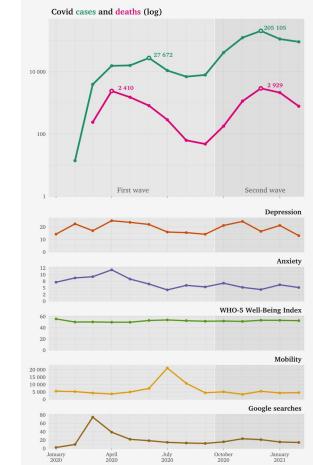
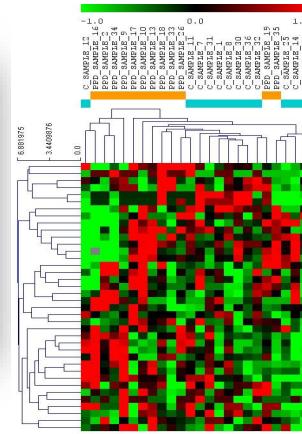
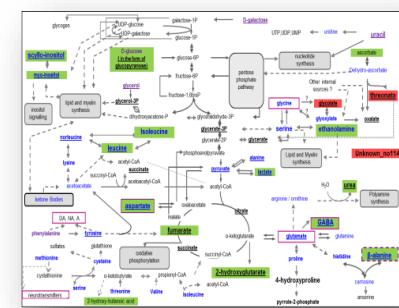
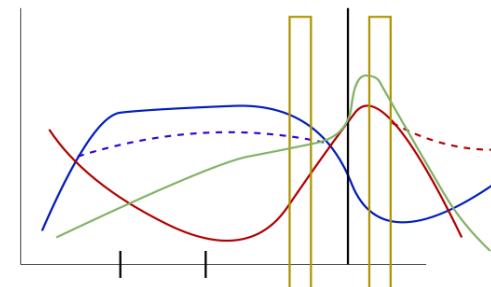


Förlossningsdepression- från molekyl till samhälle



Skalkidou, Alkistis

Instutionen för kvinnors och barns hälsa



UPPSALA
UNIVERSITET

Jäv

- Inget jäv



UPPSALA
UNIVERSITET

DEPRESSION HOS KVINNER

► Kvinnor löper ökad risk för humörstörningar under perioder med hormonella fluktuationer

- premenstruellt
- postpartum
- perimenopausalt

Women have 1.5-2.5 x rate of depression vs. men
Lifetime prevalence: 21.3% women and 12.7% men

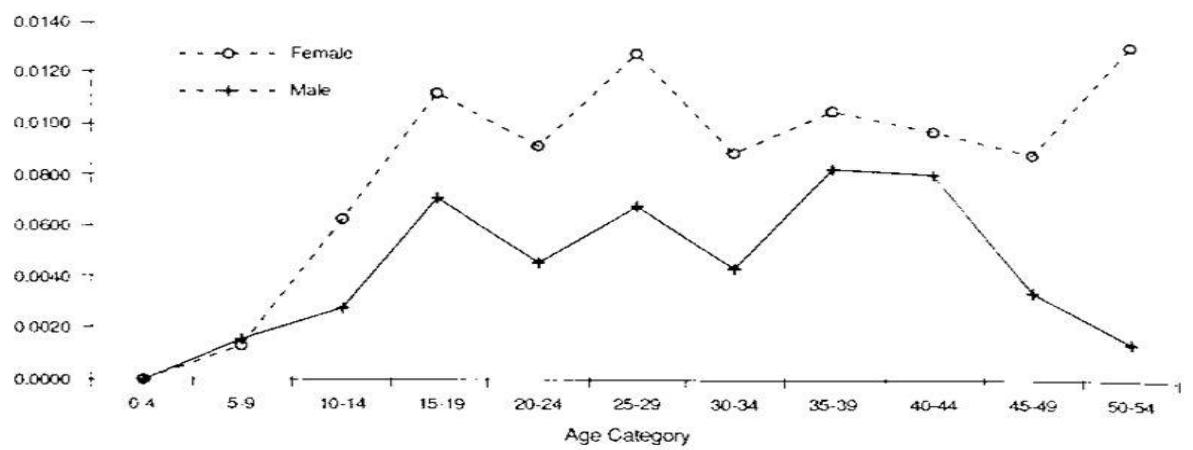


Fig. 1. MDE hazard rates by age and sex.

WOMHER

Women's
Mental Health
during the
Reproductive
Lifecycle

CENTRUM FÖR
KVINNORS PSYKISKA
HÄLSA - WOMHER

Utlysning av doktorandtjänster

Världsunik satsning på kunskap om kvinnors psykiska hälsa

POSTPARTUM DEPRESSION

- Hela 12-20% av alla kvinnor
- Depressionen kan börja så tidigt som 24 timmar eller så sent som flera månader efter förlossningen
- Ofta underdiagnosticerad, underbehandlad



Gavin et al, Obstet Gynecol, 2005



UPPSALA
UNIVERSITET

Etablerade riskfaktorer

- depressionshistoria
- **depression** och ångest under graviditeten
- **neuroticism**
- dåligt självförtroende
- postpartum blues
- **stressiga** livshändelser (inklusive barnomsorgsrelaterade stressfaktorer)
- dåligt förhållande
- dåligt **socialt** stöd
- låg socioekonomisk status (SES)
- vara singel
- oönskad graviditet
- **obstetriska** stressfaktorer
- **svårt spädbarnstemperament**

O'Hara & McCabe, Annu Rev Clin Psychol, 2013



UPPSALA
UNIVERSITET

Varför viktigt ?

- Förstå mekanismer bakom depression
- Förebygga
 - obstetriska komplikationer
 - framtida depressiva episoder/ sjukskrivning hos unga kvinnor
 - negativa effekter på barnen
 - Suicid
 - sociala/ekonomiska konsekvenser



SPECTRUM OF POSTPARTUM MOOD DISORDERS

Postpartum Blues

50-85% mothers in first 2 weeks postpartum

Symptoms: irritability, anxiety, fluctuating mood, & increased emotional reactivity

Mild & spontaneously remits, not considered psychiatric disorder

Postpartum Depression

13% mothers in first year postpartum

Symptoms: excessive guilt, anxiety, anhedonia, depressed mood, insomnia/hypersomnia, suicidal ideation, & fatigue

Moderate to severe symptoms, prolonged course

Postpartum Psychosis

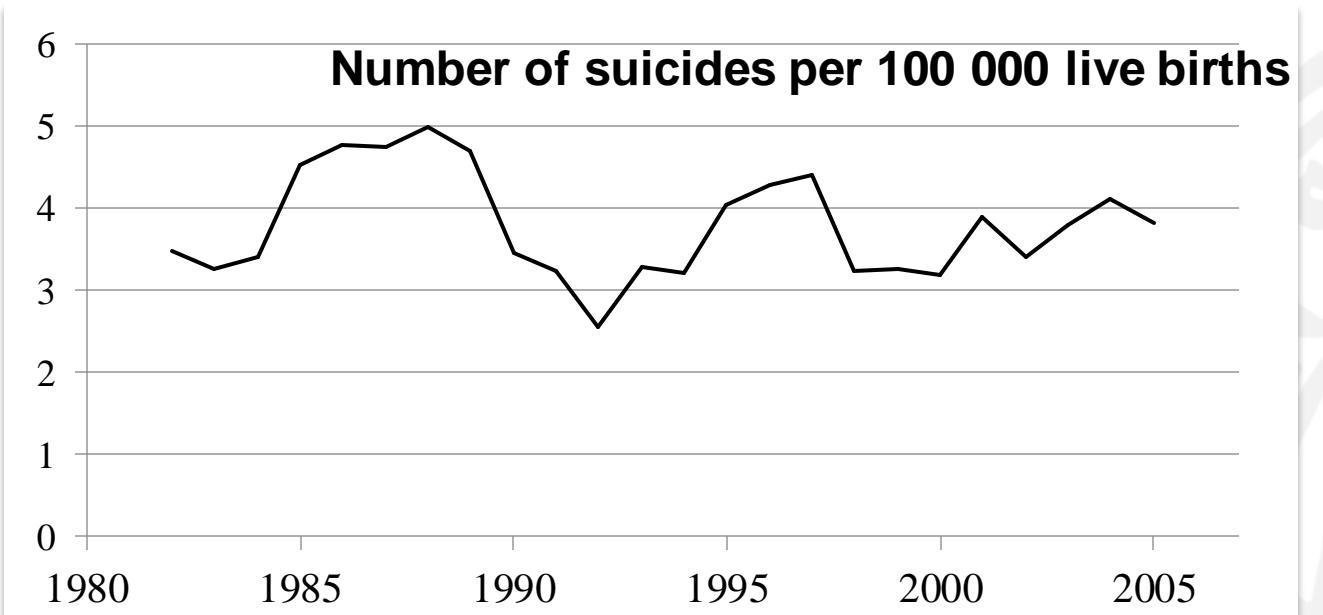
0.01% mothers in first 3 months postpartum

Symptoms: mixed or rapid cycling, agitation, delusions, hallucinations, disorganized behavior, cognitive impairment, & low insight

Severe, considered psychiatric emergency: Often necessitates hospitalization



Maternal suicides in Sweden



Esscher A, Essen B, Innala E, Papadopoulos FC, Skalkidou A, Sundstrom-Poromaa I, et al. The British journal of psychiatry : the journal of mental science. 2016;208(5):462-9.



UPPSALA
UNIVERSITET



Call to ACT

U.S. News WORLD REPORT

NEWS » News Best Countries Best States Healthiest Communities Cities America 2020 The Racial Divide Photos Events The Report

Healthcare of Tomorrow » A U.S. News virtual event series where industry leaders will discuss common priorities and perspectives on the future of healthcare. Learn more >>

[Home](#) / [News](#) / [Best States](#) / [New York News](#)

NYC Program Will Provide Home Visits to First-Time Parents

First-time parents in New York City will be entitled to up to six home visits from a health care or social services professional under a new program announced by first lady Chirlane McCray.

By Associated Press, Wire Service Content Feb. 5, 2020, at 2:24 p.m.



NEW YORK (AP) — First-time parents in [New York](#) City will be entitled to up to six home visits from a health care or social services professional under a program announced Wednesday.



