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Review article

Correlates of cortisol in human hair: implications for epidemiologic studies on health effects of chronic stress

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ABSTRACT

Assessment of cortisol concentrations in hair is one of the latest innovations for measuring long-term cortisol exposure. We performed a systematic review of correlates of cortisol in human hair to inform the design, analysis, and interpretation of future epidemiologic studies. Relevant publications were identified through electronic searches on PubMed, WorldCat, and Web of Science using keywords, "cortisol," "hair," "confounders," "chronic," "stress," and "correlates." Thirty-nine studies were included in this review. Notwithstanding scarce data and some inconsistencies, investigators have found hair cortisol concentrations to be associated with stress-related psychiatric symptoms and disorders (e.g., post-traumatic stress disorder), medical conditions indicating chronic activation of the hypothalamic-pituitary-adrenal axis (e.g., Cushing's syndrome), and other life situations associated with elevated risk of chronic stress (e.g., shiftwork). Results from some studies suggest that physical activity, adiposity, and substance abuse may be correlates of hair cortisol concentrations. In contrast to measures of short-term cortisol release (saliva, blood, and urine), cigarette smoking and use of oral contraceptives appear not to be associated with hair cortisol concentrations. Studies of pregnant women indicate increased hair cortisol concentrations across successive trimesters. The study of hair cortisol presents a unique opportunity to assess chronic alterations in cortisol concentrations in epidemiologic studies.

Introduction

"It is not stress that kills us; it is our reaction to it."

-Hans Selye (stress research pioneer)

Overview of the stress response

Despite its extensive study, psychosocial stress (hereafter called stress) remains challenging to describe. Investigators acknowledge stress as a process whereby a stimulus imposes demands or overwhelms an organism's ability to cope, causing physiological and psychological responses [1–3]. The magnitude, duration, and quality of these responses are contingent on the individual's interpretation of the stressor and how well the individual adapts or copes with the stressor [3].

Two neuroendocrine pathways are activated in stress response: one, the sympathetic-adrenal-medullary axis is activated rapidly—its activation has been described elsewhere [1]. The other, the hypothalamic-pituitary-adrenal (HPA) axis, is activated less swiftly: the hypothalamus discharges corticotrophin-releasing hormone, stimulating the dispensation of adrenocorticotropin-releasing hormone by the pituitary into systemic circulation, which then triggers the release of cortisol by the adrenal cortex [1]. Cortisol has emerged as an important objective biological measure of stress.

Cortisol and health

Cortisol helps maintain homeostasis in the body by aiding metabolism and immune response [4–6]. The human body

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secretes approximately 10 mg of cortisol daily; however, excess or insufficient amounts of cortisol are synthesized and released into systemic circulation under stressful conditions [1,7–9]. Although acute alterations in cortisol concentrations may not immediately cause disease, long-term alterations of the HPA axis are associated with adverse health outcomes. For example, high concentrations of cortisol have been associated with Cushing disease [10], diabetes complications [11], adverse perinatal outcomes [12], and myocardial infarction [13]. Low cortisol concentrations have been associated with Addison disease [14], endometriosis [15], chronic pelvic pain [15,16], and psychiatric disorders including post-traumatic stress disorder (PTSD) [17].

Limitations of cortisol concentrations obtained from saliva, blood, and urine

- Only inform about short-term cortisol concentrations (24–36 hours)
- Easily influenced by individual and environmental characteristics
- Can be invasive, especially for blood
- Require repeated measurements during 24 hours over several days to obtain average chronic concentrations of cortisol

Measuring chronic cortisol concentrations: traditional matrices of cortisol

Saliva, blood, and urine, the predominant matrices from which cortisol is obtained, have been useful in establishing the diurnal profile of circulating cortisol and in elucidating the relationship between aberrations in diurnal cortisol patterns and various disorders. But these matrices have several limitations. First, they only informed about short-term cortisol concentrations, that is, cortisol released within a few hours or 1 day [18]. Second, cortisol concentrations obtained using these specimens are easily influenced by a host of factors including study procedures [19], time of the day [20], and food consumption [21]. Third, the process of specimen collection can be invasive, particularly for blood, which in itself may induce stress and corresponding cortisol levels. Fourth, to deal with variability and the need to obtain approximate measurements of chronic cortisol concentrations, researchers need to take repeated measurements during 24 h for several days [22]. This need for repeat sampling is expensive, burdensome for study participants, and likely to increase incomplete sample collection and loss to follow-up. Given these limitations, investigators have searched for matrices that can ensure better, less invasive measurements of long-term cortisol concentrations. The most recent innovation is the isolation of cortisol from hair.

Why hair? why now?

To the best of our knowledge, Raul et al. [23] were the first to examine cortisol concentrations in human hair. Previously, three investigative teams [24–26] provided evidence of hair as a matrix for various glucocorticoids, for example, hair was used to detect exposure to corticosteroids, amphetamines, and anabolic steroids in athletes [26]. Hair allows for retrospective assessment of long-term cortisol concentrations because it grows over weeks, months, and years (e.g., 18-month hair cortisol concentrations were assessed in refs. [27,28]). Collecting hair is less invasive than obtaining blood and hair can be stored easily (Table 1). The proposed mechanisms by which cortisol is incorporated into hair is beyond the scope of this review. However, we refer interested readers to a highly relevant review on this topic [29].

Correlations of hair cortisol concentrations with other measures of chronic stress

In efforts to assess the validity of hair cortisol as a biological marker of chronic stress, investigators have examined the correlations of hair cortisol concentrations (HCCs) with cortisol concentrations from repeated samplings of other matrices. Van Holland et al. [30] found that HCC was moderately correlated with mean salivary cortisol concentrations taken on 3 days ($r = 0.41$, $P = .03$, samples were taken at six time points on each day). Similarly, Vanaelst et al. [31] found that HCC was significantly correlated with area under the curve for salivary cortisol collected over two consecutive days (samples were taken at four time points on each day). Statistically significant correlation between 24-hour urinary cortisol concentrations and HCC has been reported [32], although no statistically significant correlations were found between HCC and cortisol in one-time samples of morning blood serum [32] and blood serum collected after an overnight fast [31]. Additionally, investigators have examined correlations of HCC with scores on the perceived stress scale, a widely used self-reported measure of chronic stress over a 4-week period. Overall, results have been mixed with some investigators reporting correlation coefficients of less than 0.10 in studies of young adults [33] and in a racially diverse adult sample [34] and correlations of 0.2 in adrenal insufficiency (AI) patients [35], 0.24 in chronic pain patients and controls [36], and 0.47 in pregnant women [37]. On balance, available evidence suggests positive associations of HCC with perceived stress scale scores and repeated measures of cortisol from other matrices.

Correlates of hair cortisol

A previous review from 2012 [29] found limited data on relevant correlates of HCC. Yet, as this is a rapidly developing field, we performed a systematic review of all relevant literature to

Table 1
Comparison of hair with other matrices of cortisol

Characteristics	Hair	Other matrices (saliva, blood, and urine)
Length of cortisol information	Chronic	Acute
Storage	Can be stored at room temperature	Require specific storage (e.g., refrigeration or freezing)
Situational and intraindividual variability	Cortisol in hair is not easily influenced by acute situational and individual factors—although evidence suggests that it might be influenced by hair hygiene and cosmetic-related behavior (e.g., hair treatment and hair dyeing)	Measurements are vulnerable to factors such as time of the day, cigarette smoking, and acute stress
Repeated measurements	Less need for repeated measurements—although some individuals might be unwilling to give hair	Need for repeated measurements—expensive, burdensome for study participants, and likely to increase incomplete sample collection and loss to follow-up
Invasiveness	Small amount of hair is needed; not invasive	Although saliva and urine are less invasive, obtainment of blood can be invasive and painful for participants.

Adapted from Stalder et al. [29] and Russell et al. [106].

shed light on correlates of HCC, broadly encompassing factors that may be important determinants, confounders, effect modifiers, interactions, and mediators that could influence the relationship between HCC and covariates of interest in epidemiologic studies.

First, it is inevitably of principal interest to understand how hair-related factors (e.g., natural hair color, frequency of hair wash) might affect cortisol concentrations in hair. Second, it is important to examine whether hair cortisol concentrations reflect an individual's subjective experience of chronic psychological stress and related morbidities or disorders. Finally, the relationships between cortisol concentrations in hair and important sociodemographic and lifestyle factors should be assessed. Our systematic review summarizes evidence from existing literature on the correlates and determinants of HCC. The findings will be used to inform the design, analysis, and interpretation of clinical- and population-based studies that may use HCC as measures of chronic hypo- or hyperactivation of the HPA axis.

Methods

Literature search and article identification

Pertinent publications on hair cortisol, published before September 2013, were identified from PubMed, WorldCat, and Web of Science using keywords, "cortisol," "hair," "confounders," "chronic," "stress," "correlates," and "determinants." We also perused references of identified publications to find other relevant articles. We included articles published in English and in peer-reviewed journals.

Article selection, data extraction, and data synthesis

Human studies were the primary consideration in this systematic review. For studies to be included, the investigators had to have specified the length and weight of hair analyzed, the cortisol extraction methods, participant recruitment procedures, and comprehensible quantitative figures on the primary relationships of interest. Finally, hair must have been taken from the posterior vertex region. Hair from the posterior vertex region is the standard for hair analysis [38]. It has been shown to have higher cortisol content and lower interindividual variability compared with hair sampled from other regions [39]. We grouped the findings according to the following themes: hair-specific characteristics, stress-related correlates, lifestyle, and behavioral factors.

Results

Characteristics of studies included

After elimination of duplicates, abstracts and articles that did not meet the inclusion criteria, 39 studies were chosen for inclusion in this review (Fig. 1). Studies were conducted in multiple countries: Brazil, Canada, China, France, Germany, Israel, The Netherlands, Switzerland, Uganda, and the United States (Supplementary Table). Approximately 33% of the studies were from Germany, published by pioneers who integrated hair cortisol measurement in their clinical- and population-based studies [40–52]. In the sections that follow, we provide summary results of studies that assessed HCC in relation to hair-specific characteristics, stress-related correlates, and lifestyle and behavioral factors.

