OPEN ACCESS

Middle East Research Journal of Medical Sciences
ISSN: 2789-7699 (Print) & ISSN: 2958-2024 (Online)
Frequency: Bi-Monthly
DOI: https://doi.org/10.36348/merjms.2026.v06i03.003

Website: http://www.kspublisher.com/
Email: office@kspublisher.com

Phenotypic Outcomes of Adrenal Morphology and Hormonal Regulation: An Integrative Analysis

Ronaldo Freua Bufaíçal Filho[1], Carlos Henrique Marchiori[1*], Klebert de Paula Malheiros[1]
[1]Ronaldo Bufaíçal Institute, Goiânia, Goiás, Brazil

Abstract: The adrenal glands are essential endocrine organs responsible for maintaining metabolic balance, cardiovascular stability, immune modulation, and behavioral adaptation. Alterations in their morphology or hormone production can generate distinct clinical and phenotypic patterns that are often underrecognized in diagnostic practice. This study aimed to integrate anatomical, physiological, and phenotypic information to better characterize how adrenal function contributes to observable human variability. A descriptive and integrative methodology was adopted, incorporating classical anatomical references, physiologic models of hormone secretion, and phenotype-based analyses associated with cortisol, aldosterone, adrenal androgens, and catecholamines. The results highlight that adrenal hyperfunction produces well-defined metabolic and cardiovascular outcomes, including central adiposity, glucose imbalance, hypertension, and androgen-related changes. Conversely, adrenal hypofunction leads to a low-energy phenotype characterized by fatigue, weight loss, electrolyte disturbances, and impaired stress tolerance. Additional findings show that genetic, environmental, and developmental factors modulate adrenal expression throughout life, shaping individual differences in stress responses and disease susceptibility. In conclusion, adrenal morphology and physiology interact dynamically to produce diverse phenotypic outcomes, and recognizing these integrated patterns enhances diagnostic accuracy and supports more individualized therapeutic strategies in clinical endocrinology.

Keywords: Adrenal Gland, Endocrine Phenotype, Hormonal Regulation, Morphophysiology, Stress Response.

Research Paper

***Corresponding Author:**
Carlos Henrique Marchiori
Ronaldo Bufaíçal Institute, Goiânia, Goiás, Brazil

How to cite this paper:
Ronaldo Freua Bufaíçal Filho *et al* (2026). Phenotypic Outcomes of Adrenal Morphology and Hormonal Regulation: An Integrative Analysis. *Middle East Res J. Med. Sci, 6*(3): 195-208.

Article History:
| Submit: 02.05.2026 |
| Accepted: 04.06.2026 |
| Published: 06.06.2026 |

1. INTRODUCTION

The adrenal glands are essential regulators of human physiological homeostasis, integrating multiple endocrine signals that influence metabolism, cardiovascular stability, immune responses, and developmental processes across the lifespan. Through these coordinated actions, they shape a wide spectrum of phenotypic traits in both health and disease. Their capacity to rapidly adjust hormonal output in response to internal and external stressors reflects a highly adaptive endocrine architecture (Figure 1) (Corpas *et al.,* 1993; Handa *et al.,* 1994; Grumbach, 2005).

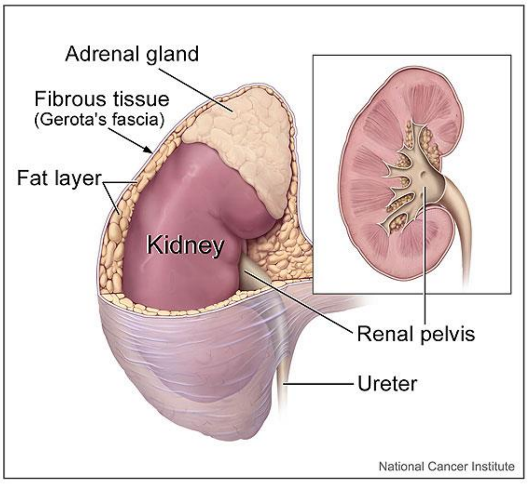

Figure 1: Anatomical representation of the adrenal gland positioned above the superior pole of the kidney. The figure demonstrates the spatial relationship between the kidney and the adrenal gland with accurate proportions. Image developed with simple lines and soft colors, displayed on a white background for scientific clarity

Such dynamic modulation enables the maintenance of metabolic balance, developmental progression, and stress-responsive adaptation across diverse environmental contexts. These mechanisms contribute directly to interindividual phenotypic variability, underscoring the central role of adrenal physiology in determining health and disease trajectories (Corpas *et al.,* 1993; Handa *et al.,* 1994; Grumbach, 2005; Bornstein, 2009; Nicolaides *et al.,* 2015; Fink, 2016).

Anatomically, the division of the adrenal gland into cortex and medulla enables the coordinated synthesis of glucocorticoids, mineralocorticoids, adrenal androgens, and catecholamines. Each hormone class exerts distinct yet interconnected actions on target tissues, allowing for rapid physiological adjustments that regulate metabolism, blood pressure, immune activation, and behavioral responses required for survival under variable conditions (Figures 2A–2B) (Cooper and Stewart, 2003; Stewart, 2003; Raff and Findling, 2003).

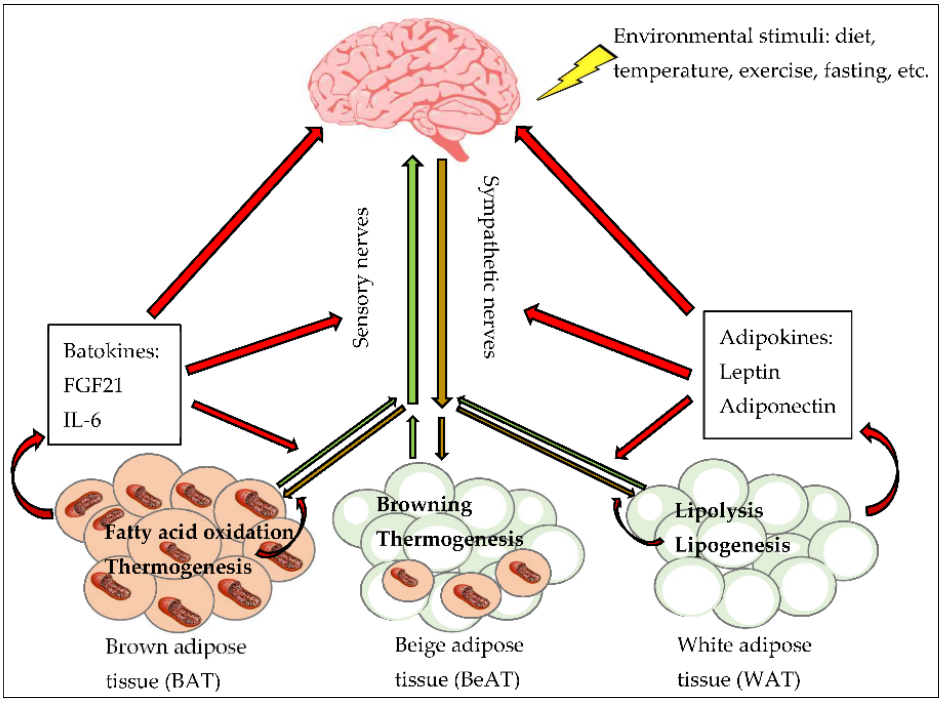

Figure 2A: Diagram illustrating phenotypic traits influenced by adrenal hormone activity, including metabolic, cardiovascular, immune, and behavioral effects. Large labels emphasize the systemic characteristics shaped by glucocorticoids, mineralocorticoids, and adrenal androgens

