THE MOST COMMON FORMS OF PSEUDO-CUSHING: PCOS AND DEPRESSION

Nora Albiger
U.O.C Endocrinology
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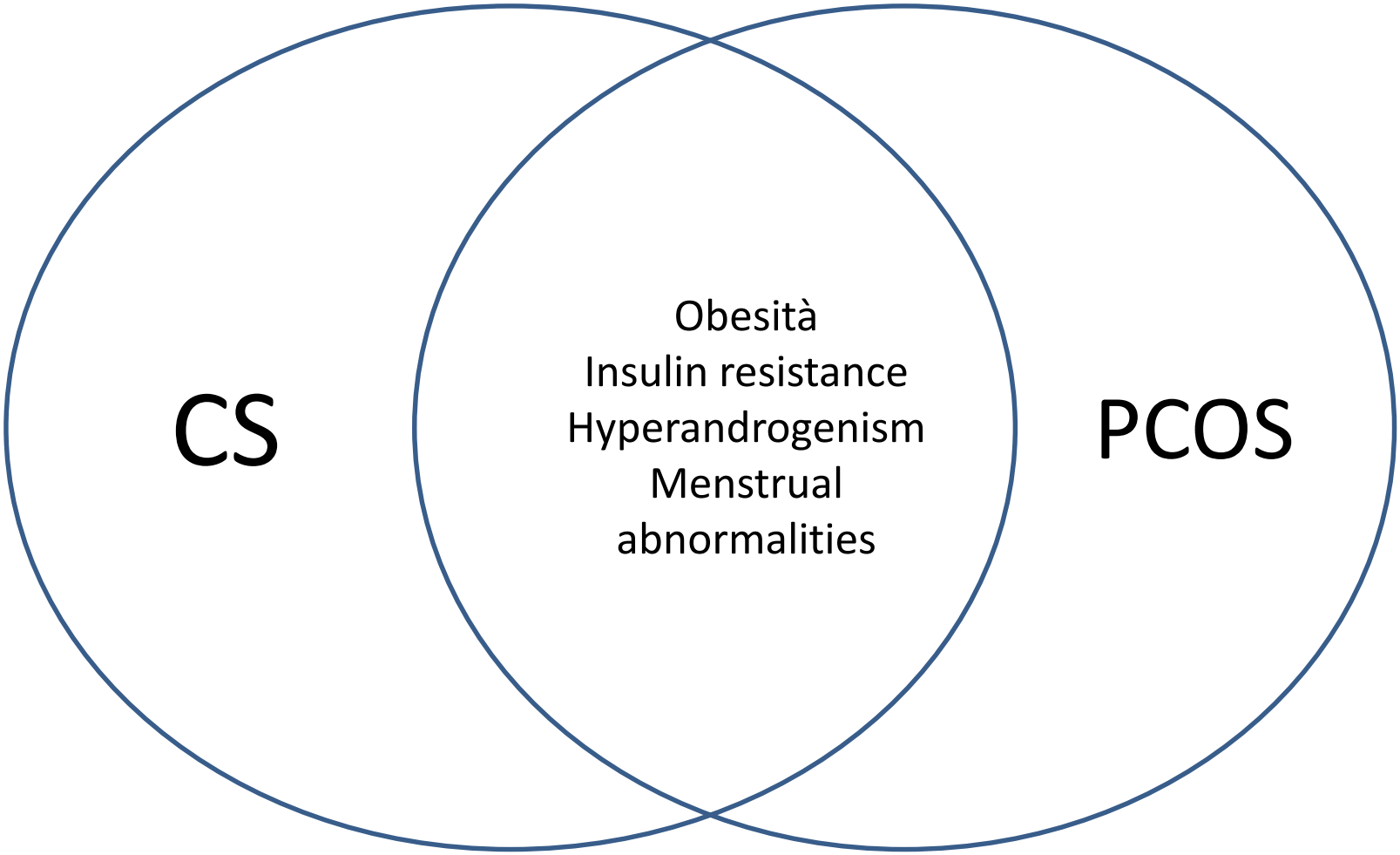


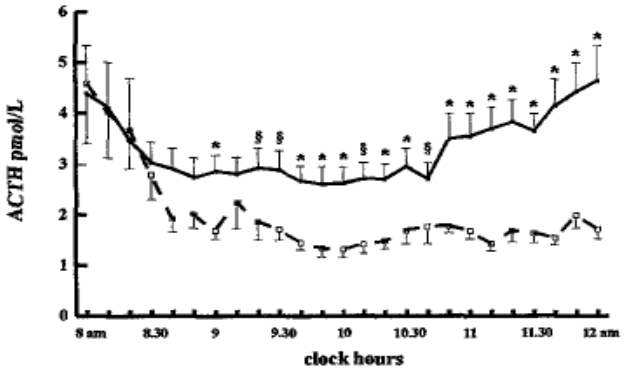
76–100 case / million/year
F > M

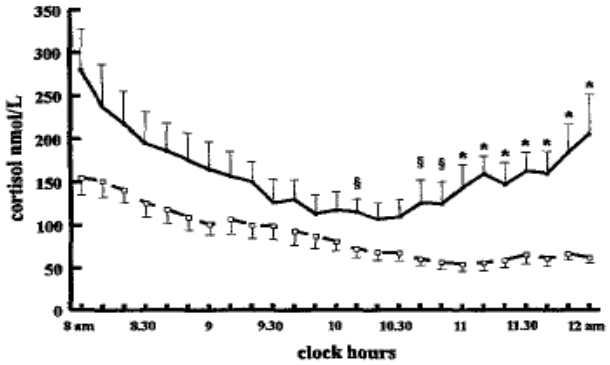
10% women of reproductive age

Mean 4-hour plasma ACTH and cortisol profiles in PCOS women and controls

16 PCOS BMI: 20 to 24 kg/m 2; 17 to 35 years
16 controls (BMI, 18 to 20 kg/m 2) 24 to 32 years

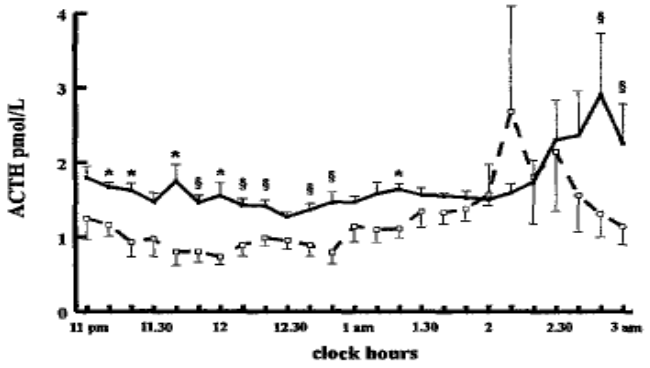
8 AM and 12 AM (9 PCOS, 8 controls)

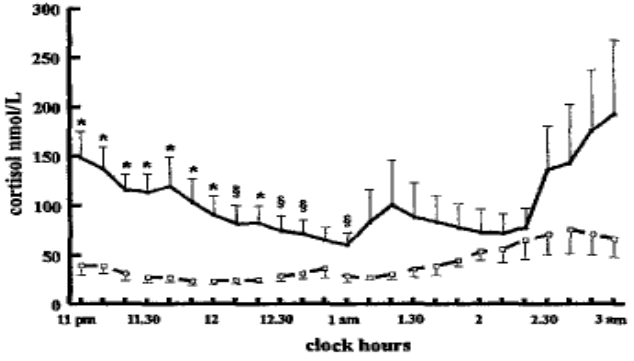




AUC	PCOS	control	P
ACTH	760 ± 85.3	472 ± 40.6	<0.05
F	36.9 ± 6.25	21,1 ± 2.3	<0.05

