mindfulness) that could possibly affect the relationship between cortisol and telomere length (unless baseline data were provided prior to the intervention); (2) used any pharmacological challenges to induce HPA axis activation (unless baseline data were provided prior to the challenge); and, (3) focused on pregnant women (unless data before pregnancy were available).

2.2. Data extraction and quality assessment

Article screening and data extraction were conducted using Covidence (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia; www.covidence.org). Two authors independently screened the articles, first by title and abstract and then by reading the full text. Disagreements were resolved by discussion until consensus was reached. After screening, two authors independently extracted the following information: (1) authors; (2) year of publication; (3) study location; (4) study design; (5) sample size and gender composition; (6) participants' age; (7) sample characteristics (see Table 1 for more details); (8) type of cortisol measure (i.e., basal, reactivity, circadian parameters); (9) the specimen type for cortisol assay; (10) time of day for cortisol sample collection; (11) cell types used for telomere length assay; and (12) telomere length assay method.

Study quality was assessed independently by two authors using the quality assessment tool for observational cohort and cross-sectional studies providing by the National Institute of Health (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools). Six aspects were used to assess study quality: study population, population recruitment, different levels of the exposure of interest, cortisol measurement, telomere length measurement, and statistical analysis. The criteria for evaluating the quality of cortisol and telomere length measurement were chosen based on previous studies in this field (Calvi et al., 2017; Mathur et al., 2016). Disagreements were solved by discussion until a consensus was reached. More information about quality assessment can be found in Supplemental Table 1.

2.3. Quantitative data synthesis and statistical analyses

Meta-analytic procedures were performed for basal cortisol levels (i.e., salivary and blood cortisol measured at a specific time point during the day or prior to a stressor and urinary cortisol) and salivary cortisol reactivity to psychosocial stress. Due to the small number of available effect sizes, no meta-analytic synthesis could be performed for longitudinal studies and for studies focusing on other measures of basal cortisol levels (i.e., total daily cortisol output) and cortisol circadian rhythm parameters (i.e., CAR, diurnal cortisol slope). However, available effect sizes based on baseline data from the longitudinal studies were included in the meta-analysis.

Some rules were followed to extract effect sizes for the meta-analysis. When data from the same sample were reported in multiple studies, the one with the largest sample size was selected. When both continuous and dichotomized correlations (e.g., between high and low

Table 1
Studies included in the review.

						Cortisol measurement			Telomere measurement	
Studies	Study location	Study design	Sample size (% female)	Mean age (SD), years	Sample characteristics	Measures	Specimen types	Time of day	Cell types	Assay methods
Nelson et al., 2018	USA	Prospective (15 months)	48 (60.4%)	6-12 months	Infants, predominantly from low SES families	Cortisol reactivity (Still Face experiment and Strange situation)	Saliva	Afternoon	Saliva	qPCR
Aulinas et al., 2014*	Spain	Case-control	154(81.8%)	48.5(12.7)	Adults, Cushing's syndrome patients (n = 77) and matched controls	Basal cortisol levels	Urine, blood	Morning	Leukocyte	TRF
Barha et al., 2017*	Canada	Cross-sectional	55(100%)	39.8(5.8)	Adults, some experienced the loss of a child (n = 25)	Basal cortisol levels	Urine	Morning, every other day over 7 weeks	Buccal	qPCR
Boeck et al., 2017*	Germany	Cross-sectional	30(100%)	31.2(6.0)	Adults, women in postpartum, some experienced child maltreatment (N = 15)	Basal cortisol levels	Blood	between 12: 30 pm to 2:00 pm	PBMCs, immune cells	qFISH
Buss et al., 2014	USA	Cross-sectional	47(100%)	40.0(7.3)	Adults, overweight (n = 25) and obese women	CAR, diurnal slope	Saliva	Waking, 30-minute post awakening, prior to bedtime, over 4 days	PBMCs	qPCR
Czamanski-Cohen et al., 2015*	Israel	Case-control	30(100%)	29.1 (4.0)	Adults, women with vitro verbalization treatment (n = 20) and healthy controls without fertilization problems	Basal cortisol levels	Blood	Morning	Lymphocyte	qPCR
Epel et al., 2006	USA	Cross-sectional	62(100%)	38.2(1.1)	Adults, healthy mothers of either a health child (n = 22) or a chronically ill child	Basal cortisol levels	Urine	Morning	PBMCs	qPCR
Fair et al., 2017*	USA	Case-control	31(64.5%)	35.9(9.9)	Adults, with unmediated major depressive disorder (n = 16) and healthy controls	Basal cortisol levels	Urine	8:00 am	Leukocyte	qPCR
Gotlib et al., 2015*	USA	Cross-sectional	97(100%)	12.0(1.5)	Children, healthy daughters of depressed mothers (n = 47) and of non-depressed mothers	Basal cortisol levels, cortisol reactivity (subtraction task and Ewart Social competence interview)	Saliva	Average at 2:37 pm	Saliva	qPCR
Kroenke et al., 2011*	USA	Cross-sectional	78(59.0%)	5-6 years	Children from diverse ethical background	Cortisol reactivity (a structured interview, a digital span recitation task, lemon juice placed on tongue, and a fear-evoking videotape)	Saliva	NA	Buccal	qPCR
Liu et al., 2017*	China	Cross-sectional	821(48.4%)	At birth	Newborn infants, a subsample from a larger cohort study recruiting from two hospitals	Basal cortisol levels	Blood	NA	Leukocyte	qPCR
Parks et al., 2017	USA	Cross-sectional	647(100%)	35-75 years	Adults, women with at least a sister diagnosed with breast cancer	Basal cortisol levels	Urine	Soon after waking	Leukocyte	qPCR
Révész et al., 2016*	Netherlands	Prospective (6 years)	2936(66.4%)	41.8(13.1)	Adults, a subsample of the Netherlands Study of Depression and Anxiety	Basal cortisol levels, cortisol suppression ratio, CAR	Saliva	Upon waking, 30, 45, 60 minutes after waking, at 10:00 pm and 11:00 pm	Leukocyte	qPCR
Savolainen et al., 2015*	Finland	Cross-sectional	283(50.5%)	63.5(2.7)	Adults, a subsample of the Helsinki Birth Cohort Study	Cortisol reactivity (TSST)	Saliva, blood	NA	Leukocyte	qPCR
Steptoe et al., 2017*	UK	Prospective (3 years)	411(52.3%)	63.3(5.6)	Adults, a subsample of Whitehall II Cohort	Cortisol reactivity (Stroop color-word interference task, mirror tracing)	Saliva	Between 8:30 am and 9:30 am and between 1:30 pm and 2:30 pm	Leukocyte	qPCR
Tomiyama et al., 2012*	USA	Cross-sectional	23(100%)	62.0(6.5)	Adults, postmenopausal women caring for a partner with dementia (n = 14) and non-caregiving	Basal cortisol levels, CAR, diurnal slope, cortisol reactivity (modified TSST)	Saliva, urine	Waking, waking + 30 min, bedtime, and between 2:00 pm-5:00 pm for cortisol reactivity	PBMCs	qPCR