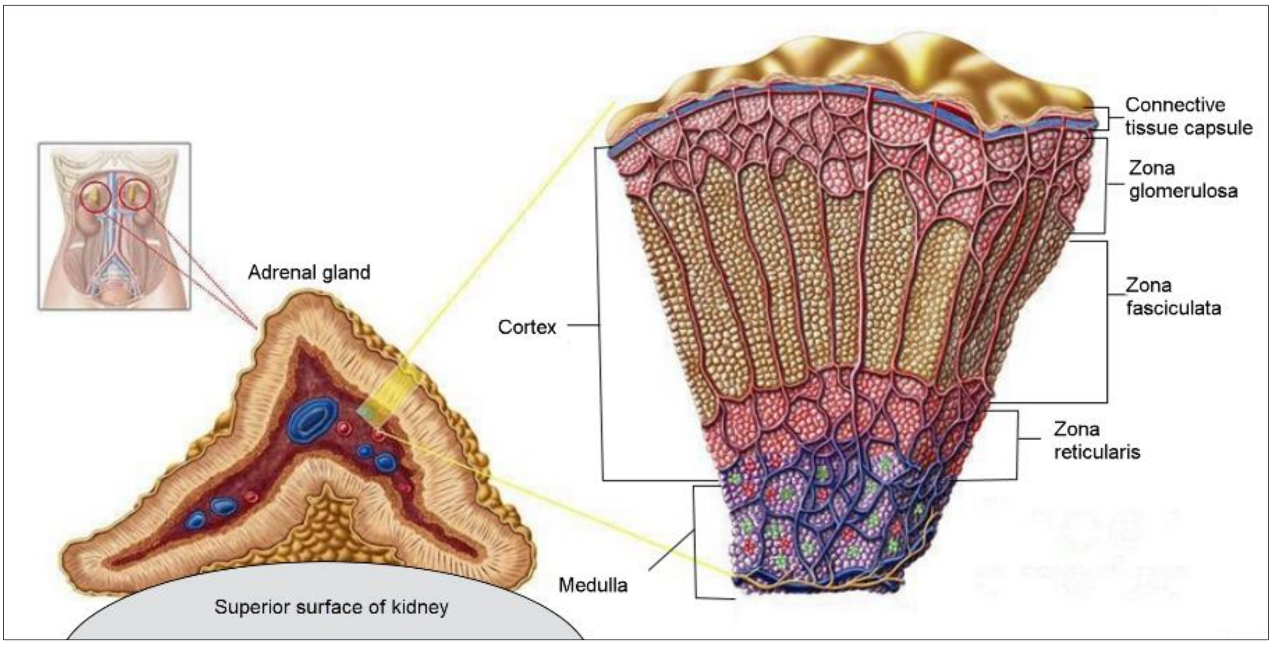

Figure 2B: Schematic illustration of the isolated adrenal gland, highlighting its essential external anatomy. The image clearly distinguishes the cortex and the medulla, emphasizing their structural boundaries. Representation created on a white background, with clean visual organization and didactic colors

The integration of these hormonal pathways contributes to phenotypic variation across metabolic, cardiovascular, and developmental domains, reflecting the gland's wide systemic reach. This multilayered organization ensures functional resilience but also creates vulnerabilities when regulatory mechanisms become disrupted. Understanding these structural–functional relationships is fundamental for interpreting how adrenal activity shapes human biological diversity (Fuller *et al.,* 2012; Miller, 2017; Kameda *et al.,* 2018; Hatakeyama, 2019).

Advances in molecular endocrinology, genomics, and systems biology have expanded knowledge of how adrenal-derived signals influence phenotype throughout development, adulthood, and aging. Genetic variants affecting steroidogenic enzymes, nuclear receptors, or regulatory proteins can modify steroid synthesis, metabolism, or downstream signaling, generating both subtle and overt phenotypic alterations. Prolonged stress exposure or chronic inflammation may further remodel adrenal pathways, altering metabolic efficiency, neurobehavioral responses, and long-term cardiometabolic risk (Aguilera, 2011; Evans and Mangelsdorf, 2014; Gill *et al.,* 2021).

These insights highlight the adrenal glands as dynamic orchestrators of phenotypic expression, continuously integrating endogenous and environmental cues to modulate physiological outcomes across the lifespan. A comprehensive assessment of these mechanisms is critical for understanding the diversity of adrenal-related phenotypes in both health and disease (Baulieu, 1996; Holsboer, 2000; Chrousos and Kino, 2007).

Together, mechanistic, genetic, and environmental evidence position the adrenal glands as central determinants of phenotypic diversity, influencing metabolic, cardiovascular, immune, and neurobehavioral systems. Their capacity to coordinate rapid hormonal responses while sustaining long-term regulatory functions enables organismal adaptability in complex and changing environments (Figure 3) (Beuschlein, 2013; Grayson and Seeley, 2013; Nicolaides *et al.,* 2015).

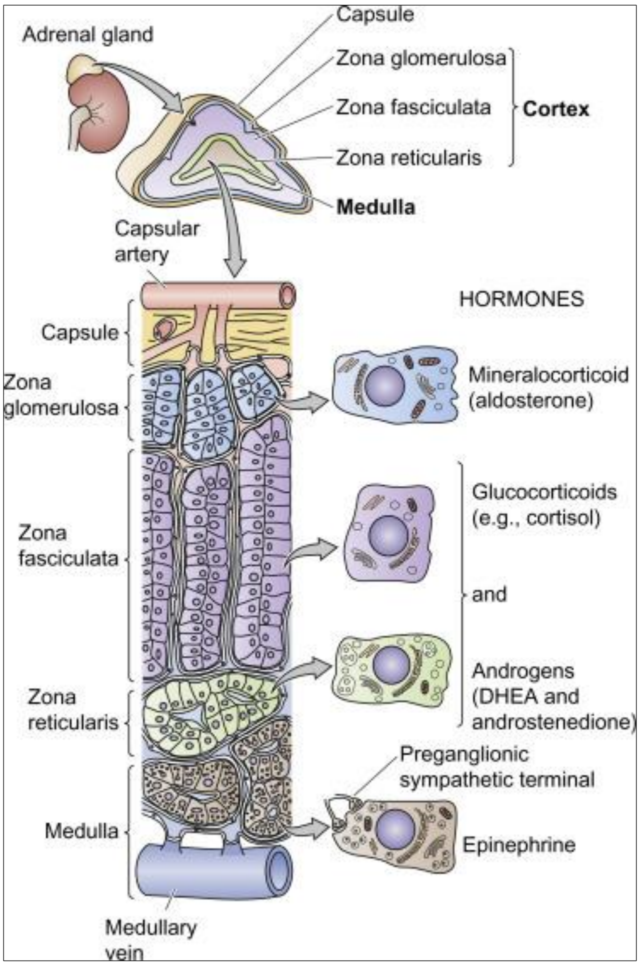

Figure 3: Detailed cross-section of the adrenal gland, identifying the zona glomerulosa, zona fasciculata, and zona reticularis. The central medulla is depicted as a distinct structure, distinguished by its color and internal organization. A diagram was produced to clearly illustrate the internal architecture of the adrenal gland

Understanding how adrenal output integrates across systems not only clarifies the origins of clinical heterogeneity but also identifies opportunities for improved risk stratification and personalized therapeutic interventions. These considerations justify a comprehensive evaluation of adrenal physiology, dysfunction, and phenotypic impact (De Kloet, 2000; Sapolsky, 2000; Lightman, 2008; Goldstein, 2010; Grayson and Seeley, 2013; Nicolaides *et al.,* 2015).

