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Invited Review

Determinants of hair cortisol concentration in children: A systematic review

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ABSTRACT

Background: Several factors are known contribute to hair cortisol concentration (HCC) in adults. However, there is less research on determinants of HCC in children and adolescents. HCC is a valuable tool for medical research pertaining to the hypothalamic-pituitary-adrenal (HPA) axis. This review aims to assess the extent to which established determinants of HCC in adults have been consistently reported in children (birth – 18 years) and to identify determinants of HCC specific to this age group.

Methods: Eligible studies were identified, selected and appraised as per PRISMA-P guidelines and as detailed in our systematic review protocol, registered on PROSPERO (registration number CRD42017056220). In view of contrasting methods and measures, a meta-analysis could not be done but a qualitative synthesis was performed.

Results: Thirty-six studies were included in the analysis. Higher HCC is associated with male sex and anthropometry, particularly increased body mass index and waist circumference. There is preliminary evidence to suggest that socio-economic status is inversely related to child HCC, particularly with reference to caregiver education and income. Of note, most of the studies analysing socio-economic variables were performed in relatively equal societies. Hair wash frequency and use of hair products and treatments do not affect HCC when proximal segments of hair are used. There is conflicting evidence regarding the relationship between HCC and age in children and adolescents. Further investigation is required to better delineate if and how the following are associated with HCC in children: hair colour, hair type, exposure to trauma and stressors, psychiatric illness, atopic illness, steroid use (including topical and inhaled steroids) and perinatal variables.

Conclusions: Sex and anthropometry are potential confounders and should be considered for adjustment in hair cortisol research. Hair wash frequency and use of hair products and treatments are not important confounders when proximal hair segments are used. A better understanding of HCC in children in relation to exposure to trauma and stressors is required before it can be used as a biomarker, particularly in terms of vulnerable developmental stages, definition and measurement of stress, and temporal relationship to stressors. Age, SES and other correlates also warrant further investigation.

1. Introduction

Hair cortisol concentration (HCC) is increasingly used as a marker of hypothalamic-pituitary-adrenal (HPA) axis activity particularly in psychoneuroendocrine research (Stalder et al., 2017). It is crucial to know the determinants of HCC so that potential confounders can be adjusted for. A meta-analysis (Stalder et al., 2017) comprehensively analysed 66 independent studies published up until 25 September 2015 comprising n = 10289 hair samples. A significant ($p < 0.05$) positive correlation was reported between HCC and male sex, stress-related anthropometry (body mass index, waist to hip ratio and systolic blood pressure), physical stressors and ongoing chronic stress. A significant negative correlation was found between HCC and hair wash frequency and anxiety disorders (a composite of generalised anxiety disorder and post-traumatic stress disorder). Interestingly, HCC was significantly positively correlated with age only in the meta-analysis of within-study correlation coefficients, and not in the meta-regression.

A subsequent publication detailed results of HCC analyses in n = 3507 participants aged 59–83 years from the Whitehall II cohort study (Abell et al., 2016). Consistent with the above meta-analysis, mean HCC was significantly lower in women than in men. Significantly lower mean HCC was reported in participants who used hair dyes, and

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there were significant changes by season and duration of sample storage. Significantly higher mean HCC was found for black ethnicity, diabetes mellitus, use of systemic (but not local) steroids and presence of depressive symptoms. Differences in mean cortisol per age group were not significant, nor were differences in mean cortisol per hair wash frequency.

Much less work has however been published on determinants of HCC in children and adolescents. In the above mentioned meta-analysis (Stalder et al., 2017), only 13 of 124 sub-samples (7.45% of the total sample) had a mean participant age of under 18 years. Furthermore, additional studies on HCC in children have since been published. To the best of our knowledge, no systematic review has been undertaken to establish the determinants of hair cortisol in children. It is therefore not known whether the determinants of HCC in adults are generalizable to a younger population. It is also not known whether determinants specific to children have been consistently reported.

The aim of this review is therefore to assess which baseline characteristics, diseases and environmental exposures are related to HCC in children.