11 PM and 3 AM (7 PCOS, 8 controls)



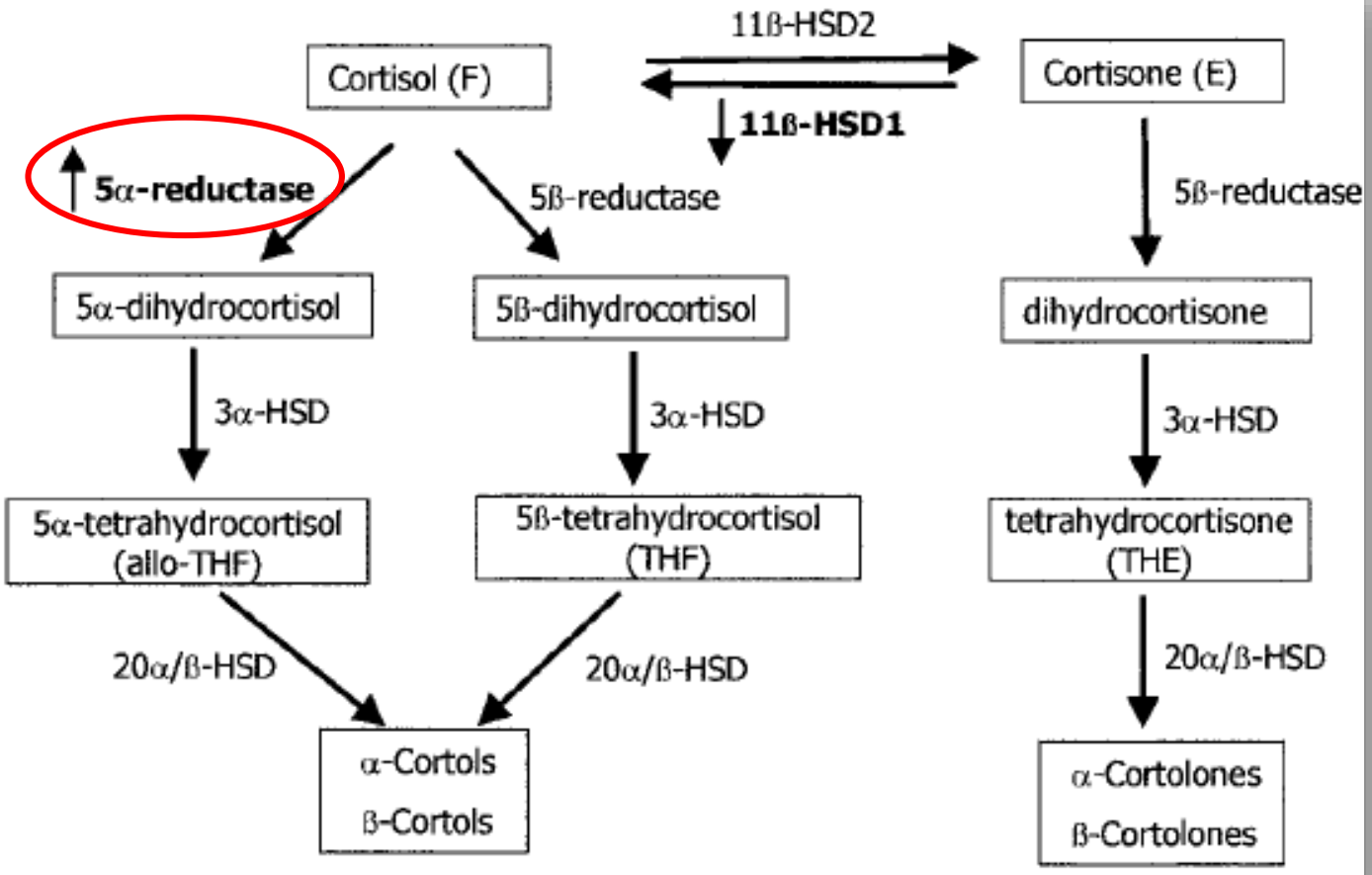


AUC	PCOS	control	P
ACTH	399 ± 19.7	295 ± 35.1	<0.05
F	23.7 ± 5.45	9.74 ± 1.21	<0.05

Invitti et al Metabolism 1998

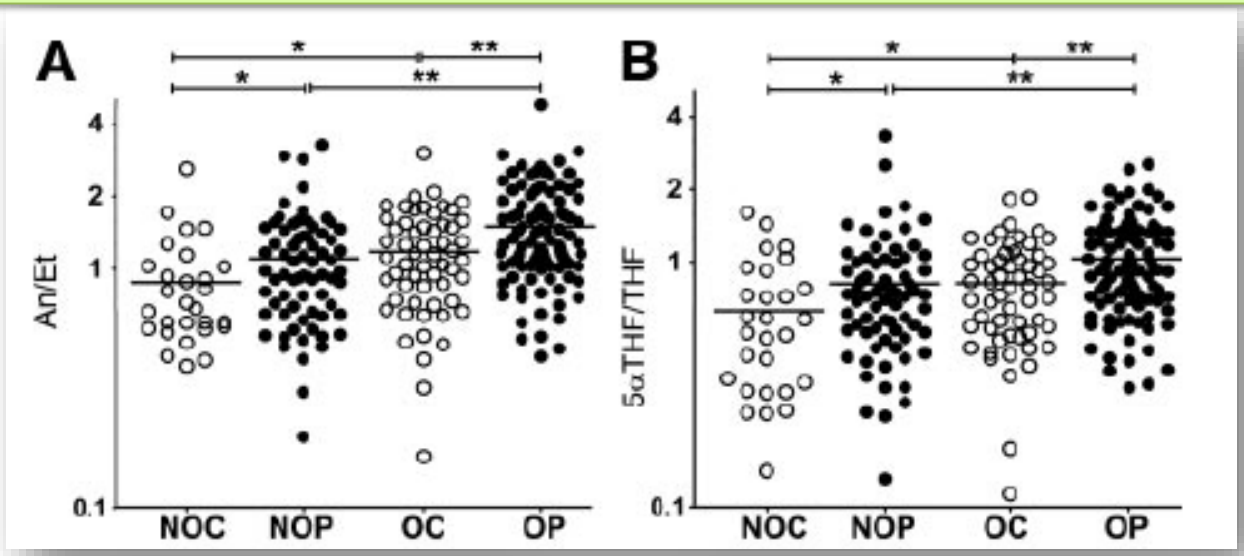
Increased 5α-Reductase Activity and Adrenocortical Drive in Women with Polycystic Ovary Syndrome

Dimitra A. Vassiliadi, Thomas M. Barber, Beverly A. Hughes, Mark I. McCarthy, John A. H. Wass, Stephen Franks, Peter Nightingale, Jeremy W. Tomlinson, Wiebke Arlt, and Paul M. Stewart



JCEM 2009

Increased 5α reductase activity (An/Et (androsterone/etiocholanolone) and 5αTHF/5βTHF ratios) in PCOS patients

