Treatment Challenges with Glucocorticoid Dosing in Congenital Adrenal Hyperplasia (CAH)

What is Physiologic Glucocorticoid Dosing?

Note: We refer to classic CAH as CAH; deviations from classic CAH are denoted by using specific terminology (e.g., non-classic CAH).

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GC Therapy Currently Has Dual Purpose in CAH

CAH is characterized by[1]:

- Deficiency in cortisol and often aldosterone
- Excessive production of ACTH, corticosteroid precursors, and adrenal androgens

Dual Role of GC Therapy[2]:

Supraphysiologic doses of GCs are used to **BOTH**

✓ **REPLACE** deficient endogenous cortisol and

REDUCE ACTH and adrenal androgens

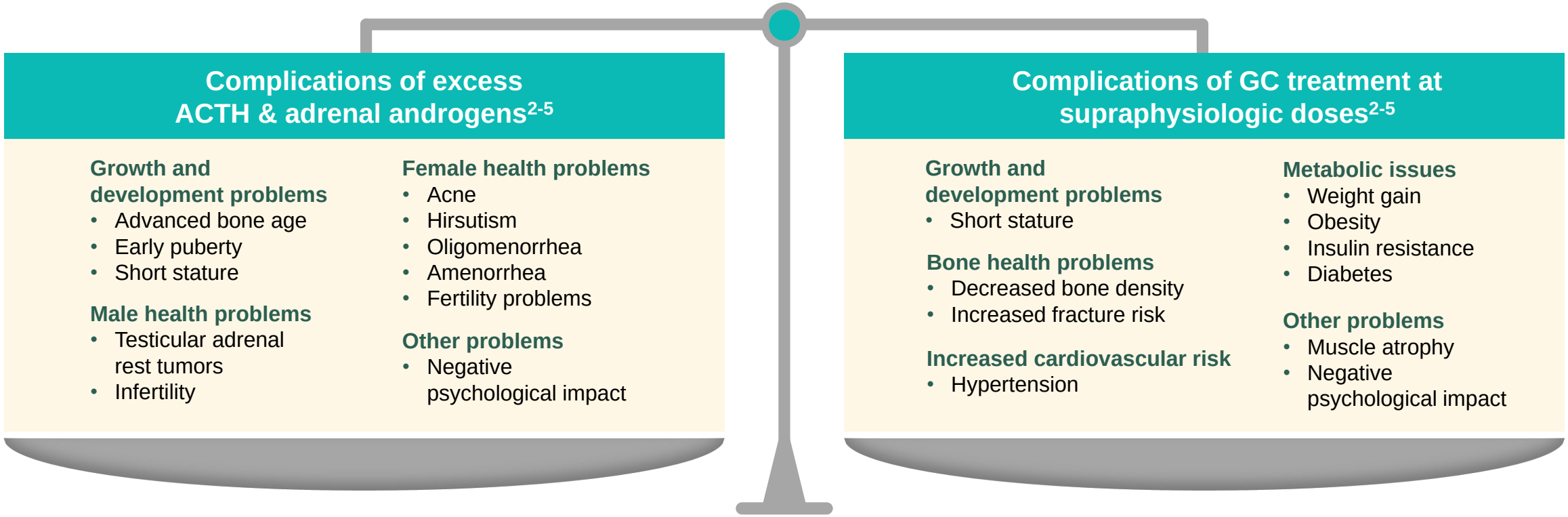
Mineralocorticoids may also be used to help replace deficient hormones[1]

ACTH, adrenocorticotropic hormone; CAH, congenital adrenal hyperplasia; GC, glucocorticoid.

1. Speiser PW, et al. *J Clin Endocrinol Metab*. 2018;103(11):4043-4088. 2. Mallappa A, Merke DP. *Nat Rev Endocrinol.* 2022;18(6):337-352.