2. Methods

2.1. Protocol and registration

Details of the protocol for this systematic review were registered on PROSPERO and can be accessed at www.crd.york.ac.uk/PROSPERO/display_record.asp?ID = CRD42017056220. This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. (Moher et al., 2015) In view of contrasting methods and measures, a meta-analysis could not be done. However, a qualitative synthesis was performed. We concluded that a variable was significantly related to HCC if it was reported on by 5 or more studies, methods used to assess the variable were sufficiently homogenous, there were no inconsistencies regarding the directionality of the relationship and more than 25% reported a significant association. We used the same criteria to conclude that a variable was not related to HCC, but here all studies had to conclude that there was no overall significant relationship. The authors agreed to make an exception to report that there was no significant relationship between HCC and use of hair products and treatments, despite that fact that only 3 studies analysed these variables. This was because of the inclusion of a study based on an exceptionally large sample size of 2484.

2.2. Eligibility criteria

The search (detailed below) included studies of all designs published in English peer-reviewed journals with human participants aged from birth to 18 years (studies on both adults and children were included only if the data on children was reported separately). HCC had to be an outcome of interest rather than salivary, urinary or serum cortisol or hair cortisone. Baseline characteristics, environmental exposures and diagnoses of disease were included as variables for comparison. Hair had to be sampled from the posterior vertex (except in neonates and infants where sparse hair may make this impossible) as this area has been shown to have the lowest co-efficient of variation (Sauve et al., 2007). Hair had to be cut as close to the scalp as possible. A maximum 6 cm proximal hair segment had to be specified, because inclusion of studies using longer segments may introduce confounding due to a 'wash-out effect' (Stalder and Kirschbaum, 2012). An exception was made for neonatal hair samples as it was assumed that neonatal hair would not exceed 6 cm in length. Method of cortisol measurement e.g. enzyme-linked immunosorbent assay (ELISA) also had to be specified.

2.3. Search strategy, study selection and data extraction

On the 4th July 2017, we conducted a systematic electronic literature search without date restrictions. We searched PubMed, Scopus, and Web of Science for peer-reviewed articles in English. We also searched references of previous reviews and all included articles. Two authors reviewed titles and abstracts of all articles from the literature search using the pre-defined inclusion criteria. The full texts of potential articles were then assessed to confirm study eligibility. Thereafter, two authors (NG and LV) independently extracted data using a standardized data extraction form and inconsistencies were resolved by discussion, and when necessary, by inclusion of a third author (AD). Analysis was mostly qualitative, although proportions are also presented.

3. Results

3.1. Search

Results of the study selection process are summarised in Fig. A1. After screening 157 articles, we ultimately included 36 studies. Total sample sizes ranged from 18 to 2484 and ages ranged from the neonatal period through to adolescence. 22 studies came from Europe, 11 from North America and 2 from Australia. The remaining study was from Brazil.

3.2. Laboratory techniques

Cortisol concentrations in the hair samples were measured using two types of analyses: immunoassays or mass spectrometry (supplementary Table 2). Of the 36 studies, most used immunoassays including ELISA (19 studies or 52.8%), immunoassay with chemiluminescence detection (CLIA) (4 studies or 11.1%) and radioimmunoassay (RIA) (2 studies or 5.6%). The remainder (9 studies or 25% percent) used liquid chromatography mass spectrometry (LCMS). Most studies (34 studies or 94.4%) specified that hair sampling included the proximal ≤ 3 cm while the remainder (2 studies or 5.6%) included the proximal ≤ 6 cm. Using more proximal segments reduces the potential for a 'wash-out effect' which relates to declining cortisol levels in distal segments due to the effects of ultraviolet radiation and hair care practices (Stalder and Kirschbaum, 2012). The mass of hair used for analysis was highly variable, with a range of 2.5 mg to 50 mg for ELISA and 1.25 mg to 20 mg for LCMS; one outlying study used a mean of 137 mg hair for LCMS from cases (Kamps et al., 2014). The inter-assay coefficient of variability (cv) was not specified in 10 studies (27.8%), was 10% or less in 23 studies (63.9%) and ranged from 10.1-15% in the remaining 3 studies (8.3%). The intra-assay cv was not specified in 12 studies (33.3%), was 10% or less in 23 studies (63.9%) and was 15% in the remaining study. These inter- and intra-assay cvs indicate low variability between measurements using different plates or tests and between duplicate samples on the same plate, respectively.

3.3. Basic determinants of HCC

3.3.1. Age

As summarised in Table B1, 14 studies analysed age as a predictor of HCC. Ten studies (71.4%) found no significant association between age and HCC (Boeckel et al., 2017; Focker et al., 2016; Gerber et al., 2017;