(*continued on next page*)

Table 1 (*continued*)

					Cortisol measurement			Telomere measurement	
Vasunilashorn and Cohen, 2014	Taiwan	Cross-sectional	943(43.0%)	68.3(8.5)	Adults, general elderly population	Urine	Morning	Leukocyte	qPCR
Känel et al., 2017*	South Africa	Cross-sectional	203(52.2%)	49.8(8.7)	Adults, general urban African and Caucasian primary and secondary school teachers	Blood	One hour after waking	PMBCs	qPCR
Wikgren et al., 2012	Sweden	Case-control	542(52.1%)	59.1(11.9)	Adults, with major depressive disorder (n = 91) and general controls	Blood	Between 8:00 am and 10:00 am	Leukocyte	qPCR
Woody et al., 2017*	USA	Cross-sectional	77(47.0%)	19.8(2.0)	Adults, general healthy college students	Saliva	Between noon and 6:00 pm	Buccal	qPCR
Zahran et al., 2015	India	Cross-sectional	46(50.0%)	35.89, ages from19 to 60 years	Adults, Indian conservation refugees	Saliva	Morning and evening and sometimes in the afternoon	Buccal	TEL-FISH and 3D imaging
Zalli et al., 2014	UK	Cross-sectional	333(50.5%)	63.2(5.5)	Adults, a subsample of Whitehall II Cohort	Saliva	Morning or afternoon	PBMCs	qPCR

Note. CAR, cortisol awakening response; DST, dexamethasone suppression test; TSST, Trial Social Stress Test; PBMCs, peripheral blood mononuclear cells; qPCR, quantitative polymerase chain reaction; qFISH, quantitative fluorescence in situ hybridization; TRF, telomere restriction fragment analysis; TEL-FISH, telomere–fluorescence in situ hybridization; NA, not available.

* Studies included in meta-analysis.

levels of cortisol and high and low levels of telomere length based on median split) were reported, the former was selected. When multiple regression coefficients from different statistical models were reported, the model with fewest covariates was selected. One study (Révész et al., 2016) reported a cross-sectional correlation between cortisol and telomere length elsewhere (Révész et al., 2014). Here, we reported the effect size from Révész et al.'s study (2014). One study (Boeck et al., 2017) reported different effect sizes for the relationship between cortisol and telomere length depending on the types of cells from which telomere length was assessed. In this case, we reported the effect size for the cell type that was mostly reported by other studies (i.e., peripheral blood mononuclear cells). In addition, one study (Savolainen et al., 2015) measured both salivary and blood cortisol reactivity, we selected the effect size for salivary cortisol reactivity, given that no other studies reported values for blood cortisol reactivity.