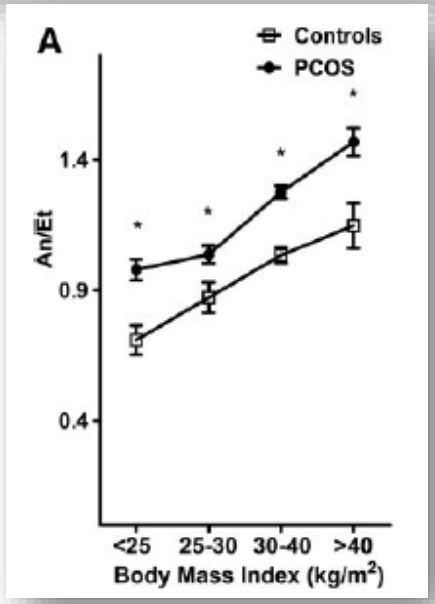


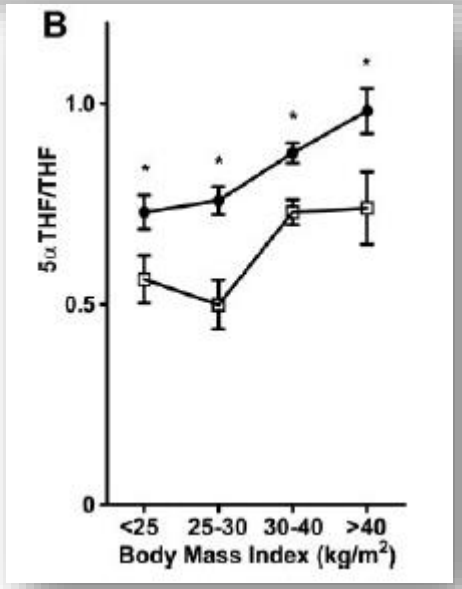
NOC, Non-obese controls

NOP, non-obese PCOS

OC, obese controls

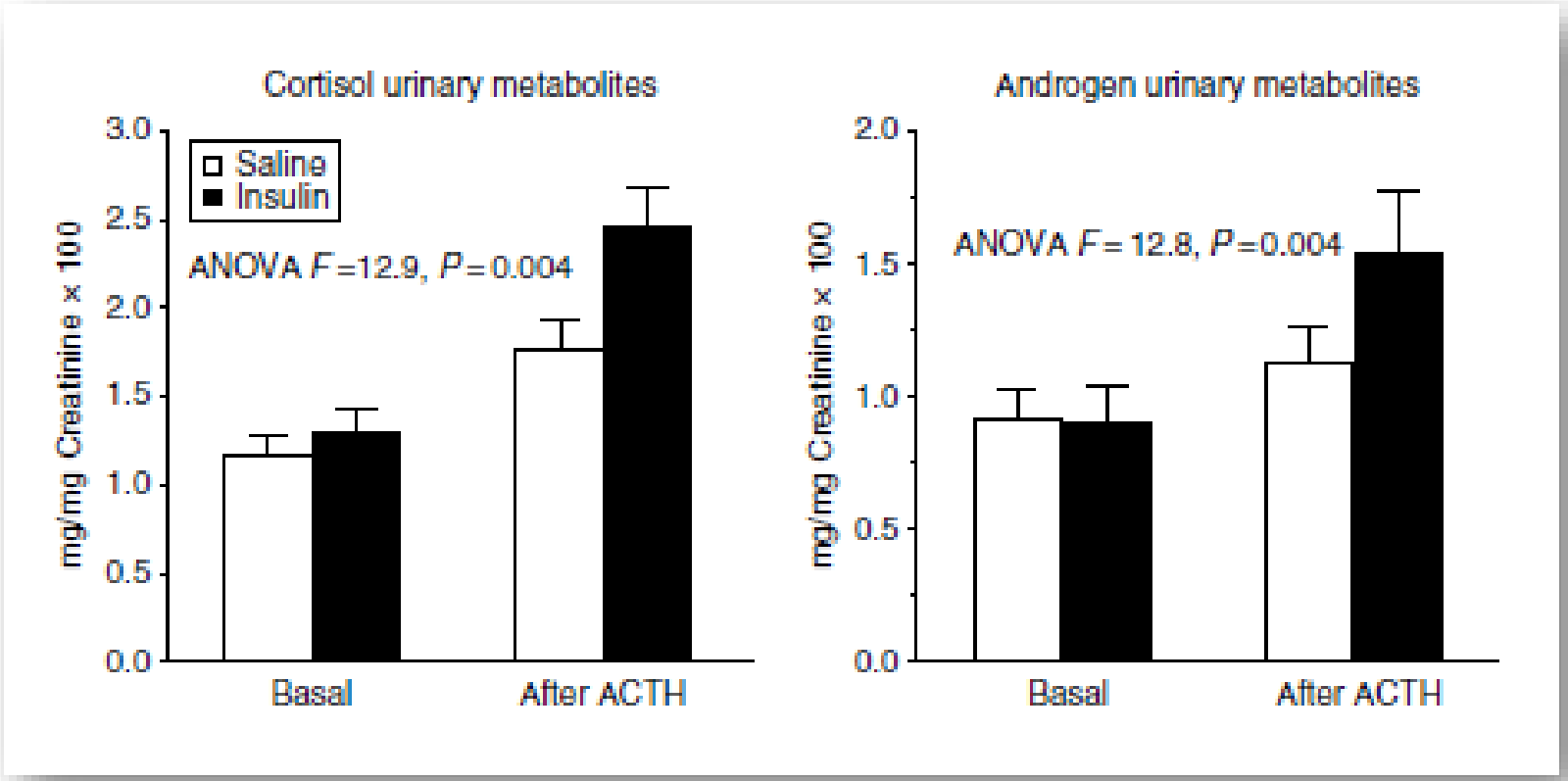
OP, obese PCOS





Vassiliadi DA, et al JCEM 2009

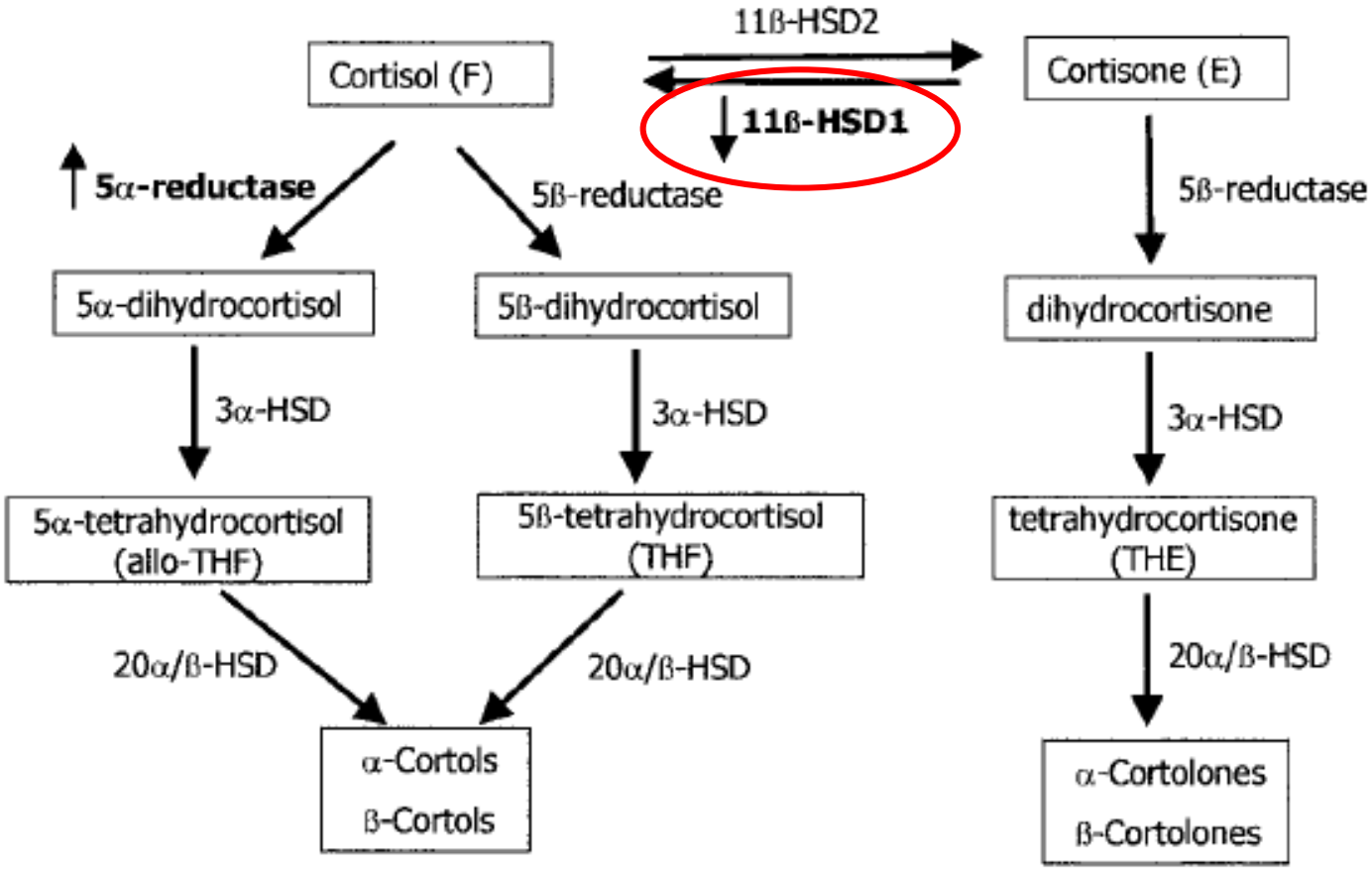
Insulin enhances ACTH-stimulated androgen and glucocorticoid metabolism in hyperandrogenic women



Tosi F..Moghetti P et al EJE 2011

Increased 5α-Reductase Activity and Adrenocortical Drive in Women with Polycystic Ovary Syndrome

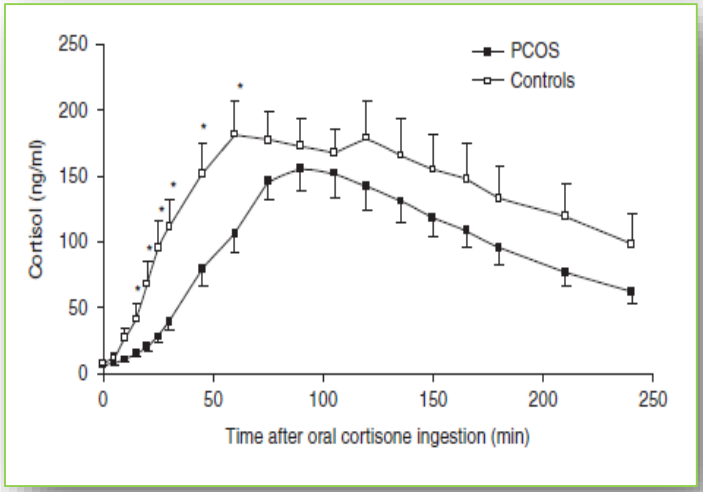
Dimitra A. Vassiliadi, Thomas M. Barber, Beverly A. Hughes, Mark I. McCarthy, John A. H. Wass, Stephen Franks, Peter Nightingale, Jeremy W. Tomlinson, Wiebke Arlt, and Paul M. Stewart

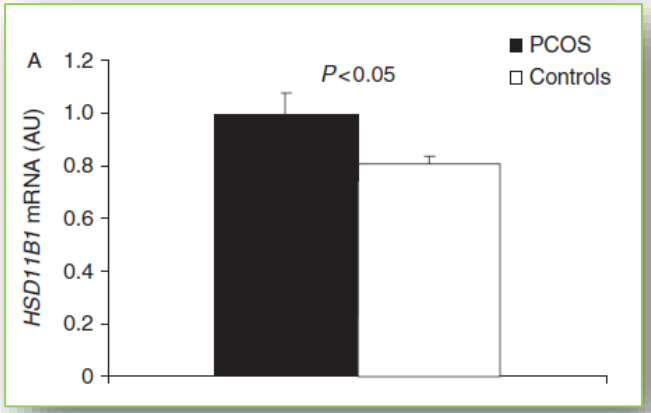


JCEM 2009

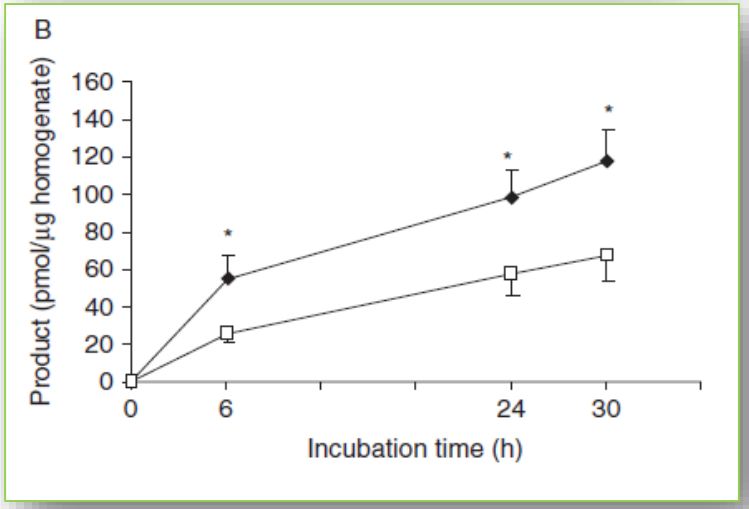
Tissue-specific dysregulation of 11*b-HSD* type 1 in overweight/obese women with PCOS and weight-matched controls

Liver HSD11B1 activity, significantly lower in PCOS cases





Subcutaneous abdominal adipose tissue:
HSD11B1 mRNA levels and
11b- HSD1 activity,
significantly higher in PCOS cases