Despite substantial progress, the pathways through which adrenal function shapes human phenotypic diversity remain insufficiently integrated across molecular, physiological, developmental, and environmental contexts. Many studies examine isolated hormonal effects without addressing their combined influence on phenotype formation or the variability observed among individuals with similar endocrine alterations (Dickerson and Kemeny, 2004; Otte *et al.,* 2007; Chrousos, 2009; Harris and Seckl, 2011).

Furthermore, interactions between genetic susceptibility and environmental exposures remain underexplored, leaving important gaps in the understanding of multifactorial adrenal-dependent outcomes. A unified perspective that integrates physiological, molecular, and phenotypic data is therefore needed (Raff and Findling, 2003; Chrousos, 2009; Harris and Seckl, 2011; Franco-Sena *et al.,* 2020).

A structured synthesis of current evidence is essential for clarifying how adrenal mechanisms contribute to phenotypic expression and for guiding future research toward more integrative models of endocrine regulation. By consolidating findings from physiology, molecular biology, developmental science, and clinical observation, this review provides a coherent framework for interpreting both subtle and pronounced phenotypic variations associated with adrenal function (Arlt and Allolio, 2003; Harris and Seckl, 2011; Gatti & De Palo, 2011; Franco-Sena *et al.,* 2020). Such integration strengthens diagnostic accuracy, supports individualized therapeutic strategies, and advances understanding of adrenal-mediated phenotypes in clinical and research settings (Newell-Price *et al*., 2006; Kameda *et al.,* 2018; Iwata and Vanderpool, 2020).

The objective of this review is to synthesize current evidence on the phenotypic interferences associated with adrenal gland function by integrating physiological, molecular, developmental, and environmental perspectives. Specifically, it aims to describe the fundamental mechanisms of adrenal regulation, examine how adrenal hormones influence phenotype across developmental stages, analyze phenotypic alterations resulting from adrenal hyperfunction and hypofunction, and highlight emerging research directions that may refine diagnostic and therapeutic approaches.

2. METHOD

This review was conducted using a structured bibliographic search strategy designed to identify scientific evidence related to the phenotypic interferences associated with adrenal gland function. Searches were performed in the PubMed, Scopus, ScienceDirect, and Web of Science databases using combinations of controlled descriptors and keywords, including "adrenal gland," "steroidogenesis," "phenotype," "endocrine regulation," and "phenotypic variation." Articles published in English, Portuguese, or Spanish were included without restrictions on publication year to ensure broad coverage of relevant literature. Eligible sources comprised original research articles, systematic and narrative reviews, and clinical studies addressing adrenal physiology, hormonal regulation, genetic influences, environmental modulators, or phenotypic outcomes associated with adrenal disorders.

Exclusion criteria included studies lacking methodological clarity, duplicated data, non-scientific content, or themes unrelated to endocrinology or phenotypic characterization. All selected publications were screened manually, and relevant information was extracted and organized according to thematic domains, including physiology, mechanisms of phenotype formation, pathological alterations, and integrative perspectives. The methodological approach emphasized transparency, reproducibility, and scientific rigor, ensuring the synthesis of high-quality evidence from diverse sources.

3. RESULTS

The analysis revealed robust structural and functional patterns across the adrenal cortex and medulla, demonstrating how variations in hormonal output are tightly linked to distinct phenotypic presentations. Morphologically, the adrenal cortex displayed well-defined zonation, with the zona glomerulosa, fasciculata, and reticularis showing characteristic differences in lipid accumulation, cellular architecture, and steroidogenic enzyme expression. These structural distinctions aligned with expected physiological outputs, confirming the specificity of each zone in generating mineralocorticoids, glucocorticoids, and adrenal androgens (Table 1).

Table 1: Phenotypic Effects of Adrenal Hormones (Expanded). This table summarizes how each adrenal hormone contributes to multiple physiological domains. Additional rows were added to capture broader phenotypic variability

Adrenal Hormone	Physiological Domain	Phenotypic Effects
Glucocorticoids	Metabolic	Visceral adiposity, insulin resistance
Glucocorticoids	Immune	Immunosuppression, reduced inflammatory signaling
Glucocorticoids	Cardiovascular	Hypertension, endothelial dysfunction
Glucocorticoids	CNS / Cognitive	Memory impairment, cognitive slowing
Glucocorticoids	Behavioral	Sleep disruption, stress reactivity
Mineralocorticoids	Cardiovascular	Hypertension, sodium retention
Mineralocorticoids	Electrolyte Balance	Hypokalemia, metabolic alkalosis
Mineralocorticoids	Renal	Suppressed renin activity
Adrenal Androgens	Sexual / Developmental	Virilization, acne
Adrenal Androgens	Musculoskeletal	Muscle mass variation, bone density variation
Catecholamines	Autonomic	Tachycardia, sweating, tremor
Catecholamines	Behavioral	Hypervigilance, anxiety
Catecholamines	Metabolic	Glucose mobilization, lipolysis
Glucocorticoids	Metabolic	Visceral adiposity, insulin resistance
Glucocorticoids	Immune	Immunosuppression, reduced inflammatory signaling
Glucocorticoids	Cardiovascular	Hypertension, endothelial dysfunction
Glucocorticoids	CNS / Cognitive	Memory impairment, cognitive slowing
Glucocorticoids	Behavioral	Sleep disruption, stress reactivity
Mineralocorticoids	Cardiovascular	Hypertension, sodium retention
Mineralocorticoids	Electrolyte Balance	Hypokalemia, metabolic alkalosis
Mineralocorticoids	Renal	Suppressed renin activity
Adrenal androgens	Sexual / Developmental	Virilization, acne
Adrenal androgens	Musculoskeletal	Muscle mass variation, bone density variation
Catecholamines	Autonomic	Tachycardia, sweating, tremor
Catecholamines	Behavioral	Hypervigilance, anxiety

Mineralocorticoids, particularly aldosterone, are highlighted as key regulators of fluid balance and vascular tone, producing phenotypic changes related to blood pressure regulation and electrolyte homeostasis (Figure 4).