Current Management of CAH

Adequate adrenal androgen reduction should be balanced against the risks of chronic supraphysiologic GC exposure[1]



Complications of excess ACTH & adrenal androgens[2-5]

Growth and development problems
- Advanced bone age
- Early puberty
- Short stature

Male health problems
- Testicular adrenal rest tumors
- Infertility

Female health problems
- Acne
- Hirsutism
- Oligomenorrhea
- Amenorrhea
- Fertility problems

Other problems
- Negative psychological impact

Complications of GC treatment at supraphysiologic doses[2-5]

Growth and development problems
- Short stature

Bone health problems
- Decreased bone density
- Increased fracture risk

Increased cardiovascular risk
- Hypertension

Metabolic issues
- Weight gain
- Obesity
- Insulin resistance
- Diabetes

Other problems
- Muscle atrophy
- Negative psychological impact

Supraphysiologic doses of GCs are usually needed for adrenal androgen reduction[2]

ACTH, adrenocorticotropic hormone; CAH, congenital adrenal hyperplasia; GC, glucocorticoid.

1. Speiser PW, et al. *J Clin Endocrinol Metab*. 2018;103(11):4043-4088. 2. Mallappa A, Merke DP. *Nat Rev Endocrinol.* 2022;18(6):337-352. 3. Finkielstain GP, et al. *J Clin Endocrinol Metab*. 2012;97(12):4429-4438. 4. Arlt W, et al. *J Clin Endocrinol Metab*. 2010;95(11):5110-5121. 5. Merke DP, Auchus RJ. *N Engl J Med*. 2020;383(13):1248-1261.

CAH Treatment

CAH management varies widely and often results in the challenging balance of[1-4]:
- Supraphysiologic GC daily doses that may not align to physiologic circadian variation
- Poorly controlled adrenal androgens

- These doses and schedules from the Endocrine Society Guidelines are meant as examples and should not be construed as a restrictive menu of choices for the individual patient[5]

	Growing		Fully grown	
Drugs	**Total daily dose ranges**	**Daily dosing frequency**	**Total daily dose ranges (mg/d)**	**Daily dosing frequency**
Hydrocortisone	10-15 mg/m^2	3	15-25	2-3
Prednisone	–	–	5-7.5	2
Prednisolone	–	–	4-6	2
Methylprednisolone	–	–	4-6	2
Dexamethasone	–	–	0.25-0.5	1
Fludrocortisone	0.05-0.2 mg	1-2	0.05-0.2	1-2
Sodium chloride supplements	1-2 g (17-34 mEq) in infancy	Divided into several feedings		

Click for Delphi study data

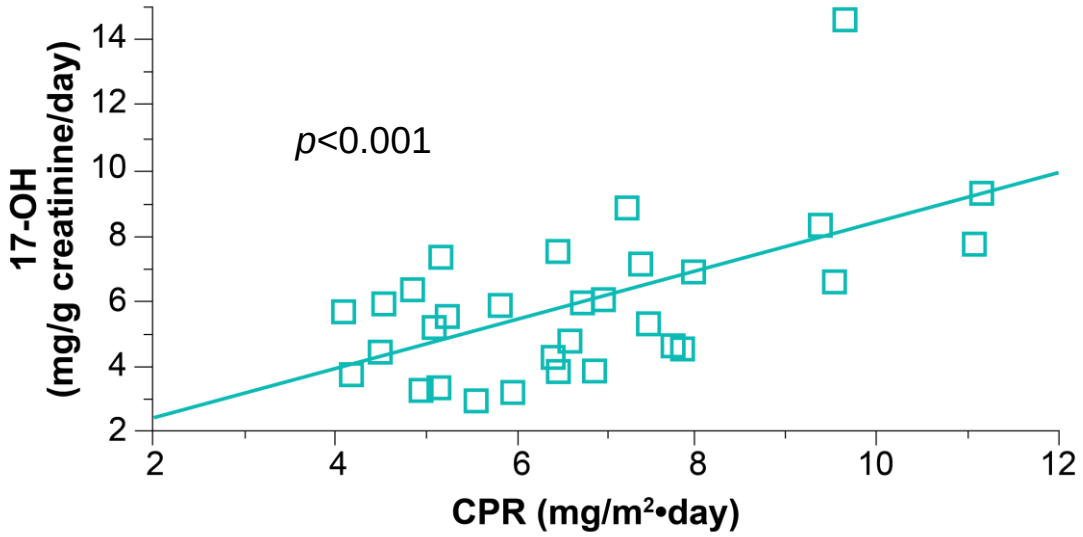
CAH, congenital adrenal hyperplasia; GC, glucocorticoid; mEq, milliequivalent.