Gambineri EJE 2014

PCOS

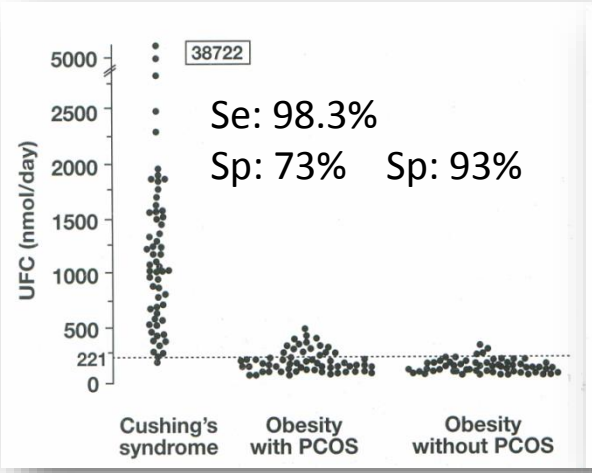
CS

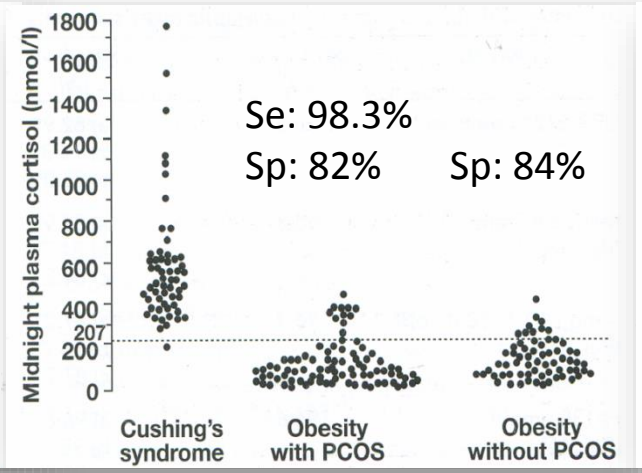
Screening for CS in obese women with and without PCOS

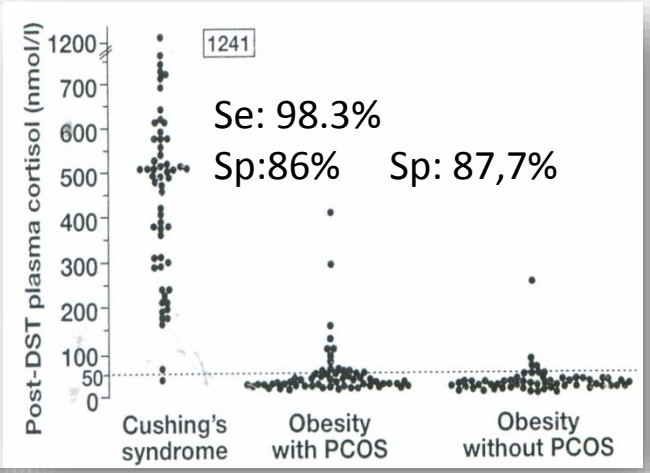
Table 1 - *Characteristics of the study subjects.*

Subjects	Age yr	BMI kg/m²	Plasma cortisol, nmol/l 08:00 h	17:00 h	24:00 h	1-mg DST	08:00/24:00 h ratio	UFC nmol/24 h
Cushing's syndrome	34.3±1.01**	30.6±1.26**	589.5±28.92**	597.1±43.79**	578.5±39.26**	470.6±30.06**	1.1±0.05**	1831.0±661.60**
Obese with PCOS	24.4±0.73	36.0±0.92*	392.3±19.65	233.4±18.00	130.0±14.18	41.1±8.10	6.3±0.87	173.6±12.19*
Obese without PCOS	4.5±1.20	39.2±1.09	345.1±15.82	209.4±22.61	109.6±12.63	28.1±4.67	5.8±0.78	123.0±7.71

**p<0.0001 vs obese patients with and without polycystic ovary syndrome (PCOS); *p<0.005 vs obese patients without PCOS.







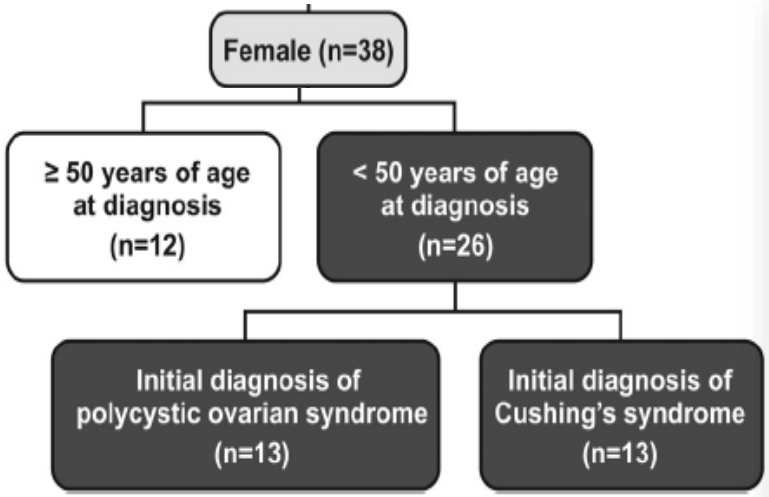
PCOS: 60; simple obesity: 58; CS: 57 patients

Putignano P et al JEI 2003

Polycystic ovarian syndrome and Cushing's syndrome: a persistent diagnostic quandary

Jessica Brzana [a], Christine G. Yedinak [b,c], Nadia Hameed [a], Adeline Plesiu [a], Shirley McCartney [b,c], Maria Fleseriu [a,b,c,*]

[a] Department of Medicine, Division of Endocrinology, Portland, OR, USA
[b] Department of Neurological Surgery, Portland, OR, USA
[c] Northwest Pituitary Center, Oregon Health & Science University, Portland, OR, USA



Prevalence of clinical symptoms and signs based on initial diagnosis.

Symptom/sign	CD after PCOS ($n=13$)	CD (no PCOS) ($n=13$)	P value
Hirsutism	100.0%	69.2%	0.03
Menstrual irregularities	100.0%	72.7%	0.02
Facial rounding	100.0%	76.9%	0.08
Supraclavicular fullness	100.0%	76.9%	0.07
Dorsocervical fullness	92.3%	84.6%	0.56
Weight gain	92.3%	100.0%	0.33
Central adiposity	92.3%	92.3%	1.0
Facial plethora	84.6%	69.2%	0.37
Acne	84.6%	53.8%	0.09
Depression	69.2%	53.8%	0.44
Easy bruising	69.2%	61.5%	0.69
Violaceous striae	61.5%	61.5%	1.0
Alopecia	61.5%	30.8%	0.13
Subjective proximal weakness	53.8%	61.5%	0.70
Hypertension	53.8%	69.2%	0.44
Sleep disturbance	46.2%	61.5%	0.45
Diabetes mellitus	30.8%	15.4%	0.37

European Journal of Obstetrics & Gynecology and Reproductive Biology 175 (2014)

How common are polycystic ovaries and the polycystic ovarian syndrome in women with Cushing's syndrome?

G. A. Kaltsas*, M. Korbonits*, A. M. Isidori*, J. A. W. Webb†, P. J. Trainer*, J. P. Monson*, G. M. Besser* and A. B. Grossman*

13 premenopausal women with CS
(32 yrs range 18-39 yrs)

Hyperandrogenism	13/13 (100%)
Irsutism	13/13 (100%)
Acne	7/13 (53%)
male pattern alopecia	5/13 (39%)
Acanthosis nigricans	0/13
Menstrual irregularity	9/13 (70%)
oligomenorrhoea	4/9
amenorrhoea	4/9
polymenorrhoea	1/9
Normal menstrual pattern	4/13 (30%)
Succesful pregnancies	4/13 (31%)
Spontaneous abortion	1/13 (8%)
Obesity (BMI > 30)	2/13 (15%)
DBT or IGT	0/3

Table 3 Ovarian ultrasonographic characteristics in 13 patients with Cushing's syndrome

CS patients	Ovarian size (ml)		Ovarian morphology		
	Right	Left	Right	Left	Diagnosis
1	3·9	2·3	Normal	Normal	
2	11·6	7·4	Normal	Normal	? PCO R
3	2·8	2·7	Normal	Normal	
4	4·5	3·3	Normal	Normal	
5	12·8	4·9	Normal	Normal	
6	6·3	5·6	Multiple follicles	Multiple follicles	PCO
7	12·6	13	Multiple follicles	Multiple follicles	PCO
8*	7·3	9·6	Multiple follicles	Multiple follicles	PCO
9*	11	Not seen	5 follicles	–	
10*	7·1	9·3	Normal	Multiple follicles	PCO
11*	3·1	3·3	Normal	Normal	
12*	8·5	3·9	Multiple follicles	Multiple follicles	
13*	12	7·3	Normal	Multiple follicles	PCO

* Women with CS and oestradiol levels > 140 pmol/l.

