

Health Concerns Associated with an Abnormal Cortisol Awakening Response (CAR)

- **Addictive Behaviors¹**
 - Research suggests an attenuated CAR could be a physiological biomarker associated with vulnerability to addictive behaviors.
- **Attention-Deficit/Hyperactivity Disorder (ADHD)²**
 - Research suggests children with ADHD present with a blunted CAR. The results of one clinical study revealed children with ADHD combined (ADHD-C) had a lower mean CAR than children with ADHD inattentive (ADHD-I). Moreover, the mean CAR was also lower in children with ADHD-I than in the control group.
- **Alcohol Consumption^{1,3}**
 - A clinical study of thirty-four female college students discovered those with riskier drinking habits who consumed more alcohol had an attenuated CAR. Another small clinical trial determined longer abstaining patients with alcohol dependence showed a more robust CAR, suggesting recent alcohol consumption could be associated with a reduced CAR.
- **Anxiety^{4,5}**
 - A small clinical study that included patients with knee osteoarthritis discovered those with a relatively blunted CAR had significantly higher anxiety levels. Another clinical study that included moderately depressed patients with coronary artery disease determined those with anxiety had a more robust CAR. More research is needed.
- **Asthma⁶**
 - The results of one small study suggest individuals with better asthma control have a larger CAR. The study also suggests young adults with asthma have a blunted CAR, which is consistent with other literature showing children and adults with asthma produce less cortisol throughout the day.
- **Autoimmune Disease⁷**
 - Research suggests those with autoimmune disorders have a blunted CAR when compared to healthy controls.
- **Borderline Personality Disorder (BPD)^{8,9}**
 - Research suggests an elevated cortisol awakening response that increases with age is present in female, but not male, patients with BPD compared to healthy controls.
- **Central Serous Chorioretinopathy (CSC)^{10,11}**
 - The results of one clinical study suggest the CAR values of patients with CSC are significantly higher than those of healthy controls. Another clinical study suggests adult male patients with CSC show a remarkably blunted CAR compared to healthy controls. More research is needed.
- **Chronic Fatigue Syndrome (CFS)^{12,13,14,15,16}**
 - Research suggests individuals with CFS exhibit a blunted CAR compared to healthy controls. One clinical trial discovered women with CFS were more likely to have a significantly attenuated morning cortisol profile compared to men with CFS and healthy controls. Results of another clinical study reveal CFS patients with a greater amplitude CAR experience less post-exertional malaise and have higher Perceived Stress Management Skills (PSMS).
- **Chronic Infection^{17,18}**
 - Research suggests that chronic infection with HIV, *Histoplasma capsulatum*, *Mycobacterium tuberculosis*, cytomegalovirus, SARS-CoV-2 (long-COVID), and other pathogens could contribute to adrenal insufficiency, low cortisol levels, and/or pituitary damage. More research is needed to directly assess the CAR in populations with chronic infection.

- **Chronic Stress**^{19,20}
 - Research shows chronic stress could decrease the CAR in healthy young men and middle-aged women.
- **Cognitive Impairment**^{21,22,23}
 - Research suggests that overall, a greater average CAR is associated with better average memory and executive function, though the results of some clinical studies conflict at times. More research is needed.
- **Conduct Disorder**²⁴
 - A small clinical trial discovered girls with conduct disorder secrete less cortisol 30 minutes after awakening, suggesting an attenuated CAR.
- **Coronary Heart Disease (CHD)**²⁵
 - A small clinical study suggests patients with CHD have an attenuated CAR compared to healthy controls.
- **Crohn's Disease**²⁶
 - A small observational study suggests those with Crohn's Disease have an attenuated CAR compared to healthy controls.
- **Cushing's Disease**²⁷
 - Research suggests patients with active Cushing's Disease have a blunted CAR compared to healthy controls and Cushing's Disease patients in remission.
- **Depression**^{28,29,30,31}
 - More research is needed since some data suggest patients with depression have an exaggerated CAR while other data suggest patients with depression have a blunted CAR. Additional studies show no relationship, possibly due to the inconsistent findings. The severity and duration of depression could contribute to the magnitude of the CAR, but more research is needed to clarify the association.
- **Developmental Delay**³²
 - A clinical study that included 364 infants with a median age of 14.2 months suggests a more positive CAR is associated with a lower risk of delay in language comprehension and nonverbal cognitive development and a lower risk of nonoptimal fine motor development.
- **Diabetes**^{33,34}
 - Some research suggests individuals with diabetes have a blunted CAR.
- **Extremely Preterm Birth (EPT)**³⁵
 - Research suggests a blunted cortisol awakening response is associated with memory and inattention problems in EPT children.
- **Fatigue**^{36,37}
 - Significant positive correlations were present between the magnitude of the CAR and fatigue in a clinical study that included 18 healthy girls aged 13–16 years. Results of a clinical study that included 130 adult women recently diagnosed with early-stage breast cancer suggest more ongoing fatigue is associated with a higher awakening cortisol level and a lower CAR. More research is required.
- **Functional Neurological Disorder (FND)**³⁸
 - Research suggests a flattened CAR might represent a trait marker for FND.
- **Hypertension**^{39,40}
 - The results of one clinical study suggest patients with hypertension demonstrate relative attenuation in the CAR and HPA-axis feedback sensitivity following dexamethasone suppression compared to healthy controls. Another study included 85 participants and described similar findings, with results that suggest mean CAR values correlate negatively with diastolic and systolic blood pressure levels.