UPPSALA
UNIVERSITET

Longitudinella, populations-baserade studier i Uppsala

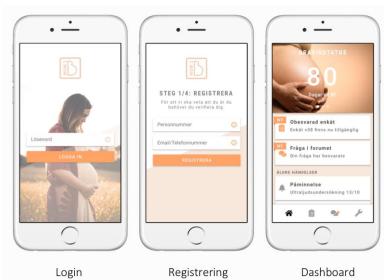
- UPPSAT studie
- BASIC/U-BIRTH studie
- Mom2B studie
pågående, n=20.000



n= 2.318



n= 6.478



UPPSALA
UNIVERSITET

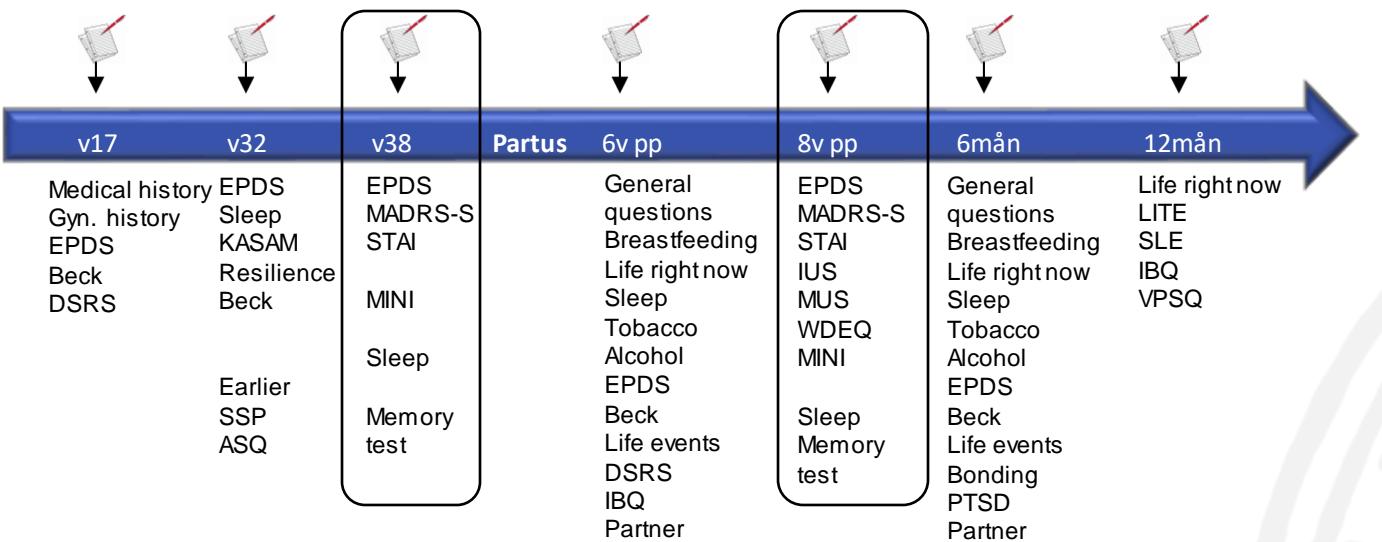
BASIC-studien



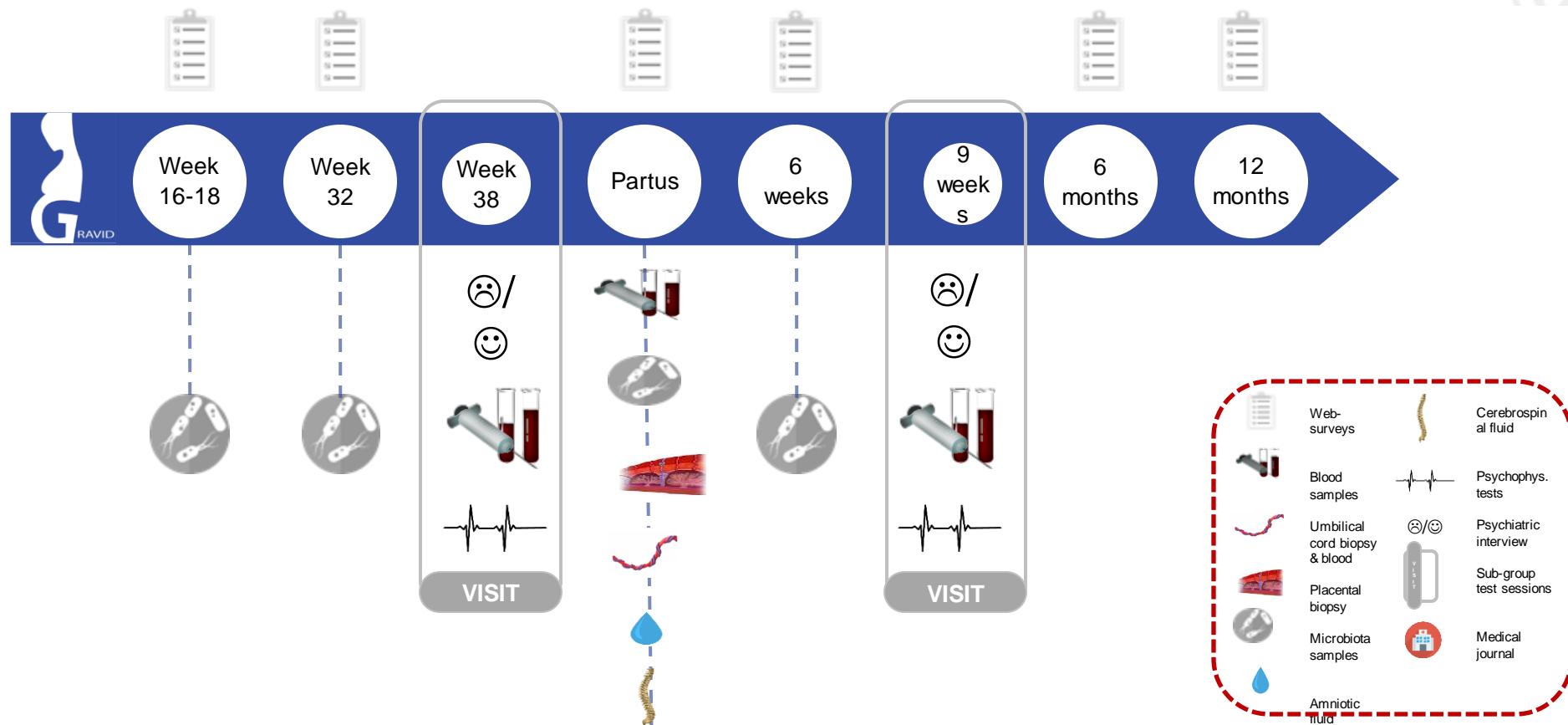
Syftet med BASIC studien är att studera biopsychosociala processer involverade i peripartum depression (PPD)