Clinical Endocrinology (2000) **53**, 493–500

Testosterone and Bioavailable Testosterone Help to Distinguish between Mild Cushing's Syndrome and Polycystic Ovarian Syndrome*

CS= 20 patients; PCOS= 20 patients

Test	Cushing's syndrome	PCOS	p-Value
age (years)	34.0±6.7	29.8±7.6	0.08
BMI (kg/m^2)	37.7±1.7	37.7±1.6	0.99
total testosterone (nmol/L)	0.75±0.08	1.75±0.17	<0.0001
bioavailable testosterone (nmol/L)	0.29±0.08	0.56±0.08	0.02
SHBG (nmol/L)	28.4±4.1	28.0±4.6	0.95
FAI (testosterone/SHBG)	3.43±0.66	9.30±1.60	0.003

All values are mean±SEM, except age, which is mean±SD

Parameter (cut-off)	Sens. %	Spec. %
TT (1.39 nmol/l)	95	70
BT (0,24 nmol/l)	75	80
FAI (5,7)	88	60

Pall ME et al Horm Metab Res 2008

Conclusions 1

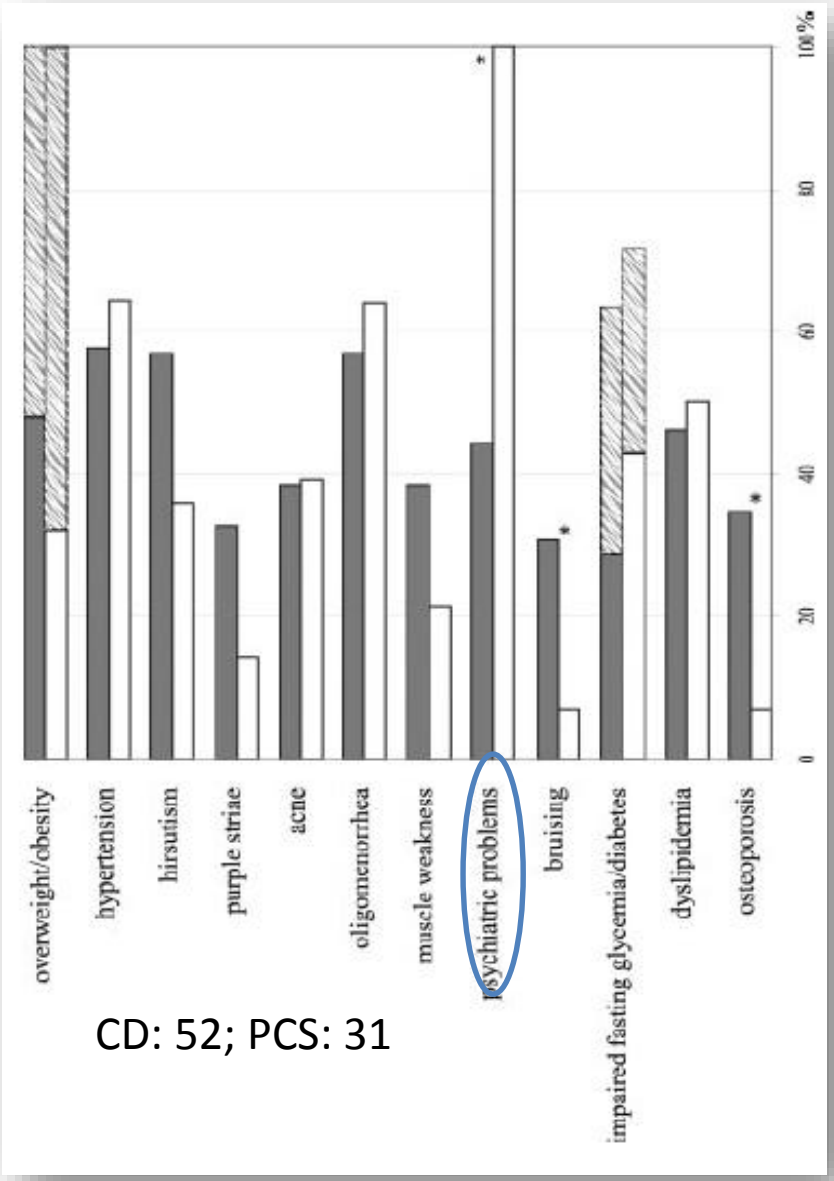
- Among the uncertainties surrounding the etiology of PCOS the role of altered cortisol metabolism is prominent

- PCOS may be a manifestation of CS and the likelihood of a diagnosis of CS increases, however, as the overlap of clinical features increases

- Compared to the high prevalence of PCOS, CS is relatively uncommon but should always be considered in the differential diagnosis to avoid the long-term consequences of a delay diagnosis of CS

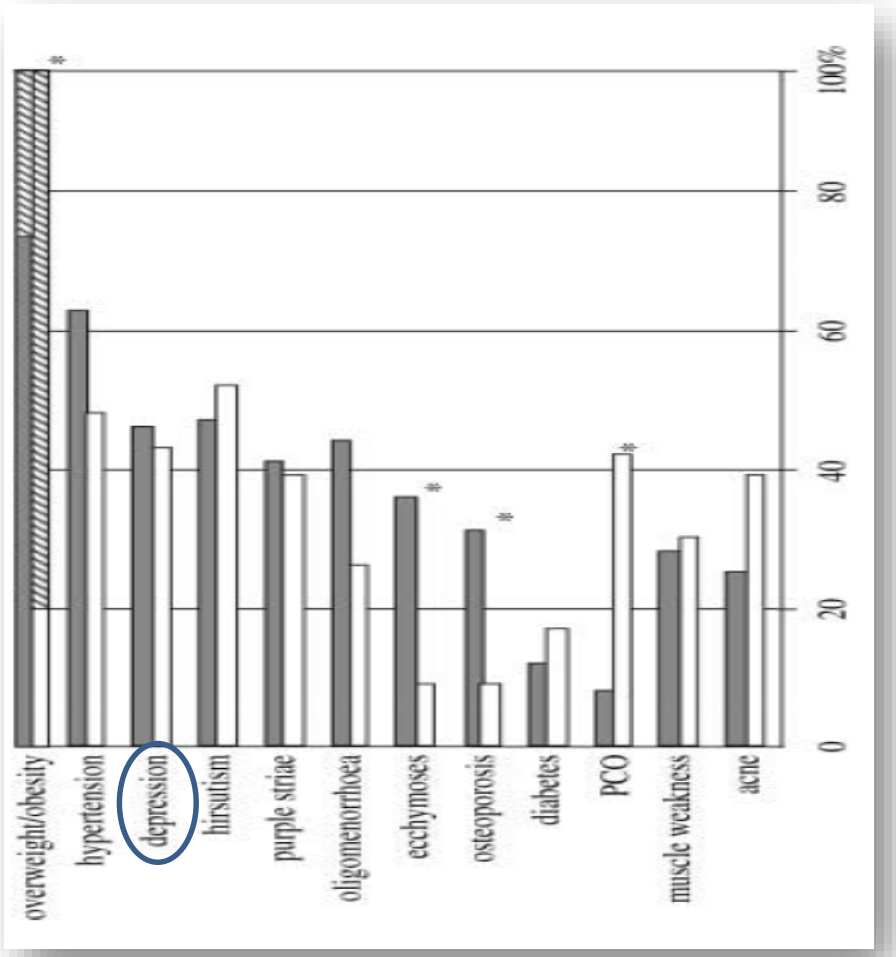
PSEUDO-CUSHING AND DEPRESSION

Clinical charcteristic in patients with CS (grey bar) and with PCS (white bar)



CD: 52; PCS: 31

Tirabasi et al JCEM 2010



Pecori Giraldi et al Clin Endocrinol 2007

Cortisol in the onset and course of major depression disorder (MDD)

- Diurnal rhythms in cortisol are disturbed in around half the cases of MDD *(Sachar et al. 1973)*
- There is increased resistance to the feedback action of GC on the activity of the HPA axis in a proportion of cases *(Carroll et al. 1968; Carroll, 1982);*
- The post-awakening surge in cortisol is accentuated in those at risk for MDD *(Portella et al. 2005);*

FUNCTIONAL HYPERCORTICISM

epiphenomena of depression?

role in the onset, recovery or course of a depressive episode?

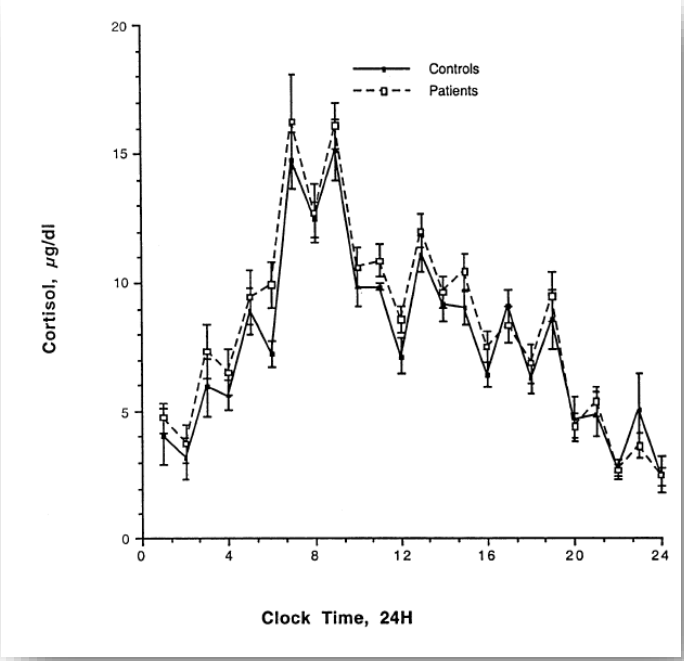
Twenty-Four-Hour ACTH and Cortisol Pulsatility in Depressed Women

Elizabeth A. Young, M.D, Nichole E. Carlson, M.S., and Morton B. Brown, Ph.D.