1. Auchus RJ, et al. *Front Endocrinol (Lausanne).* 2022;13:1005963. 2. Finkielstain GP, et al. *J Clin Endocrinol Metab*. 2012;97(12):4429-4438. 3. Arlt W, et al. *J Clin Endocrinol Metab*. 2010;95(11):5110-5121. 4. Mallappa A, Merke DP. *Nat Rev Endocrinol.* 2022;18(6):337-352. 5. Speiser PW, et al. *J Clin Endocrinol Metab*. 2018;103(11):4043-4088.

What Is a Physiologic GC Dose, Based on Cortisol Production Rates?

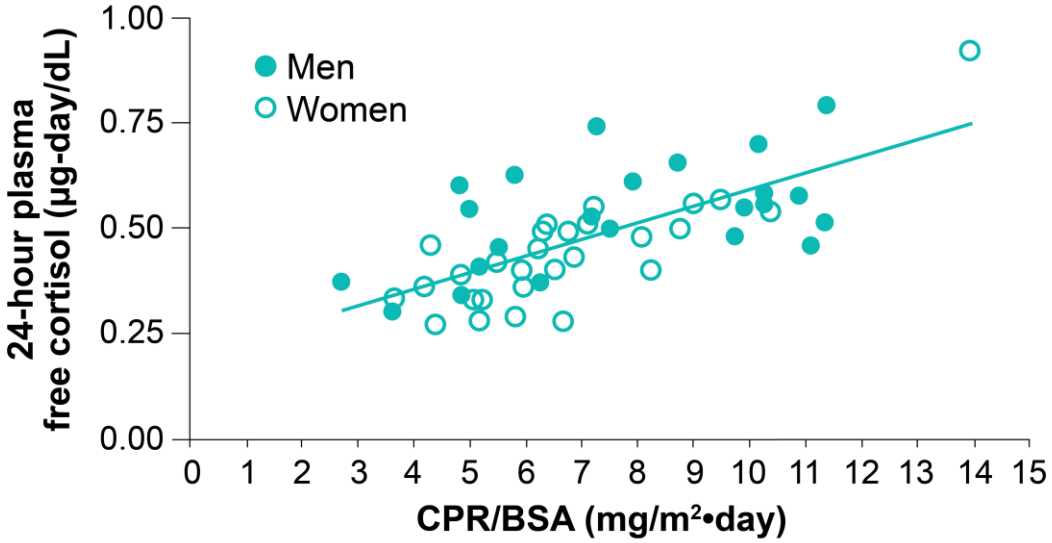
Literature shows a broad range of daily cortisol production rates in healthy individuals[1,2]:

Linder et al, 1990[a]: ~4-12 mg/m²•day



- Study of children and adolescents (8-17 years, N=33)[1]
- Figure depicts the range of cortisol production rates on the x axis.

Purnell et al, 2004[b]: 2.7-14 mg/m²•day



- Study of adults (19-70 years, N=54)[2]
- Figure depicts the range of cortisol production rates on the x axis.

[a]Reprinted from *J Pediatr*, 117/6, Linder BL, et al, Cortisol production rate in childhood and adolescence, 892-896, copyright 1990, with permission from Elsevier.
[b]Reprinted from *J Clin Endcrinol Metab*, 89/1, Purnell JQ, et al, Association of 24-hour cortisol production rates, cortisol-binding globulin, and plasma-free cortisol levels with body composition, leptin levels, and aging in adult men and women, 281-287, copyright (2004), with permission from The Endocrine Society.
17-OH, 17-hydroxysteroid; BSA, body surface area; CPR, cortisol production rate; GC, glucocorticoid.
1. Linder BL, et al. *J Pediatr*. 1990;117(6):892-896. 2. Purnell JQ, et al. *J Clin Endocrinol Metab*. 2004;89(1):281-287.