N= 6 478 graviditeter

Webb-Enkäter



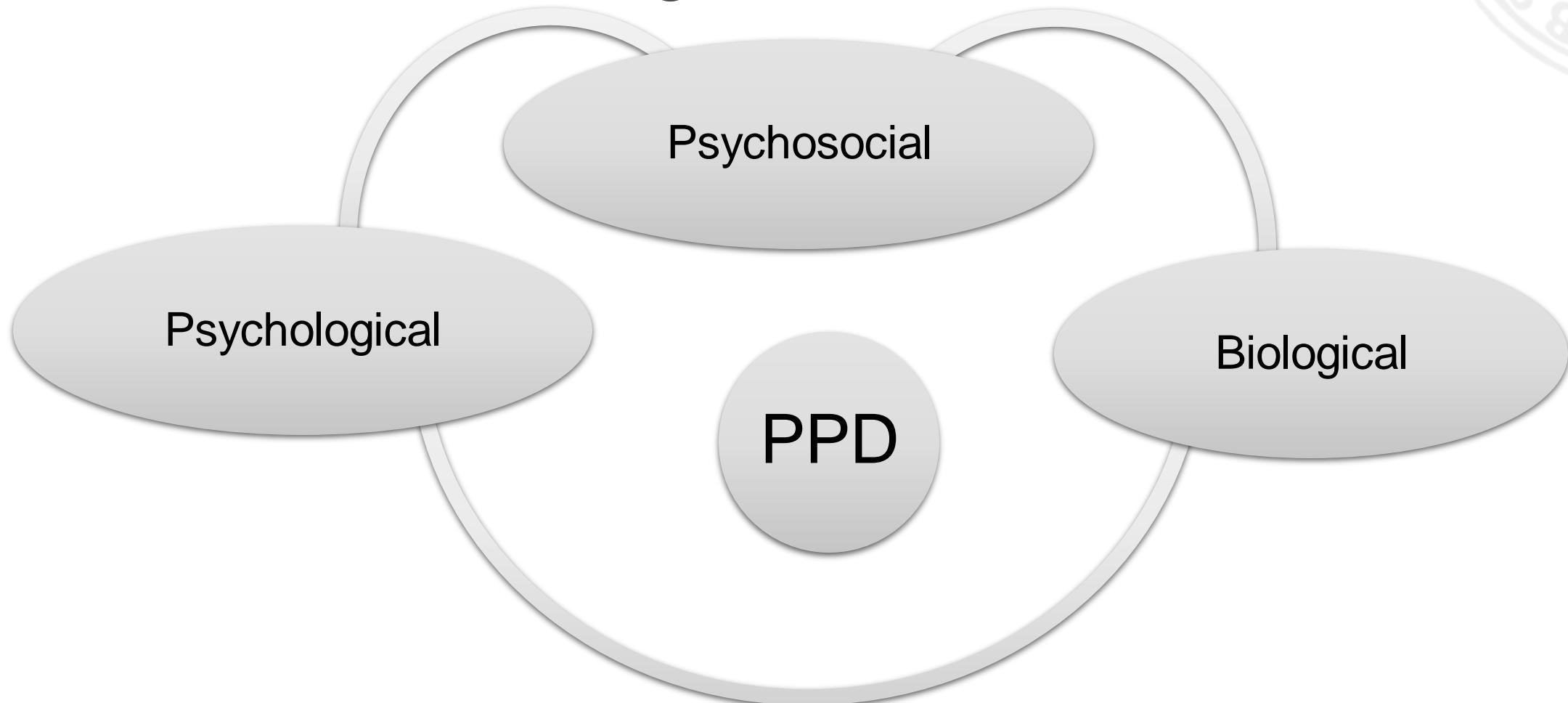
BASIC Provsamling



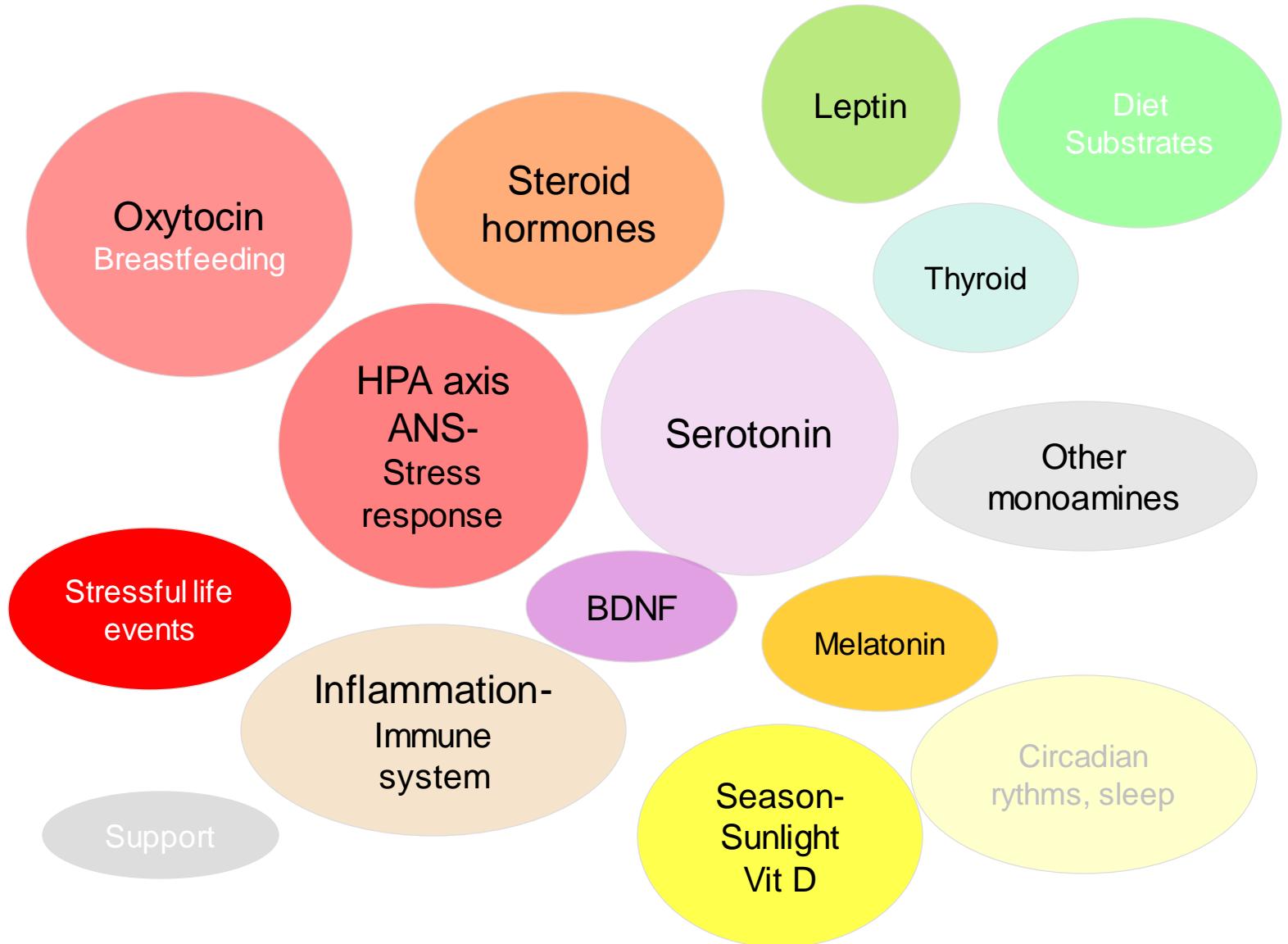
UPPSALA
UNIVERSITET



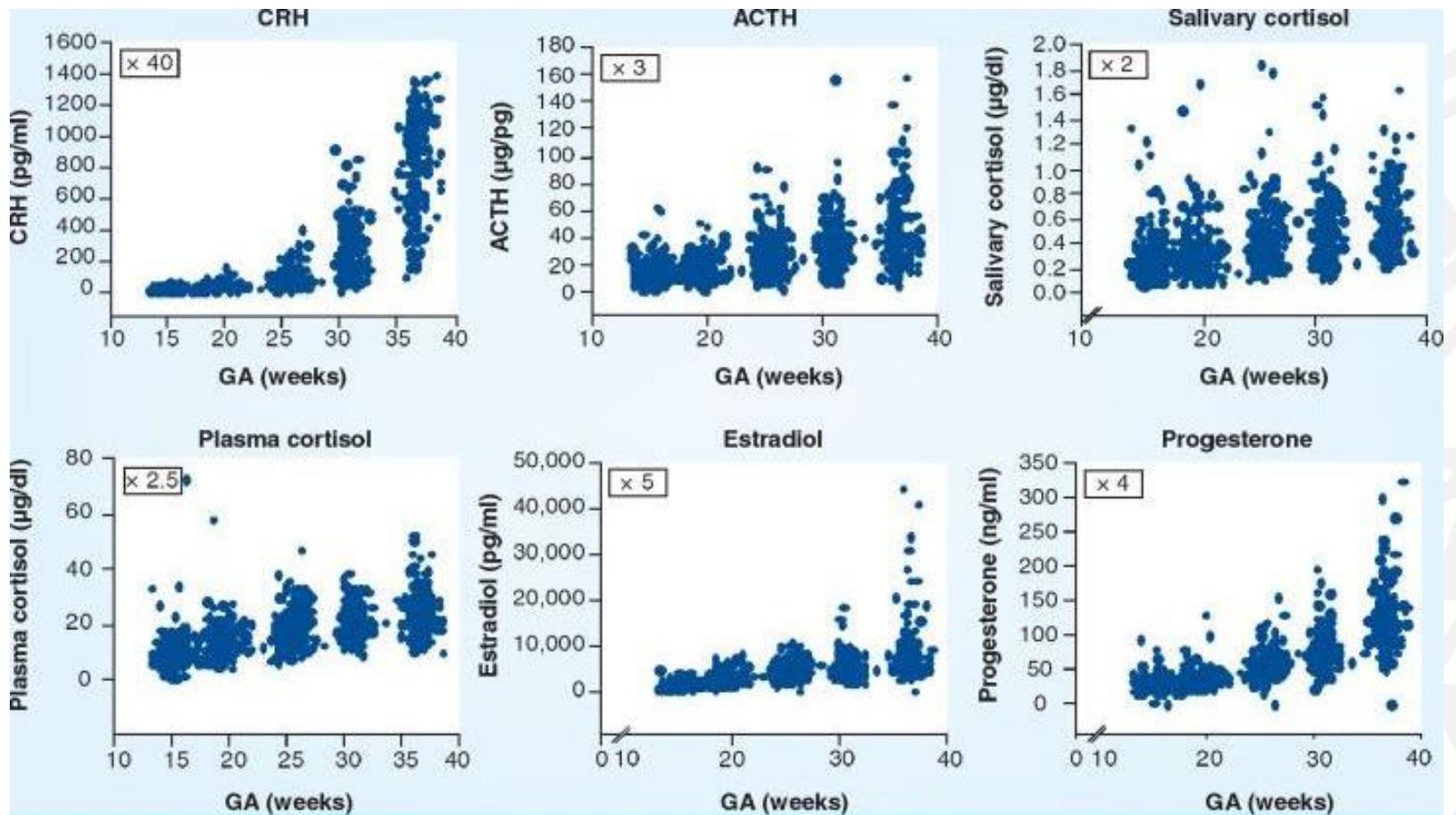
Etiologiska modellen



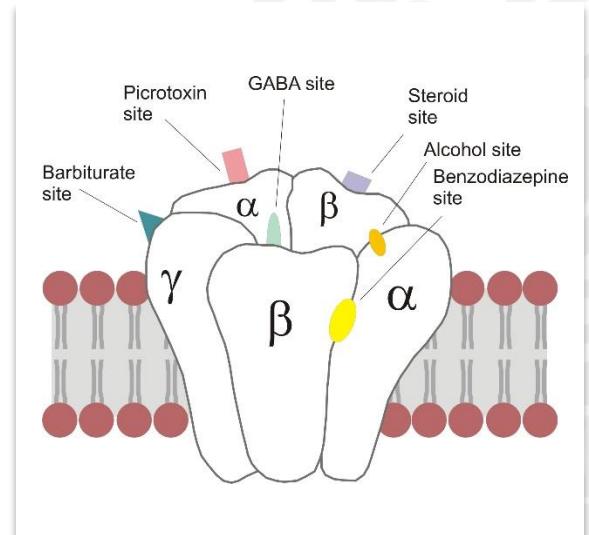
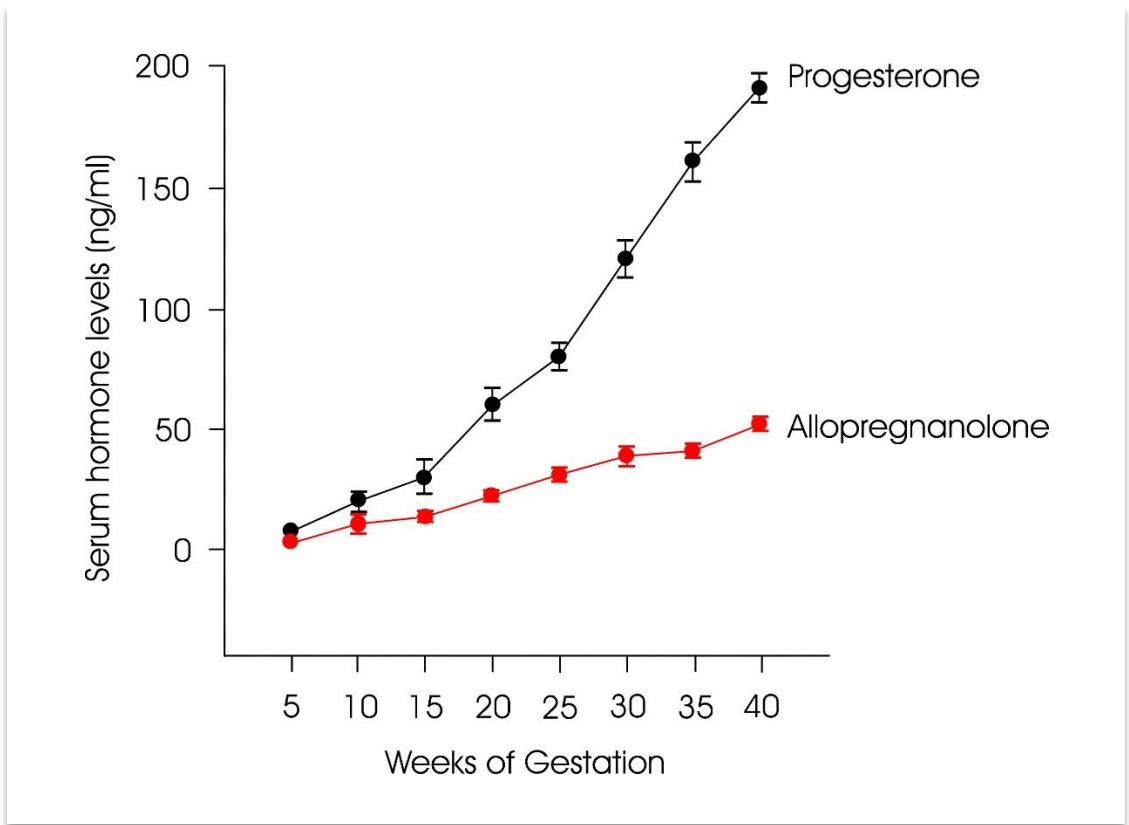
Biologin bakom PPD



Graviditetsendokrinologi



Neurosteroider under graviditet



Luisi et al, J Clin Endo Metab 2000; 85: 2429-33.