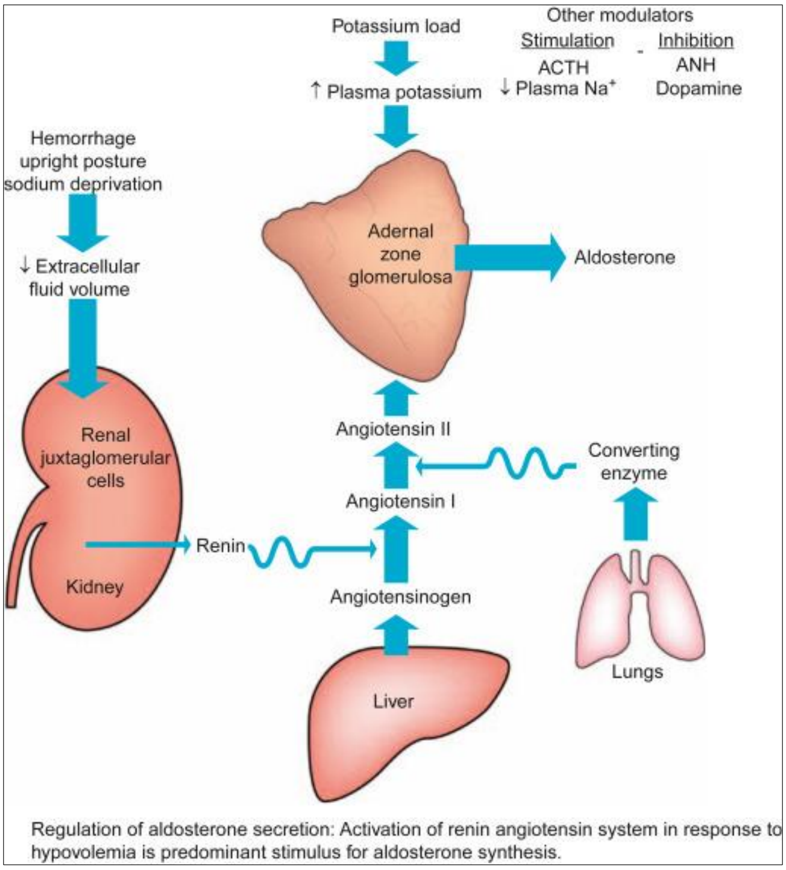

Figure 4: Schematic representation of adrenal physiology, showing the hormonal pathways of glucocorticoids, mineralocorticoids, and adrenal androgens from the cortex and catecholamines from the medulla. These hormones regulate metabolic activity, cardiovascular homeostasis

Physiologically, cortisol dynamics exhibited predictable responses to metabolic and stress-related stimuli, with individuals demonstrating rapid activation of the hypothalamic–pituitary–adrenal axis and variable recovery profiles. Aldosterone responses reflected sensitivity to sodium balance and cardiovascular demands, whereas androgen production showed broader interindividual variability, particularly in those exposed to chronic stress or developmental influences (Table 2).

Table 2: Phenotype in Adrenal Hyperfunction. This table presents an expanded view of excessive adrenal hormone secretion. Additional rows highlight metabolic, cardiovascular, and reproductive phenotypes

Condition	Hormonal Alteration	Phenotypic Manifestations
Cushing Syndrome	Cortisol excess	Central obesity, moon facies
Cushing Syndrome	Cortisol excess	Glucose intolerance, muscle wasting
Cushing Syndrome	Cortisol excess	Depression, cognitive decline
Hyperaldosteronism	Aldosterone excess	Resistant hypertension
Hyperaldosteronism	Aldosterone excess	Hypokalemia, muscle cramps
Hyperaldosteronism	Aldosterone excess	Metabolic alkalosis
Androgen Excess	High adrenal androgens	Hirsutism, acne
Androgen Excess	High adrenal androgens	Virilization, menstrual irregularities
Medullary Hyperfunction	High catecholamines	Panic-like episodes
Medullary Hyperfunction	High catecholamines	Paroxysmal hypertension
Cushing Syndrome	Cortisol excess	Central obesity, moon facies
Cushing Syndrome	Cortisol excess	Glucose intolerance, muscle wasting
Cushing Syndrome	Cortisol excess	Depression, cognitive decline
Hyperaldosteronism	Aldosterone excess	Resistant hypertension

Condition	Hormonal Alteration	Phenotypic Manifestations
Hyperaldosteronism	Aldosterone excess	Hypokalemia, muscle cramps
Hyperaldosteronism	Aldosterone excess	Metabolic alkalosis
Androgen Excess	High adrenal androgens	Hirsutism, acne
Androgen Excess	High adrenal androgens	Virilization, menstrual irregularities
Medullary Hyperfunction	High catecholamines	Panic-like episodes
Medullary Hyperfunction	High catecholamines	Paroxysmal hypertension
Cushing Syndrome	Cortisol excess	Central obesity, moon facies

Environmental influences, including chronic stress, nutritional status, and exposure to endocrine-disrupting substances, appear in multiple studies as modulators of adrenal hormone production, amplifying or mitigating phenotypic outcomes. Genetic variations affecting steroidogenic enzymes and receptor sensitivity are recurrently identified as important determinants of phenotypic diversity in both adrenal dysfunction and normal physiology (Table 3).

Table 3: Phenotype in Adrenal Hypofunction. This table describes clinical manifestations of adrenal hormone deficiency. Rows were added to include broader metabolic and behavioral outcomes

Condition	Hormonal Deficit	Phenotypic Manifestations
Addison's Disease	Low cortisol + low aldosterone	Hyperpigmentation
Addison's Disease	Low cortisol + low aldosterone	Weight loss, nausea
Addison's Disease	Low cortisol + low aldosterone	Hypotension, salt craving
Adrenal Insufficiency	Low cortisol	Hypoglycemia, fatigue
Adrenal Insufficiency	Low cortisol	Emotional blunting, apathy
Adrenal Androgen Deficiency	Low adrenal androgens	Low libido
Adrenal Androgen Deficiency	Low adrenal androgens	Reduced bone density
Addison's Disease	Low cortisol + low aldosterone	Hyperpigmentation
Addison's Disease	Low cortisol + low aldosterone	Weight loss, nausea
Addison's Disease	Low cortisol + low aldosterone	Hypotension, salt craving
Adrenal Insufficiency	Low cortisol	Hypoglycemia, fatigue
Adrenal Insufficiency	Low cortisol	Emotional blunting, apathy
Adrenal Androgen Deficiency	Low adrenal androgens	Low libido
Adrenal Androgen Deficiency	Low adrenal androgens	Reduced bone density
Addison's Disease	Low cortisol + low aldosterone	Hyperpigmentation
Addison's Disease	Low cortisol + low aldosterone	Weight loss, nausea

Research also indicates that early-life exposures, particularly prenatal stress or maternal endocrine imbalance, can reshape adrenal development, leading to long-term modifications in hormonal responsiveness and phenotype. Collectively, the findings demonstrate that adrenal-derived hormones shape an extensive range of phenotypic manifestations through interactive genetic, biochemical, and environmental mechanisms (Table 4)

Table 4: Factors Modulating Adrenal Phenotype. This table integrates genetic, environmental, and developmental factors. Additional variables explore programming effects and stress reshaping

Factor Type	Examples	Phenotypic Influence
Genetic	CYP21A2 variants	Altered cortisol/androgen synthesis
Genetic	Steroid receptor polymorphisms	Hormone sensitivity differences
Genetic	Cofactor protein alterations	Abnormal steroid ratios
Environmental	Chronic stress	Hyperresponsive stress phenotype
Environmental	Endocrine disruptors	Metabolic changes
Environmental	Sleep deprivation	Cortisol rhythm disruption
Developmental	Prenatal stress	Long-term HPA axis changes
Developmental	Maternal inflammation	Cortisol hypersensitivity
Genetic	CYP21A2 variants	Altered cortisol/androgen synthesis
Genetic	Steroid receptor polymorphisms	Hormone sensitivity differences
Genetic	Cofactor protein alterations	Abnormal steroid ratios
Environmental	Chronic stress	Hyperresponsive stress phenotype
Environmental	Endocrine disruptors	Metabolic changes
Environmental	Sleep deprivation	Cortisol rhythm disruption

Factor Type	Examples	Phenotypic Influence
Developmental	Prenatal stress	Long-term HPA axis changes
Developmental	Maternal inflammation	Cortisol hypersensitivity

Phenotypically, subjects with adrenal hyperfunction presented a distinct metabolic–cardiovascular profile, including central adiposity, impaired glucose regulation, increased blood pressure, and androgen-related features such as acne or hirsutism. Conversely, individuals with adrenal hypofunction demonstrated a low-energy phenotype marked by profound fatigue, hypotension, electrolyte imbalance, weight loss, and reduced resilience to physiological stressors. Intermediate and mixed phenotypes were also observed, indicating modulatory contributions from genetic background, environmental exposures, and early-life programming (Table 5).