Correlation coefficient r was used to quantify the linear relationship between cortisol and telomere length. If r statistic was not provided, authors were contacted to obtain this information. In those cases where no response or data were provided by the authors, we computed r from regression coefficients. For studies reporting unstandardized regression coefficient b and its standard error (se), t statistics were calculated using the equation $t = \frac{b}{se}$. T statistics were further converted to r using the equation $r = \sqrt{\frac{t^2}{t^2+df}}$, where $df = N - 2$. For studies reporting standardized regression coefficient β, it was converted to r using the equation $r = 0.98\beta + 0.05a$ where a = 1 if β is nonnegative and a = 0 if β is negative (Peterson and Brown, 2005). As recommended by Hedges and Olkin, Fisher's r-to-Z transformation was used to calculate the effect size using the equation $Z = \frac{1}{2}ln\left(\frac{1+r}{1-r}\right)$. The standard error of the z value was calculated using the equation $Z_{se} = \frac{1}{\sqrt{N-3}}$ where N indicates the sample size.

All analyses were performed using STATA 14.0 software package (Stata Corporation, College Station, TX, USA), with user-contributed commands for meta-analysis: metan, metabias. Two separate analyses were conducted: one to assess the relationship between basal cortisol levels and telomere length, and one to assess the relationship between cortisol reactivity and telomere length. Because heterogeneity was expected in terms of study populations as well as cortisol and telomere length measurements, random effects models were used to calculate the pooled z value. The pooled z value was transformed into an r correlation coefficient using the equation $r = \frac{e^{2z}-1}{e^{2z}+1}$. In addition, a subgroup analysis based on the specimen type for cortisol assay (blood vs. saliva vs. urine) was conducted among studies on basal cortisol levels. Subgroup analyses were also conducted to assess the influence of age, gender composition, type of laboratory paradigms used for psychosocial stress induction (TSST vs. other paradigms), and study quality on the pooled effect size. Following Cohen's recommendations (Cohen, 1969), effect sizes were considered small when $r \leq 0.10$, medium when $r = 0.25$, and large when $r \geq 0.40$.

The presence of heterogeneity across studies was assessed by the Cochran Q test, and the degree of inconsistency was measured using I^2 values (Higgins and Thompson, 2002). A p value less than 0.05 for the Cochran Q test or a I^2 value greater than 50% were considered indicators of moderate to high heterogeneity. Sensitivity analyses were also performed to examine whether one specific study would significantly impact the overall pooled effect size if the presence of heterogeneity was indicated. Lastly, the Begg's funnel plot and the Begg's test were used to assess publication bias (Begg and Mazumdar, 1994).

3. Results

3.1. Characteristics of included studies

Fig. 1 shows the PRISMA flow diagram, and Table 1 displays the characteristics for the identified 22 studies meeting the inclusion

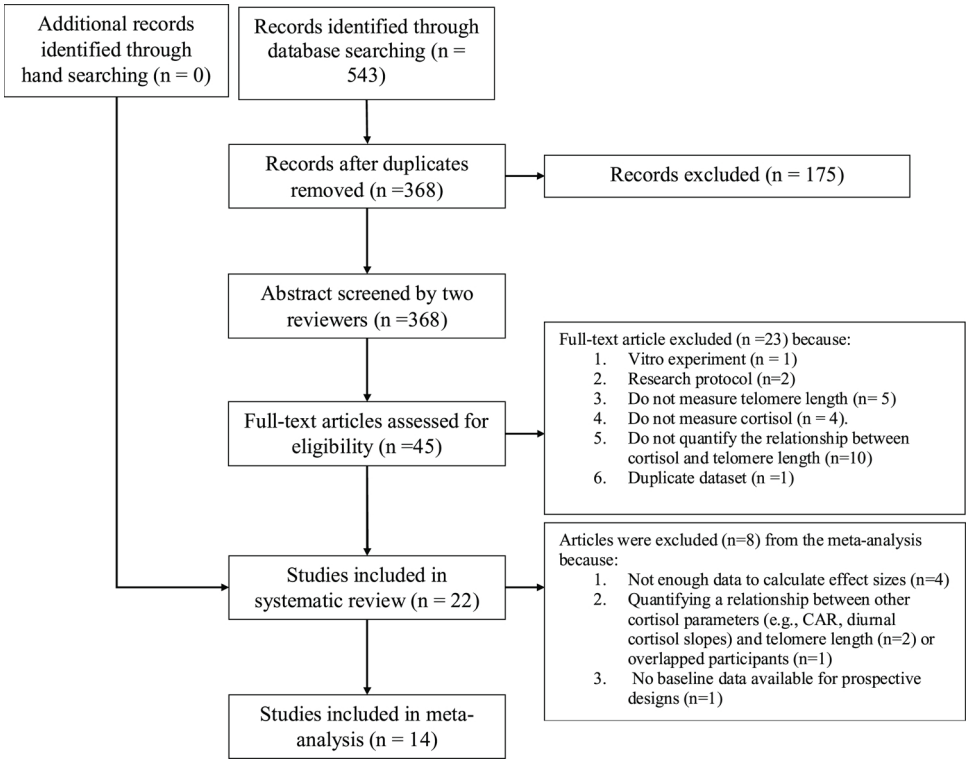

Fig. 1. The PRISMA flow diagram.