UPPSALA
UNIVERSITET

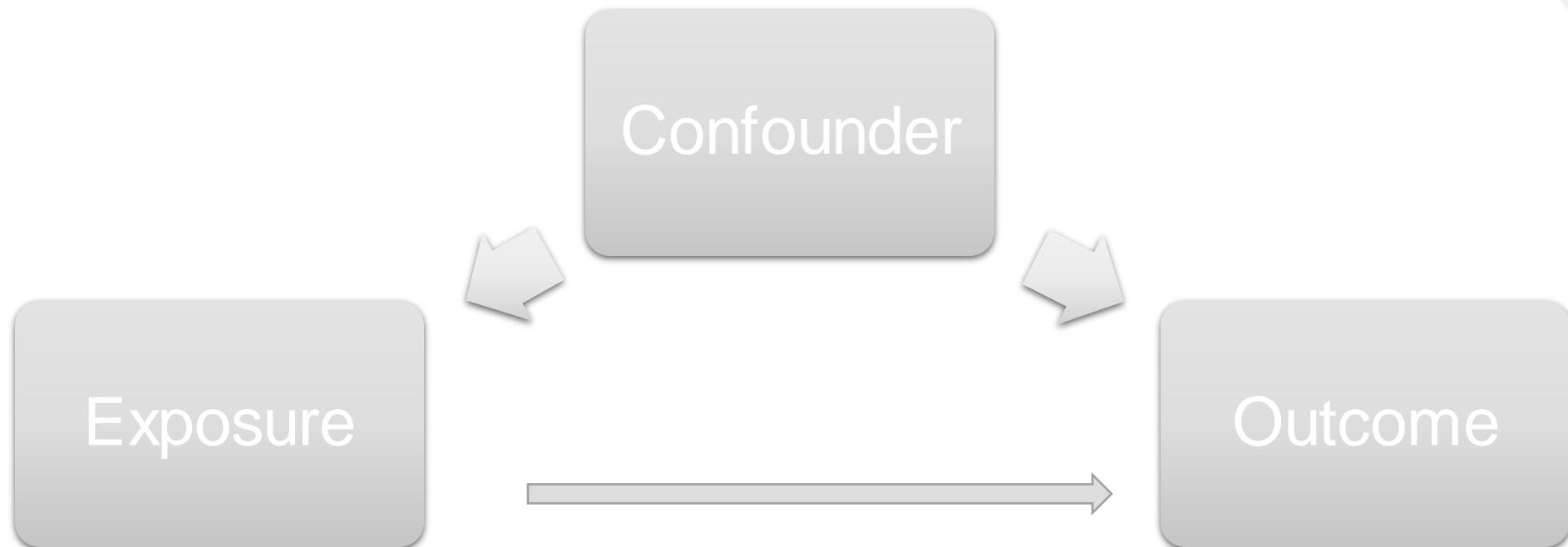
Postpartum dropp



Chrousos et al., 1998

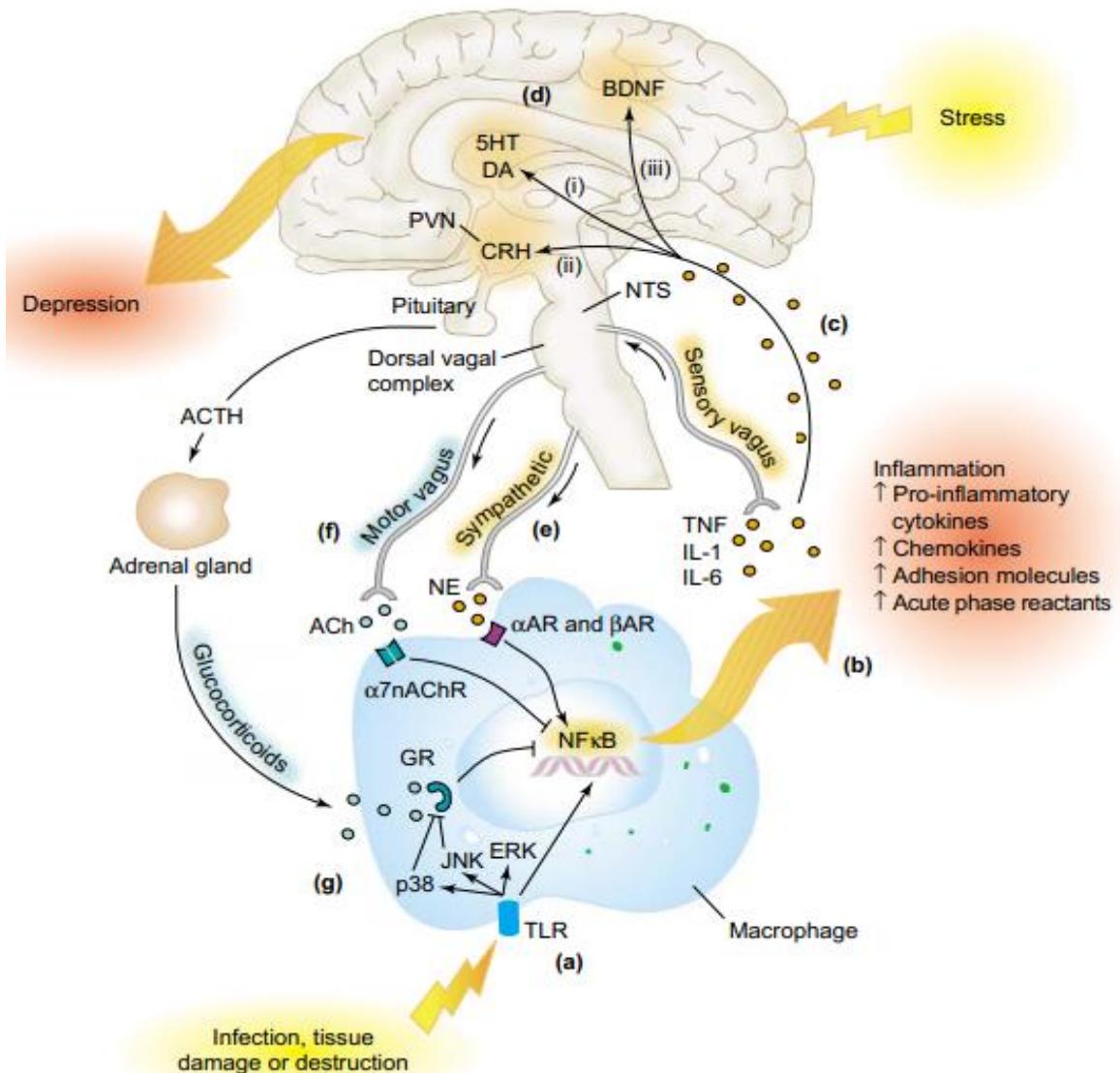


UPPSALA
UNIVERSITET



Från hormoner till depression...

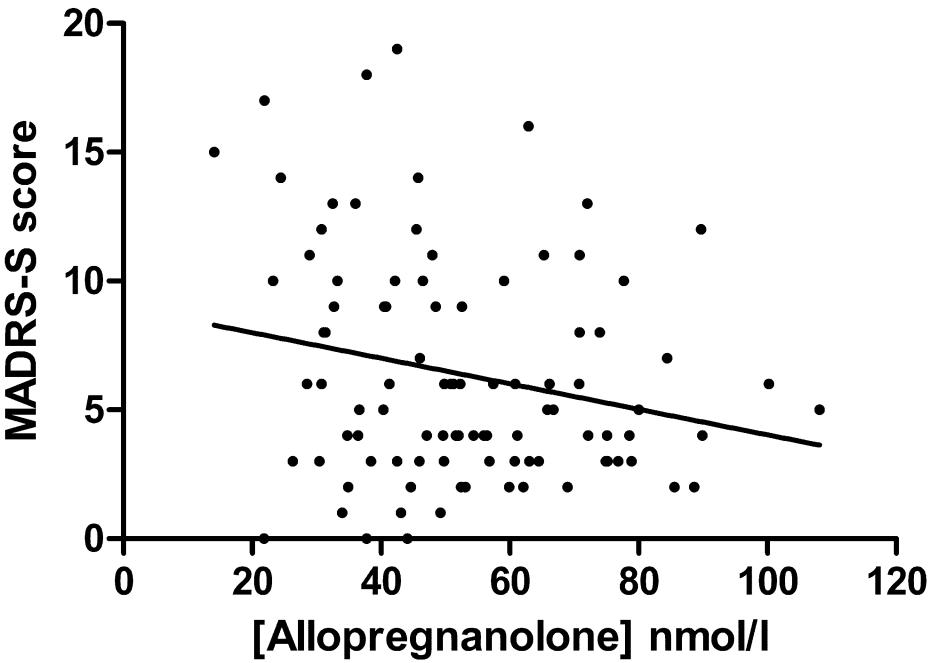
- Serotonergic system
- Dopaminergic system
- Inflammatory response
- BDNF system
- Brain plasticity and neurogenesis



Low serum allopregnanolone is associated with symptoms of depression in late pregnancy



Hellgren et al. 2013,
Neuropsychobiology



UPPSALA
UNIVERSITET



Received: 11 July 2016 | Revised: 3 November 2016 | Accepted: 2 February 2017
DOI: 10.1002/hup.2576

WILEY

SHORT COMMUNICATION

Open-label, proof-of-concept study of brexanolone in the treatment of severe postpartum depression

Stephen J. Kanes¹ | Helen Colquhoun¹ | James Doherty¹ | Shane Raines² | Ethan Hoffmann¹ | David R. Rubinow³ | Samantha Meltzer-Brody³

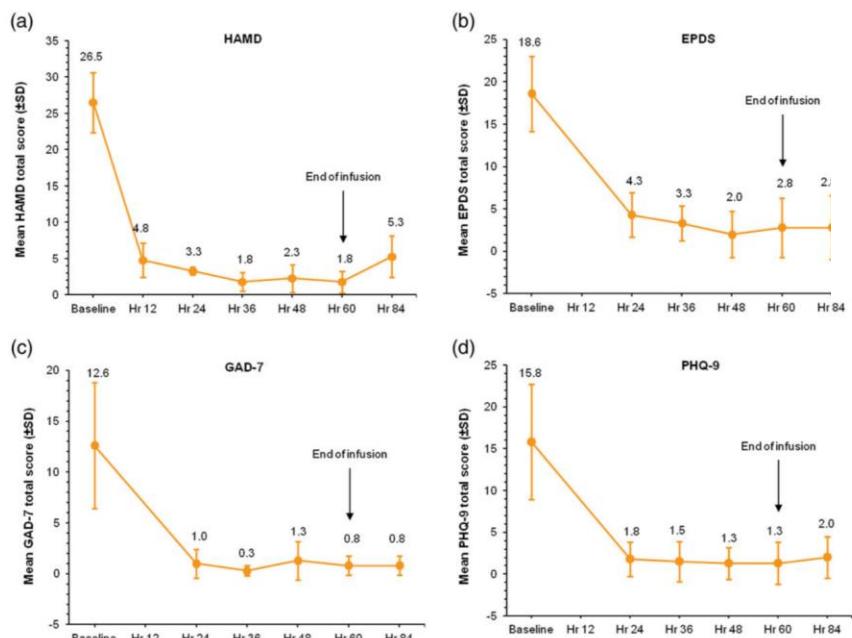
¹Sage Therapeutics, Inc., Cambridge, MA, USA
²b Analytics, Wallingford, PA, USA

³Department of Psychiatry, University of North Carolina, Chapel Hill, NC, USA

Correspondence
Samantha Meltzer-Brody, Campus Box #7160,
Department of Psychiatry, University of North
Carolina, Chapel Hill, NC 27599, USA.
Email: samantha_meltzer-brody@med.unc.edu

Abstract

Objective Preclinical evidence indicates that rapid changes in levels of allopregnanolone, the predominant metabolite of progesterone, confer dramatic behavioral changes and may trigger postpartum depression (PPD) in some women. Considering the pathophysiology of PPD (i.e., triggered by reproductive steroids), the need for fast-acting, efficacious treatments and the negative consequences of untreated PPD, there is an increasing focus on developing PPD therapies. Brexanolone (USAN; formerly SAGE-547 Injection), a proprietary injectable allopregnanolone formulation, was evaluated as a treatment for severe PPD in a proof-of-concept, open-label study.



THE LANCET

ARTICLES | VOLUME 392, ISSUE 10152, P1058-1070, SEPTEMBER 22, 2018

Brexanolone injection in post-partum depression: two multicentre, double-blind, randomised, placebo-controlled, phase 3 trials

Samantha Meltzer-Brody, MD Helen Colquhoun, MD Robert Riesenbergs, MD Prof C Neill Epperson, MD Kristina M Deligiannidis, MD Prof David R Rubinow, MD et al. Show all authors

Published: August 31, 2018 DOI: [https://doi.org/10.1016/S0140-6736\(18\)31551-4](https://doi.org/10.1016/S0140-6736(18)31551-4)



UPPSALA
UNIVERSITET



The estrogen sensitivity hypothesis



Epigenetic PPD biomarkers across disease and hormone levels
L Osborne et al
1652

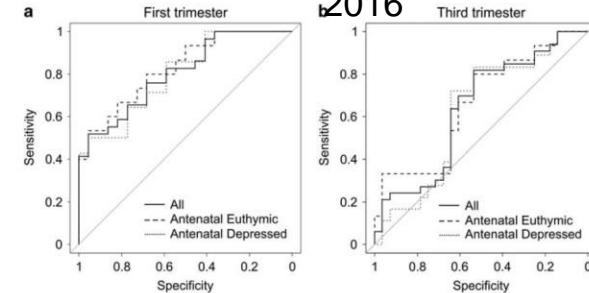


Figure 1 Receiver operator characteristic curves of prospective PPD prediction. Receiver Operator Characteristic (ROC) curves depicting the sensitivity (y axis) as a function of specificity (x axis) for prediction of PPD status in the Prospective Gene Expression cohort during the first (a) and third (b) trimesters.



