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How stable are diurnal cortisol activity indices in healthy individuals? Evidence from three multi-wave studies

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Summary
Background: Indices of cortisol activity, including the cortisol awakening response (CAR), diurnal slope, and cortisol output across the day (total daily output), are often studied as mechanistic indicators that could link stress with health. Yet there is a paucity of data speaking to their temporal features, particularly whether they behave in a more state- or trait-like manner across time.
Methods: To address this issue, data from 3 studies were used to assess CAR, diurnal slope and total daily output stability over different age groups and time spans: 130 healthy children and adolescents collected salivary cortisol samples 5 times/day (1, 4, 9 and 11 h after wake) over 2 days at 5 visits spaced 6 months apart (Study 1); 147 adolescent girls collected saliva 6 times/day (wake, 1, 4, 9 and 14 h after wake) for 2 days at 3 visits, each a year apart (Study 2); and 47 healthy, primarily middle age adults collected saliva 6 times/day (wake, 1, 4, 9 and 14 h after wake) for 3 days at 4 visits spaced 2—3 months apart (Study 3). Stability was estimated by multilevel model-derived intraclass correlation coefficients (*ICC*s).
Results: Across studies, approximately 50% of the variance in cortisol indices was attributable to day-to-day fluctuations, suggesting state-like properties. Of the indices, total daily output emerged as the most stable over time, followed by diurnal slope and CAR, but stability estimates were generally quite modest regardless of index and sample. Over time spans of >1 year, *ICC*s were $\leq .13$.
Conclusions: Most of the variance in CAR, diurnal slope and total daily output reflects day-to-day fluctuation; there was little evidence for more stable trait-like influences. These findings suggest that future research should focus on short-term fluctuations in stress, cortisol and health, as opposed to lengthy disease processes.

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1. Introduction

Cortisol, a steroid hormone and glucocorticoid, is a key-end product of hypothalamic-pituitary-adrenal (HPA) axis activation. It is essential for life, and is best known in health psychology and related disciplines for its role in regulating the stress response cascade (Sapolsky, 2000). Much of the interest in cortisol revolves around its role as a proposed intermediary linking chronic stress with health problems (Miller et al., 2007; Adam and Kumari, 2009), including diabetes mellitus and the metabolic syndrome (Anagnostis et al., 2009; Champaneri et al., 2012), affective difficulties (Stetler and Miller, 2005; Adam et al., 2010; Stetler and Miller, 2011), clinical and sub-clinical heart disease (Matthews et al., 2006; Dekker et al., 2008; Hajat et al., 2013), cardiovascular disease mortality (Kumari et al., 2011), chronic fatigue syndrome (Strickland et al., 1998), arthritis (Chikanza et al., 1992; Catley et al., 2000), and asthma (Chen et al., 2003; Fei et al., 2004).

Cortisol is secreted in pulses over the course of the day. Typically, there is a steep rise in cortisol output during the first 30—45 min following awakening, followed by a steady decline across the morning, afternoon, and evening hours, with the daily nadir typically occurring around midnight (Kirschbaum and Hellhammer, 1989; Pruessner et al., 1997). To capture this variability in daily life most researchers have participants collect saliva samples 2—6 times during the waking hours. After cortisol has been measured in saliva, various indices can be extracted from different portions of the diurnal curve. Three of the most commonly used are the cortisol awakening response (CAR), diurnal cortisol slope (diurnal slope), and total daily cortisol output. The CAR is defined as the increase in cortisol concentrations during the first 30 min post-awakening, relative to waking cortisol values. It is believed to represent a physiological boost needed to meet the expected demands of the day, and evincing either high or blunted CARs has been linked to maladaptive outcomes (Stetler and Miller, 2005; Adam et al., 2010; Champaneri et al., 2012). The diurnal slope attempts to capture cortisol circadian fluctuations; it is usually operationally defined as the line resulting from regression of cortisol values collected across the day onto hours since awakening, excluding the morning awakening response. A negative diurnal slope is generally considered indicative of healthy HPA axis function (although some exceptions exist, see Smyth et al., 1997; Stone et al., 2001), with flattened or positive diurnal slopes suggestive of potential HPA axis dysfunction. Finally, total daily cortisol output, or total area-under-the-curve (total daily output), is defined as the area between ground and cortisol values taken across the day. Often, but not always, the morning awakening response is excluded from these calculations, to prevent morning awakening responses from having undue influence on calculated values. Total daily output is thought to reflect cumulative tissue exposure to cortisol across the day: Persistently high total daily output may create "wear and tear" on various bodily tissues, resulting in structural or functional changes that could affect disease vulnerability (McEwen, 1998).

Despite extensive research on these cortisol output indices, important questions about their determinants and characteristics remain unanswered. Of particular relevance to stress and health research is whether these indices possess relatively state-like vs. trait-like properties. If diurnal cortisol indices fluctuate widely across days, or are more state-like, they are probably best suited to explaining phenomenon that operate along similarly brief timeframes, like why arthritis symptoms wax and wane in concert with daily mood states (e.g., Schanberg et al., 2000). By contrast, if the cortisol indices are relatively stable over time, or are more trait-like, they could be well poised to explain processes that evolve over more lengthy time periods, for example why some enduring stressors, such as an abrasive marriage, bolster risk for heart disease (e.g., Orth-Gomer, 2000), a condition that develops over the course of multiple decades.

Surprisingly little is known about the stability of various cortisol indices. To the best of our knowledge, only two studies have examined stability over periods longer than 1 month. Both of these focused on adolescents and assessed a single domain of cortisol activity (i.e., cortisol following awakening or the diurnal rhythm of output). In a sample of 410 adolescents, CARs were assessed annually over three consecutive years. Analyses yielded a standard tracking coefficient of $\beta = .17$, which can be interpreted as indicating low stability (Platje et al., 2013). In another study, diurnal slopes were assessed biannually over 6 years in 357 children. Results indicated that 13% of the total variance in diurnal slopes was trait-like or between persons. The remainder was attributable to day-to-day or within-day fluctuations (Shirtcliff et al., 2012).

Although they provide initial evidence regarding cortisol's temporal stability, these studies leave open several important questions. First, to what extent does stability vary across the indices (CAR, diurnal slope, total daily output)? If it does, there could be significant implications for theory and methods in this area, with researchers attempting to match the temporal characteristics of cortisol indices with those of the phenomenon being studied. Second, to what extent does the stability of cortisol indices vary across the lifespan? All of the stability research to date has focused on adolescents, so it remains unclear whether patterns differ at other ages. Again, if they did, it would have significant implications for theory and methods in this literature, potentially leading researchers to focus on specific cortisol indices for specific populations or age groups. The purpose of this article is to begin addressing these questions, using cortisol datasets that were collected in three distinct multi-wave longitudinal studies spanning from childhood into the adult years.

2. Methods

We used data from three independent studies to assess cortisol index stability over various timeframes (see Table 1 for a summary of protocols and samples). Participants across the studies were recruited from the Vancouver, BC, Canada area through a combination of print and online advertisements. In order to be included, all participants had to be currently healthy and free of any history of major physical or psychiatric disorders. All projects were approved by the University of British Columbia Research Ethics Board. Written consent was obtained from all participants, and a parent or guardian also provided consent for participants under 18.