NEUROPSYCHOPHARMACOLOGY 2001

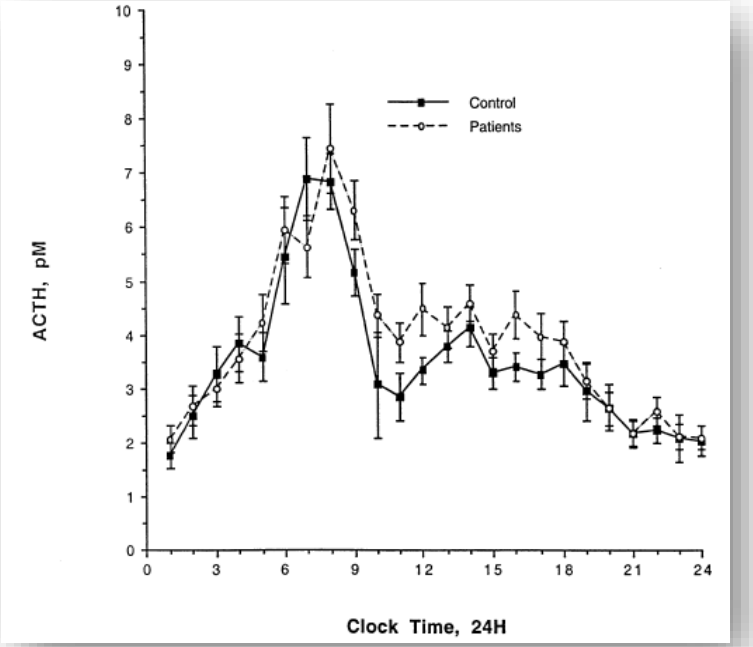
25 premenopausal depressed; 25 controls

AUC: 10,712 ± 3,611 (SD) in controls
AUC 12,051 ± 4,023 (SD) in patients (p 0.089)
Baseline AUC p= 0.064



Hypercortisolism in 24% of patients
(22-38% other studies)

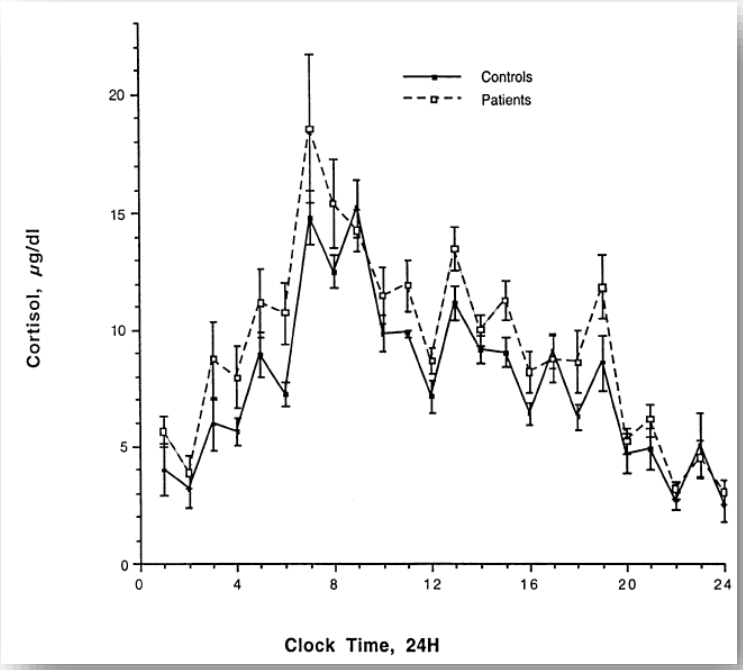
AUC 4,950 ± 1,875 (SD) in controls
AUC 5,635 ± 2,104 (SD) in patients
Baseline AUC p=0.045



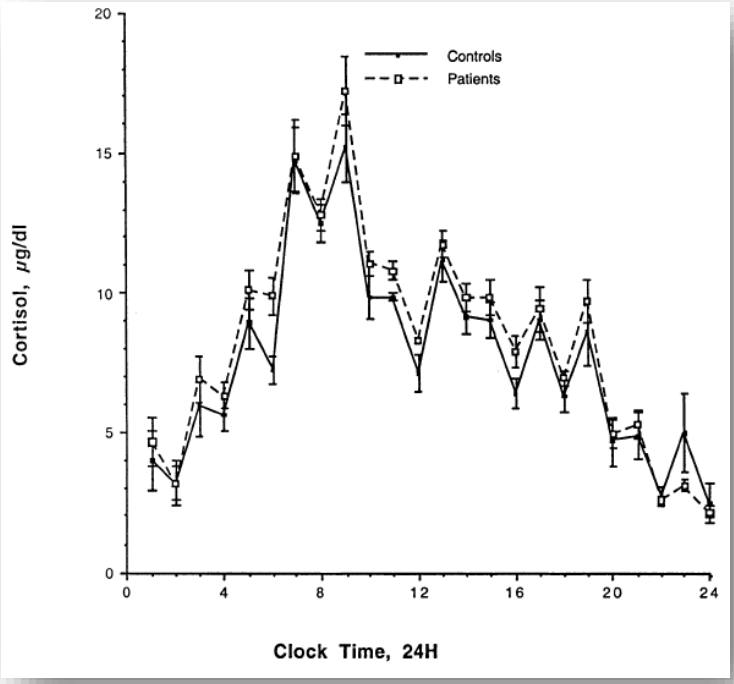
AUC per cortisolo e ACTH è significativa solo per i valori basali (p.064 ep.045)

Cortisol profile by subtype of depression

Endogenous Depression (n=6)



Atypical Depression (n=6)



Mean values during day

- *overall group: 8.36 ±2.9 mcg/dl*
- *atypical depression: 8.38 ± 1.9 mcg/dl*
- *endogenous depression: 12.17 ± 4 mcg/dl*

No correlation between severity and cortisol levels (F 2.46, r=0.11, p=0.13).

Young et al. NEUROPSYCHOPHARMACOLOGY 2001

Diurnal Activity and Pulsatility of the Hypothalamus-Pituitary-Adrenal System in Male Depressed Patients and Healthy Controls

MICHAEL DEUSCHLE, ULRICH SCHWEIGER, BETTINA WEBER, ULRIKE GOTTHARDT, ANDREAS KÖRNER, JURGEN SCHMIDER, HARALD STANDHARDT, CLAAS-HINRICH LAMMERS, AND ISABELLA HEUSER

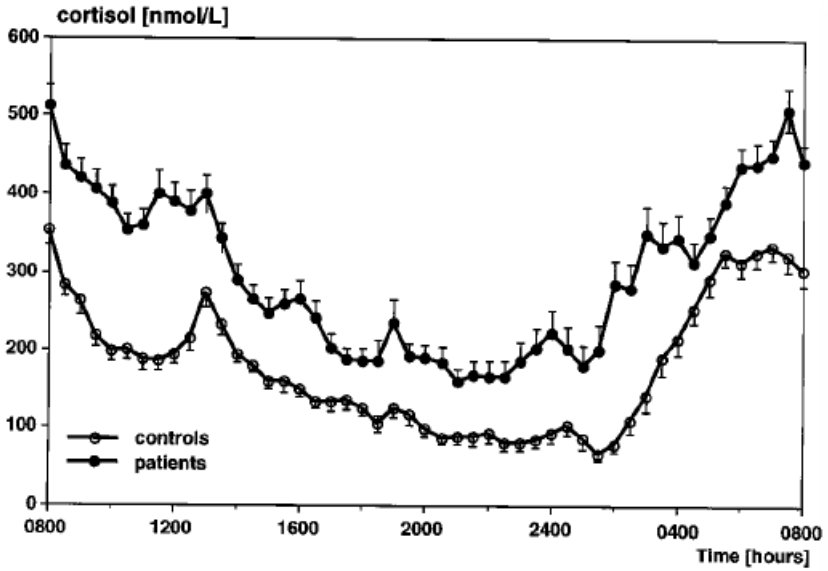


FIG. 1. Diurnal profiles of mean plasma cortisol in depressed patients and healthy controls (mean ± SEM).

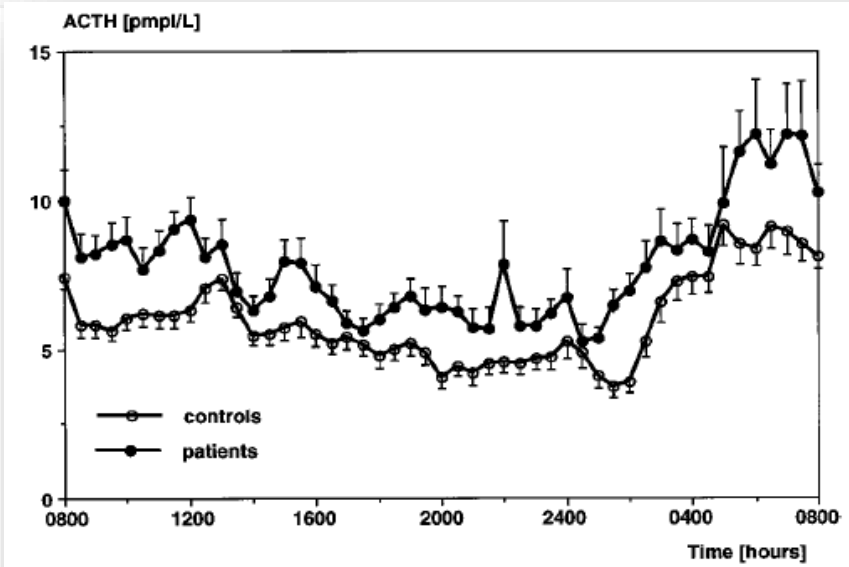
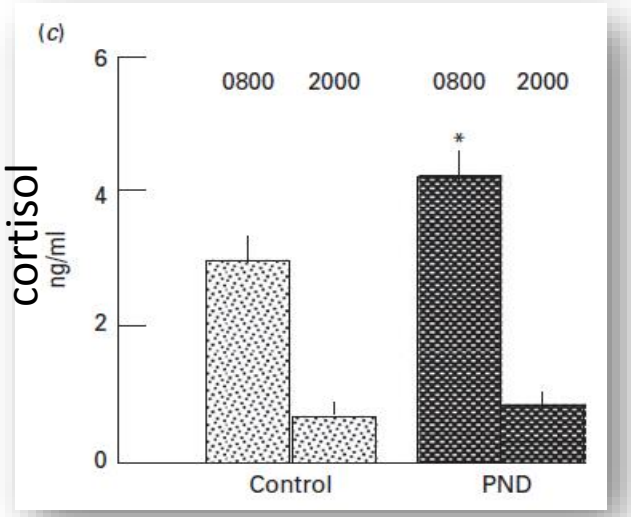


FIG. 2. Diurnal profiles of mean plasma ACTH in depressed patients and healthy controls (mean ± SEM).