EPODES-study

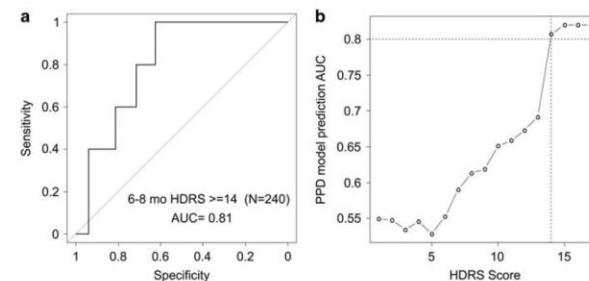
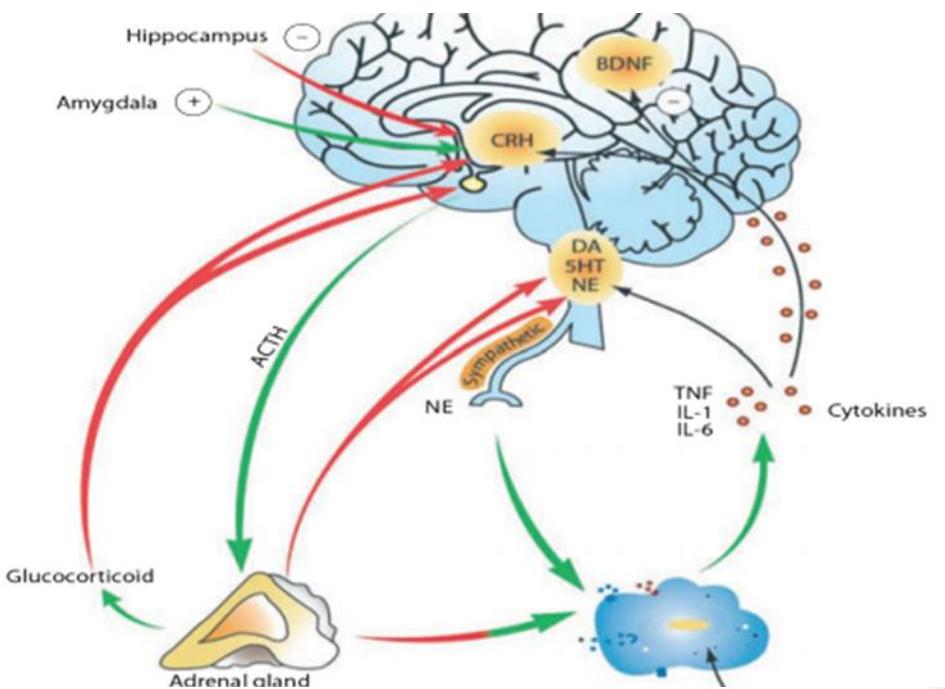


Figure 2 PPD prediction in women without a psychiatric history. (a) Receiver operator characteristic (ROC) curves depicting the sensitivity (y axis) as a function of specificity (x axis) for prediction of 6–8 months HDRS scores ≥ 14 status in the FRAMES cohort of women from the general population. (b) A plot of the performance of PPD model prediction as measured by AUC (y axis) as a function of the HDRS cutoff signifying affected individuals (x axis). The horizontal line denotes the threshold of a 'good' biomarker at an AUC of 0.80, whereas the vertical dashed line denotes an HDRS cutoff of 14.

"PPD is mediated by differential gene expression and epigenetic sensitivity to pregnancy hormones and that modeling proxies of this sensitivity enable accurate prediction of PPD"



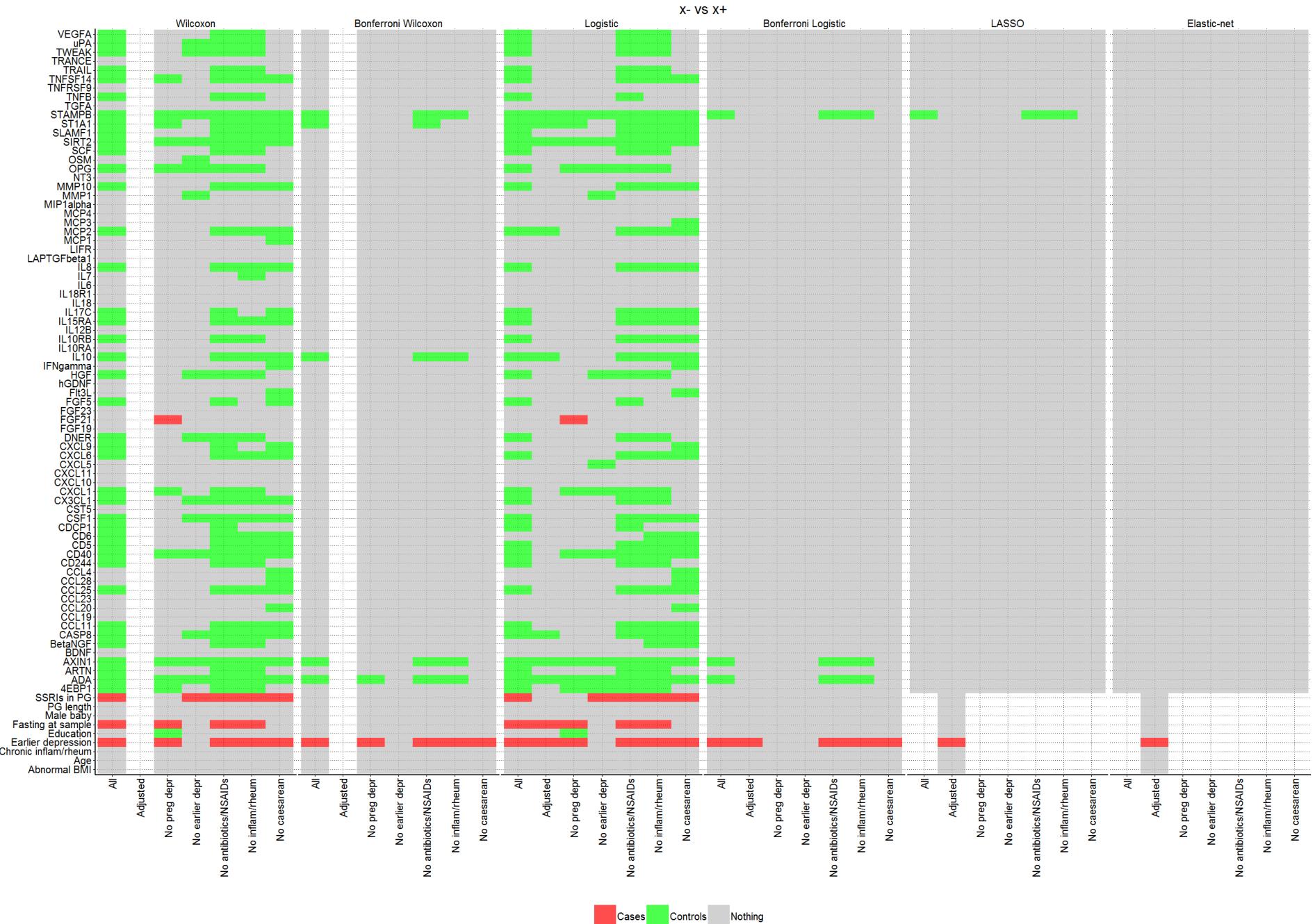
Den inflammatoriska hypotesen av depression



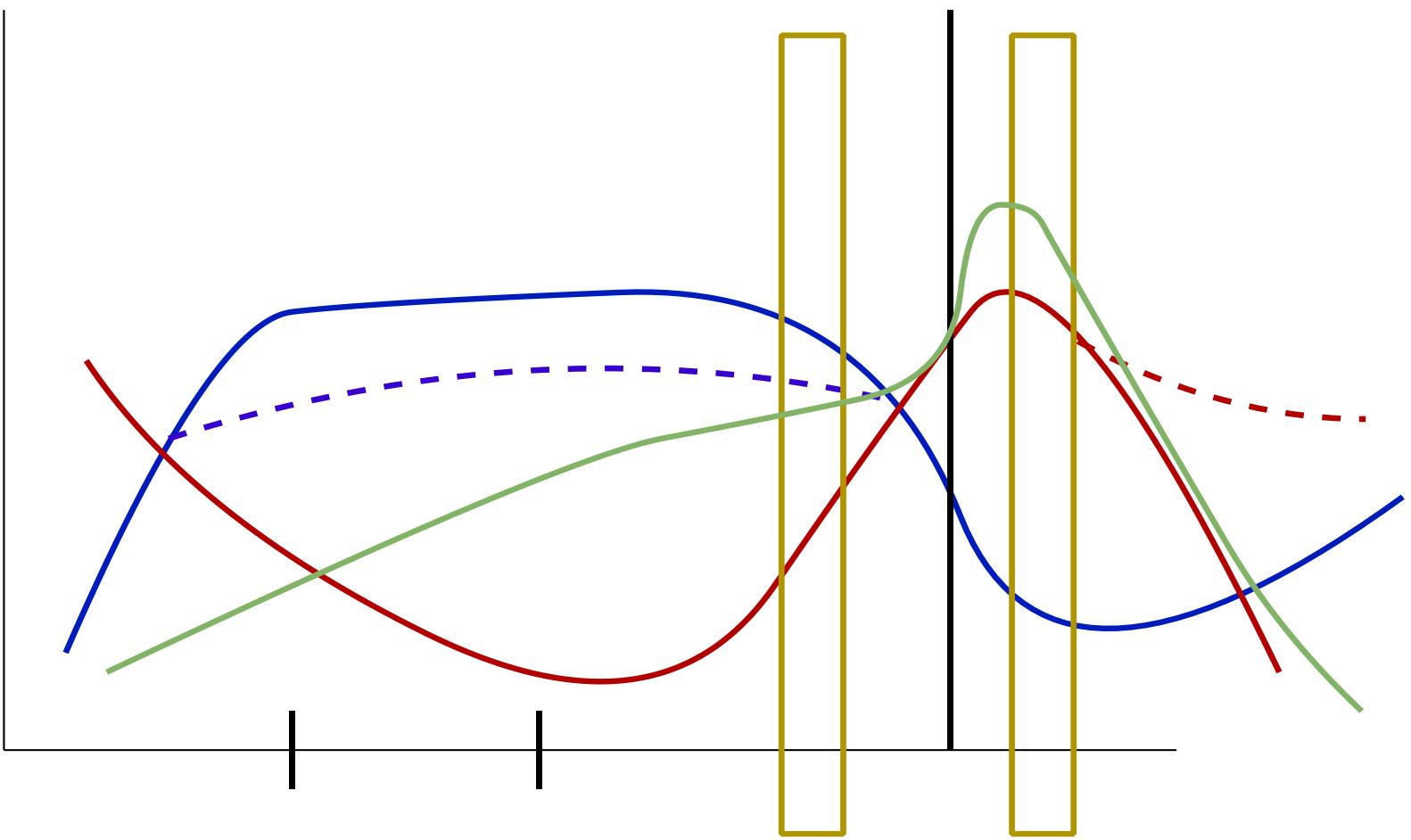
Maletic et al. Neurobiology of depression. Int J Clin Pract. 2007 December; 61(12):2030–2040.