Click to learn more on CPR

Summary: Treatment Challenges with GC Dosing in CAH

Dual Role of Supraphysiologic GC Therapy[1]:

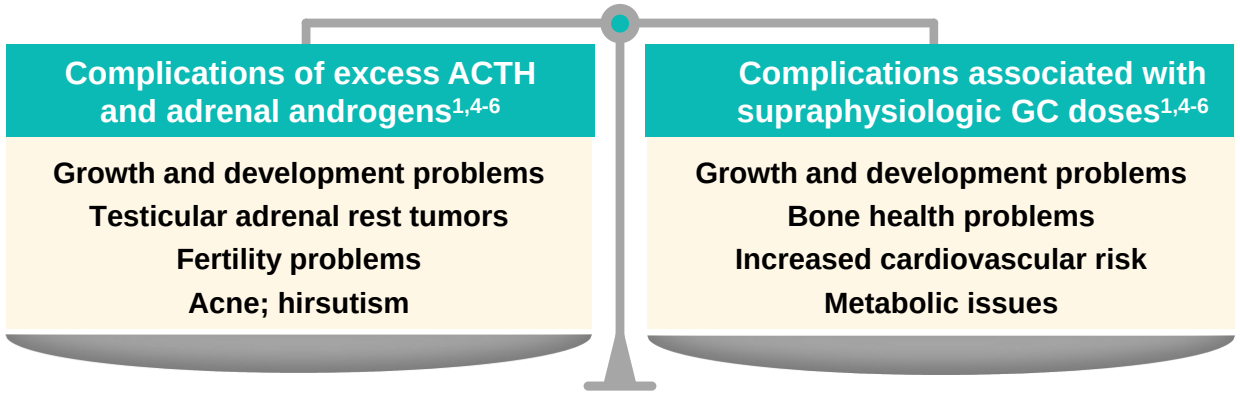
- ✓ **REPLACE** deficient endogenous cortisol
- ✓ **REDUCE** excess ACTH and adrenal androgens

Physiologic GC doses vary between patients[2,3]

Literature shows a broad range of daily cortisol production rates in healthy individuals[2,3]

Purnell et al, 2004:	**2.7-14 mg/m²•day**
Linder et al, 1990:	**~4-12 mg/m²•day**

Supraphysiologic GC doses are usually needed for adrenal androgen reduction and can lead to complications[1]



ACTH, adrenocorticotropic hormone; CAH, congenital adrenal hyperplasia; GC, glucocorticoid.

1. Mallappa A, Merke DP. *Nat Rev Endocrinol.* 2022;18(6):337-352. 2. Purnell JQ, et al. *J Clin Endocrinol Metab*. 2004;89(1):281-287. 3. Linder BL, et al. *J Pediatr*. 1990;117(6):892-896.
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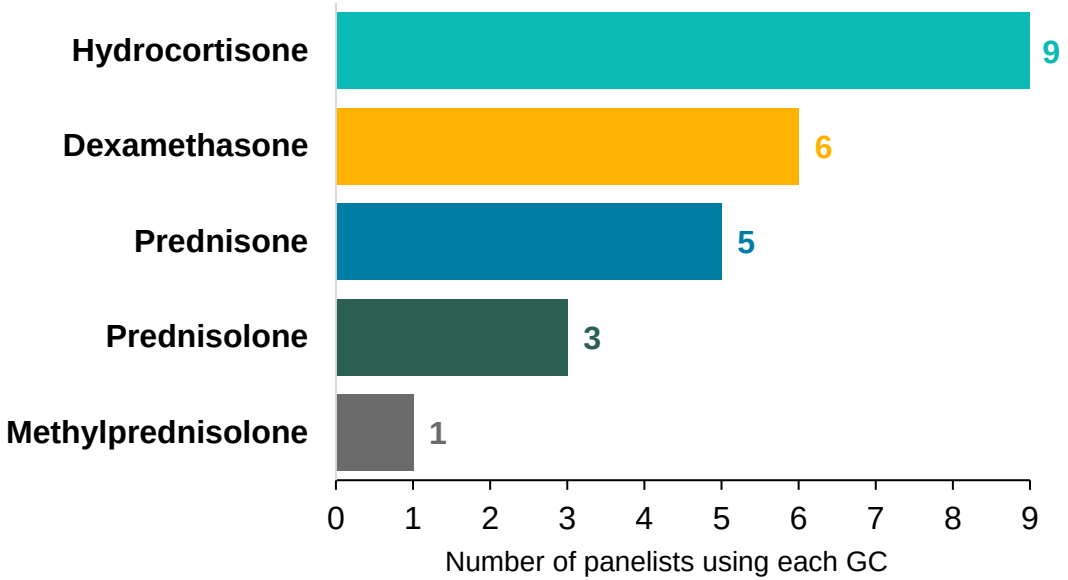
Appendix