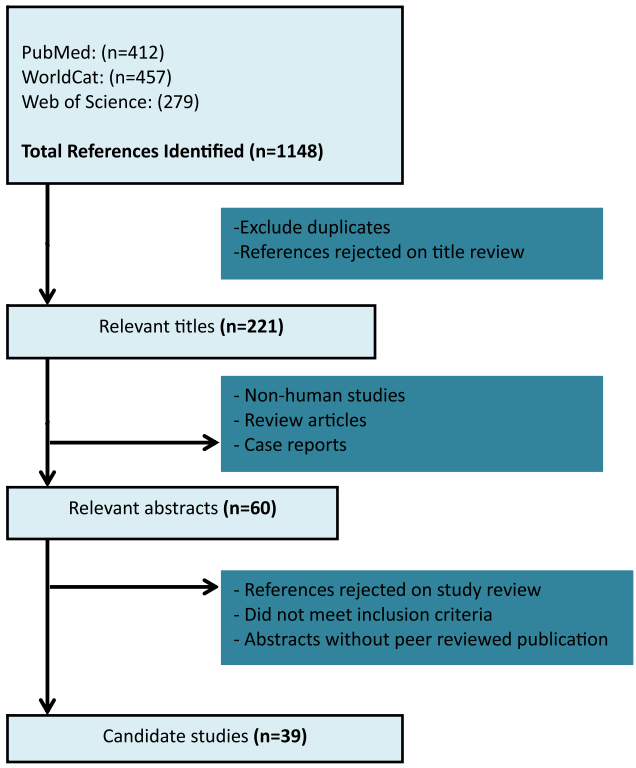

Fig. 1. Assessment of eligibility.

Hair-related characteristics

Natural hair color, frequency of hair washing, hair dyeing, and treatment

Natural hair color appears not to be associated with HCC in humans. In their early study, Raul et al. [23] reported no association between natural hair color and HCC. Other investigators have confirmed these findings [27,32,41,42,53]. On balance, it appears reasonable to conclude that natural hair color is not a correlate or determinant of HCC.

Investigators have speculated that the frequency and temperature at which hair is washed may be inversely associated with HCC. However, most [27,43,46,51,53] although not all [39] studies on this topic indicated no association between HCC and hair washing. Li et al. [39] found that in a subsample of three participants, mean HCC decreased from 30.5 $\pm$ 9.6 pg/mg to 6.5 $\pm$ 5.9 pg/mg in hair immersed in shampoo solution for 4 hours. Furthermore, in a subsample of eight participants, cortisol concentrations progressively declined after immersion of hair in hot water at 40°C, 65°C, and 80°C (Table 2) [39].

As with frequency of hair washing, findings on the relationship between hair treatment and HCC have been inconsistent. Some investigators [27,32,51,54] but not all [33,46,55] have documented substantial influences of hair dye and other hair treatments on HCC. Manenschijn et al. [27] found that treated hair had lower HCC compared with untreated hair while use of hair product (e.g., spray, mousse, gel, and wax) on the day of hair sample collection was not significantly associated with mean HCC. In aggregate, available data suggest modest influence of hair dyes and other treatments on HCC. Hence, investigators may consider collecting information on these behaviors in future large-scale epidemiologic studies that rely on HCC as a biomarker of chronic stress.

Table 2
Correlates of hair cortisol concentrations

Study	Sample size for analysis	Summary of findings
Hair-related factors		
Natural hair color		
Raul et al. [23]	8 black, 3 blond, 24 brown, 7 gray	No differences in HCC of different hair colors ($P = .9773$)[*,†] Mean ± SD: black: 16.63 ± 7.99 pg/mg; blond: 16.97 ± 6.84 pg/mg; brown: 15.52 ± 7.85 pg/mg; gray: 15.86 ± 5.21 pg/mg
Sauvé et al. [32]	4 blond, 4 brown, 4 black	No difference in HCC of different hair colors[‡,§]
Kirschbaum et al. [43]	142 women[‖]	No difference in HCC of different hair colors ($P > .20$)[‡,§]
Manenschijn et al. [27]	10 black, 75 brown, 94 blond, 6 red, 9 gray	No difference in HCC of different hair colors ($P = .413$)[§]
Dettenborn et al. [42]	33 light blond, 36 dark brown	No difference in HCC of different hair colors ($P = .524$) Mean ± SD: light blond: 20.22 ± 11.2 pg/mg; dark brown: 21.88 ± 10.4 pg/mg
Dettenborn et al. [42]	79 light-middle blond, 71 dark blond-light brown, 84 middle-dark brown	No significant difference in HCC of different hair colors $F_{(2,232)} = 2.538$, $P = .081$[§]
Groeneveld et al. [53]	42 children (mean age, 50.1 mo, SD = 0.42 mo, 45% boys)[‖]	HCC was not significantly related to hair color[‡,§]
Hair wash frequency and temperature		
Kirschbaum et al. [43]	142 women[‖]	No significant association between frequency of hair washes per week and HCC ($P > .20$)[‡,§]
Manenschijn et al. [27]	50 hair samples (≤2 times per week) 143 hair samples (≥3 times per week)	No significant association between frequency of hair washes per week and HCC ($P = .673$)[§]
Dettenborn et al. [42]	Frequency of hair washing: (0–1, 1.5–2, 2.5–3, 3.5–4, 4.5–5, 5.5–6, 6.5–9 times per week)	No significant association between frequency of hair wash and HCC in first two segments: (first 3-cm segment: $r = -0.061$, $P = .335$, $n = 249$), (second 3-cm segment: $r = -0.102$, $P = .168$, $n = 184$). However, in third segment, HCC was inversely correlated with frequency of hair wash ($r = -0.248$, $P = .008$, $n = 113$)
Li et al. [39]	3 participants	After immersion in shampoo solution for 4 h, HCC decreased from 30.5 ± 9.6 to 6.5 ± 5.9 pg/mg[§] Mean ± SD cortisol loss ratio was 75.5 ± 27.4%, range: 45.1%–98.4%
	8 participants	After 20-h immersion, mean HCC decreased from (at 40°C: 13.8 ± 5.8 to 4.4 ± 2.9 pg/mg, $P < .001$), (at 65°C: 8.8 ± 4.1 to 1.4 ± 0.4 pg/mg, $P < .01$) and (at 80°C: 8.8 ± 4.1 to 0.6 ± 0.2 pg/mg, $P < 0.01$)
Stalder et al. [46]	155 individuals in study I (mean ± SD of number of hair washes in the entire sample: 3.1 ± 2.3)[‖] 58 individuals in study II (mean ± SD of number of hair washes in the entire sample: 3.7 ± 1.6)[‖]	No significant association between frequency of hair washes per week and HCC ($P > .10$ in study I, $P > .30$ in study II)[‡,§]
Groeneveld et al. [53]	42 children (mean age, 50.1 mo, SD = 0.42 mo, 45% boys)[‖]	HCC was not significantly related to hair washing frequency[‡,§]
Stalder et al. [51]	1258 men and women[‖]	HCC was not correlated with number of hair washes per week ($r = -0.046$, $P > .05$)[‡]
Hair dyeing and other hair treatments		
Sauvé et al. [32]	25 untreated hair, 14 dyed hair	Dyed hair had lower HCC ($P = .036$)[§]
Dowlati et al. [55]	5 dyed hair, 78 nondyed hair	No difference in mean HCC of dyed and nondyed hair (4.77 ± 0.70 vs. 4.95 ± 0.57, $P = .49$)
Karlén et al. [33]	95 students (40 students had colored/permed hair)	There seemed to be a difference between mean HCC of colored/permed hair versus noncolored/permed hair (mean ± SD 13.0 ± 16.0 pg/mg vs. 24.8 ± 40.9 pg/mg, $P = .09$), but it was not statistically significant
Manenschijn et al. [27]	152 untreated hair, 43 treated hair (women) 90 used hair products, 104 did not use hair products	Treated hair (dyed, bleached, permanent waved/straightened) had lower mean HCC than untreated hair (24.27 vs. 29.38 pg/mg, $P = .051$) Use of hair product (hair spray, mousse, gel, wax) on the day of hair collection was not significantly associated with HCC: 24.83 pg/mg (product use) vs. 28.44 pg/mg (no product use), $P = .109$
Manenschijn et al. [54]	96 healthy, nonobese controls, 14 patients with CS, 6 patients suspected of cyclic CS[‖]	HCC was slightly lower in healthy women with treated hair, that is, hair dyeing or bleaching ($P = .06$)[§] No difference between HCC of treated and untreated hair in Cushing patients[‡,§]
Stalder et al. [46]	Study I: 59 treated hair, 96 untreated hair Study II: 21 treated hair, 37 untreated hair	Study I: no difference between treated semipermanent color, coloration or permanent wave) and untreated hair ($P > .10$)[‡,§] Study II: no difference between treated (as described above) and untreated hair ($P > .30$)[‡,§]
Stalder et al. [51]	1258 men and women[‖] (15.5% reported use of hair treatment)	HCC was negatively associated with hair treatment after adjustment for sex ($F_{1,\ 1195} = 4.22$, $P = .04$, $\eta p^2 = 0.004$)
Hair segment		
Xie et al. [57]	8 female participants	Average linear HCC decline rate of 2.9 ± 0.6 pg/mg ($r = -0.948$, $P < .05$) per centimeter in the first five 1-cm hair segments
Manenschijn et al. [27]	28 healthy women	HCC was not significantly different in six consecutive 3-cm segments ($P = .249$)[§]