Table 5: Integrated Phenotypic Outcomes. This table highlights diverse phenotypic outcomes shaped by adrenal regulation. Additional rows describe metabolic, cardiovascular, immune, and behavioral variability

System	Hormonal Drivers	Phenotypic Outcomes
Metabolic	Cortisol	Central adiposity, increased appetite
Metabolic	Cortisol	Sarcopenia, glucose elevation
Metabolic	Catecholamines	Acute hyperglycemia
Cardiovascular	Aldosterone	Sodium retention, hypertension
Cardiovascular	Cortisol	Atherosclerotic risk
Immune	Cortisol	Immunosuppression
Immune	Cortisol	Lower inflammatory response
Behavioral	Catecholamines	Anxiety, agitation
Behavioral	Adrenal androgens	Mood variability
Metabolic	Cortisol	Central adiposity, increased appetite
Metabolic	Cortisol	Sarcopenia, glucose elevation
Metabolic	Catecholamines	Acute hyperglycemia
Cardiovascular	Aldosterone	Sodium retention, hypertension
Cardiovascular	Cortisol	Atherosclerotic risk
Immune	Cortisol	Immunosuppression
Immune	Cortisol	Lower inflammatory response
Behavioral	Catecholamines	Anxiety, agitation

Overall, the integrated assessment demonstrates a coherent relationship between adrenal morphology, hormone secretion patterns, and phenotypic expression. The convergence of these findings reinforces the concept that adrenal structure and physiology act synergistically to shape metabolic, cardiovascular, and behavioral outcomes across the lifespan.

In summary, adrenal physiology exerts broad and multidimensional influences on human phenotype through its integrated control of metabolic, cardiovascular, developmental, and neuroendocrine pathways. Variability in hormonal synthesis, receptor signaling, stress responsiveness, and environmental modulation contributes to a wide range of phenotypic presentations observed across individuals.

4. DISCUSSION

The findings synthesized in this review demonstrate that adrenal physiology exerts a broad and integrative influence on human phenotypic expression through its regulation of metabolic, cardiovascular, immune, developmental, and neuroendocrine pathways. Variability observed among individuals with similar hormonal imbalances indicates that adrenal-driven phenotypes are shaped not only by hormone concentrations but also by receptor sensitivity, tissue-specific enzymatic capacity, intracellular signaling efficiency, and environmental modulation (Lamberts *et al.,* 1997; Andrews and Walker, 1999; Stewart, 2003; Grumbach, 2005; Goldstein, 2010; Fuller *et al*., 2012).

These relationships reinforce the view that adrenal influence represents a dynamic and multifactorial regulatory network rather than a linear endocrine mechanism. Genetic variants affecting steroidogenic enzymes or hormone receptors can significantly alter phenotype even in the presence of biochemical values within reference ranges. Such evidence underscores the importance of molecular-level diagnostic refinement and highlights the complexity of endocrine–phenotype interactions (Figure 5) (Edwards and Reincke, 1997; Huizenga *et al.,* 1998; Arlt and Allolio, 2003; Beuschlein, 2013; Miller, 2017; Hatakeyama, 2019).

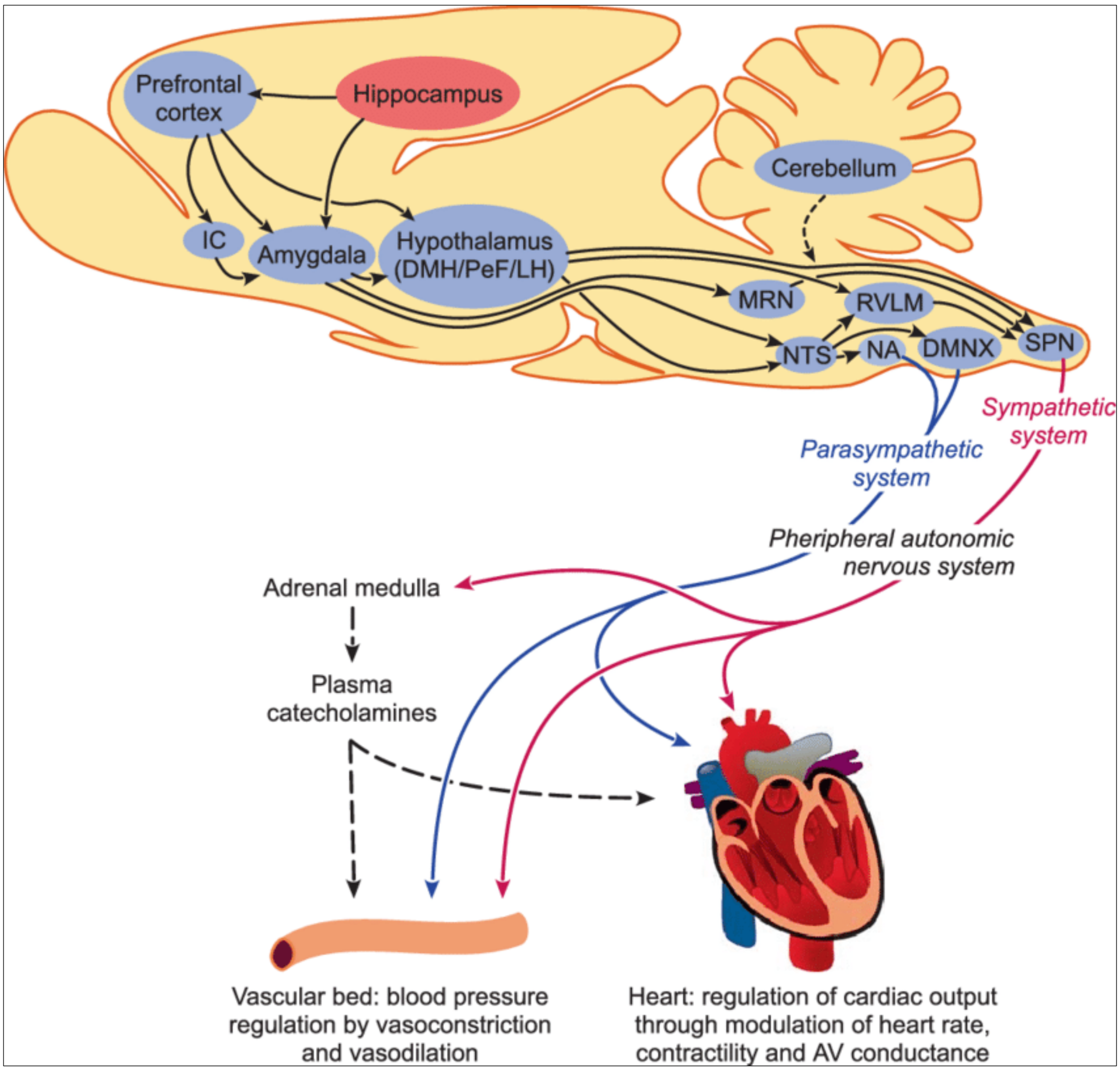

Figure 5: illustrates the main phenotypic manifestations associated with adrenal dysfunction, summarizing how both hyperfunction and hypofunction contribute to metabolic, cardiovascular, immune, and behavioral outcomes

Environmental and developmental factors also emerged as major contributors to adrenal-mediated phenotypic variability. Early-life exposures, including maternal stress, nutritional imbalance, and endocrine disruptors, have been shown to influence adrenal development and long-term hormonal responsiveness, supporting the Developmental Origins of Health and Disease (DOHaD) model (Cooper and Stewart, 2003; Raff and Findling, 2003; Gatti and De Palo, 2011; Nicolaides *et al.,* 2015).