Note: We refer to classic CAH as CAH; deviations from classic CAH are denoted by using specific terminology (e.g., non-classic CAH).

GC Treatment Practices in CAH

- A modified Delphi consensus study that assessed GC treatment practices in adults with CAH among 9 CAH experts showed wide variations in GC treatment practices[1]:



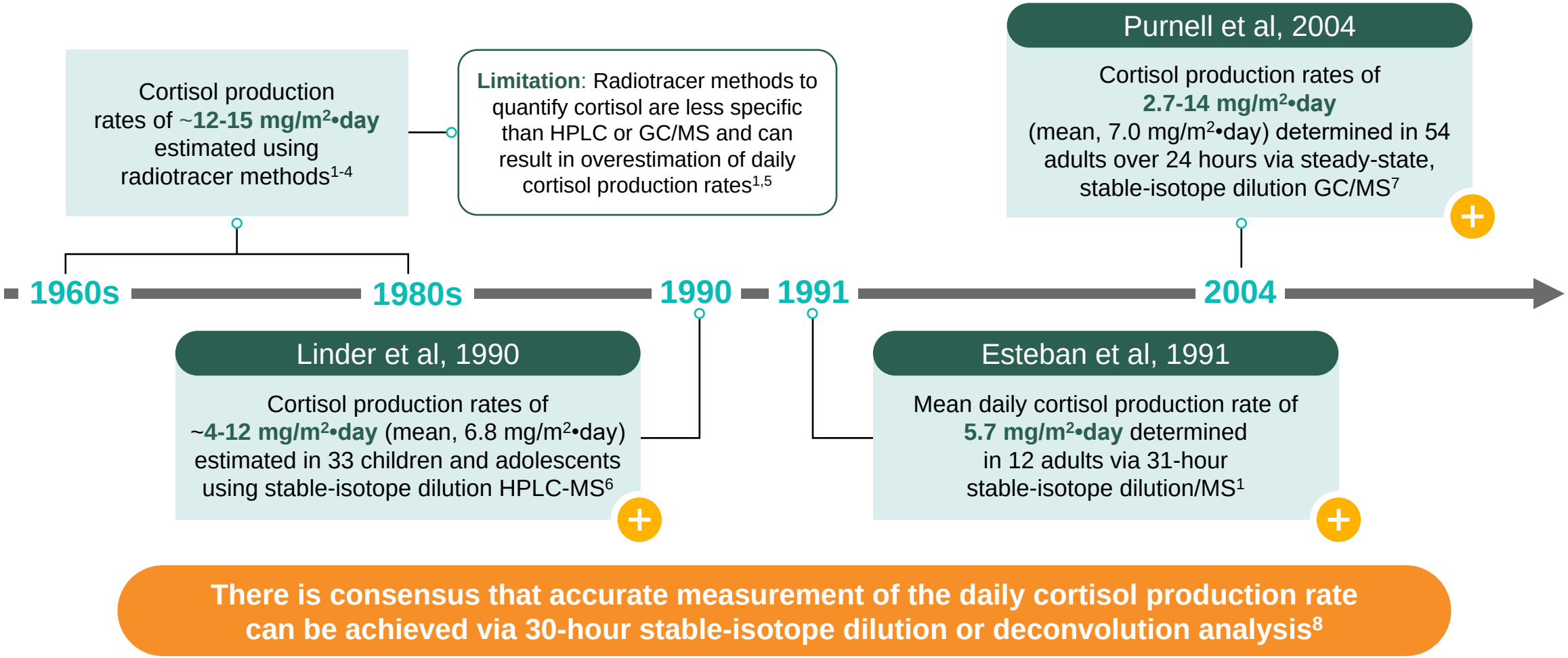
	Daily dose (mg/d), mean (SD)	Lower range, mean (SD)	Upper range, mean (SD)	Endocrine Society's recommended daily dose[2] (mg/d)
Hydrocortisone	27.2 (3.6)	14.2 (3.8)	40.8 (10.2)	15-25
Dexamethasone	0.6 (0.3)	0.4 (0.1)	1.5 (0.6)	0.25-0.5
Prednisone	4.9 (1.5)	3.8 (1.8)	7.5 (1.8)	5-7.5
Prednisolone	4.4 (0.9)	3.3 (1.7)	7.1 (2.2)	4-6
Methylprednisolone	5.4 (1.3)	3.8 (2.1)	6.5 (1.9)	4-6