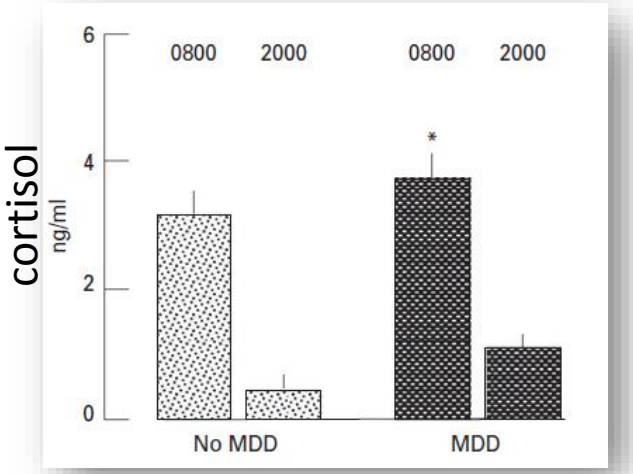
JCEM 1997

Higher levels of morning cortisol as a risk factor for subsequent MDD



Morning cortisol at age 13 in offspring of mothers with postnaltal depression (Halligan et al 2004)

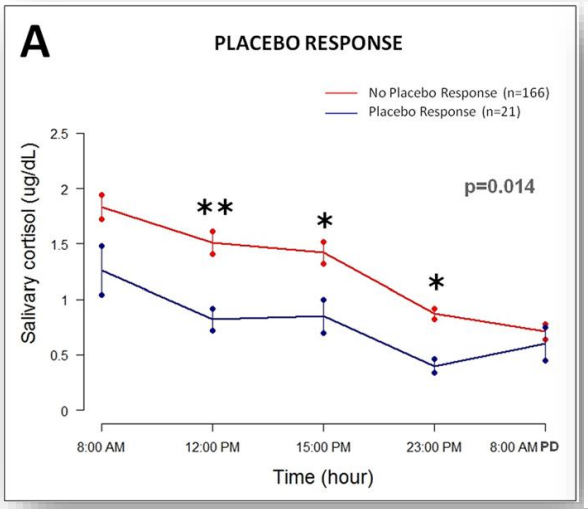
Salivary cortisol in adolescent who will develop first event of MDD during a 4 yrs follow-up (Goodyer et al 2000)

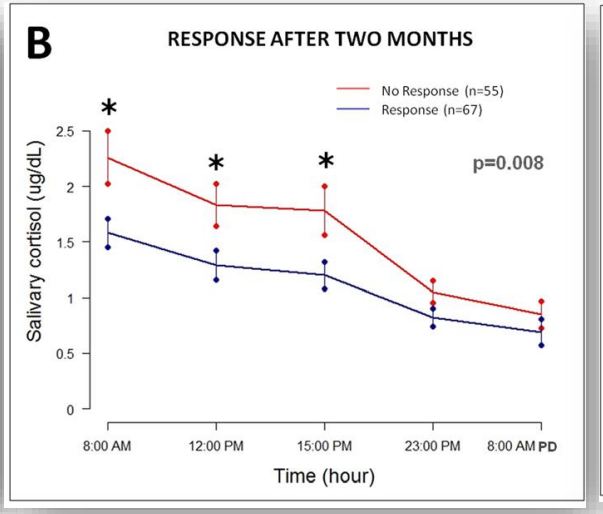


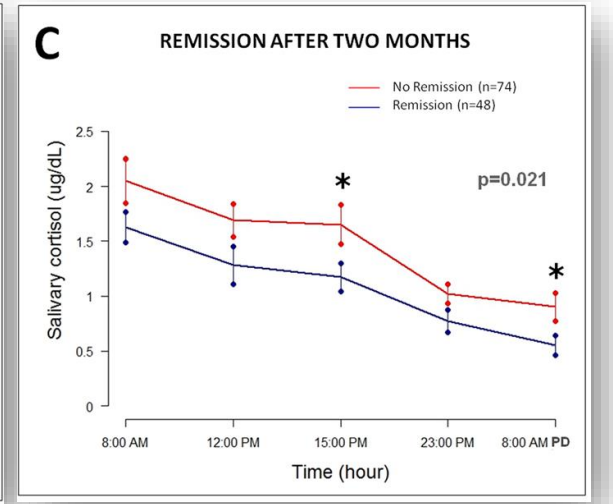
Differences in baseline circadian salivary cortisol levels between:

- placebo responders and non-responders (A),
- Fluoxetine responders and non-responders (B),
- Remitters (C)

fluoxetine







P= 0.014,

P= 0.008

P= 0.021

rs242939 polymorphism (CRHR1) associated with early response to fluoxetine

Ventura-Juncá et al. BMC Psychiatry 2014, 14:220

Concomitant Medication Use Can Confound Interpretation of the Combined Dexamethasone-Corticotropin Releasing Hormone Test in Cushing's Syndrome

Elena Valassi, Brooke Swearingen, Hang Lee, Lisa B. Nachtigall, Daniel A. Donoho, Anne Klibanski, and Beverly M. K. Biller

JCEM 94: 4851–4859, 2009

TABLE 4. Comparison between No Meds and Meds tests using different cutoff points

Test	Cutoff[a]	Sensitivity % (95% CI)			Specificity % (95% CI)		
		Meds	No Meds	*P* value	Meds	No Meds	*P* value
Post- LDDST cortisol	1.4 (38)	73.3 (64.7–81.9)	85.7 (78.9–92.5)	0.77	70 (59–81)	96.1 (92.4–99.9)	0.014
Post-LDDST cortisol	1.8 (50)	70 (61–79)	85.7 (78.9–92.5)	0.61	80 (70.7–89.3)	96.1 (92.4–99.9)	0.08
15 min post-CRH cortisol	1.4 (38)	88.2 (82.6–93.9)	93.1 (88.4–97.8)	0.88	75 (64.8–85.2)	92.3 (87–97.6)	0.10
15 min post-CRH cortisol	1.8 (50)	82.3 (75.5–89.1)	89.6 (83.9–95.4)	0.81	80 (70.6–89.3)	96.1 (92.4–99.9)	0.08
15 min post-CRH cortisol	2.5 (70)	70.5 (62.2–79)	86.2 (79.6–92.8)	0.60	90 (83.2–96.8)	96.1 (92.4–99.9)	0.87
15 min post-CRH ACTH	16 (3.5)	75 (66.3–83.7)	84.6 (77.3–91.9)	0.76	85 (76.8–93.2)	96.1 (92.4–99.9)	0.77
15 min post-CRH ACTH	27 (5.9)	64.2 (54.4–74.2)	73 (63.8–82.3)	0.75	95 (90.1–99.9)	100	0.90

receptor antagonists (3)	
Atypical antipsychotics (5)	Olanzapine, quetiapine
Proton pump inhibitors (6)	Pantoprazole, lansoprazole, omeprazole
PPARγ antagonists (3)	Pioglitazone, rosiglitazone
Antiarrhythmics (2)	Quinidine
β−Adrenoceptor blockers (2)	Propranolol
Benzodiazepine sedatives (2)	Clonazepam
Anticonvulsants (2)	Tiagabine, topiramate

PPARγ, Peroxisome proliferator-activated receptor-γ; SNRI, serotonin-noradrenaline reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors. Number of tests performed on each class of medication is indicated in *parentheses*.

Pathophysiology of Hypercortisolism in Depression: Pituitary and Adrenal Responses to Low Glucocorticoid Feedback