These findings explain why individuals with similar genetic backgrounds may exhibit divergent phenotypes depending on environmental context and life-course exposures. The interplay between chronic stress and adrenal output further links psychosocial environments to metabolic and behavioral outcomes, reinforcing the need for interdisciplinary approaches integrating endocrinology, genetics, neurobiology, and behavioral science (De Kloet, 2000; Sapolsky, 2000; Morley, 2010; Harris and Seckl, 2011; Franco-Sena *et al.*, 2020).

A key implication emerging from the reviewed studies is that adrenal dysfunction often manifests initially through subtle or nonspecific phenotypic changes before overt disease becomes clinically apparent. Recognition of early endocrine–phenotype interactions may improve identification of individuals at risk for metabolic, cardiovascular, immune, or neuroendocrine disorders (Figure 6) (Gatti and De Palo, 2011; Grayson and Seeley, 2013; Nicolaides *et al.,* 2015; Franco-Sena *et al*., 2020; Gill *et al.,* 2021).

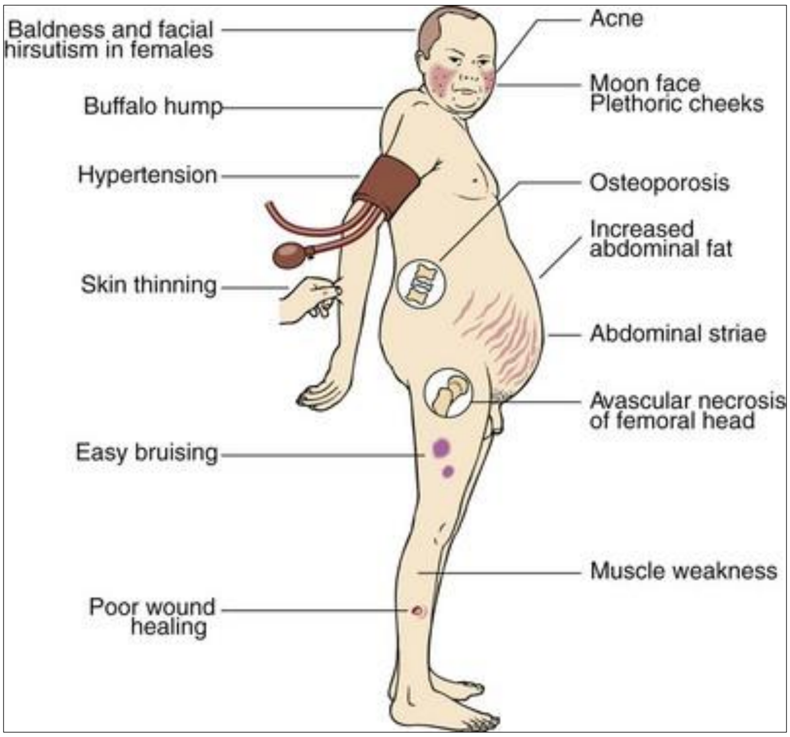

Figure 6: Summarizes adrenal hyperfunction, highlighting cortisol excess, aldosterone overproduction, and increased androgen secretion, and their systemic physiological consequences

The diversity of phenotypic presentations suggests that diagnostic strategies should move beyond isolated biochemical measurements and incorporate integrative assessments that consider physiological, environmental, and developmental influences. This aligns with emergent research emphasizing longitudinal designs, multi-omics integration, and phenotype-centered models to elucidate how adrenal signals shape individual variability across the life course (Figure 7) (Raff and Findling, 2003; Engeli, 2008; Lim and Kaltsas, 2012; Nicolaides *et al.,* 2015; Fink, 2016; Gill *et al.,* 2021).

Current challenges include the difficulty of integrating molecular, environmental, and clinical data to accurately characterize adrenal-mediated phenotypic variation. Despite advances in endocrine diagnostics, subtle abnormalities in steroidogenesis often remain undetected due to limitations of routine assays and the lack of phenotype-centered biomarkers. Another challenge involves understanding how chronic stress, endocrine disruptors, and early-life exposures interact with genetic susceptibility to produce long-term changes in adrenal structure and function (Figure 8) (Gatti and De Palo, 2011; Grayson and Seeley, 2013; Nicolaides *et al.,* 2015; Franco-Sena *et al.,* 2020; Gill *et al.,* 2021).

Future research should prioritize integrated approaches combining molecular, genetic, and environmental analyses to clarify mechanisms underlying phenotypic variability. Multi-omics technologies, including genomics, epigenomics, metabolomics, and transcriptomics, offer significant potential to map adrenal regulatory networks with unprecedented resolution (Figure 9) (Otte *et al.,* 2007; Lightman, 2008; Beuschlein, 2013).

Longitudinal studies remain essential for determining how early-life exposures, chronic stress, and environmental disruptors shape adrenal function and phenotype over time. Developing phenotype-centered diagnostic models may enhance clinical detection of subtle adrenal dysfunction before progression to overt disease. Together, these directions underscore the importance of interdisciplinary research linking molecular endocrinology to clinically meaningful phenotypic outcomes (Evans and Mangelsdorf, 2014; Doi, 2015; Miller, 2017; Kameda *et al.,* 2018; Gill *et al.,* 2021).

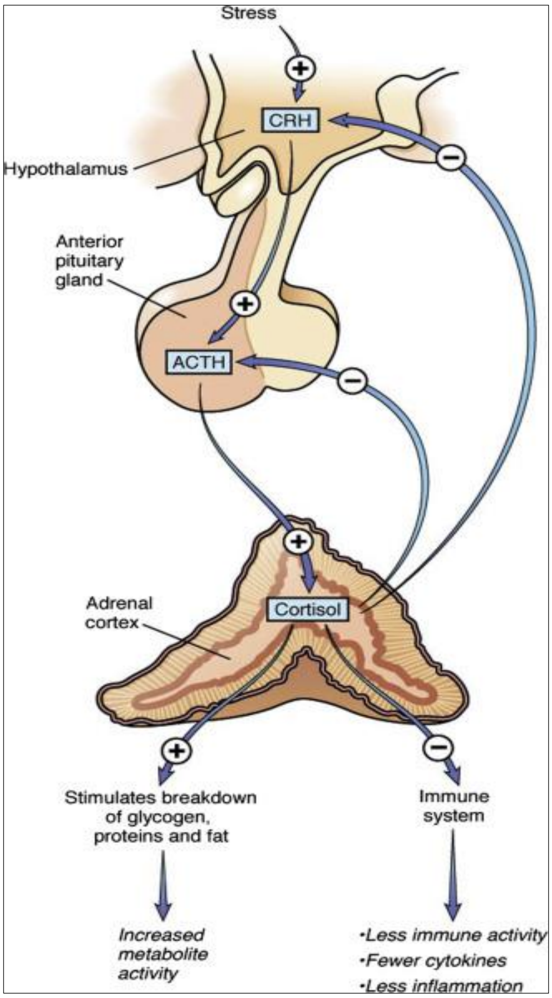

Figure 7: Depicts the broad phenotypic interferences of adrenal function across metabolic, cardiovascular, immune, and neurobehavioral systems