Among 9 clinicians with expertise in treating CAH, the average daily dose of hydrocortisone was 27.2 mg, with doses ranging from 14.2-40.8 mg[1]

CAH, congenital adrenal hyperplasia; GC, glucocorticoid; SD, standard deviation.

1. Auchus RJ, et al. *Front Endocrinol (Lausanne).* 2022;13:1005963. 2. Speiser PW, et al. *J Clin Endocrinol Metab*. 2018;103(11):4043-4088.

Prior Studies Evaluating Cortisol Production Rate in Healthy Individuals



There is consensus that accurate measurement of the daily cortisol production rate can be achieved via 30-hour stable-isotope dilution or deconvolution analysis[8]

GC, gas chromatography; HPLC, high-performance liquid chromatography; MS, mass spectrometry.

1. Esteban NV, et al. *J Clin Endocrinol Metab*. 1991;72(1):39-45. 2. Kenny FM, et al. *Pediatrics*. 1966;37(1):34-42. 3. Petersen KE. *Acta Paediatr Scand*. 1980;(Suppl 281):2-38. 4. Kenny FM, et al. *Metabolism*. 1970;19(4):280-290. 5. Björkhem I, et al. *Clin Chem*. 1981;27(5):733-735. 6. Linder BL, et al. *J Pediatr*. 1990;117(6):892-896. 7. Purnell JQ, et al. *J Clin Endocrinol Metab*. 2004;89(1):281-287. 8. Caetano CM, Malchoff CD. *Front Endocrinol (Lausanne)*. 2022;13:897211.