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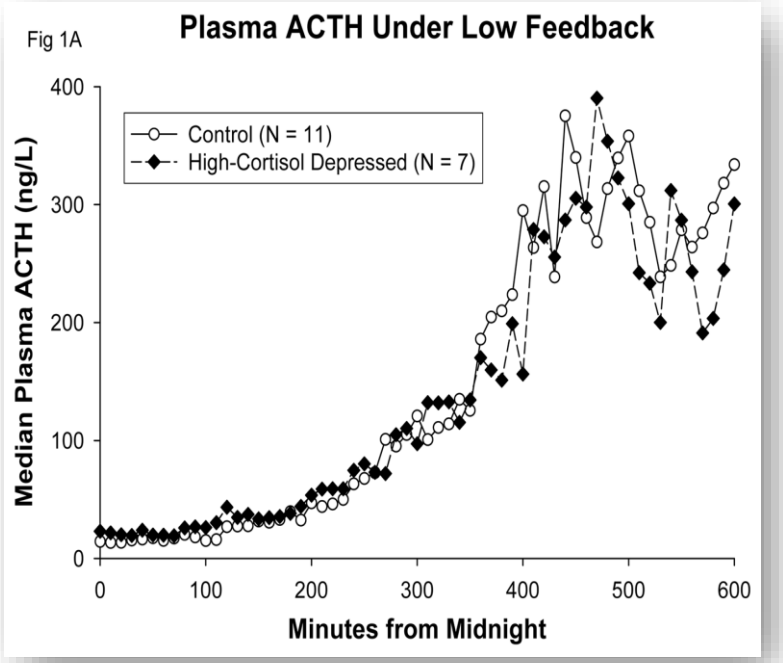
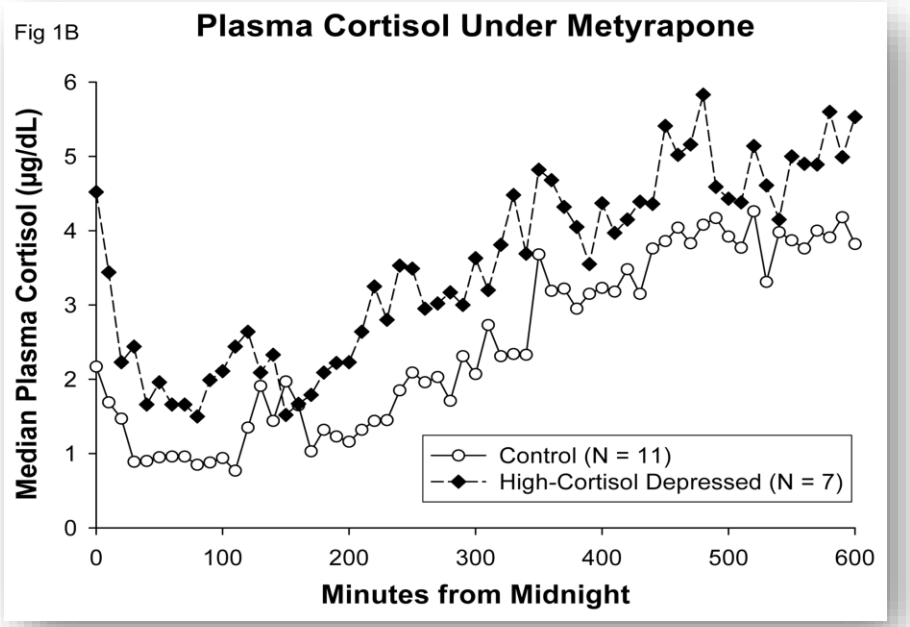
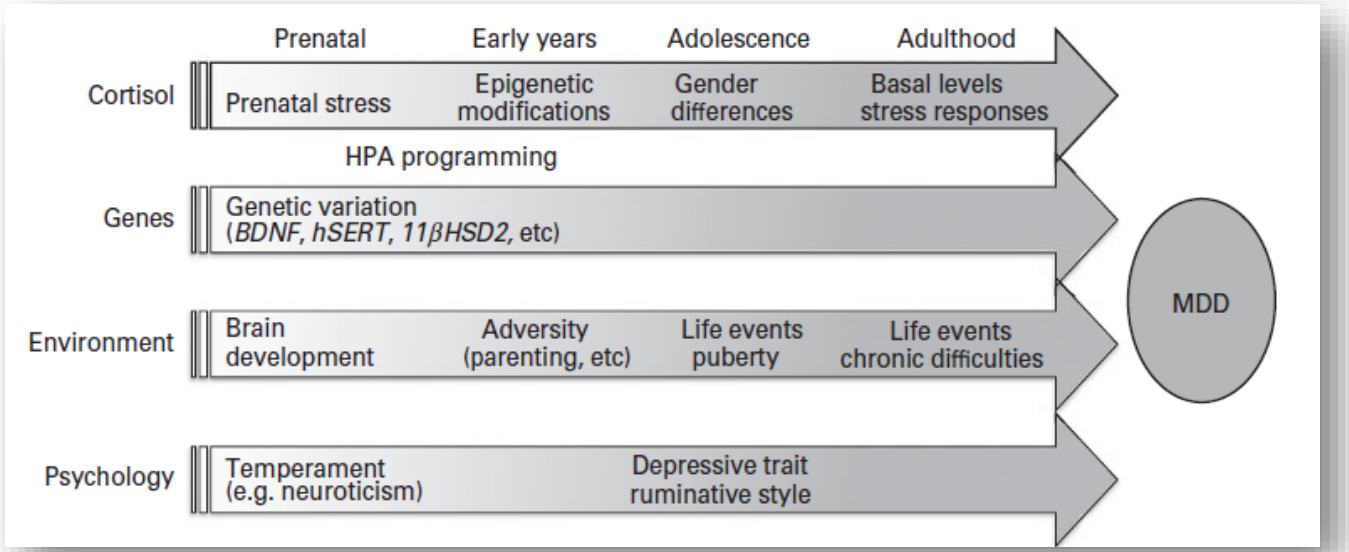




Acta Psychiatr Scand. 2012

Conclusions 2



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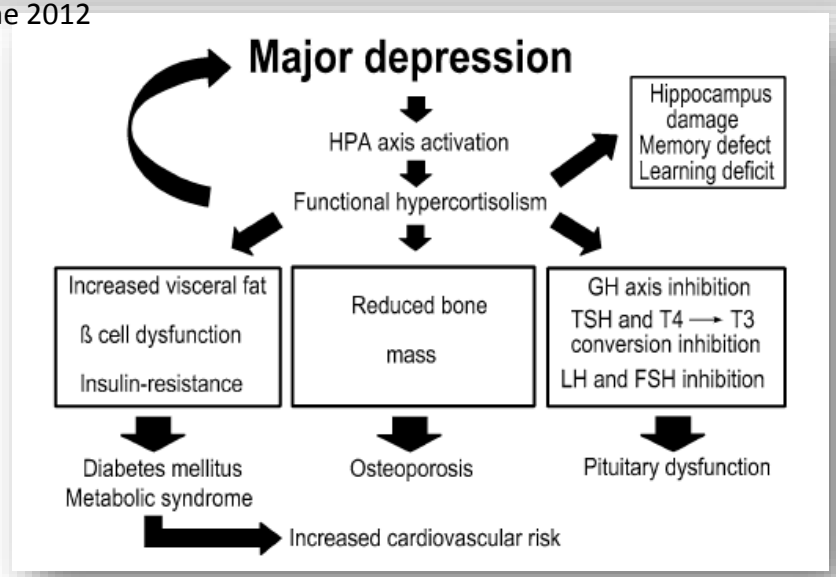

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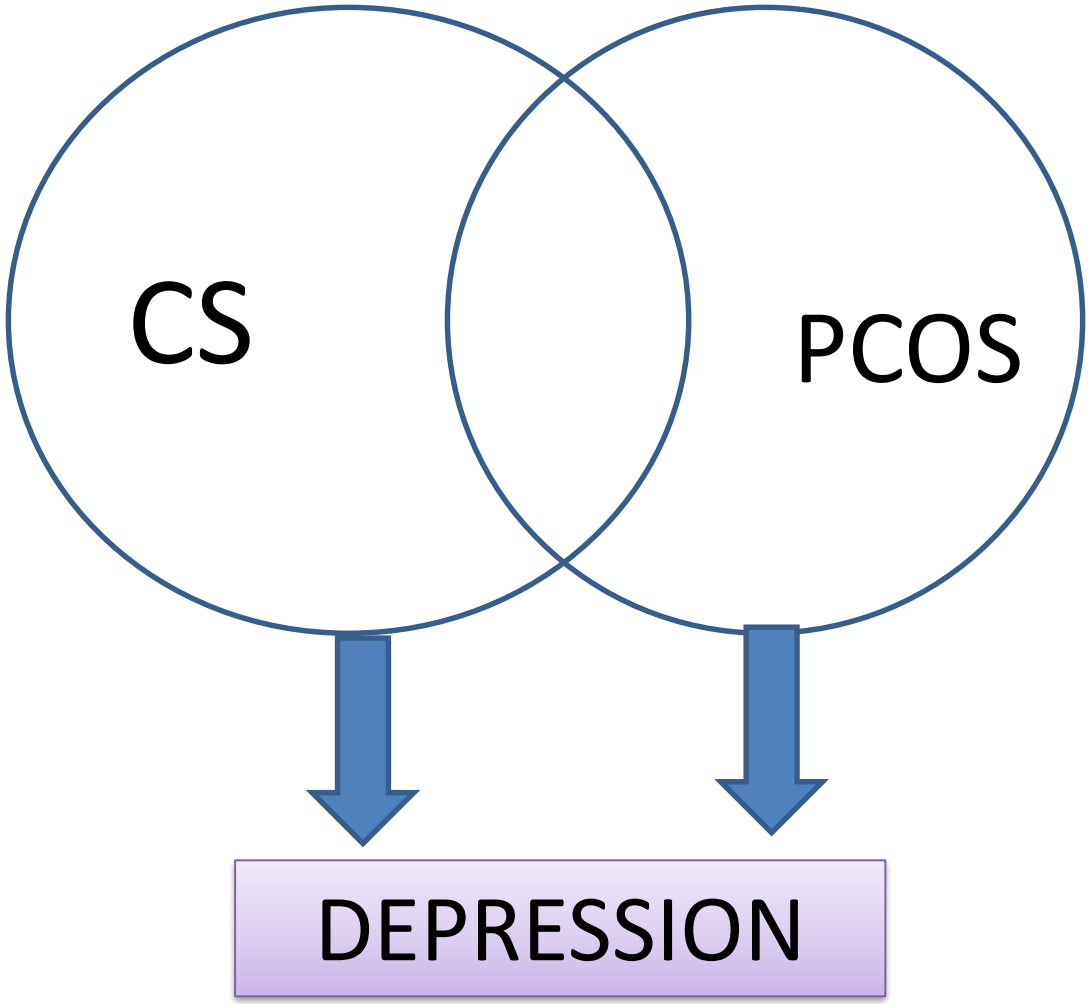
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