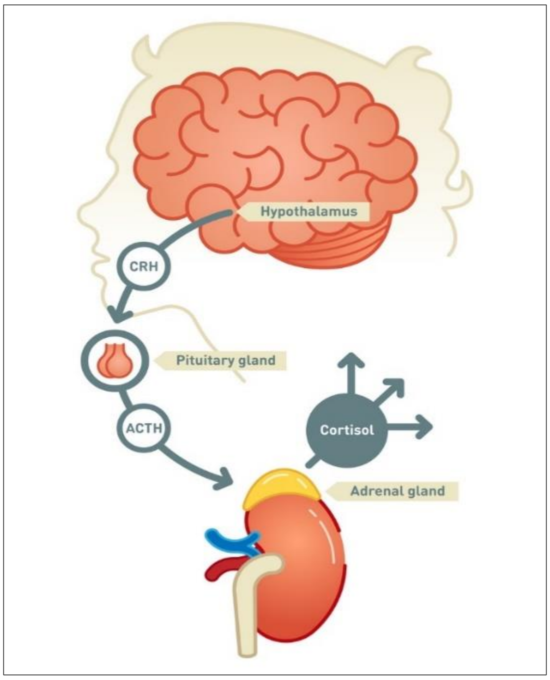

Figure 8: Summarizes adrenal hypofunction, emphasizing reduced secretion of cortisol, aldosterone, and adrenal androgens, and the associated endocrine deficits such as primary adrenal insufficiency and Addison's disease

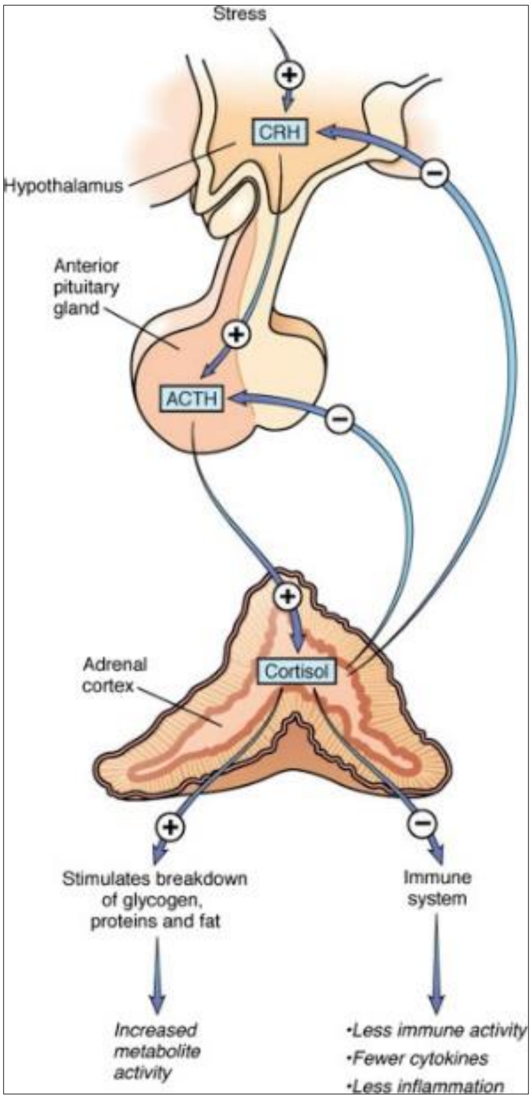

Figure 9: Highlights how adrenal hormones shape phenotypic outcomes across multiple physiological domains

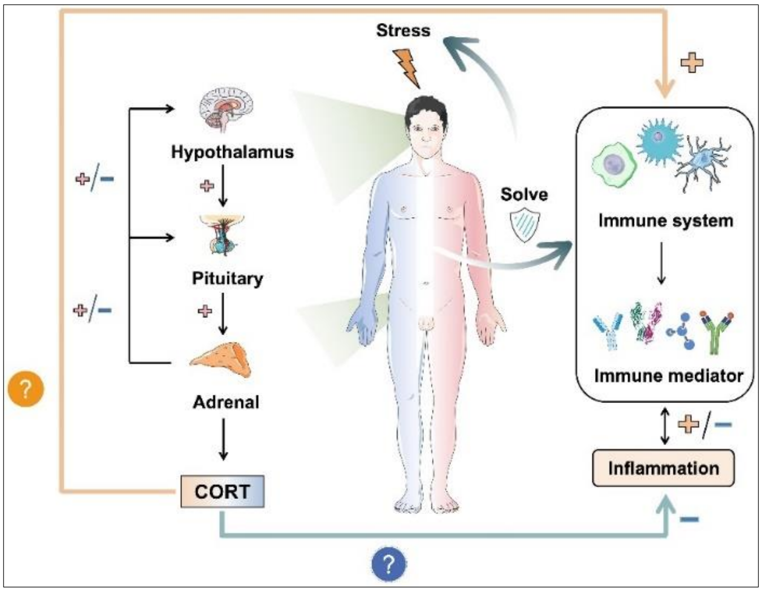

Figure 10: Provides an overview of phenotypic traits modulated by adrenal hormone activity, emphasizing metabolic, cardiovascular, immune, and behavioral dimensions

5. CONCLUSION

Adrenal physiology plays a central role in shaping human phenotypic diversity through its integrated regulation of metabolic, cardiovascular, immune, developmental, and neuroendocrine pathways. Evidence synthesized in this review demonstrates that phenotypic outcomes arise from the dynamic interaction between hormonal production, genetic susceptibility, tissue-specific signaling, and environmental exposures.

This multifactorial interplay explains the wide variability observed in clinical presentations of adrenal dysfunction and reinforces the need for diagnostic approaches that incorporate molecular, physiological, and contextual influences. A comprehensive understanding of adrenal-driven phenotypic mechanisms is therefore essential for improving early identification of endocrine-related abnormalities, guiding therapeutic strategies, and supporting the development of more integrative models capable of explaining human biological variation.