criteria. Fifteen studies were cross-sectional (Barha et al., 2017; Boeck et al., 2017; Buss et al., 2014; Epel et al., 2006; Gotlib et al., 2015; Kroenke et al., 2011; Liu et al., 2017; Parks et al., 2009; Savolainen et al., 2015; Tomiyama et al., 2012; Vasunilashorn and Cohen, 2014; von Kanel et al., 2017; Woody et al., 2017; Zahran et al., 2015; Zalli et al., 2014), four studies were case-control (Aulinas et al., 2014; Czamanski-Cohen et al., 2015; Fair et al., 2017; Wikgren et al., 2012), and three studies were prospective (Nelson et al., 2018; Révész et al., 2016; Steptoe et al., 2017). Variability in sample demographics were observed: eight studies included female participants only, whereas the remaining 14 studies included both male and female participants; Four studies examined the association between cortisol and telomere length among infants and children, whereas the remaining 18 studies focused on adults. Three of the 22 studies included participants diagnosed with physical or mental health conditions including Cushing's syndrome and major depressive disorder. There was also substantial variability in terms of cortisol assessment. Five studies measured basal cortisol levels from blood or saliva using a single sample (i.e., single-point in time assessment). Five studies assessed basal cortisol levels in urine with a single sample. Seven studies measured cortisol reactivity only. The remaining studies assessed basal cortisol levels using more than one single sample (n = 1) and reported more than one parameter for cortisol secretion (n = 4). Among eight studies assessed cortisol reactivity, three used the original TSST or a modified version of the original TSST as the laboratory paradigm to induce psychosocial stress, while the remaining five studies used other laboratory stress induction protocols (e.g., subtraction task, Stroop task). In addition, differences in cell types and assay methods for telomere length assessment were identified. Among the 22 studies, nine studies measured telomere length in leukocytes, six studies measured telomere length in peripheral blood mononuclear cells, one study measured telomere length in lymphocytes, four studies measured telomere length in buccal cells, and two studies measured telomere length in salivary cells. Nineteen of the 22 studies assayed telomere length using quantitative polymerase chain reaction, one study used terminal restriction fragment, one study used quantitative fluorescent in situ hybridization (FISH), and one study used FISH coupled with 3D imaging. Quality assessment revealed that 14 of the 22 studies did not meet all quality assessment criteria (see, Supplementary Table 1).

3.2. Meta-analysis

Fourteen studies were included in the meta-analysis. Among the 14 studies, 12 provided data quantifying the cross-sectional correlation between basal cortisol levels and telomere length, and six ($N = 958$ participants) provided data quantifying the cross-sectional correlation between cortisol reactivity and telomere length. Among the 12 studies that measured basal cortisol levels, four reported blood cortisol, four reported salivary cortisol, three reported urinary cortisol, and one reported basal cortisol levels in both blood and urine (Aulinas et al., 2014); therefore, 13 basal cortisol level analyses ($N = 3675$ participants) were extracted.

3.2.1. Basal cortisol levels and telomere length

Fig. 2 displays forest plots illustrating the correlation between basal cortisol levels and telomere length. Overall, a statistically non-significant negative correlation was found between basal cortisol levels and telomere length ($r = -0.05$, 95% CI [−0.11, 0.02]). A moderate level of heterogeneity was detected ($I^2 = 51.8\%$, $p = .015$), suggesting that there was substantial inconsistence across included studies. Results stratified by the specimen type showed no statistically significant correlation between telomere length and blood cortisol ($r = -0.02$, 95% CI [−0.07, 0.04]), salivary cortisol ($r = -0.02$, 95% CI [−0.09, 0.05]), or urinary cortisol ($r = -0.26$, 95% CI [−0.53, 0.07]). Relatively small heterogeneity was detected between studies using blood and salivary cortisol ($I^2 = 0.0\%$; $p = .546$, $I^2 = 24.1\%$, $p = .266$, respectively); however, there was high heterogeneity between studies using urinary cortisol ($I^2 = 77.9\%$, $p = .004$). No additional subgroup analyses were performed due to the small number of studies within each subgroup.