- **Hypogonadism**⁴¹
 - A small clinical trial discovered a concomitant increase in cortisol and testosterone levels post-awakening in the subgroup of male participants who exhibited a typical CAR. This finding is consistent with previous clinical trials that showed significant increases in estradiol and progesterone levels within the first hour after awakening in women with regular menstrual cycles and a typical CAR. In the subgroup of participants not exhibiting a typical CAR, there was no discernible increase in testosterone levels after the awakening period, suggesting a sub-optimal CAR could be associated with hypogonadism.
- **Hypoactive Sexual Desire Disorder (HSDD)**⁴²
 - A clinical study that included 137 women with HSDD and 138 women without HSDD determined women with HSDD display a lower CAR amplitude.
- **Irritable Bowel Syndrome (IBS)**⁴³
 - Research suggests IBS subjects have a blunted CAR compared to healthy controls.
- **Insulin Resistance (IR)**⁴⁴
 - The results of a clinical study determined adolescents with IR have a blunted CAR, smaller hippocampal volumes, and greater frontal lobe atrophy compared to controls. Furthermore, the data indicated a smaller CAR was associated with a higher body mass index (BMI).
- **Intermittent Explosive Disorder (IED)**⁴⁵
 - A small clinical study that included 78 adult participants determined the CAR is lower in individuals with IED compared with controls.
- **Low Self-Esteem**⁴⁶
 - One clinical study that included 166 participants discovered a relationship between low self-esteem and a blunted CAR when low self-esteem levels at work are stable over time.
- **Multiple Sclerosis**⁴⁷
 - Evidence suggests a greater CAR in relapsing-remitting MS (RRMS) patients with Expanded Disability Status Scale (EDSS) progression. Researchers suggest the CAR could be valuable for predicting neurological disability in patients with RRMS.
- **Obesity**^{48,49,50,51}
 - The association between obesity and the CAR requires clarification via further research. Current research suggests HPA-axis dysfunction is a risk factor for obesity and other metabolic diseases. Individuals with obesity often display blunted diurnal HPA-axis function characterized by lower morning and elevated evening cortisol levels. Research also shows BMI is inversely associated with the CAR, and mindfulness interventions may reduce abdominal adiposity by improving eating habits and the CAR.
- **Obstructive Sleep Apnea (OSA)**⁵²
 - Research suggests adult male obese subjects with severe OSA have a flattened CAR. Evidence also shows that 3 and 6 months of CPAP therapy restores the CAR and significantly reduces the difference in cortisol levels between OSA and control groups.
- **Physical Pain**^{53,54}
 - One clinical study suggests greater pain intensity and unpleasantness ratings are associated with an attenuated CAR. Another study demonstrates that an increased CAR is associated with greater pain intensity and unpleasantness. More research is necessary.
- **Premenstrual Dysphoric Disorder (PMDD)**⁵⁵
 - Research suggests PMDD is associated with a flattened diurnal cortisol slope and delayed CAR peak.

- **Premenstrual Syndrome (PMS)**⁵⁶
 - Research suggests women with PMS display a significantly attenuated CAR compared with healthy controls, regardless of the menstrual cycle phase. Evidence also shows a significant negative correlation between PMS severity and CAR magnitude in the mid-follicular phase. Thus, an attenuated CAR could be a risk factor for PMS development.
- **Psychosis**⁵⁷
 - Evidence suggests that the CAR is attenuated in patients with psychosis when compared to healthy controls.
- **Post-traumatic Stress Disorder (PTSD)**^{58,59}
 - Research shows the CAR is significantly lower in PTSD patients compared to healthy controls. Research also suggests veterans with PTSD and a service dog have a statistically significant higher CAR, which is less blunted in comparison to veterans receiving usual PTSD care. Therefore, in veterans with a blunted morning cortisol response, service dog placement could support a healthier CAR despite PTSD.
- **Schizophrenia**⁵⁷
 - Subgroup analysis of patients with psychosis in a systematic review and meta-analysis of 11 studies with 879 participants revealed a flattened CAR in patients with schizophrenia.
- **Sleep Disorders**^{60,61}
 - Research suggests a steeper morning rise in cortisol is observed in patients reporting chronic insomnia symptoms and short sleep duration compared to those who do not report sleep concerns. Also, more sleep is associated with a smaller CAR the next day.
- **Slow Walking Speed**⁶²
 - Research shows a CAR of reduced magnitude is related to slower walking speed.
- **Slow Wound Healing**^{63,64}
 - Evidence from a study that included 24 male participants suggests a significantly higher CAR the day after a biopsy in the slow-healing group compared to the fast-healing group. A different prospective observational study that included 93 patients with a diabetic foot ulcer discovered the ulcers that healed by 24 weeks were associated with a greater CAR. More research is needed to clarify the relationship between wound healing and the CAR.
- **Systemic Inflammation**^{65,66,67,68}
 - Research suggests cortisol has potent anti-inflammatory effects that prevent tissue and nerve damage associated with systemic inflammation. A study that included 689 students in 4th grade and 647 students in 5th grade discovered a correlation between cortisol levels and inflammatory cytokines. High morning cortisol was associated with high morning IL-1 β and low evening IL-1 β . Researchers hypothesize strong diurnal cycling of IL-1 β may serve as a homeostatic mechanism to optimize immune function. They also suspect that low morning cortisol, consistent with circadian misalignment, could lead to less stringent control of inflammatory networks, resulting in unchecked systemic inflammation. A clinical trial that included 38 subjects who participated in a 3-month yoga and meditation retreat discovered an increased CAR is associated with the enhancement of pro- and anti-inflammatory cytokine changes to support healthy immunological function. Another clinical study that included 266 adult participants showed an association between C-reactive protein and salivary cortisol levels during the CAR.
- **Traumatic Brain Injury (TBI)**⁶⁹
 - Research suggests a blunted CAR is associated with TBI symptom severity and neurobehavioral impairment.

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