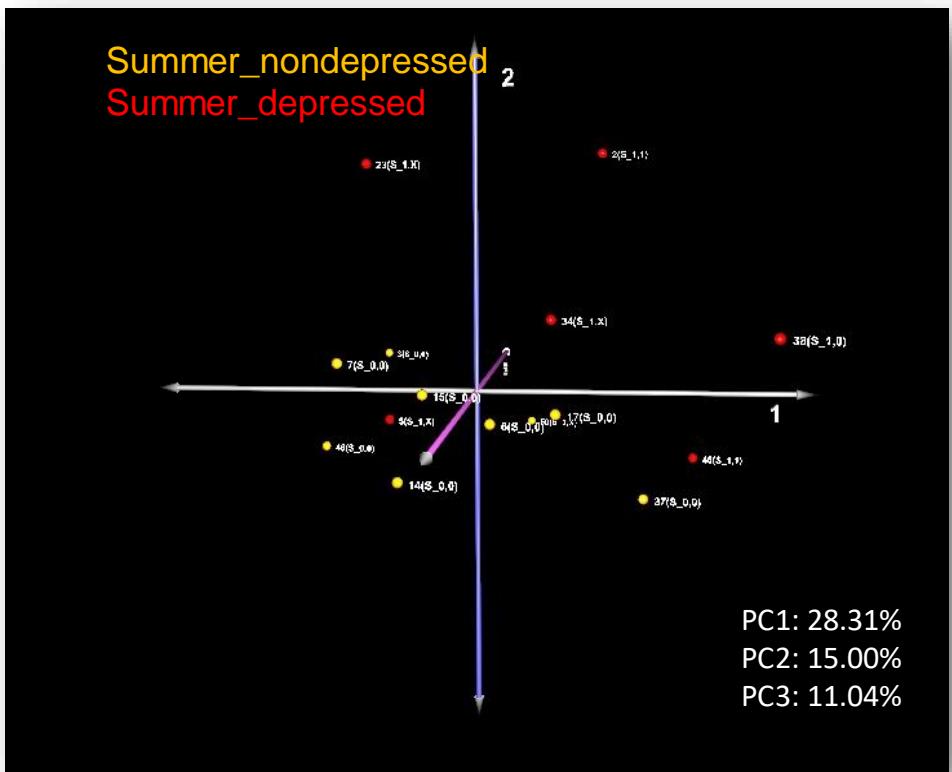
UPPSALA
UNIVERSITET



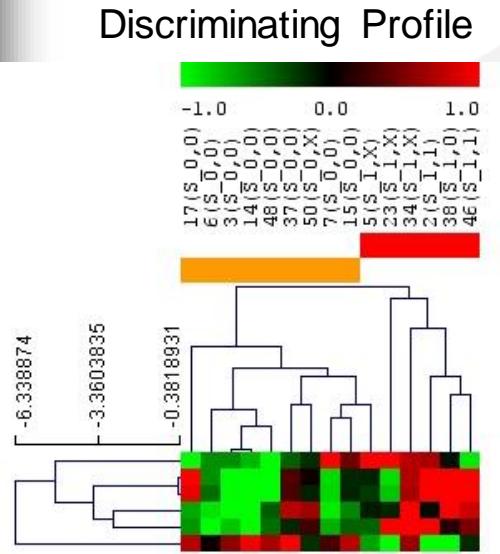
The impaired immune flexibility hypothesis



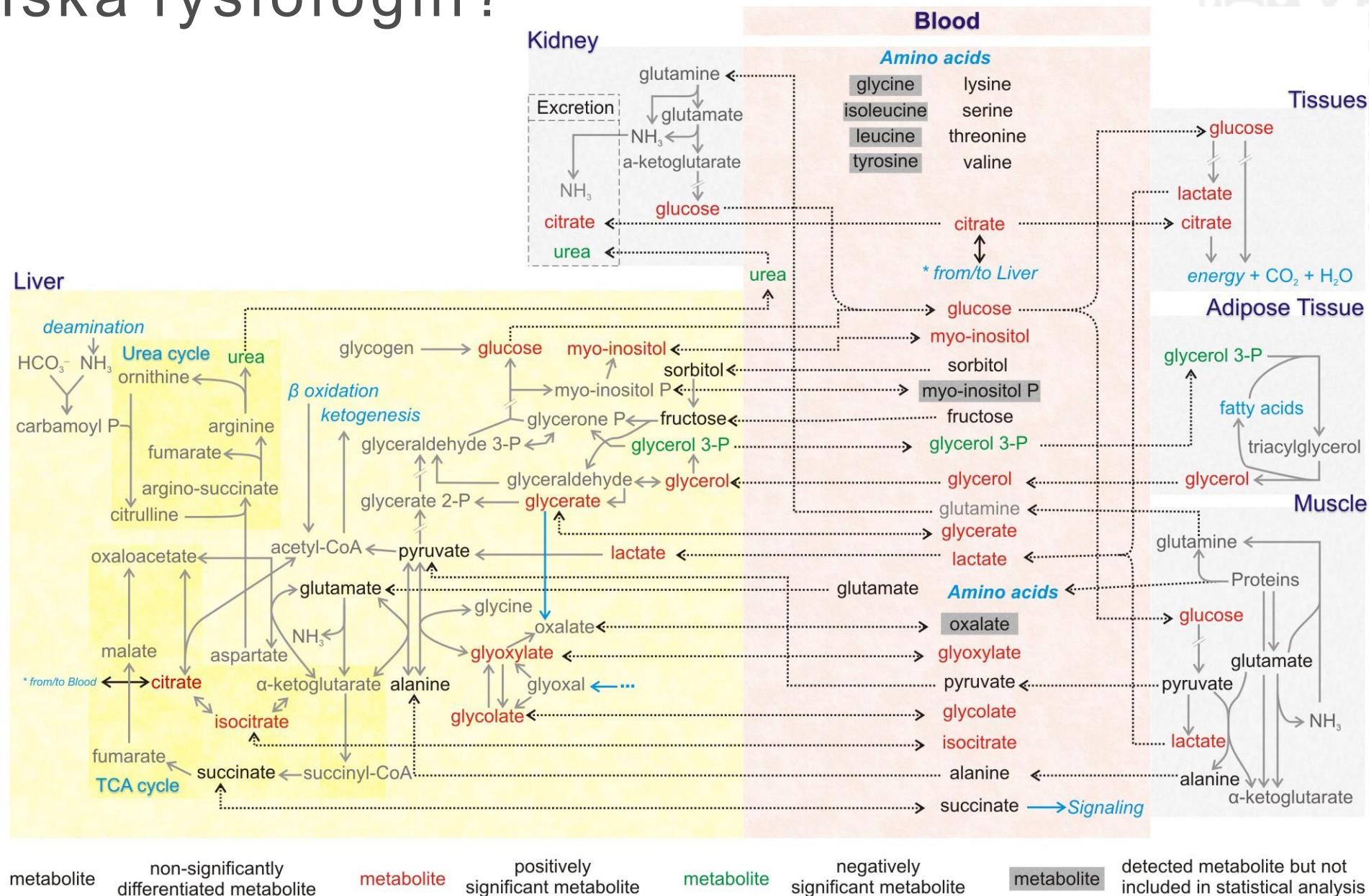
Metabolomiken



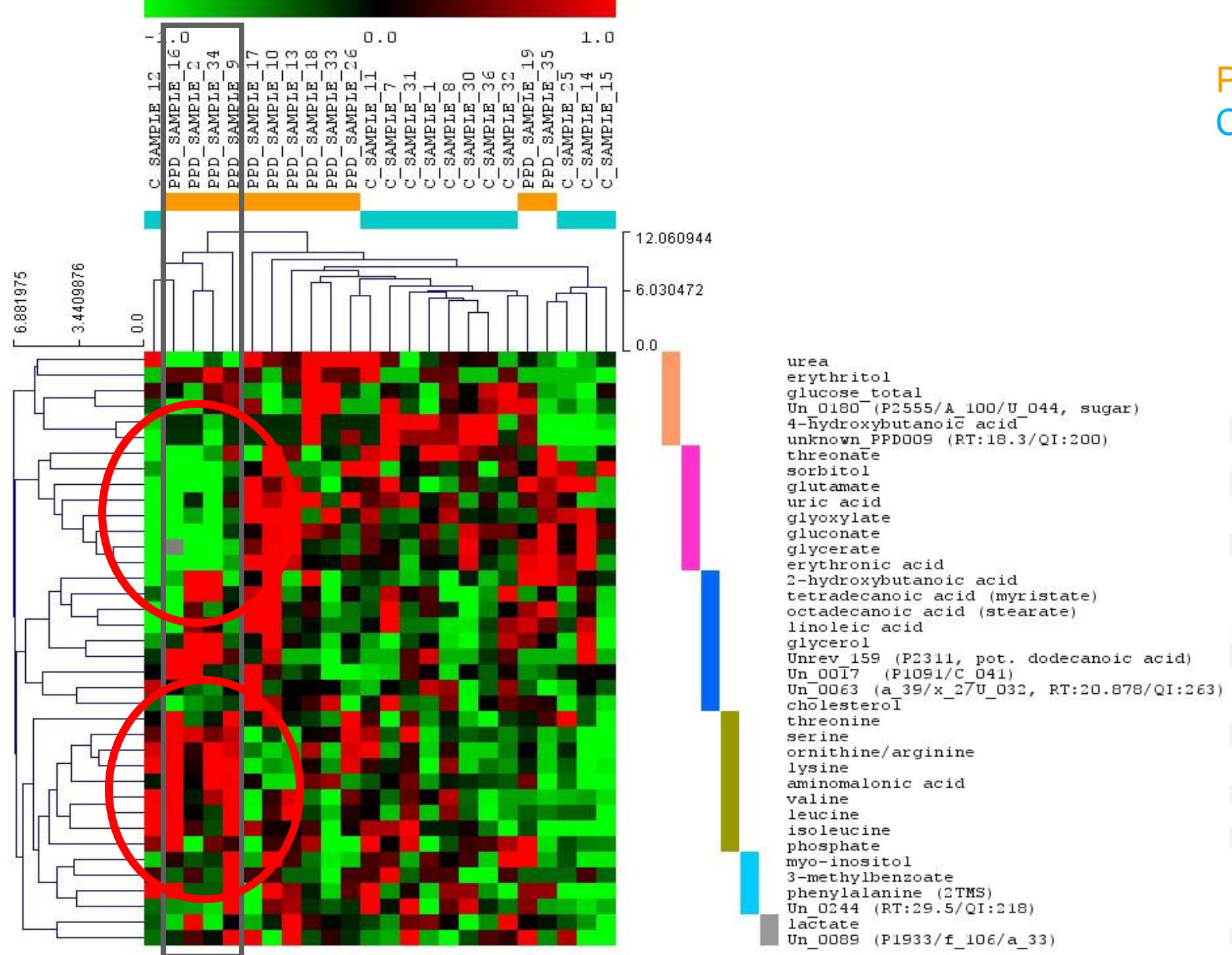
Depressed vs. Nondepressed:
Higher level of sugars and sugar acids, lower energy metabolism