The results of the Begg's test indicated no significant publication bias among the included studies ($p = 0.359$). However, the funnel plot

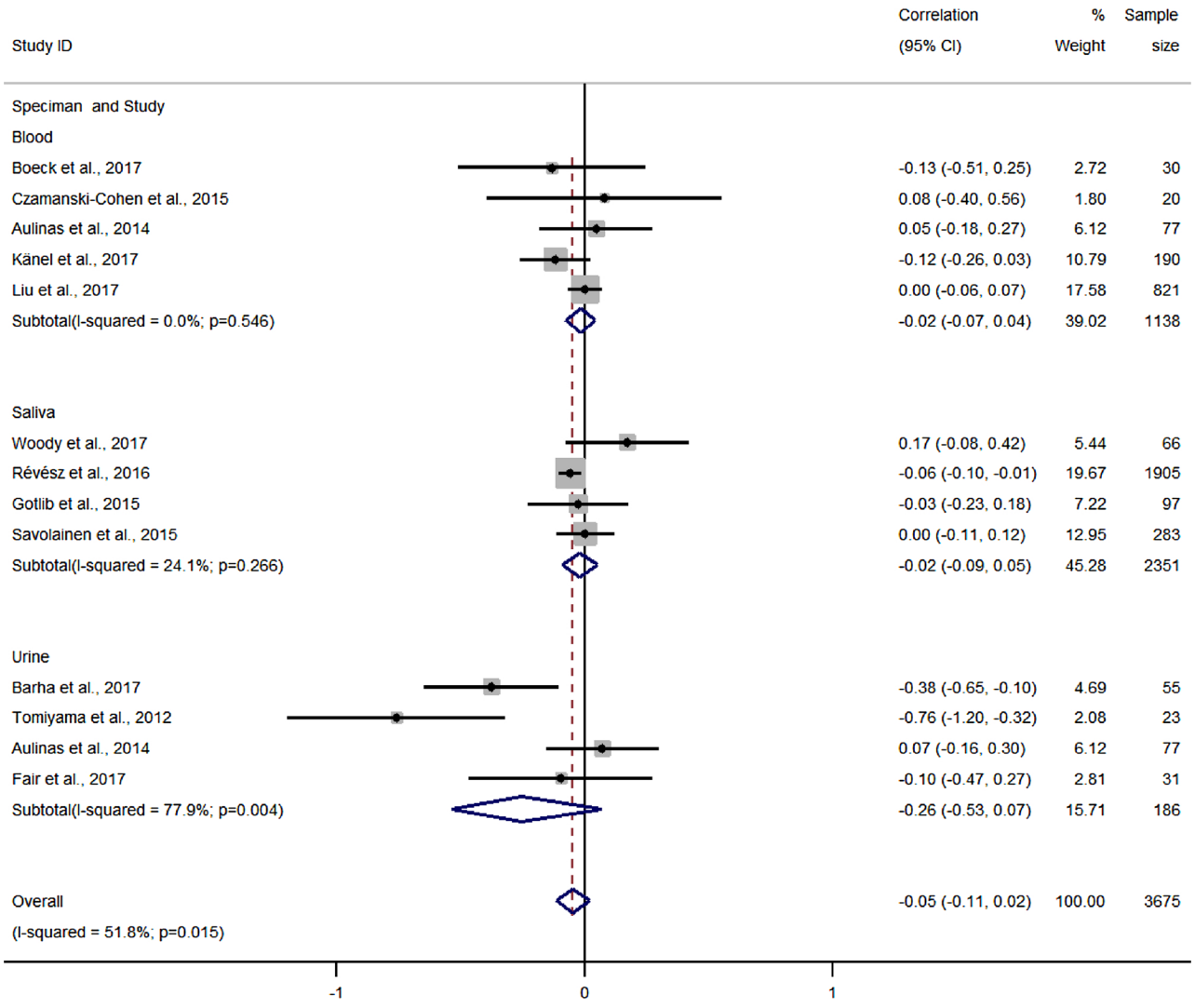

Fig. 2. Forest plots of the correlation between basal cortisol levels and telomere length by the specimen type of cortisol assay (blood, saliva, and urine).

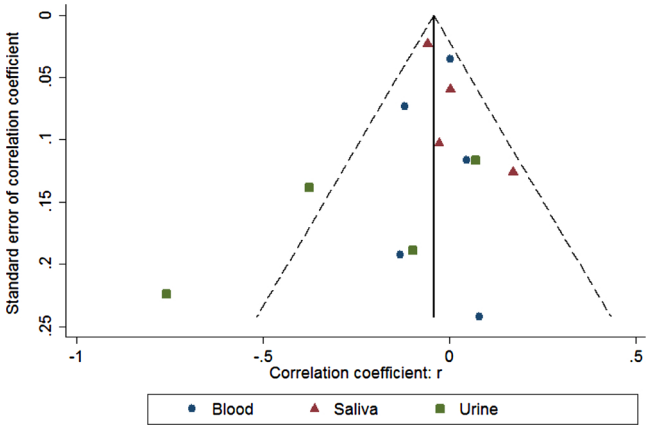

Fig. 3. Funnel plots of publication bias for the relationship between basal cortisol levels and telomere length by the specimen type of cortisol assay (blood, saliva, and urine).

indicated a relatively large deviation for studies measuring cortisol from urine (see Fig. 3). Sensitivity analyses were performed for studies reporting urinary cortisol given the high heterogeneity within this group. Results showed that no single study had significant influence on the pooled effect size, with the exception of urinary cortisol being negatively correlated with telomere length ($r = -0.37$, 95% CI[-0.62, -0.06]) when the study of Aulinas et al. (2014) was excluded.