Steudte et al. [49]	30 participants	HCC decreased 17.4% from the proximal 3-cm segment to the second 3-cm segment, then decreased 18.3% from the second 3-cm segment to the third ($P = .027$)
Dettenborn et al. [42]	155 individuals	HCC decreased by 16.32% from first 3-cm hair segment to the second hair segment ($P < .001$). HCC also decreased 12.29% from second 3-cm hair segment to third ($P < .001$)
Skoluda et al. [44]	273 individuals	HCC decreased from proximal to distal hair segments ($F_{(1.55,\ 273.05)} = 131.9$, $P < .001$)[§]
Luo et al. [56]	20 NTC[‖]	HCC linearly declined from proximal to distal in the nontraumatized control group ($F = 41.07$, $P < .0001$)
Krumbholz et al. [58]	1 woman (hair examined across pregnancy)	HCC decreased by >50% after 4 mo of hair growth
Hair texture and UV irradiation		
Kirschbaum et al. [43]	142 women[‖]	Hair curvature was not significantly related to HCC ($P > .20$)[§]
Dettenborn et al. [42]	360 individuals (70% of whom were aged 18–49 y)[‖]	There was no influence of curls ($P = .468$)[§] or waves ($P = .633$)[§] on HCC when compared with straight hair in individuals aged 18–49 y
Li et al. [39]	12 hair samples exposed to 9-h UV irradiation	HCC decreased from 26.1 ± 8.8 to 18.9 ± 8.0 pg/mg ($P = .047$) The average loss ratio in HCC was 26.5 ± 20.9% ($r = 0.616$, $P < .05$)
Stress-related factors		
Demographic, social, and occupational factors		
Dettenborn et al. [41]	31 unemployed, 28 employed	Unemployed individuals had higher HCC for first 3-cm segment ($P < .05$)[§] and second 3-cm segment ($n = 52$, $P < .05$)[§]
Manenschijn et al. [64]	33 shift workers, 89 day workers	Workers who had a fast-forward rotating shift schedule had higher mean HCC compared with those who only worked during the day (mean [95% CI]: 47.32 [38.37–58.21] vs. 29.72 [26.18–33.73] pg/mg, $P < 0.001$). However, in individuals aged <40 y, shift workers had higher HCC (mean [95% CI]: 48.53 [36.56–64.29] vs. 26.42 [22.91–30.55] pg/mg, $P < .001$), whereas for those >40 y, there was no effect of shiftwork. There were no individuals who were exactly aged 40 y
Chen et al. [62]	Cohort A (13 had elementary school education, 34 had high school education or below, 6 had college education or above) Cohort B (4 had elementary school education, 27 had high school education and below, 19 had college education or above)	No significant difference in HCC among all three educational groups in cohort A ($F = 0.31$, $P = .74$) and in cohort B ($F = 1.98$, $P = .15$)
Groeneveld et al. [53]	42 children (mean age, 50.1, SD = 0.42 mo); mean parental educational was 14.8 y (SD = 1.9)[‖]	HCC was not significantly related to parents' educational level[‡,§]
Saleem et al. [65]	56 cardiac rehabilitation patients with CAD (26 with normal HCC (median 111 ng/g) and 30 with elevated HCC (median 263 ng/g)	Normal vs. high HCC group: total years of education (mean ± SD: 16.5 ± 3 vs. 17 ± 3.5 y, $P = .45$), married (88.5% vs. 73.3%, $P = .20$)
Vaghri et al. [61]	333 preschoolers	Parental income was inversely correlated with HCC from 1 to 2 cm hair segment ($r = -0.18$, $P = .001$); in a subsample of 275 preschoolers, annual family income was not correlated with HCC ($r = -0.07$, $P = .235$)
Age		
Raul et al. [23]	44 individuals	Linear regression predicting HCC from age ($\beta = 0.0296$, standard error = 0.0541, $P = .139$)[*,†]
Manenschijn et al. [27]	195 individuals (18–63 y); Mean age: 36 y	There was no relationship between HCC and age category (mean ± SD: 0–15 y: 15.2 ± 7.1; 16–30 y: 14.4 ± 8.4; 31–50 y: 16.2 ± 7.6; 51–90 y: 17.3 ± 6.3 pg/mg, $P = .878$) HCC was not correlated with participant age ($P = .388$)[§]
Dettenborn et al. [42]	360 individuals (1–91 y)	HCC was positively related with age ($r^2 = 0.010$, $P = .030$) For children 0–5 y, age in months was negatively correlated with HCC ($r = -0.428$, $P = .023$). Children (1–9 y, $n = 28$) had significantly higher HCC compared with adults ($n = 34$, 18–38 y) ($P < .001$)[§]
Kirschbaum et al. [43]	103 mothers of newborns aged 2–4 d (mean ± SD age: 29.7 ± 5.5 y), 19 mothers of toddlers 3–9 mo (mean ± SD age: 30.4 ± 2.8 y) and 20 nonpregnant nulliparas (mean ± SD age: 25.8 ± 6.4 y)	HCC was not significantly associated with age across the entire group ($P > .20$)[‡,§]
Manenschijn et al. [54]	14 CS patients, 6 individuals with suspected cyclic CS, 96 healthy controls[‖]	HCC was not significantly related with age in either the patient or control group[‡,§]
O'Brien et al. [34]	135 adults (18–66 y)	No correlation of age and HCC ($r = 0.07$, $P > .05$) HCC was not significantly correlated with tertiles of age (age ranges: young = 18–21 y, $n = 44$; middle = 22–29 y, $n = 45$; older = 30–66 y, $n = 43$)
Stalder et al. [46]	155 individuals (18–46 y) Mean ± SD age: 24.1 ± 14.2 y	HCC was not correlated with participant age ($r = -0.02$, $P > .05$)[‡,§]
Stalder et al. [46]	58 individuals (20–70 y) Mean ± SD age: 30.5 ± 12.1 y	HCC was not correlated with participant age ($r = 0.06$, $P > .05$)[‡,§]
Vaghri et al. [61]	339 preschoolers (mean ± SD age: 4.6 ± 0.5 y)	No statistically significant correlation between age and log-transformed, winsorized HCC variable ($r = -0.09$, $P = .098$)

(*Continued on next page*)

Table 2 (*Continued*)

Study	Sample size for analysis	Summary of findings
Chen et al. [62]	Cohort A (23 participants 21–40 y; 29 participants >40 y); Cohort B (21 participants aged 21–40 y; 23 participants >40 y)	No significant difference in HCC of those aged 21–40 y and those >40 y in cohort A ($z = -0.179$, $P = .86$) and in cohort B ($z = -0.51$, $P = .61$)
Gerber et al. [70,79]	42 university male and female students	Age was not significantly associated with HCC[§]
Manenschijn et al. [69]	283 elderly adults (65–85 y)	HCC was not correlated with age ($r = -0.02$; $P = .76$)
Saleem et al. [65]	56 cardiac rehabilitation patients with CAD (26 in normal HCC (median 111 ng/g) and 30 in the elevated HCC (median 263 ng/g)	Age was not significantly associated with HCC ($P = .43$)
Stalder et al. [51]	1258 men and women[‖](age: 16–64 y)	HCC was positively correlated with age ($r = 0.11$, $P < .0001$)[‡]
Sex		
Raul et al. [23]	16 males, 26 females	No differences in HCC of males and females (mean ± SD: 15.6 ± 8.8 vs. 16.1 ± 6.3 pg/mg, $P = .859$)
Karlén et al. [33]	95 students (24 males, 71 females)	No difference in HCC of males and females (mean ± SD: 17.8 ± 13.4 pg/mg vs. 20.6 ± 37.7 ($P = .73$)
Manenschijn et al. [27]	90 men, 105 women	No significant effect of gender ($P = .353$)[§]
Manenschijn et al. [72]	Bipolar patients: 34 men, 62 women Healthy controls: 90 men, 105 women	No sex differences in HCC of bipolar patients ($P = .12$)[§] and healthy controls ($P = .87$)[§]
Steudte et al. [48]	PTSD patients: 4 men, 6 women Controls: 11 men, 6 women	No significant effects of gender on HCC ($F_{(1,23)} = 1.01$, $P = .33$, $\eta p^2 = 0.04$)[§]
Dettenborn et al. [42]	252 adults (18–49 y) 52 children (1–9 y) 25 adolescents (10–17 y) 31 elderly (50–91 y)	Males had higher HCC in first 3-cm segment compared with females for adults 18–49 y ($F_{(1,251)} = 9.573$, $P = .002$, $\eta p^2 = 0.037$).[§] Males had higher in first 3-cm segment HCC compared with females for children 1–9 y ($F_{(1,51)} = 5.304$, $P = .025$, $\eta p^2 = 0.078$).[§] No sex differences were seen in HCC of adolescents ($F_{(1,24)} = 0.837$, $P = .370$)[§] or elderly ($F_{(1,30)} = 0.064$, $P = .803$)[§]
Manenschijn et al. [54]	14 CS patients, 6 individuals with suspected CS, 96 healthy controls[‖]	HCC was not significantly related with sex in either the patient or control group[‡,§]
O'Brien et al. [34]	135 adults (60% female)	Men had slightly higher HCC compared with women $t_{(129)} = 2.91$, $P < .01$
Skoluda et al. [44]	Athletes: 304 individuals (58.9% female), controls: 70 individuals (82.9% female)	No significant differences in HCC between the sexes in athletes ($P = .06$)[§] nor in controls ($P = .62$)[§] Across the entire sample, males had higher HCC ($F_{(1,372)} = 8.13$, $P < .01$)[§]
Stalder et al. [46]	Study I: $N = 155$ (73.5% females) Study II: $N = 58$ (67.2% females)	Study I: no significant difference in HCC of males and females ($F_{(1.154)} = 0.006$, $P > .05$)[‡,§] Study II: nonsignificant linear trend for higher HCC in males compared with females ($F_{(1,57)} = 3.58$, $P = .06$, $\eta p^2 = .06$)[§]
Vaghri et al. [61]	167 preschool boys, 172 preschool girls	No statistically significant correlation between age and log-transformed, winsorized HCC variable (biserial correlation = −0.01, $P = .790$)
Chen et al. [62]	Cohort B (41 men, 9 women)	No significant gender difference in HCC ($z = -1.25$, $P = .22$)
Gerber et al. [70,79]	42 university students (22 women, 20 men)	Sex was not significantly associated with participants' HCC ($P = .346$)[§]
Groeneveld et al. [53]	42 children (mean age, 50.1 mo, SD = 0.42 mo, 45% boys)	HCC was not significantly related to gender[‡,§]
Hinkelmann et al. [52]	43 major depressive disorder patients, 41 age- and sex-matched controls[‖]	HCC was not significantly associated with sex ($P > .10$)[‡,§]
Manenschijn et al. [69]	283 elderly adults (66.1% female)	HCC were significantly higher in men than in women (median, 26.3 pg/mg hair (IQR, 20.6 −35.5 pg/mg hair) versus 21.0 pg/mg hair (IQR, 16.0–27.0 pg/mg hair); $P < .001$)
Saleem et al. [65]	56 cardiac rehabilitation patients with coronary artery disease (26 in normal HCC group (median 111.4 ng/g) and 30 in the elevated HCC group (median 262.8 ng/g)	Gender was not significantly different between normal HCC group (92.3% male) and high HCC group (80% male) ($P = .19$)
Stalder et al. [51]	1258 men and women[‖] (about 84.8% were men)	HCC was not significantly with sex ($F_{1,\ 1216} = 1.83$, $P > .05$)[‡,§]
Race and ethnicity		
O'Brien et al. [34]	135 adults categorized into two groups: minorities (African-Cuban, Afro-Cuban, Asian, Brazilian, Indian, Latino-Hispanic, and Pacific Islander [$n = 67$]); and nonminorities (European or White American [$n = 68$])	HCC was not correlated with race ($r = -0.09$, $P > .05$). However, there was significant interaction of race and socioeconomic status on HCC ($F_{(2,\ 122)} = 3.26$, $P < .05$, $\eta p^2 = 0.16$)
Psychiatric symptoms and disorders		
Dowlati et al. [55]	34 depressed patients, 87 nondepressed patients (all attending a cardiac rehabilitation center)	Mean HCC was not different between depressed and nondepressed patients (log mean ± SD: 4.96 ± 0.58 vs. 5.04 ± 0.59, $P = .53$)
Karlén et al. [33]	95 students (20 with serious life events)	Mean HCC were higher students who had experienced serious life events within the last 3 mo vs. those who had not (mean ± SD: 33.0 ± 57.0 vs. 16.3 ± 22.5 pg/mg, $P = .045$)
Steudte et al. [48]	10 traumatized individuals with PTSD, 16 TC without PTSD	Traumatized PTSD patients had significantly higher HCC compared with traumatized non-PTSD controls ($F_{(1,25)} = 5.35$, $P = .03$, $\eta p^2 = 0.18$)[§]
Steudte et al. [49]	15 GAD patients, 15 controls	HCC were significantly lower in GAD patients compared with controls for first 3-cm segment ($F_{(1,27)} = 11.80$, $P = .002$, $\eta p^2 = 0.304$)[§] and second 3-cm segment ($F_{(1,24)} = 8.894$, $P = .006$, $\eta p^2 = 0.270$).[§] A nonsignificant trend for lower HCC in GAD patients was observed for the third segment ($F_{(1,17)} = 4.138$, $P = .058$, $\eta p^2 = 0.196$)[§]