Estimated Daily Cortisol Production Rate in Children and Adolescents

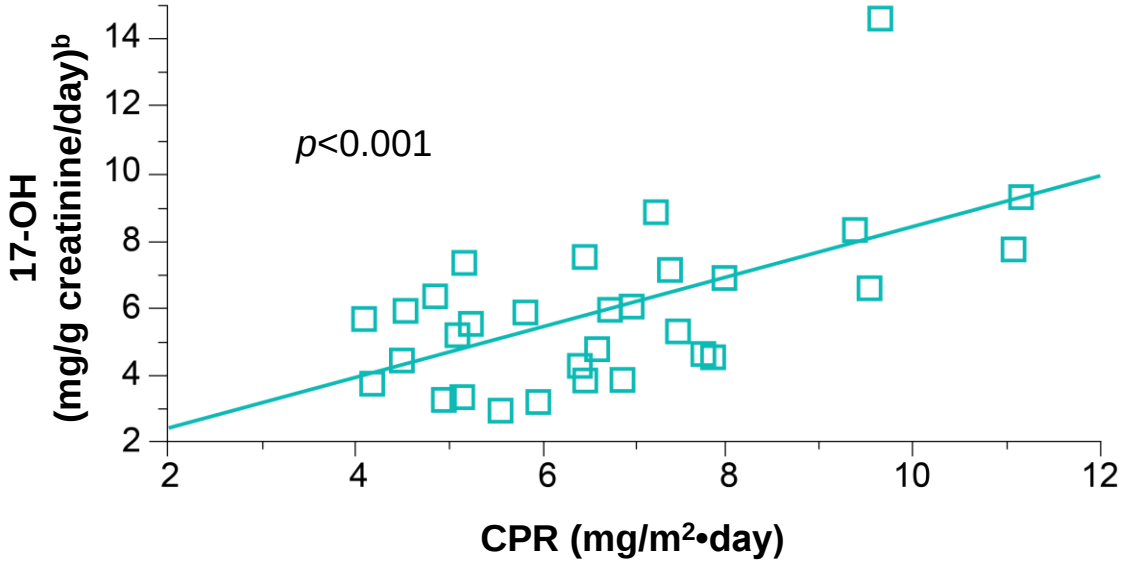
Study design

- Observational
- Healthy children and adolescents (N=33)
- **Ages:** 8-17 years
- **Height and weight:** 5th-95th percentile
- **Methods:** Cortisol production rate measured via stable-isotope dilution HPLC-MS with continuous infusion of deuterated cortisol via IV catheters for 30 hours

Results

- Mean daily cortisol production rate: **9.5 mg/day** (6.8 mg/m^2•day; range: ~4-12 mg/m^2•day)
  - This represents a **3-fold** range of cortisol production rates

Correlation between cortisol production rate and urinary 17-OH excretion, corrected for creatinine value[a]



[b]17-OH excretion rate reflects cortisol adrenal secretion

[a]Reprinted from Linder et al *J Pediatr*, 117/6, Linder BL, et al, Cortisol production rate in childhood and adolescence, 892-896, copyright 1990, with permission from Elsevier.
17-OH, 17-hydroxysteroid; CPR, cortisol production rate; HPLC, high-performance liquid chromatography; MS, mass spectrometry; PAI, primary adrenal insufficiency; IV, intravenous.
Linder BL, et al. *J Pediatr*. 1990;117(6):892-896.

Novel Approach to Quantifying Cortisol Production – Overcoming Overestimation by Radiotracer Methods

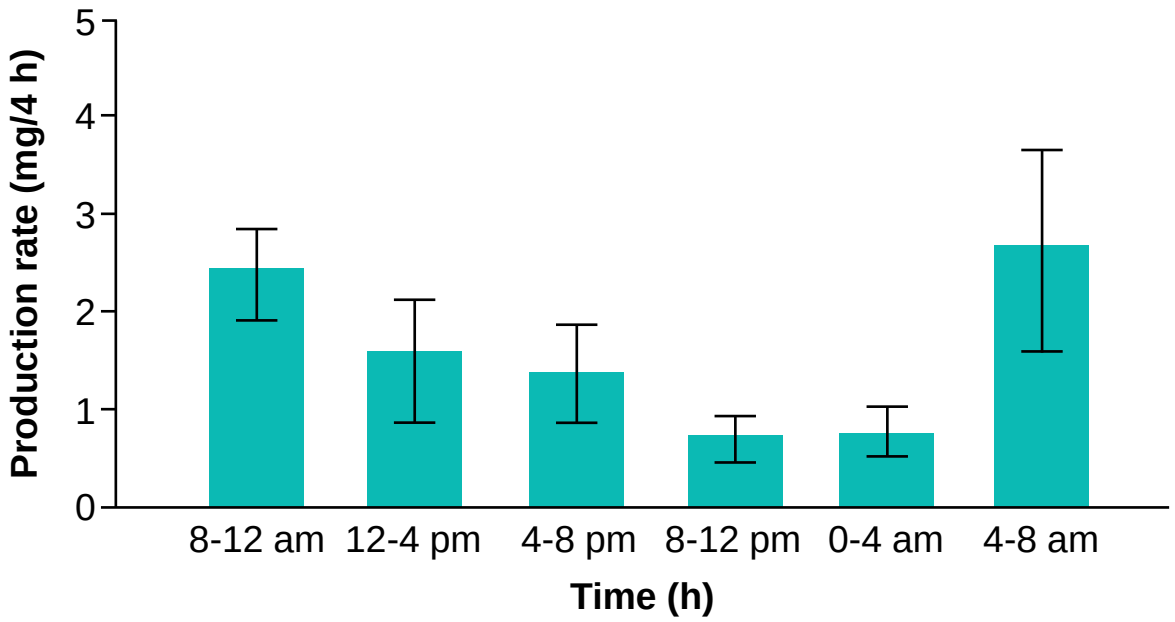
Study design

- Observational
- Healthy adults (n=12)
- **Mean age:** 28 years
- **Methods:** 31-hour stable-isotope dilution/MS used to estimate daily cortisol production rate