3.2.2. Cortisol reactivity to acute psychological stress and telomere length

Fig. 4 displays forest plots illustrating the correlation between cortisol reactivity and telomere length. Overall, a statistically significant negative correlation was found between cortisol reactivity and telomere length ($r = -0.13$, 95% CI [-0.23, -0.03]). The Cochran Q test was marginally significant ($I^2 = 51.3\%$; $p = .068$), which might suggest the presence of a moderate level of heterogeneity. The results of the Begg's test ($p = 0.091$) and the funnel plot (see Fig. 5) indicated no significant publication bias among the included articles. Sensitivity analyses showed that no single study had a significant influence on the pooled effect size.

Subgroup analyses revealed a statistically significant correlation between cortisol reactivity and telomere length in female-only studies (the number of studies $k = 2$, $r = -0.28$, 95% CI [-0.49, -0.037]), but not among studies comprising both male and female participants ($k = 4$, $r = -0.08$, 95% CI [-0.18, 0.016]). A statistically significant correlation was also found for studies focusing on children ($k = 2$, $r = -0.22$, 95% CI [-0.36, -0.07]), but not for studies focusing on adults ($k = 4$, $r = -0.09$, 95% CI [-0.21, 0.033]). Cortisol reactivity was statistically correlated with telomere length among studies using other stress induction paradigms (e.g., Stroop task, $k = 3$, $r = -0.14$, 95% CI [-0.25, -0.01]), but not among studies using TSST ($k = 3$, $r = -$

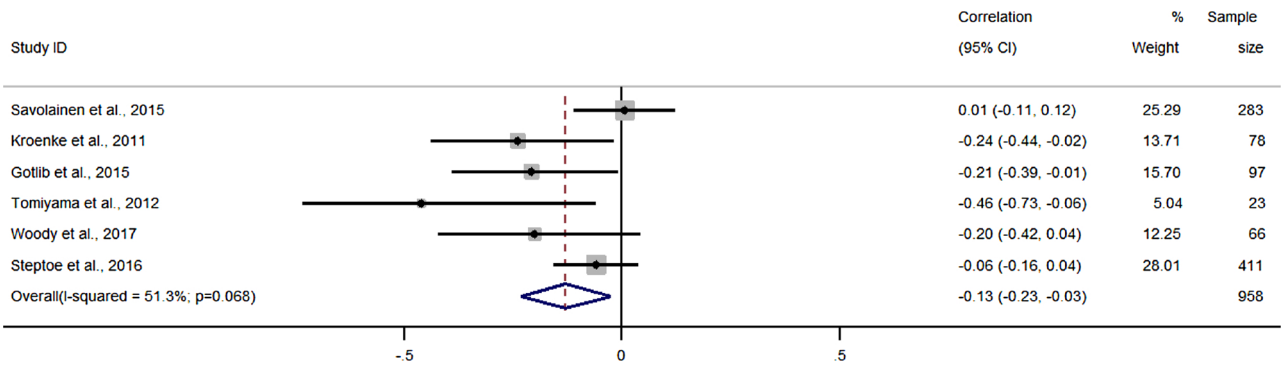

Fig. 4. Forest plots of correlation between salivary cortisol reactivity and telomere length.

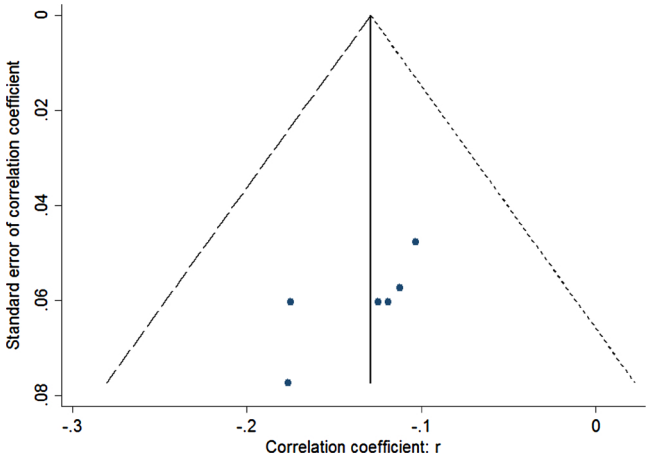

Fig. 5. Funnel plots of publication bias for the relationship between salivary cortisol reactivity and telomere length.