Dettenborn et al. [40]	23 depressed patients, 64 healthy controls	Depressed patients had elevated HCC in the first 3-cm (mean ± SD: 26.7 ± 20.8 vs. 18.7 ± 11.5 pg/mg, $P < .05$) and second 3-cm hair segments (mean ± SD: 21.9 ± 23.7 vs. 13.4 ± 9.6 pg/mg, $P < .05$) compared with controls
Luo et al. [56]	32 individuals with PTSD, 32 traumatized non-PTSD controls, 20 nontraumatized non-PTSD controls	For the hair segment corresponding to 2 mo before and 1 mo after the earthquake, HCC were elevated in traumatized individuals (PTSD and non-PTSD) compared with the nontraumatized non-PTSD controls ($F = 3.88$, $P = .0499$ and $F = 6.27$, $P = .013$, respectively).[§] For the hair segment corresponding to 2–4 mo after the earthquake, traumatized non-PTSD controls had significantly higher HCC compared with traumatized PTSD individuals ($F = 6.17$, $P = .0137$)[§] and nontraumatized non-PTSD controls ($F = 11.74$, $P = .0007$).[§] For the period corresponding to 5–7 mo after the earthquake, traumatized non-PTSD controls had higher HCC compared with traumatized individuals with PTSD ($F = 4.11$, $P = .0438$)[§]
Manenschijn et al. [72]	100 bipolar disorder patients, 195 healthy controls	No difference between mean HCC of bipolar disorder patients and that of controls (mean [95% CI]: 31.84 [28.38–35.81] vs. 28.18 [25.94–30.62] pg/mg, $P = .233$). However, in a subsample, individuals with older age of onset (≥30 y) had higher HCC compared with those with early onset (<30 y) ($\beta = 0.335$, $P = .004$)
Gerber et al. [79]	42 undergraduate students (22 women, 20 men)	HCC were negatively associated with depressive symptoms (as assessed using the Beck Depression Inventory), $\beta = -0.24$, $P = .009$
Grassi-Oliveira et al. [78]	23 treatment seeking crack cocaine-dependent women	HCC was significantly related with negative life events exposure 90 d before hospital admission ($r = 0.56$; $P = .007$) and 30 d ($r = 0.42$; $P = .048$) before admission at the hospital, but not with 60 d before admission ($r = 0.23$; $P = .293$)
Groeneveld et al. [53]	42 children (mean age, 50.1 mo, SD = 0.42 mo, 45% boys); 21 children scored high on a fearfulness questionnaire	HCC significantly increased after the start of school, but only in children who scored high for fearfulness $F_{(1, 19)} = 4.67$, $P = .04$, $\eta p^2 = 0.20$
Hinkelmann et al. [52]	43 major depressive disorder patients, 41 age- and sex-matched controls[‖]	HCC was not associated with current depression nor with atypical depression[‡,§]
Saleem et al. [65]	56 cardiac rehabilitation patients with CAD (26 in normal HCC [median 111 ng/g] and 30 in the elevated HCC [median 263 ng/g])	The prevalence of depression did not differ between the normal HCC group (26.9%) and the high HCC group (30%) ($P = .80$)
Steudte et al. [50]	25 PTSD patients, 25 TC, 28 NTC	HCC was 59% lower in PTSD patients and 51% lower in TC, compared with NTC (mean ± SD HCC: PTSD 6.44 ± 6.05 pg/mg; TC 7.78 ± 7.01 pg/mg; NTC 15.75 ± 14.77 pg/mg; $P < .05$). No differences in HCC between PTSD and TC groups ($P = .535$). HCC was not correlated with Beck Depression Inventory-II scores ($r = -0.127$, $P = .256$). HCC was inversely correlated with number of different lifetime traumatic events, frequency of traumatic experiences, time since traumatization, and severity of intrusion symptoms.
Other medical conditions		
Cardiovascular disease, cardiometabolic syndrome, and chronic pain		
Van Uum et al. [36]	15 chronic pain patients receiving opioid treatments, 39 nonobese controls	Chronic pain patients had higher HCC compared with controls (mean [range]: 83.1 [33.0–205] pg/mg vs. 46.1 [27.2–200] pg/mg, $P < .01$)
Pereg et al. [13]	56 acute myocardial infarction (AMI) patients, 56 non-AMI hospital controls	AMI patients had significantly elevated median HCC compared with non-AMI hospital controls (median [range]: 295.3 [105.4–809.3] vs. 224.9 [76.58–949.9] ng/g, $P < .01$)
Karlén et al. [33]	95 students (28 reported taking pharmaceuticals)	No difference in HCC according to use of pharmaceuticals (mean ± SD: 22.9 ± 44.9 pg/mg vs. 18.6 ± 27.2 pg/mg, $P = .57$)
Manenschijn et al. [27]	46 healthy participants	No correlation between HCC and systolic ($P = .109$)[§] or diastolic blood pressure ($P = .365$)[§]
O'Brien et al. [34]	135 adults (18–66 y, 65% female, 48% minority)	HCC was positively correlated with systolic blood pressure ($r = 0.25$, $P < .01$); however, no significant correlation was observed between HCC and diastolic blood pressure ($r = 0.08$, $P > .05$)
Manenschijn et al. [69]	283 elderly adults (age range: 65–85 y)	HCC was significantly associated with cardiovascular disease. The odds ratio was 1.9 ($P = .09$) for the second, 2.0 ($P = .08$) for the third, and 2.7 ($P = .01$) for the fourth quartile. Highest levels of HCC quartile associated with type 2 diabetes mellitus (odds ratio 3.2, $P = .04$).
Saleem et al. [65]	56 cardiac rehabilitation patients with CAD (26 in normal HCC [median 111 ng/g] and 30 in the elevated HCC [median 263 ng/g])	High baseline HCC (i.e., HCC≥153.2 ng/g) predicted less improvement in verbal memory performance after 1 y ($F_{(1, 50)} = 5.50$, $P = .02$, number of weeks since acute coronary event, percutaneous coronary intervention, and myocardial infarction did not differ between normal and high HCC groups; however, history of coronary artery bypass surgery differed. Between the normal and high HCC groups: prevalence of hypertension (53.8% vs. 63.3%, $P = .47$), diabetes (7.7% vs. 16.7%, $P = .31$), maximum heart rate (118 ± 18 vs. 121 ± 22 bpm, $P = .55$), systolic blood pressure (176 ± 24 vs. 177 ± 27 mmHg, $P = .90$), diastolic blood pressure (76 ± 9 vs. 80 ± 11 mmHg, $P = .18$), and maximal oxygen intake (20 ± 5 vs. 20 ± 5, $P = .98$) seemed to differ, although the P-values were not significant.