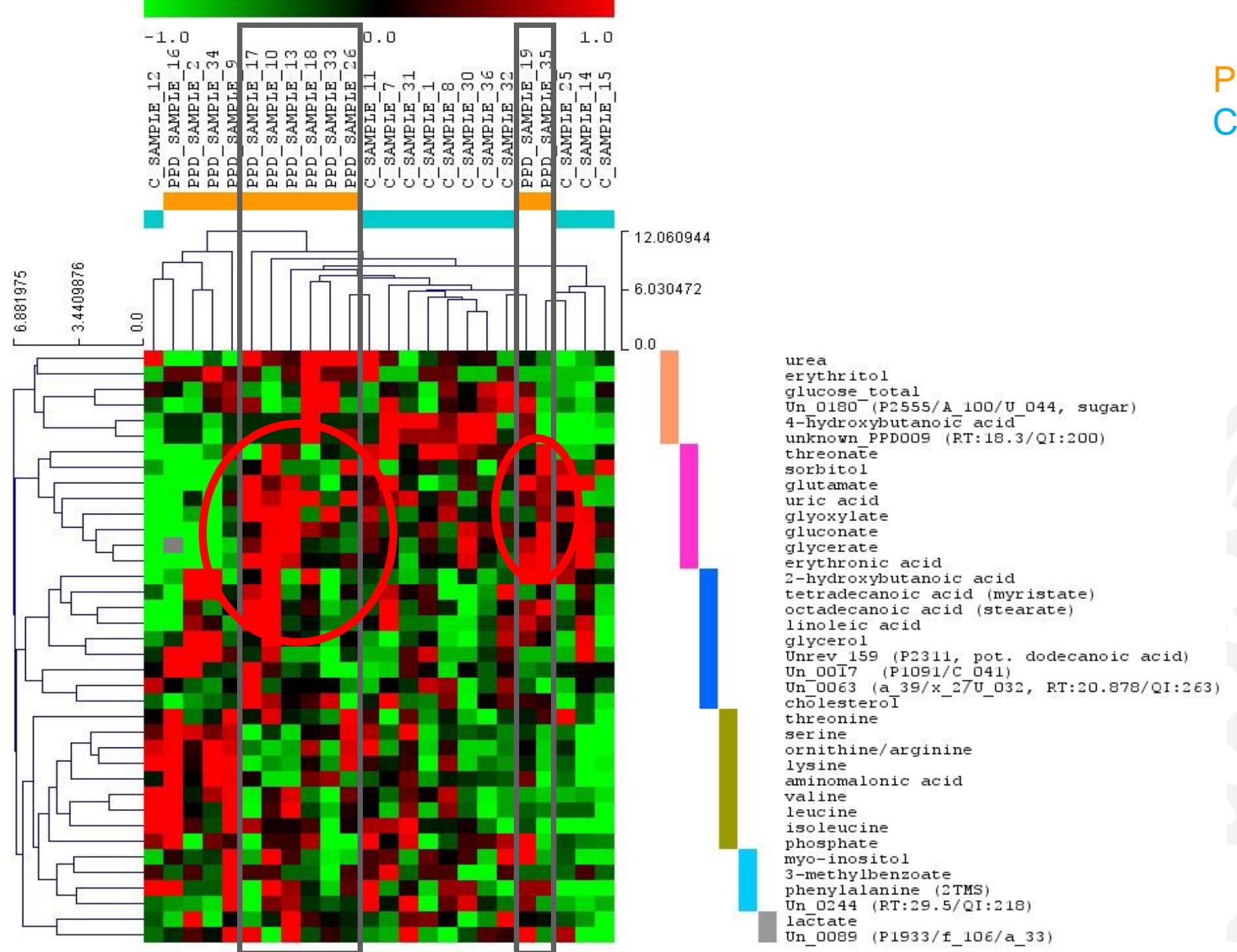
Vad indikerar dessa metabolitskillnader för den metaboliska fysiologin?



PPDS Control



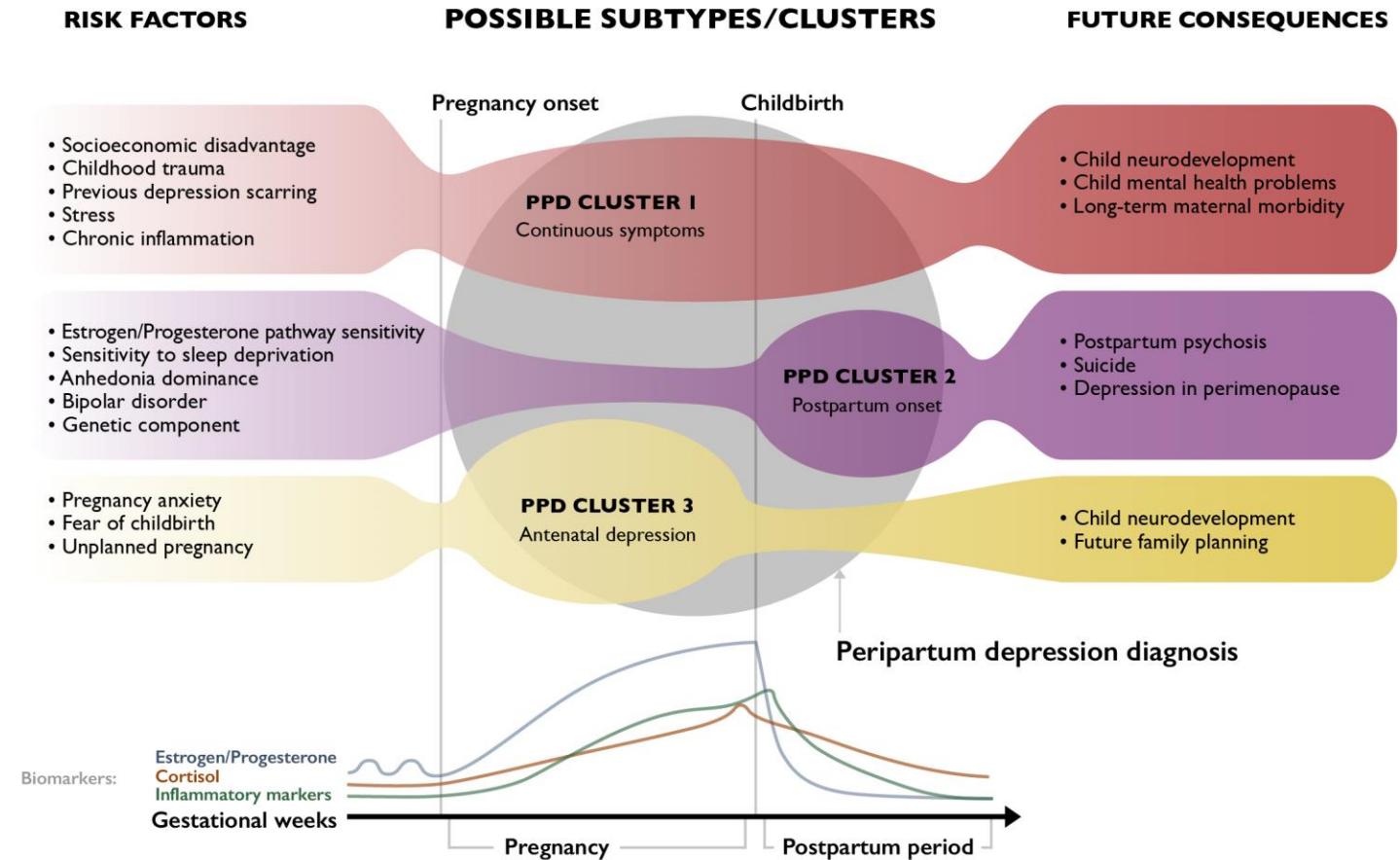
PPDS Control



Olika sub-grupper ?



Figure 1. Hypothetical description of possible PPD subtypes

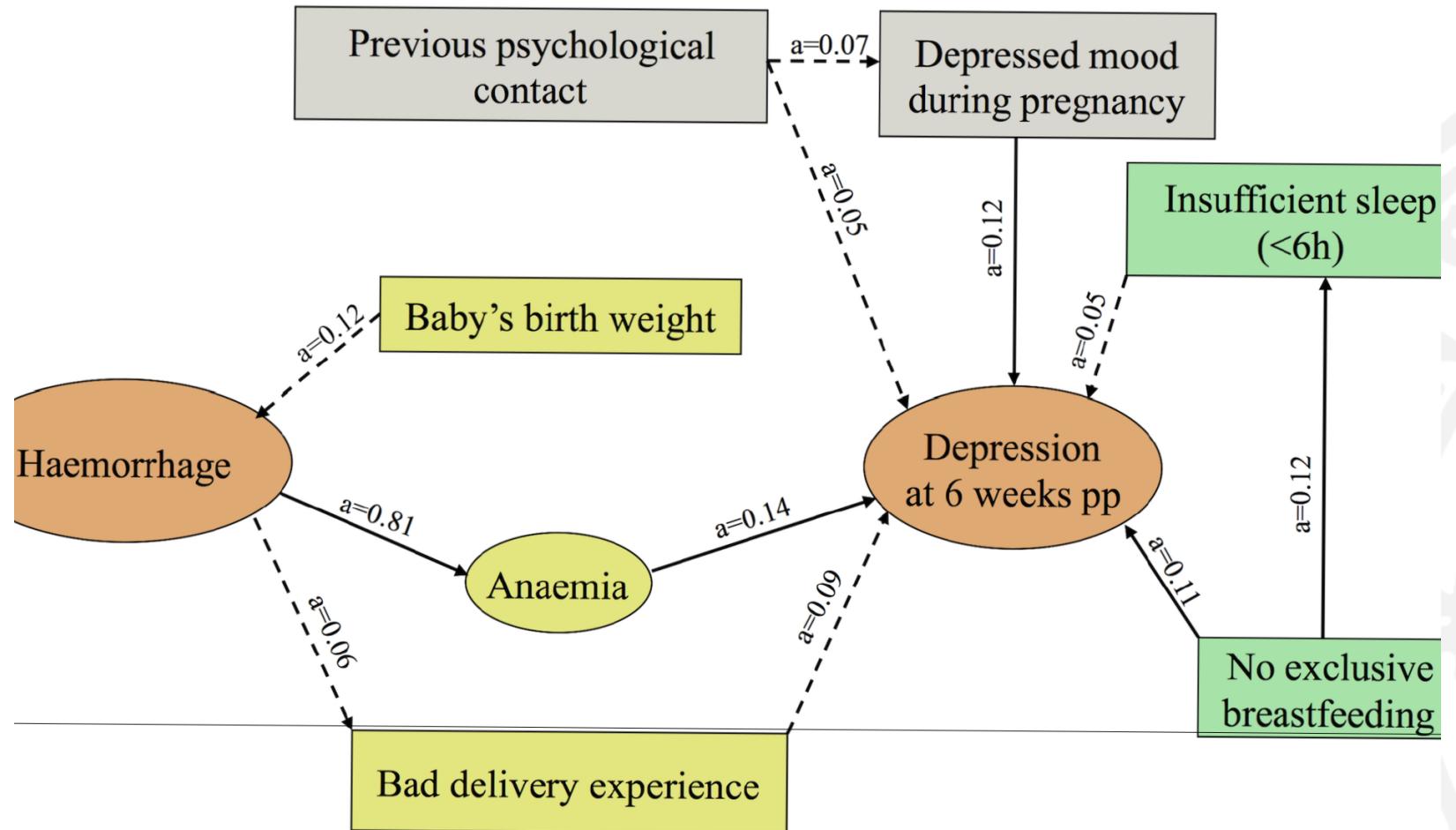


Wikman A, Skalkidou A, J Neuroscience Res 2019



UPPSALA
UNIVERSITET

Kliniska aspekter





Severe obstetric lacerations associated with postpartum depression among women with low resilience – a Swedish birth cohort study