0.16, 95% CI [-0.39, 0.09]. Marginally significant results were found for studies with high risk of bias ($k = 4$, $r = -0.14$, 95% CI [−0.27, 0.002]), but not for studies with low risk of bias ($k = 2$, $r = -0.22$, 95% CI [−0.56, 0.19]).

3.3. Associations between cortisol parameters and telomere length that were not included in the meta-analysis

None of the three studies that measured CAR found a significant relationship between CAR and telomere length (Buss et al., 2014; Révész et al., 2016; Tomiyama et al., 2012). Of the three studies that measured diurnal cortisol slopes, one study found no significant relationship between diurnal cortisol slopes and telomere length (Buss et al., 2014), while the other two studies found that blunted diurnal cortisol slopes were associated with short telomere length (Tomiyama et al., 2012; Zahran et al., 2015). Only one study measured total daily cortisol output and found no significant association between total daily cortisol output and telomere length (Tomiyama et al., 2012). Of the three prospective studies, two studies found significant associations between increased cortisol reactivity and short telomere length, respectively, at six-month follow-up and at three-year follow-up (Nelson et al., 2018; Steptoe et al., 2017), whereas one study found that neither CAR nor evening saliva cortisol predicted telomere length at six-year follow-up (Révész et al., 2016).

4. Discussion

To the best of our knowledge, this is the first systematic review and meta-analysis investigating the correlation between cortisol and telomere length in humans. Results from random effects meta-analysis showed that basal cortisol levels were not correlated with telomere length. Analyses stratified by the specimen type for cortisol assay (i.e., blood, saliva, and urine) revealed the same pattern of results. In contrast, a significant correlation between increased salivary cortisol reactivity to psychosocial stressors and short telomere length was observed.

4.1. Basal cortisol levels and telomere length

In our meta-analysis, 10 out of 12 studies assessed basal cortisol levels using a single cortisol sample. Although collection of cortisol samples at a single-point in time is a common practice in many studies, especially large epidemiological ones, this approach might not be ideal to capture long-term systemic cortisol exposure (Russell et al., 2012). Thus, to the extent to which telomere shortening is driven by chronic stress exposure (Epel et al., 2004), single-point in time assessments of cortisol might not be adequate to capture HPA axis dynamics purportedly associated with chronic stress (for a similar explanation, see Garcez et al., 2018). Data from Barha and colleagues (2017), who found that urinary cortisol measured over seven weeks was negatively associated with telomere length, support this hypothesis.

Another explanation for the observed null effect might have to do with the variability in sample composition. This might be particularly true for studies that assessed cortisol from urine, which were more heterogeneous than studies using blood and saliva samples. Within this group, there was a study conducted among people affected by Cushing's syndrome (Aulinas et al., 2014), a medical condition characterized by prolonged and excessive exposure to cortisol. Notably, when this study was excluded from the analyses, we observed a significant relationship between urinary cortisol and telomere length, supporting the existence of a correlation between urinary cortisol and telomere length among individuals without Cushing's syndrome. This result may suggest that atypical basal cortisol levels due to medical conditions are not necessarily associated to short telomere length, and that only stress-related elevations of urinary cortisol are linked to accelerated telomere shortening. Despite intriguing, this interpretation awaits further corroboration as well as a proper description of the mechanisms as to why stress-related cortisol elevations, but not cortisol elevations due to medical conditions, would be related to telomere shortening.

4.2. Cortisol reactivity to acute psychosocial stress and telomere length

Contrary to the results on basal cortisol levels, our meta-analysis found a correlation between elevated cortisol reactivity to acute laboratory stressors (e.g., TSST, Stroop task) and short telomere length. Thus, although limited to cortisol reactivity, our findings provide support for previous studies hinting at the possible mediating role played by the HPA axis in linking stress exposure to accelerated telomere shortening (Barha et al., 2017; Nelson et al., 2018; Shalev, 2012). This hypothesis is mechanistically corroborated by existing in vitro

experiments in human T lymphocytes that reported a causal link between elevated cortisol exposure and accelerated telomere erosion (Choi et al., 2008; Vartak et al., 2014), potentially through the down-regulating influences of cortisol on telomerase activity (Choi et al., 2008).

Interestingly, our results suggested that the correlation between cortisol reactivity and telomere length might be further qualified by certain sample demographics (i.e., age and gender), the type of laboratory stress induction paradigm used, and the quality of the study at hand. For example, subgroup analyses showed that a correlation between cortisol reactivity and telomere length was more evident in studies including only female participants compared to studies including both genders. Sex differences in stress sensitivity observed in non-human animal studies might help to explain this finding. For example, studies among rodents have shown that these female mammals have greater physiological stress responses to external stressors than males (Handa et al., 1994). Somewhat complementary, some population studies have found that women are more vulnerable to psychosocial stress with respect to telomere length than men (e.g., family violence; Drury et al., 2014, 2012). Our results also showed that the correlation between cortisol reactivity and telomere length was present in samples including children but not in samples including adults. This finding is in line with recent reviews indicating that accelerated telomere shortening could occur early in life, particularly among children exposed to stressors (Coimbra et al., 2017). However, the null relationship between cortisol reactivity and telomere length in adults is more puzzling. One possible explanation is that cortisol reactivity might be prospectively, rather than cross-sectionally, associated with changes in telomere length. This possibility was first suggested in a recent longitudinal study among older adults, which found that elevated cortisol reactivity significantly predicted accelerated telomere shortening three years later, after controlling for baseline telomere length. In the same study, no association was found between cortisol reactivity and telomere length at baseline (Steptoe et al., 2017).