(*Continued on next page*)

Table 2 (*Continued*)

Study	Sample size for analysis	Summary of findings
Stalder et al. [51]	1258 men and women‖ (about 24% had MetS)	HCC was positively associated with MetS: [mean (±SD), no MetS: 7.70 (±8.12) pg/mg; MetS: 10.78 (±11.37) pg/mg, $P < .0001$]. Furthermore, in the adjusted partial correlations, HCC was not significantly associated with mean arterial pressure ($r = 0.047$, $P > .05$), high-density lipoprotein cholesterol ($r = -0.037$, $P > .05$), triglycerides ($r = -0.015$, $P > .05$), and glucose ($r = 0.005$, $P > .05$). However, HCC was associated with low-density lipoprotein cholesterol ($r = -0.080$, $P < .01$), and glycated hemoglobin ($r = 0.116$, $P < .001$)
Adrenocorticoidal conditions		
Thomson et al. [28]	6 female CS patients, 32 healthy controls (21 females, 11 males)	Cushing patients had significantly higher HCC compared with controls: (median [range]: 679 [279–2500] vs. 116 [26–204] ng/g, $P < .001$)
Gow et al. [35]	93 AI patients on hydrocortisone replacement therapy, 62 household partners	AI patients had higher median HCC than controls (median [range]: 230.7 [22.7–1377] vs. 184.7 [57.7–1479] ng/g, $P = .08$), although the result was not significance. Hydrocortisone dose was also correlated with HCC ($r = 0.03$, $P = .004$)
Manenschijn et al. [27]	195 healthy controls, 9 hypercortisolemic	Hypercortisolemics had significantly elevated HCC compared with healthy controls ($P < .0001$)‡,§
Manenschijn et al. [54]	14 patients with CS, 6 patients with cyclic CS, 96 nonobese healthy controls	Patients with CS (excluding cyclic CS patients) had significantly elevated mean HCC compared with healthy individuals (mean [95% CI]: 399.7 [171.8–930.0] vs. 27.3 [24.6–30.4] pg/mg, $P < .0001$)
Adiposity		
Manenschijn et al. [64]	39 shift workers, 89 day workers	HCC positively correlated with participant BMI ($\beta = 0.262$, $P < .05$). HCC increased across BMI groups as follows: (mean [95% CI]: BMI < 25 kg/m^2: 31.26 [26.79–36.48]); (BMI = 25–30 kg/m^2: 36.06 [30.48–42.76]); (BMI >30 kg/m^2: 60.95 [43.95–84.72] pg/mg, $P = .002$)
Manenschijn et al. [27]	195 healthy people, 9 hypercortisolemic, 1 hypocortisolemic	HCC was positively correlated with waist circumference ($r = 0.392$, $P < .05$) and waist-to-hip ratio ($r = 0.425$, $P < .05$). HCC was not significantly correlated with BMI ($P = .646$) or hip circumference ($P = .096$)
Manenschijn et al. [72]	Bipolar patients: 100 individuals; BMI median (IQR): 25.3 (23.5–28.0 kg/m^2) Healthy controls: 195 people: BMI median (IQR): 23.7 (21.7–26.5 kg/m^2)	No significant relationship between HCC and BMI in bipolar ($r = 0.163$, $P = .11$) and control individuals ($r = 0.042$, $P = .59$)
O'Brien et al. [34]	135 adults	HCC was not significantly correlated with waist-to-hip ratio ($r = -0.03$, $P > .05$)
Stalder et al. [46]	155 adults; BMI: (mean ± SD: 22.2 ± 3.4; range: 16.5–35.8) kg/m^2	HCC positively correlated with participant weight ($r = 0.29$, $P \leq .001$) and BMI ($r = 0.33$, $P \leq .0001$)
Stalder et al. [46]	58 men and women; BMI: (mean ± SD: 24.0 ± 4.9; range: 16.9–42.1) kg/m^2	HCC positively correlated with participant weight ($r = 0.36$, $P < .05$) and BMI ($r = 0.42$, $P \leq .001$)
Manenschijn et al. [69]	283 elderly adults (65–85 y, 66.1% female)	No significant correlation between HCC and BMI ($r = 0.06$, P =.36), waist circumference ($r = 0.11$, $P = .08$)
Saleem et al. [65]	56 cardiac rehabilitation patients with CAD (26 in normal HCC [median 111 ng/g] and 30 in the elevated HCC [median 263 ng/g])	Between the normal and high HCC groups, mean ± SD of BMI did not differ (27.1 ± 5.0 kg/m^2 vs. 27.4 ± 3.5 kg/m^2, $P = .75$), neither did waist circumference (96.2 ± 10.1 cm vs. 98.8 ± 8.8, $P = .29$)
Pregnancy		
D'Anna-Hernandez et al. [86]	21 nonsmoking pregnant women (<17 wk gestational age)	HCC increased across successive trimesters and then decreased during the first 2–3 mo postpartum. HCC in third trimester was higher than in the first ($t = 4.1$, $P = .001$)§ as well as postpartum ($t = 2.9$, $P = .004$)§
Kirschbaum et al. [43]	103 mothers with newborn aged 2–4 d, 19 mothers of toddlers 3–9 mo, 20 nonpregnant nulliparous women ($n = 20$).	HCC of mothers of newborns aged 2–4 d (their hair corresponded with the third trimester) was significantly elevated in the first 3-cm segment compared with that of control women ($t_{(1,120)} = 4.77$, $P < .0001$)§; however, there was no significant difference in HCC of the two groups of women for segments 2 and 3
Krumbholz et al. [58]	1 woman (HCC over a pregnancy)	The highest HCC (13.4 pg/mg) was observed for the hair segment that reflected the last month of pregnancy and first month postpartum
Early life adversity		
Yamada et al. [87]	60 NICU infants > 25 wk gestational age, NICU term infants, healthy term infants	HCC for NICU infants was elevated compared with HCC for healthy term infants (mean ± SD: 2.06 ± 2.05 vs. 0.11 ± 0.42 nmol/g, $P = .004$). Total number of days on the ventilator was associated with HCC (increased 0.2 nmol/g, $P = .03$, on average, for each additional day). There was no difference between HCC of term infants in NICU and HCC of preterm infants in NICU
Grassi-Oliveira et al. [78]	23 treatment seeking crack cocaine-dependent women	No correlation between HCC and severity of early life stress‡,§
Hinkelmann et al. [52]	43 major depressive disorder patients, 41 age- and sex-matched controls‖	HCC was lower in subjects who experienced childhood maltreatment compared with controls ($F_{1,71} = 4.11$, $P = .05$)‡,
Steudte et al. [50]	25 PTSD patients, 25 TC, 28 NTC‖	No significant correlation was observed between HCC and childhood trauma scores ($r = -0.144$, $P = .197$)
Lifestyle and behavioral factors		

Alcohol use		
Stalder et al. [45]	23 alcoholics in acute withdrawal, 25 abstinent alcoholics, 20 controls	HCC (mean ± SD) was highest in acute withdrawal alcoholics (51.99 ± 43.30 pg/mg), compared with abstinent alcoholics (13.98 ± 10.63 pg/mg, $P < .001$) and controls (16.35 ± 12.59 pg/mg, $P < .001$). No difference between HCC of abstinent alcoholics and controls ($P = .91$)
Manenschijn et al. [69]	283 elderly adults (17.4% who had never drank, 52.8% light drinkers, 26.2% moderate drinkers, 3.6% (very) excessive drinkers)	HCC was positively associated with alcohol consumption. HCC were 21.2 pg/mg hair (IQR, 15.2–29.4) in nondrinkers, 21.7 pg/mg hair (IQR, 16.9–28.9) in light drinkers, 24.5 pg/mg hair (IQR, 17.1–36.3) in moderate drinkers, and 30.4 pg/mg hair (IQR, 25.0–45.0) in excessive drinkers ($P = .05$)
Stalder et al. [51]	1258 men and women‖ (43% reported regular consumption of ≥3 alcoholic drinks/wk)	No association between HCC and self-reported alcohol consumption ($F_{1,\ 1208} = 0.11$, $P > .05$)§; HCC was positively associated with serum γ-glutamyltransferase, ($r = 0.11$, $P < .0001$)
Cigarette smoking		
Dettenborn et al. [42]	18–49 y‖	No influence of smoking status on HCC ($P = .836$)§
Stalder et al. [46]	Study I: 155 adults (17.6% smokers) Study II: 58 men and women (27.6% smokers)	Study I: No association between smoking status and HCC ($P > .10$)§ Study II: No association between smoking status and HCC ($P > .30$)§
Skoluda et al. [44]	304 amateur endurance athletes (7.1% habitual smokers); 70 controls (20% habitual smokers)	Smoking was not associated with HCC ($F_{(1,\ 364)} = 0.02$, $P = .88$)§
Hinkelmann et al. [52]	43 major depressive disorder patients; 41 age- and sex-matched controls‖	HCC was not significantly associated with smoking status ($P > .10$)‡,§
Manenschijn et al. [69]	283 elderly adults (38.2% never smoked; 52.7% former smokers, 8.8% current smokers)	No difference in HCC based on smoking status. HCC were 21.2 pg/mg hair (IQR, 16.6–26.9) in those who never smoked, 22.1 pg/mg hair (IQR, 17.4–33.6) in former smokers, and 26.3 pg/mg hair (IQR, 18.7–32.3) in current smokers ($P = .22$)
Stalder et al. [51]	1258 men and women‖ (33.5% smokers)	HCC was not associated with smoking status ($P > .05$)‡,§
OCs and medication intake		
Dettenborn et al. [42]	(16.7% used OCs)‖ 252 individuals aged 18–49 y‖ 29 elderly individuals (medication intake analysis)‖	No influence of OC use on HCC in 18- to 49-y-old women ($P = .110$)§ No influence of overall medication intake on HCC in 18–49 y ($P = .610$)§ No influence of medication intake in elderly group ($F_{(1,29)} = 0.245$, $P = .625$)§
Stalder et al. [46]	Study I: 72 OC users, 42 not taking OCs Study II: 16 OC users, 23 not taking OCs	Study I: No association between OC use and HCC ($P > .10$)§ Study II: No association between OC use and HCC ($P > .30$)§
Groeneveld et al. [53]	42 children (mean age, 50.1 mo, SD = 0.42 mo, 45% boys)‖	HCC of children was not related to use of corticosteroids or other medications‡,§
Hinkelmann et al. [52]	43 major depressive disorder patients, 41 age- and sex-matched controls‖	HCC was not associated with antidepressant treatment ($P > .1$)§
Saleem et al. [65]	56 cardiac rehabilitation patients with CAD (26 in normal HCC [median 111 ng/g] and 30 in the elevated HCC [median 263 ng/g])	Use of concomitant medications seemed to differ with specific drugs between normal and high HCC groups; however, no statistically significant difference was observed; beta-blocker (80.8% vs. 70%, $P = .35$); calcium channel blocker (26.9% vs. 10%, $P = .10$); diuretics (23.1% vs. 20%, $P = .78$); antihypertensives (50% vs. 63.3%, $P = .32$); antidiabetics (3.8% vs. 16.7%, $P = .12$); antidepressants (3.8% vs. 10%, $P = .37$); anxiolytics (11.5% vs. 3.3%, $P = .23$)
Steudte et al. [50]	25 PTSD patients (36% used RM), 25 TC (20% used RM), 28 NTC (29% used RM)‖	No relationship between HCC and medication intake ($P > .31$)§
Steudte et al. [50]	25 PTSD patients (96% female, 7 women used OC), 25 TC (92% female, 4 used OC), 28 NTC (89 female, 9 used OC)‖	No relationship between HCC and OC use ($P > .31$)§
Physical activity		
Skoluda et al. [44]	304 amateur endurance athletes, 70 controls	On average, athletes had higher HCC compared with controls (mean ± SD: 18.18 ± 9.6 vs. 12.43 ± 6.2 pg/mg; and gender did not alter the effect of endurance sports on HCC, $P = .048$). Additionally, they observed a significant correlation between HCC and training kilometers run per week ($r = 0.32$, $P < .001$), training hours per week ($r = 0.22$, $P < .001$) and number of competitions per year ($r = 0.29$, $P < .001$), but not with number of training years ($r = 0.008$, $P = .89$).
Stalder et al. [51]	1258 men and women‖ (physical activity score range: 3–15)	No association of HCC with physical activity ($P > .05$)‡,§
Gerber et al. [70]	42 university students (vigorous physical activity: 0–213 weekly minutes; moderate physical activity: 164–775 weekly minutes)	HCC positively correlated with vigorous physical activity ($\beta = 0.33$, $P < .05$, $\Delta R^2 = 0.106$). HCC was not significantly correlated with moderate physical activity ($r = -0.08$, $P > .05$)
Diet		
Stalder et al. [51]	1258 men and women‖ (self-reported daily fruit and vegetable consumption)	No association between HCC and fruit and vegetable consumption ($P > .05$)‡,§