Results

- Mean daily cortisol production rate: **9.9 ± 2.7 mg/day** (5.7 mg/m^2•day)
- Methodology overcomes difficulties associated with radiotracer techniques leading to overestimation of cortisol production rates

Circadian pattern of cortisol production in healthy adults[a]



[a]Reprinted from *J Clin Endocrinol Metab*, 72/1, Esteban NV, et al, Daily cortisol production rate in man determined by stable dilution/mass spectrometry, 39-45, copyright (1991), with permission from The Endocrine Society.
MS, mass spectrometry.
Esteban NV, et al. *J Clin Endocrinol Metab*. 1991;72(1):39-45.

Estimated Daily Cortisol Production Rate in Adults

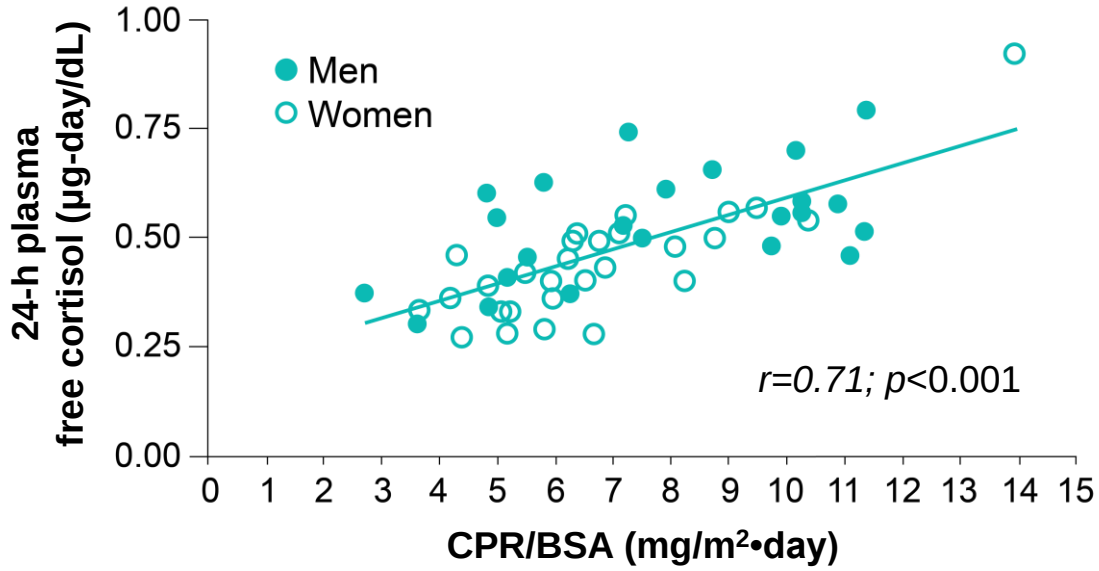
Study design

- Observational
- Healthy men (n=24) and women (n=30)
- **Ages:** 19-70 years
- **BMI:** 19-64 kg/m^2
- **Methods:** Cortisol production rate assessed over 24 hours via steady-state, stable-isotope dilution GC/MS, alongside measurements of free cortisol and CBG levels

Results

- Mean daily cortisol production rate: **14.5 mg/day** (7.0 mg/m^2•day; range: 2.7-14 mg/m^2•day)
  - This represents a **5.2-fold** range of cortisol production rates

Correlation between CPR/BSA and 24-hour plasma free cortisol levels in adults[a]



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Purnell JQ, et al. *J Clin Endocrinol Metab*. 2004;89(1):281-287.