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PLASMA CORTISOL AS A CLINICALLY TRANSFORMATIVE PRECLINICAL BIOMARKER FOR COGNITIVE DECLINE

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Emerging research evidences highlight plasma cortisol - a central biomarker of hypothalamic-pituitary-adrenal (HPA) axis dysregulation, as a critical predictor of preclinical cognitive impairment. Chronic hypercortisolemia is involved in neurotoxic mechanisms, such as neuroinflammation, hippocampal atrophy, synaptic dysfunction and amyloid-beta dysregulation, which are characteristic of Alzheimer's disease (AD) and vascular dementia. This review proposes that plasma cortisol, a readily accessible and minimally invasive biomarker, holds particular potential as a preclinical marker of cognitive decline as a clinically relevant strategy for the determination of at-risk individuals many years in advance of the development and manifestation of cognitive symptoms

Integrating evidence to facilitate the introduction of plasma cortisol into clinical practice as a marker of preclinical cognitive impairment. Specific aims are: (1) integrating neurobiological evidence of how cortisol dysregulation relates to neurodegeneration, (2) determining cortisol's predictive validity in heterogeneous populations, (3) resolving confounders (e.g., circadian rhythms, depression), and (4) proposing standard protocols to enhance its clinical utility.

Evidence for analysis of tested correlation were carefully gathered by running a search on academic research databases. Then the gathered sources were studied to further narrow down the materials with data more specific to the aim. The review critically examines 20 longitudinal and cross-sectional studies from the past 10 years (2015-2025), highlighting robust correlations between elevated plasma cortisol and accelerated cognitive decline.

Meta-analysis of 12 prospective studies (n = 15,892) yields a pooled hazard ratio of 1.67 (95% CI: 1.41–1.98) for cognitive decline per standard deviation increase in cortisol. Subgroup analyses highlight stronger associations in women (HR = 1.82 vs. 1.51 in men) and adults aged 60–75. Critically, cortisol outperforms traditional risk factors (e.g., hypertension) in predicting hippocampal volume loss ($\beta = -0.41$, $p < 0.001$). Interventions such as mindfulness-based stress reduction (MBSR) lower cortisol by 18–22% and are linked with stabilized cognitive scores, emphasizing its modifiable impact.

Analysis of the chosen studies demonstrates recurrent results of associations of elevated plasma cortisol and accelerated cognitive decline. Longitudinal cohorts show that individuals with cortisol in the highest quartile have 2.3-fold risk of developing AD from mild cognitive impairment during 3–5 years ($p < 0.001$). The predictive value of cortisol is increased by APOE-ε4 carrier status and metabolic syndrome status, suggesting synergistic neuroendocrine-metabolic dysregulation. However, methodological variability, single-timepoint data and inconsistent adjustment for diurnal cycle affect reproducibility. Promising advances like hair cortisol analysis (reflecting chronic exposure) and machine learning models integrating cortisol trajectories can be used in enhancing predictive precision.

Plasma cortisol is a clinically significant, cost-effective biomarker with transformative potential for dementia prevention. There is an urgent need to standardize cortisol measurement (e.g., time-staggered sampling, standardized assays) and to validate its application in conjunction with neuroimaging and genetic profiling. Primary care-based cortisol screening may deliver the infrastructure for introducing targeted interventions (e.g., HPA axis modulation, lifestyle therapies) for preventing neurodegeneration. Clinicians and policymakers must prioritize this tool if we are to effectively counter the epidemic of dementia.