AI = adrenal insufficiency; AMI = acute myocardial infarction; BMI = body mass index; CI = confidence interval; CS = Cushing syndrome; GAD = generalized anxiety disorder; HCC = hair cortisol concentrations; IQR = interquartile range; MetS = metabolic syndrome; NICU = neonatal intensive care unit; NTC = nontraumatized control; OC = oral contraceptive; PTSD = post-traumatic stress disorder; RM = regular medication; SD = standard deviation; TC = traumatized control. Studies are organized by year, then by alphabetical order.

* We used SAS 9.2 to calculate these values.

† We excluded two outlier values.

‡ Authors did not report exact *P*-values.

§ Authors did not report mean HCC, median HCC, correlation, or odds ratio.

‖ Sample size used in analysis might be different from total sample size (and/or) authors did not specify the proportion of subjects in comparison groups.

Hair segment

HCC has been shown to decrease as one moves distally from the scalp [42,44,49,56–58]. This attenuation in cortisol concentration has been attributed to exposure to water, sunlight, and other elements. Of note, Steudte et al. [49] reported that HCC decreased 17.4% from the proximal 3-cm segment to the second 3-cm segment and then decreased 18.3% from the second 3-cm segment to the third. Manenschijn et al. [27], however, found no difference in HCC among six consecutive 3-cm segments of hair from healthy women (Table 2).

Other factors

Other hair-related factors that have been studied include hair texture and ultraviolet (UV) irradiation. Although HCC appears not to be influenced by curls, hair curvature, or waves [42,43], investigators have reported that 9-hour UV irradiation, compared with no exposure, is associated with statistically significant reductions in HCC (Table 2) [39]. More studies are needed to further examine the effect of hair texture and UV irradiation on HCC.

Taken together, although the available data suggest that natural hair color and texture are not associated with HCC, data are still scarce or inconclusive on the relationship between the various hair treatments and HCC. Thus, investigators may consider collecting information on these behaviors along with precisely defining hair segment for collection and analysis in future large-scale epidemiologic studies that rely on HCC as a biomarker of chronic stress.

Stress-related correlates

Demographic, social, and occupational stressors

Socioeconomic factors such as income, educational level, occupation, and neighborhood characteristics are important determinants of health and are closely related with psychosocial stress [59]. Results of studies exploring the association between these factors and cortisol concentrations in saliva, urine, and blood serum have been mixed [60]. To date, only a few studies have examined the relationship between HCC and socioeconomic factors. In a sample of 333 children from 23 neighborhoods in Vancouver, Canada, Vaghri et al. observed that maternal and paternal education were both inversely correlated with HCC ($r = -0.18$, $P = .001$). However, in a subsample of 275 preschoolers, annual family income was not significantly correlated with HCC ($r = -0.07$, $P = .235$) (Table 2) [61]. Chen et al. [62] observed no relationship between HCC and educational level in a study of adults in Nanjing, China.

With regard to employment-related factors, shiftwork is of increasing importance in health studies, particularly because chronic shiftwork alters the circadian rhythm of cortisol production leading to HPA dysfunction [63]. In a small but important early study, investigators observed elevated mean HCC in participants who had a fast-forward rotating shift schedule compared with those who only worked during the day (47.32 vs. 29.72 pg/mg, $P < .001$) [64]. However, there appeared to be an effect of age on the relationship between HCC and shiftwork (Table 2) [64]. Unemployment has also been examined in relation to HCC. Dettenborn et al. [41] found higher HCC in unemployed individuals compared with those employed.

Age

Results of studies on the relationship between age and cortisol in other matrices have been quite mixed with investigators reporting both positive [66,67] and negative associations [68]. With regard to the hair cortisol literature, some [23,27,34,43,46,53,54,61,62,65,69,70] but not all [42,51] investigators have reported no relationship between age and HCC. However, inferences from most studies documenting no associations are hindered by limited variability in the age of study participants. A study of 360 individuals aged 1–91 years suggests a complex nonlinear relationship between age and HCC [42]. Across the age spectrum, the authors found that HCC were elevated in children aged younger than 10 years and in adults aged 50–91 years [42]. Furthermore, HCC was inversely related with age (in months) of children 5 years or younger ($r = -0.428$, $P = .023$).

In a smaller study with a comparable age range (2–90 years), Raul et al. [23] found no association of age with HCC. Available data suggest a complex relationship of HCC with age. Studies of individuals across broader age spectrums are needed to more thoroughly explore the relationship between age and HCC.

Sex

Findings on the relationship between sex and cortisol concentrations in other matrices have been inconsistent with some investigators finding higher concentrations in men [71] and others finding higher cortisol concentrations in women [66]. HCC studies on this topic have also been mixed with some investigators finding associations between HCC and sex [34,42,44,46,69] and others finding none [23,27,33,51–54,61,62,65,70,72]. Dettenborn et al. found higher HCC among males than among females in two age groups: adults aged 18–49 years and children aged younger than 10 years. However, no differences were found in adults older than 49 years nor in individuals aged 10–17 years (Table 2) [42].

Race and ethnicity

Race and ethnicity are important indicators of exposure to social stressors [73]. Equally vital, they are determinants of hair texture and hair growth rate [74]. Yet, race and ethnicity have not been adequately studied in HCC studies. The average rate of hair growth used in most hair cortisol studies and other hair analysis is 1 cm/mo; however, hair growth is known to vary between 0.7 and 3.6 cm/mo [75]. Loussouarn et al. [74] observed lower hair density and hair growth rate in Africans compared with Caucasians. These findings are consistent with racial differences in hair growth characteristics. In a study by O'Brien et al. [34], participants were classified into two groups: minorities (African-Cuban, Afro-Cuban, Asian, Brazilian, Indian, Latino-Hispanic, and Pacific Islander) and nonminorities (European or white American), and investigators observed no relationship between racial category and HCC. However, the authors found a significant interaction of race and socioeconomic status on HCC with minorities having elevated HCC at low and high socioeconomic status [34]. Additional studies are needed to ascertain variations in hair growth rate among diverse populations. Considering inconsistencies in findings concerning HCC in relation to gender and given the importance of race and ethnicity as important indicators of social stressors, hair texture, and hair growth rate, investigators should account for sex, race, and ethnicity in the design, analysis, and interpretation of hair cortisol studies.

Psychiatric symptoms and disorders

Despite some inconsistencies, findings from studies examining cortisol concentrations in saliva, blood, and urine generally point to a relationship between HPA dysregulation, psychiatric disorders, and aberrations in cortisol concentrations or diurnal cycles [17,56,76,77]. A meta-analysis of 47 studies that examined salivary, blood plasma/serum, and urinary cortisol showed that compared with no-trauma controls, PTSD patients had suppressed morning cortisol concentrations and afternoon/evening cortisol concentrations [17]. Studying the association of HCC with stressful events and psychological symptoms or disorders is particularly important

for establishing the validity of hair cortisol as a biomarker of chronic stress.

Using hair samples that corresponded to 1–2 months after the 2008 Wenchuan earthquake, Luo et al. determined that HCC were elevated in PTSD and traumatized controls (TC) compared with nontraumatized controls (Table 2). Furthermore, for an additional 2–4 months after the earthquake, TC had the most elevated average HCC compared with the other two groups (Table 2) [56]. Steudte et al. [48] also observed higher HCC in individuals with PTSD compared with TC (60% of PTSD patients and 22.2% of TC experienced traumatic events in the past year). However, in a separate study, Steudte et al. [50] observed lower HCC in PTSD patients and TC compared with nontraumatized controls (75% of participants had experienced their most traumatic event >5 years ago) and no difference in HCC of PTSD patients and TC. Furthermore, they found no associations between salivary cortisol levels and traumatization or PTSD [50]. On balance, available data indicate that trauma exposure and PTSD are associated with aberrant HCC and that while cortisol levels may rise shortly after trauma, they may decrease over time. Like trauma, serious adverse life events, frequently precursors to impaired mental health, have also been associated with HCC [33,78].