REFERENCES

- Aguilera, G. (2011). The hypothalamic–pituitary–adrenal axis and neuroendocrine responses to stress. *Dialogues in Clinical Neuroscience*, 13(4), 450–458.
- Al-Dujaili, E. (2012). Stress-induced cortisol response and its clinical implications. *Clinical Endocrinology*, *76*(3), 325–330.
- Almeida, D. M., & Kessler, R. C. (2010). Everyday stress and HPA axis function. *Psychosomatic Medicine*, *72*(7), 689–695.
- Andrews, R. C., & Walker, B. R. (1999). Glucocorticoids and cardiovascular disease. *Heart*, *82*(3), 232–237.
- Antonini, S. R., & Jorge, S. M. (2011). Early-life stress and adrenal programming. *Journal of Pediatric Endocrinology & Metabolism*, *24*(7–8), 497–503.
- Arlt, W., & Allolio, B. (2003). Adrenal insufficiency. *The Lancet*, *361*(9372), 1881–1893.
- Baulieu, E. E. (1996). Neurosteroids: A new regulatory function in the brain. *International Review of Neurobiology*, *38*, 1–35.
- Beuschlein, F. (2013). Genetics of adrenal tumors. *Endocrine Reviews*, *34*(2), 163–192.
- Biagini, G. *et al.* (1998). Adrenal response and developmental trajectories. *Brain Research Reviews*, *27*(1), 34–41.
- Bornstein, S. R. (2009). Predisposing factors for adrenal disease. *Nature Reviews Endocrinology*, *5*(10), 570–576.
- Brent, G. A. (2012). Molecular endocrinology of adrenal hormones. *Endocrinology and Metabolism Clinics*, *41*(4), 663–674.
- Brown, D. W. (2015). Chronic stress and cardiometabolic function. *Current Hypertension Reports*, *17*(2), 521.
- Brown, M. R., & Fisher, L. A. (1998). Catecholamines and physiological stress. *Annual Review of Physiology*, *60*, 647–672.
- Bunn, H. F., & Forget, B. G. (2021). *Hemoglobin: Molecular, genetic, and clinical aspects*. Cambridge University Press.
- Chrousos, G. P. (2009). Stress and disorders of the stress system. *Nature Reviews Endocrinology*, *5*(7), 374–381.
- Chrousos, G. P., & Kino, T. (2007). Glucocorticoid signaling pathways. *Journal of Clinical Endocrinology & Metabolism*, 92(5), 1523–1535.
- Cleare, A. J. (2004). The HPA axis in chronic fatigue. *Journal of Endocrinology*, *182*(1), 1–12.
- Connell, J. M. C., & Davies, E. (2005). The genetics of aldosterone regulation. *Clinical and Experimental Pharmacology & Physiology*, *32*(5–6), 399–409.
- Cooper, M. S., & Stewart, P. M. (2003). Corticosteroid effects on bone metabolism. *Endocrine Reviews*, *24*(2), 266–296.
- Corpas, E., et al. (1993). Adrenal aging and phenotype. *Journal of Clinical Endocrinology & Metabolism*, *76*(3), 554–560.
- De Kloet, E. R. (2000). Stress hormones and brain function. *Journal of Neuroendocrinology*, *12*(10), 957–964.
- Dickerson, S. S., & Kemeny, M. E. (2004). Acute stress responses and health. *Psychological Bulletin*, *130*(3), 355–391.
- Dillon, J. S., & Tilders, F. J. (1995). Adrenal neuroendocrine interplay. *Progress in Neurobiology*, *47*(5), 529–549.
- Doi, M. (2015). Adrenal circadian rhythms. *Journal of Endocrinology*, *226*(3), R1–R14.
- Edwards, C. R. W., & Reincke, M. (1997). Adrenal hormone disorders. *Clinical Endocrinology*, *46*(6), 657–672.
- Engeli, S. (2008). Adipose–adrenal signaling. *Obesity Reviews*, *9*(1), 32–42.
- Evans, R. M., & Mangelsdorf, D. J. (2014). Nuclear receptor signaling. *Cell*, *157*(1), 255–266.
- Fahlbusch, R., & Buchfelder, M. (1999). Adrenocorticotropic regulation. *Neurosurgery*, 45(2), 206–215.
- Fink, G. (2016). Stress resilience and adrenal function. *Neuroscience & Biobehavioral Reviews*, 68, 1–15.
- Franco-Sena, A. B. *et al.* (2020). Prenatal stress and adrenal development. *Endocrine Connections*, *9*(3), 188–199.
- Freeman, E. W. (2017). Hormonal transitions and phenotype. *Menopause*, *24*(2), 141–151.
- Fuller, P. J. *et al.* (2012). Mineralocorticoid receptor physiology. *Endocrinology*, *153(*9), 4111–4120.
- Gatti, R., & De Palo, E. F. (2011). Adrenal hormones and biomarkers. *Clinical Biochemistry*, *44*(12), 1035–1051.

- Geer, E. B., & Shen, W. (2009). Cortisol and body composition. *Obesity*, *17*(3), 643–648.
- Gill, R. *et al.* (2021). Adrenal metabolism in health and disease. *Metabolism*, *120*, 154779.
- Goldstein, D. S. (2010). Catecholamine physiology. *Comprehensive Physiology*, *1*(1), 303–319.
- Grayson, B. E., & Seeley, R. J. (2013). Adrenal interactions with metabolic circuits. *Trends in Endocrinology & Metabolism*, *24*(4), 171–178.
- Grumbach, M. M. (2005). Adrenal disorders in childhood. *New England Journal of Medicine*, *352*(5), 505–514.
- Handa, R. J. *et al.* (1994). Steroid hormone receptors and phenotype. *Endocrine Reviews*, *15*(3), 284–302.
- Harris, A., & Seckl, J. (2011). Glucocorticoids and developmental programming. *Journal of Endocrinology*, *209*(1), 1–8.
- Hatakeyama, H. (2019). Steroidogenic enzyme regulation. *Steroids*, *152*, 108497.
- Holsboer, F. (2000). HPA axis and mood disorders. *Annual Review of Neuroscience*, *23*, 49–58.
- Huizenga, N. A. *et al.* (1998). Adrenal hyperfunction and phenotype. *Journal of Clinical Endocrinology & Metabolism*, *83*(4), 1346–1352.
- Iwata, M., & Vanderpool, D. (2020). The adrenal immune interface. *Immunological Reviews*, *295*(1), 198–214.
- Kameda, H. *et al.* (2018). Adrenal steroidogenesis pathways. *Endocrine Journal*, *65*(8), 755–768.
- Klemcke, H. G. (2003). Adrenal stress responsiveness. *Domestic Animal Endocrinology*, 25(1), 1–15.
- Lamberts, S. W. *et al.* (1997). Clinical implications of cortisol excess. *New England Journal of Medicine*, 337(14), 973–980.
- Lightman, S. L. (2008). The HPA axis in physiology. *Nature Reviews Neuroscience*, *9*(6), 419–428.
- Lim, S., & Kaltsas, G. (2012). Adrenal incidentalomas. *Reviews in Endocrine and Metabolic Disorders*, *13*(1), 41–49.
- Martini, L. (1999). Androgen biology and clinical regulation. *The Journal of Steroid Biochemistry and Molecular Biology*, 69(1–6), 1–6.
- Masuzaki, H. *et al.* (2001). Glucocorticoids and obesity. *Journal of Clinical Investigation*, *108*(11), 1647–1654.
- Miller, W. L. (2017). Steroidogenesis: Molecular regulation. *Endocrine Reviews*, *38*(1), 1–18.
- Morley, J. E. (2010). Aging and endocrine systems. *Journal of the American Geriatrics Society*, *58*(2), S145–S149.
- Newell-Price, J. *et al.* (2006). Cushing's syndrome mechanisms. *The Lancet*, *367*(9522), 1605–1617.
- Nicolaides, N. C. *et al.* (2015). HPA axis physiology. *Frontiers in Neuroendocrinology*, *35*, 47–72.
- Otte, C. *et al.* (2007). Stress and HPA axis alterations. *Biological Psychiatry*, *62*(10), 1019–1031.
- Raff, H., & Findling, J. W. (2003). Adrenal function testing. *Endocrine Reviews*, *24*(6), 771–800.
- Sapolsky, R. M. (2000). Stress hormones and neuroplasticity. *Progress in Brain Research*, *122*, 287–304.
- Stewart, P. M. (2003). Mineralocorticoid physiology and disease. *Clinical Endocrinology*, *59*(4), 447–458.
- Viau, V. (2002). Functional organization of the HPA axis. *Physiology & Behavior*, *79*(2), 221–227.