We also found that the correlation between cortisol reactivity and telomere length was more evident in studies that did not employed the TSST as the stress-inducing paradigm. These results appear surprising, given that TSST is treated as the gold standard for psychosocial stress induction in laboratory settings (Allen et al., 2017). One possible explanation for this result might be the variability in samples' composition. Studies that did not use the TSST were disproportionally focused on children. Given the potential age influences in the correlation between cortisol reactivity and telomere length discussed above, it is possible that differences in the correlation between cortisol reactivity and telomere length by stress induction paradigms were confounded, and possibly driven, by age differences. Our subgroup analyses also indicated that the correlation between cortisol reactivity and telomere length might have been affected by the quality of the study at hand. Specifically, we found that cortisol reactivity was marginally correlated with telomere length in studies with high risk of bias, but not in studies with low risk of bias. Overall, although interesting, results from these subgroup analyses should be interpreted with caution given the limited number of studies available.

4.3. Limitations

The present meta-analysis is not without limitations. First, the evidence collected from existing studies is merely correlational, and the small number of available prospective studies makes any speculation about causality conjectural. Second, the large variability in cortisol measurements across the included studies makes it difficult to compare effect sizes and to draw definitive conclusions from this modest body of research. Further, as reported above, most of the studies on basal cortisol levels considered a single-point in time measure of cortisol, which is arguably a suboptimal measure of activity of the HPA axis (Rotenberg et al., 2012; Russell et al., 2012). Third, the relatively small number of studies included in this review limits the ability to explore potential important moderators of the link between basal cortisol levels and telomere length.

4.4. Recommendations for future studies

Some recommendations for future research might be drawn from the present meta-analysis. First, it is possible that the observed correlation between cortisol reactivity and telomere length — but not between basal cortisol levels and telomere length — is simply a byproduct of the adopted sampling regime (i.e., multiple saliva samples used to assess cortisol reactivity vs. a single sample used to assess basal cortisol levels). This explanation could be corroborated or ruled out by future research on basal cortisol levels based on multiple cortisol measurements. Research on the link between basal cortisol levels and telomere length might also benefit from considering relatively new specimen types for cortisol measurement, such as hair and nails. Hair cortisol (Russell et al., 2012) and nail cortisol (Frugé et al., 2018) are thought to reflect long-term HPA axis activity and, thus, might be more valid and reliable indicators of chronic physiological stress.

A recent meta-analysis supported the idea that flattened cortisol slopes are robust predictors of a plethora of poor physical and mental health outcomes, including telomere length (Adam et al., 2017). Large studies on the association between dysregulated diurnal cortisol rhythm and telomere length appear to be a promising avenue for future research, despite the inconsistent correlations between diurnal cortisol slopes and telomere length found in our review (Buss et al., 2014; Tomiyama et al., 2012; Zahran et al., 2015), which might have been due to the small sample size of the reviewed studies (less than 60).

Moreover, there is a need to examine the correlation between HPA axis functioning and telomere length using prospective research designs. Although two existing longitudinal studies reported an association between cortisol reactivity to psychosocial stress and telomere length (Nelson et al., 2018; Steptoe et al., 2017), whether individual differences in basal cortisol levels, CAR, and diurnal cortisol slopes predict long-term changes in telomere length is still an open question. An important step toward this direction has been taken by Révész and colleagues (2016), who examined the effect of CAR and evening cortisol on telomere length changes over 6 years.

5. Conclusion

The results of this systematic review and meta-analysis found a negative correlation between cortisol reactivity to psychosocial stressors and telomere length; however, no association emerged between basal cortisol levels and telomere length. Correlations between cortisol reactivity and telomere length were more evident in studies among children (vs. adults) and in studies that included female participants only (vs. both genders). Overall, the findings of this study support the existence of a relationship between salivary cortisol reactivity and telomere shortening.

Author contributions

YJ conceived the study, YJ, WD, GI acquired the data, YJ and WD prepared the data analysis plan, WD analyzed the data, YJ, SZ, and WD wrote the manuscript, XL, SQ, QZ critically revised the manuscript.

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Conflict of interest

The authors declare that they have no conflict of interest with respect to the authorship or the publication of this manuscript.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.psyneuen.2019.01.022.

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