Depression has also been studied in relation to HCC; however, the results have been mixed. One study found that depressed patients had elevated HCC compared with healthy controls [40]. In another study of cardiac rehabilitation patients, investigators observed no significant difference in HCC between depressed and nondepressed subjects [55]. The authors suggested that the absence of an association may be due to already elevated stress and cortisol levels in the cardiac rehabilitation population [55]. Investigations of the relationship between HCC and scores on the Beck Depression Inventory have found both negative associations [79] and no associations [50,65]. Saleem et al. [65] found no difference in the prevalence of depression between normal HCC and high HCC subjects.

Other psychiatric conditions that have been studied in hair cortisol research include bipolar disorder and generalized anxiety disorder (GAD). Manenschijn et al. [72] found no overall difference between mean HCC of bipolar disorder patients, most of whom were receiving pharmacologic treatment, compared with healthy controls. However in a subsample, it was observed that individuals with older age of onset (≥30 years) had higher HCC compared with those with early onset (<30 years) (Table 2). The authors suggested that stressful life events and HPA axis dysregulation may play a role in later development of bipolar disorder, whereas early onset may be related to genetics or fluctuations in sex hormones [72]. Finally, Steudte et al. examined cortisol concentrations for GAD patients and controls. Although they found no difference in area under the diurnal curve for 24-hour salivary cortisol concentrations between the two groups, GAD patients had lower HCC compared with controls (Table 2) [49]. The investigators suggested that the experience of participating in a study might have contributed to acute fluctuations in salivary cortisol concentrations such that no differences in salivary cortisol concentrations were detectable. They also reasoned that HCC might be a more accurate measure of long-term HPA axis activity as it is not easily susceptible to acute influences [49].

Finally, in a sample of young school children, HCC significantly increased after school entry, but only in children who scored high on the fearfulness subscale of the Child Behavior Questionnaire [53]. Collectively, findings suggest that trauma exposure, psychiatric disorders, serious adverse life events, and symptoms of negative moods and emotions may be associated with HCC. More studies are needed to firmly establish HCC as a clear biomarker of chronic stress and elucidate the temporal relationship of HCC deviations with psychiatric disorders while jointly considering the mediating effects of stressors and stress response.

Other medical conditions

Adrenocorticoidal conditions

Cushing syndrome, Addison disease, and other conditions affecting the hypothalamus, pituitary, or adrenal cortex are associated with aberrations in cortisol concentrations or diurnal patterns in saliva, blood serum/plasma, and urine [80]. Studies examining HCC and adrenocorticoidal conditions have been consistent with these findings. In a study of AI patients receiving hydrocortisone replacement therapy and household partner controls, AI patients had higher HCC than controls. HCC was also positively correlated with glucocorticoid dose [35]. The authors speculated that patients with AI may be overtreated and could be at risk for adverse effects of elevated cortisol concentrations.

Investigators examining the relationship between Cushing syndrome and HCC have found significantly higher HCC in Cushing patients compared with healthy controls (Table 2) [27,28,54]. In their study of nonobese healthy controls and patients with cyclic Cushing syndrome, Manenschijn et al. [54] observed 86% sensitivity and 98% specificity for Cushing syndrome, using the upper-limit reference range for nonoverweight healthy controls (75.9 pg/mg hair). These findings on Cushing syndrome lend support to the capability of hair as a valid matrix of chronic cortisol exposure.

Chronic pain, cardiovascular disease, and metabolic syndrome

Results support an association between aberrations in cortisol concentrations from other matrices and cardiovascular disease [81–83], cardiometabolic syndromes [84], and chronic pelvic pain [15,16]. Positive significant associations have been observed of high HCC with severe chronic pain [36], 1-year verbal memory, and history of coronary artery bypass graft surgery in cardiac rehabilitation patients [65] and cardiovascular disease and events [13,69].

The results on cardiometabolic parameters have been mixed. HCC has not been associated with diastolic blood pressure [27,34,65], and although O'Brien et al. [34] found a significant positive correlation between HCC and systolic blood pressure ($r = 0.25$, $P < .01$), two other studies observed no significant association [27,65]. Stalder et al. observed a positive correlation in unadjusted analysis of HCC and mean arterial pressure, but after adjustment, the correlation did not exist ($r = 0.047$, $P > .05$). They also observed mixed results between HCC and cardiometabolic parameters (Table 2) [51]. In one study, mean values of various cardiometabolic fitness parameters did not differ between normal and high HCC groups [65]. To date, HCC has not been associated with cancer, osteoporosis, and chronic nonspecific lung diseases [69].

On balance, HCC appears to be associated with chronic disorders, particularly disorders that are strongly associated with stress (e.g., chronic pain and cardiovascular disease). There is a need for prospective studies to further elucidate the relationship of HCC with incident disease and disease progression. For example, epidemiologic studies that investigate the relationship between HCC and adrenocorticoidal conditions should take into account the duration for which individuals have had the condition, the duration of treatment, and the type of treatment that individuals receive as all these factors may influence the relationship between HCC and adrenocorticoidal conditions.

Pregnancy

Evidence of increased cortisol production during pregnancy is well established [43,85]. Findings on the relationship between HCC and pregnancy have been consistent with a positive association. D'Anna-Hernandez et al. [86] studied HCC among pregnant women and found that HCC was significantly higher in the third trimester compared with the first and then decreased during the first 2–3 months postpartum (Table 2). In their study of mothers of newborns

aged 2–4 days, mothers of toddlers aged 3–9 months, and control women who were nulliparous and nonpregnant, Kirschbaum et al. [43] found that mean HCC among mothers of newborns aged 2–4 days (their hair samples corresponded with the third trimester) was two-fold higher than that of nonpregnant nulliparous women (Table 2). Krumbholz et al. [58] also found significantly elevated HCC in hair segment reflecting the last month of pregnancy and first month of delivery. Given well-documented evidence of a relationship between pregnancy and cortisol increase, investigators should exclude pregnant women from hair cortisol studies unless of course when pregnancy is the focus of the research.

Early life adversity

In their study of term infants and preterm infants who were older than 25 weeks gestational age at birth, Yamada et al. found that neonatal intensive care unit (NICU) infants had significantly higher HCC compared with healthy term (≥37 weeks) infants (mean ± standard deviation: 2.06 ± 2.05 vs. 0.11 ± 0.42 nmol/g, $P = .004$). Total number of days on the ventilator was associated with HCC and there was no significant difference in HCC for NICU term infants and NICU preterm infants [87]. In a study of depressed patients and healthy subjects, Hinkelmann et al. [52] observed lower mean HCC in subjects who experienced childhood maltreatment. However, Grassi-Oliveira et al. [78] did not observe a correlation between severity of early life stress and HCC in a sample of women seeking treatment for substance abuse.

Although studies on early life adversity and HCC in humans have been few, compelling results have been observed in studies of nonhuman primates. Two studies that examined monkeys showed that those separated from their mothers in early life had aberrant HCC when placed in new social environments compared with those that were reared by their mothers [88,89]. Additionally, Laudenslager et al. [90] observed that monkeys whose social groups were relocated during the perinatal period had elevated HCC compared with monkeys raised in a constant environment. On balance, results from studies of humans and nonhuman primates suggest that early life adversity may influence cortisol concentrations and have long-term negative effects on development. Thus, investigators should consider early life adversity in studies of HCC where necessary. There is a need for more studies to elucidate the relationship between HCC and perinatal and other early life experiences.

Adiposity

Results of studies examining relationships between adiposity and cortisol in blood, urine, and saliva have been varied. Investigators have reported no association [91], inverse [92–94] and positive associations [95,96] of cortisol concentrations with a full range of measures meant to reflect body fatness or adiposity. In Table 2, we provide a summary of the relatively sparse literature devoted to assessing HCC in relation to different measures of adiposity. Of note, some [27,46,51,64] but not all [34,72] available studies have found positive relationships between HCC and at least one adiposity measure including body mass index (BMI), waist circumference (WC), and waist-to-hip-ratio.

Positive associations between HCC and BMI have been reported in various populations including fast-forward rotating shift workers [64], university students [46], and adults [46,51]. However, other studies have found no relationship between HCC and BMI [27,65,69,72] or WC [65]. Still, others have shown HCC to be positively correlated with WC [27,51,69] and waist-to-hip-ratio [27,51] but not with hip circumference [27]. Despite some inconsistencies, available data suggest that HCC may be associated with adiposity in some but not all populations studied to date. Studies with objective measures of adiposity and central obesity are needed to further clarify suggested associations.

Lifestyle and behavioral factors

Alcohol use

Studies of other matrices suggest that aberrations in cortisol concentrations are associated with alcoholism [97] and alcohol relapse [98]. Two studies have found positive associations between HCC and high alcohol intake [45,69]. A third study reported no association between HCC and regular alcohol consumption (≥3 d/wk), but observed positive associations between HCC and serum γ-glutamyltransferase [51]. Overall, these findings suggest a positive relationship between high alcohol intake and HCC. More studies are needed to explore the relationship between HCC and alcohol use or abuse. Investigators should ascertain alcohol consumption among study participants and examine alcohol's effect on HCC where necessary.

Cigarette smoking

Evidence suggests that nicotine alters the HPA axis and acutely increases cortisol concentrations in saliva, urine, and blood plasma [99–103]. However, the association may only be acute [100]. Thus far, HCC has not been associated with cigarette smoking [42,44,46,51,69]. More studies are needed to provide further evidence about the relationship between cigarette-smoking status and HCC, especially because smokers report higher levels of stress than nonsmokers [104].

Oral contraceptives and other medications

The results of studies examining the effect of oral contraceptive use on cortisol concentrations in other matrices have been inconsistent. A summary of the relationship between oral contraceptive use and cortisol concentrations in blood plasma and saliva is given by Dettenborn et al. [42]. So far, investigators have reported no significant positive or negative relationships between HCC and oral contraceptive use [42,46,50]. See Table 2 for report of findings on the association between HCC and other medications.

Physical activity

Investigators have previously reported on the influence of moderate-to-high intensity physical activity to acutely raise concentrations of circulating cortisol in blood [105]. Positive associations have been observed for HCC and participation in endurance sports [44] and vigorous physical activity [70]. However, no associations have been observed for moderate physical activity [70]. Furthermore, Stalder et al. [51] observed no association between HCC and physical activity level as assessed by summing up 5-point frequency ratings in the areas of mild, moderate, and vigorous physical activity over the preceding 6 months. On balance, evidence suggests an association between HCC and vigorous physical activity.

Discussion

The study of correlates of hair cortisol concentrations is still at an early stage. Yet, available data obtained through this systematic review are suggestive of the validity of this biomarker. Importantly, our findings suggest that hair cortisol may be associated with early life adversity, stress-related psychiatric conditions, and medical conditions indicating chronic activation of the HPA axis or high stress levels. Further research is needed to underpin the validity of the biomarker as well as to obtain deeper understanding of its potentially different associations to reactive psychiatric conditions versus psychiatric disorders with stronger hereditary etiology.

The literature suggests that some factors (e.g., natural hair color, cigarette smoking, oral contraceptive use, and medication use) may not have important influences on HCC. Other factors, such as sex, adiposity, hair treatments, and substance abuse, may be potential determinants of HCC and thus investigators may want to include these measures in future studies. For a number of other factors (e.g., age, physical activity, and hair texture), available evidence are

insufficient, particularly because most existing hair cortisol studies assess the effect of sociodemographic and hair-specific behaviors secondary to some other primary outcomes. As such, studies were not usually conducted in ways that maximized opportunities for comprehensive assessments of these secondary covariates

Gaps in current hair cortisol research

- Lack of prospective studies to elucidate the association of HCC with major disease risk as well as how HCC change over preclinical and clinical manifestations of disease and with pharmacologic and nonpharmacologic treatments
- Other understudied areas include the effects of diet, hair loss, and seasonal variations on HCC, and the extent to which the different methods of laboratory analysis affect HCC observed and reported in studies
- Little racial/ethnic variation in current studies

[42]. Over the last decade, hair as a measure of cortisol has emerged as a promising biomarker of chronic stress and alterations of the HPA axis. Hair cortisol concentrations have shown favorable intraindividual variability in some studies. In one study, Stalder et al. [47] observed a relatively strong correlation between HCC after an average 375.3-day interval ($r = 0.78$, $P < .0001$, adjusted for perceived stress scores, and number of competitions per year). Three repeated measurements at 2-month intervals showed correlation coefficients ranging from 0.53 to 0.79 ($P < .001$) [47]. These findings support the reliable intraindividual stability of HCC.

Many gaps in understanding the fidelity and determinants of hair cortisol remain. One major limitation of current hair cortisol research is that most studies have been cross-sectional. Little is known about how HCC change across the human life course; the degree with which HCC changes across preclinical and clinical manifestations of disease; how HCC change with pharmacologic and nonpharmacologic treatments of conditions including mood and anxiety disorders; and how time since last episode and severity of illness influence HCC.

Other understudied areas include the influences of diet, hair loss, and seasonal variations on HCC and the extent to which different methods of laboratory analysis affect HCC observed and reported in studies [74,75,106]. To date, there have been few studies of large representative populations and few studies have included ethnically, racially, and economically diverse populations. Studies conducted in increasingly diverse populations will enrich the literature and provide investigators with much needed information that can be used to design, analyze, and interpret HCC in clinical- and population-based studies.

Our assessment of correlates of HCC suggests that hair cortisol may indeed constitute an important biomarker of HPA-axis dysregulation and chronic psychosocial stress. Investigators who elect to integrate this emerging biological marker into their studies should be strategic about accounting for covariates that may confound or modify associations of primary interests. Results of hair cortisol studies should be interpreted with consideration of appropriate factors including study size and segments of hair studied. The assessment of cortisol in hair presents unique strengths and challenges that if overcome may revolutionize the study of the potential health effects of chronic stress in large-scale epidemiologic studies.

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Supplementary Table
Overview of studies included in this review

Author, Ref.	Country	Total sample size	Sample population	Covariates
Chen et al. [62]	China	53 (cohort A) 50 (cohort B)	Adults from suburbs of Nanjing, China	Sociodemographics
D'Anna-Hernandez et al. [86]	United States	21	Nonsmoking pregnant women (aged 18–45 y) who are at <17 wk gestational age and experiencing noncomplicated pregnancies	Trimester of pregnancy
Dettenborn et al. [41]	Germany	59	Employed and unemployed adults	Unemployment; hair-related characteristics
Dettenborn et al. [40]	Germany	87	Depressed patients, healthy controls	Depression
Dettenborn et al. [42]	Germany	360	Healthy individuals (1–91 y)	Hair-related characteristics; sociodemographics and lifestyle factors
Dowlati et al. [55]	Canada	121	Depressed and nondepressed patients attending a cardiac rehabilitation center	Depression; hair-related characteristics
Gerber et al. [70,79]	Switzerland	42	University students	Sociodemographics; psychiatric symptoms; physical activity; and other lifestyle factors
Gow et al. [35]	Canada; USA	187	Adults with adrenal insufficiency, household controls (all within the age range of 18–70 y)	Adrenal insufficiency; sex; hydrocortisone; drugs for osteopenia/osteoporosis
Grassi-Oliveira et al. [78]	Brazil	23	Treatment seeking crack cocaine-dependent women	Negative life events; early life stress
Groeneveld et al. [53]	The Netherlands	42	Children entering school	School entry; hair-related characteristics; sociodemographics; fearfulness; medication intake
Hinkelmann et al. [52]	Germany	84	Major depressive disorder patients, controls	Major depression; childhood maltreatment
Karlén et al. [33]	Sweden	99	Students	Sociodemographics; serious life events
Kirschbaum et al. [43]	Germany	142	Mothers with newborns aged 2–4 d, mothers of toddlers 3–9 mo, nonpregnant nulliparous women	Pregnancy; postpartum; being the mother of a toddler; age; frequency of hair washing
Krumbholz et al. [58]	Germany	1	Hair samples were collected over a pregnancy cycle	Pregnancy; hair segment
Li et al. [39]	China	58	Healthy male adolescents (mean ± SD age: 16.2 ± 1.2 y), healthy males (mean ± SD age: 27.3 ± 2.5 y)	Ultraviolet exposure; hot water immersion; shampoo immersion; location of hair on the head
Luo et al. [56]	China	84	Women with PTSD who experienced the earthquake, women without PTSD who did not experience earthquake, controls (from an area not significantly affected by earthquake)	PTSD
Manenschijn et al. [72]	Netherlands	295	Bipolar disorder patients, healthy controls	Bipolar disorder; adiposity; sex
Manenschijn et al. [64]	Netherlands	122	Workers who worked in a fast-forward rotating shift, workers who only worked during the day	Shiftwork; adiposity
Manenschijn et al. [27]	Netherlands	205	Healthy adults, hypercortisolemic, and a hypocortisolemic	Cushing's syndrome; adiposity; sociodemographics; hair-related characteristics; blood pressure
Manenschijn et al. [54]	Netherlands	116	Patients with Cushing's syndrome, patients with cyclic Cushing's syndrome, nonobese healthy controls	Cushing's syndrome; sociodemographics
Manenschijn et al. [69]	The Netherlands	283	Elderly adults	Cardiovascular disease; sociodemographics; adiposity; lifestyle factors
O'Brien et al. [34]	United States	135	Adults	Sociodemographics; subjective stress; adiposity; blood pressure
Pereg et al. [13]	Israel	112	Acute myocardial infarction patients, hospitalized controls	Acute myocardial infarction
Raul et al. [23]	France	44	Healthy individuals	Hair-related characteristics; sociodemographics
Saleem et al. [65]	Canada	56	Cardiac rehabilitation patients	1-y verbal memory; sociodemographic factors; psychiatric symptoms; adiposity; medication intake
Sauvé et al. [32]	Canada	39	Healthy individuals	Hair-related characteristics; sex
Skoluda et al. [44]	Germany	395	Amateur endurance athletes, controls	Endurance sports; cigarette smoking; gender
Stalder et al. [45]	Germany	76	Alcoholics in acute withdrawal, abstinent alcoholics, gender- and age-matched controls	Alcoholism
Stalder et al. [46]	Germany	155 (study I) 58 (study 2)	Healthy individuals	Stress related measures; adiposity; hair-related characteristics; sociodemographics; lifestyle factors
Stalder et al. [47]	Germany	45 (study I) 68 (study 2)	Healthy individuals	Intraindividual stability of hair cortisol concentrations
Stalder et al. [51]	Germany	1258	Employees of an aerospace company	Metabolic syndrome; cardiometabolic parameters; hair-related characteristics; sociodemographics; lifestyle factors
Steudte et al. [49]	Germany	30	Generalized anxiety disorder patients and gender- and age-matched controls	Generalized anxiety disorder
Steudte et al. [48]	Uganda	27	PTSD patients, traumatized controls without PTSD	PTSD; gender
Steudte et al. [50]	Germany	78	PTSD patients, traumatized controls, nontraumatized controls	PTSD; trauma; lifestyle factors
Thomson et al. [28]	Canada	38	Cushing's syndrome patients, healthy controls	Cushing's syndrome
Vaghri et al. [61]	Canada	333	Healthy preschoolers	Parental income; maternal and paternal education; age; gender

(*Continued on next page*)

Supplementary Table (*continued*)

Author, Ref.	Country	Total sample size	Sample population	Covariates
Van Uum et al. [36]	Canada	54	Chronic pain patients, nonobese controls	Chronic pain
Xie et al. [57]	China	40	Nonobese healthy male graduate students (aged 22–30 y), female participants	Hair segment
Yamada et al. [87]	Canada	60	NICU infants >25 wk gestational age, NICU term infants, healthy term infants	Stay in NICU

NICU = neonatal intensive care unit; PTSD = Post-traumatic stress disorder.