S Asif,^a A Mulic-Lutvica,^a C Axforss,^a P Eckerdal,^a SI Iliadis,^a E Fransson,^{a,b,*} A Skalkidou^{a,*}

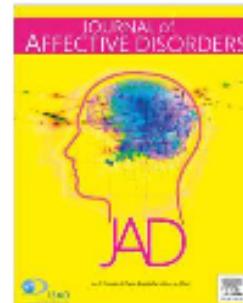
	Crude	Adjusted
All women (<i>n</i> = 2990)	OR (95% CI)	OR (95% CI)
Severe perineal lacerations*	1.4 (0.6–3.5)	1.4 (0.5–3.6)
BMI (kg/m ²)		
<18.5 (versus 18.5–24.9)		0.6 (0.4–1.0)
≥25 (versus 18.5–24.9)		0.8 (0.3–2.3)
Education >12 years (versus lower education)		0.6 (0.4–0.8)
Nulliparous (versus multiparous)		1.1 (0.7–1.5)
Vacuum extraction		1.3 (0.7–2.3)
Women with low resilience** (<i>n</i> = 310)		
Severe perineal lacerations	4.8 (1.2–20)	5.5 (1.2–26)
BMI (kg/m ²)		
<18.5 (versus 18.5–24.9)		0.8 (0.4–1.4)
≥25 (versus 18.5–24.9)		1.5 (0.3–8.0)
Education >12 years (versus lower education)		0.5 (0.3–1.0)
Nulliparous (versus multiparous)		1.1 (0.6–2.0)
Vacuum extraction		0.8 (0.2–2.5)



Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad



Research paper

Maternal perinatal depressive symptoms trajectories and impact on toddler behavior – the importance of symptom duration and maternal bonding



Emma Fransson^{a,b,*,#}, Ferdinand Sörensen^{c,d,#}, Theodora Kunovac Kallak^a, Mia Ramklint^e, Patricia Eckerdal^a, Magdalena Heimgärtner^c, Ingeborg Krägeloh-Mann^c, Alkistis Skalkidou^a

^a Department of Women's and Children's Health, Uppsala University, Uppsala, Sweden

^b Department of Microbiology, Tumor and Cell Biology, Karolinska Institutet, Stockholm, Sweden

^c Pediatric Neurology & Developmental Medicine, University Children's Hospital Tübingen, Germany

^d Eberhard Karls University Tübingen, Werner Reichardt Centre for Integrative Neuroscience, Germany

^e Department of Neuroscience, Psychiatry, Uppsala University, Uppsala, Sweden



UPPSALA
UNIVERSITET



RESEARCH

Open Access



DNA methylation in cord blood in association with prenatal depressive symptoms

Theodora Kunovac Kallak^{1*} , Emma Bränn¹, Emma Fransson¹, Åsa Johansson², Susanne Lager¹, Erika Comasco³, Robert Lyle⁴ and Alkistis Skalkidou¹

Differential DNA methylation was observed in children born to mothers exposed to
-comorbid PND with anxiety symptoms compared with healthy controls
-on SSRIs (unclear if underlying more severe depression)

Sites involved in brain development and glucocorticoid stress response



UPPSALA
UNIVERSITET

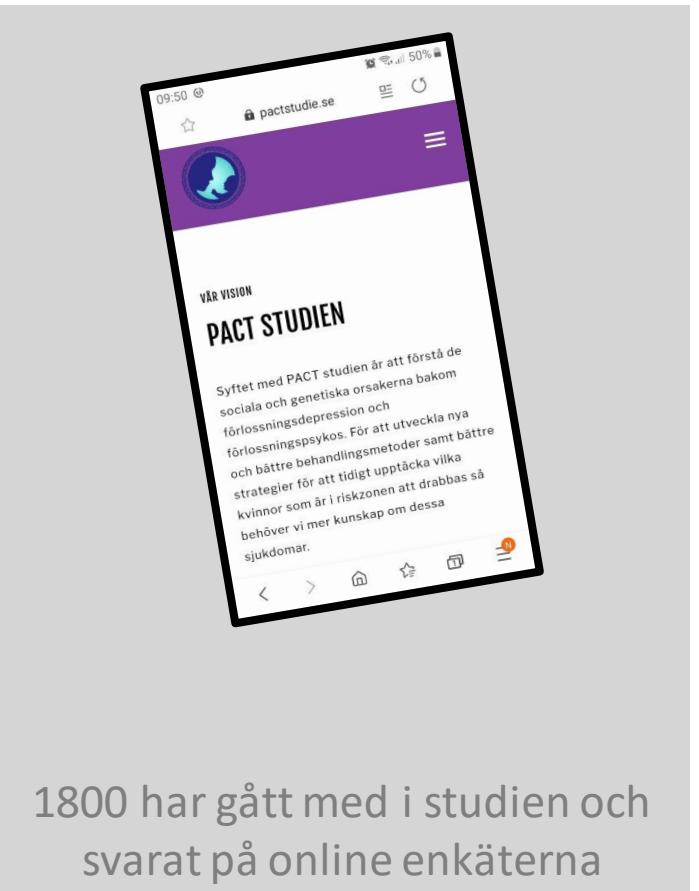
PACT-studien



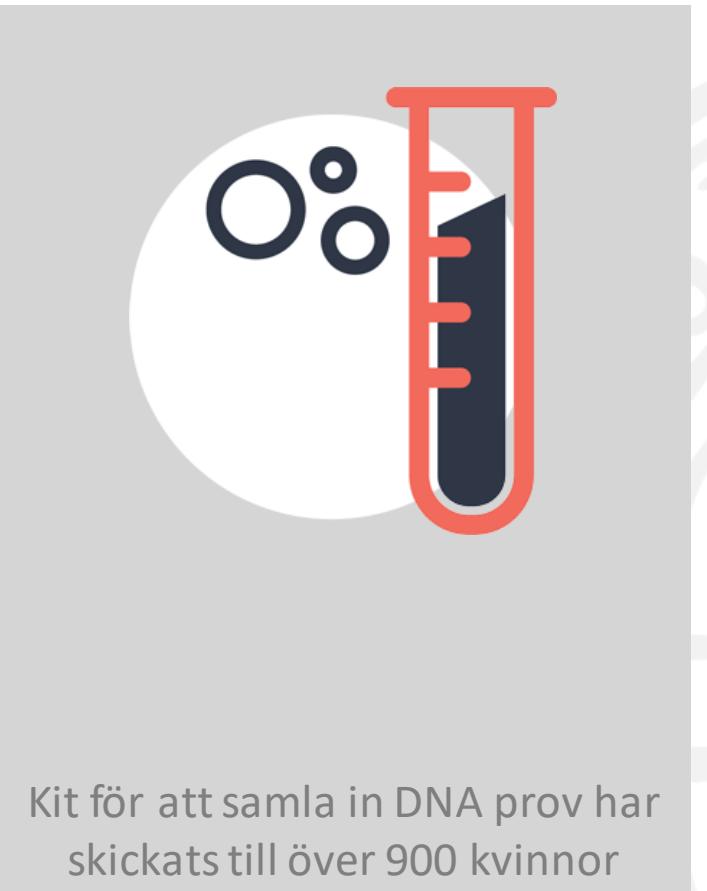
International collaboration –PACT consortium
Målet är att samla in över 100 000 DNA prover

Syftet med PACT studien är att förstå sociala och genetiska
aspekter av måendet kring förlossningen

PACT-studien i Sverige



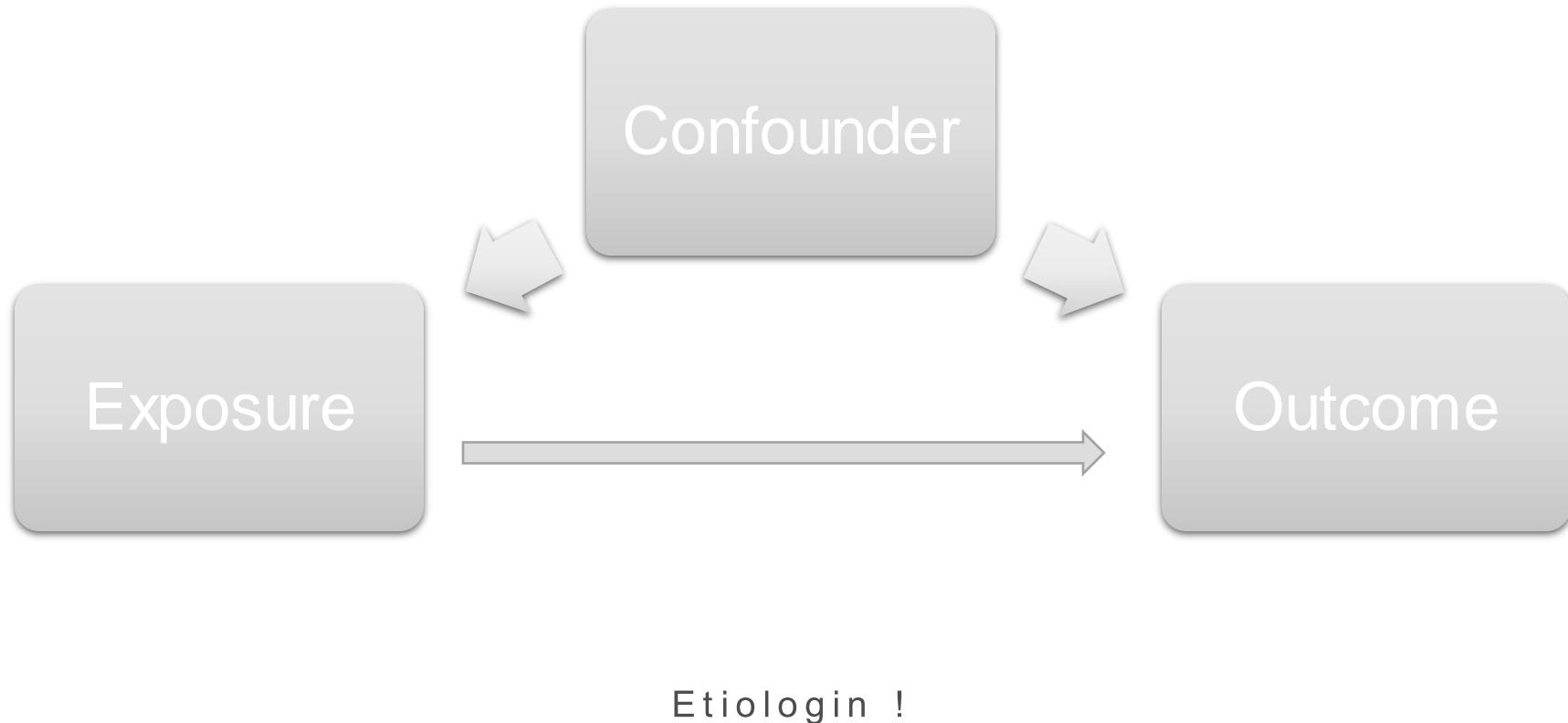
1800 har gått med i studien och
svarat på online enkäterna



Kit för att samla in DNA prov har
skickats till över 900 kvinnor

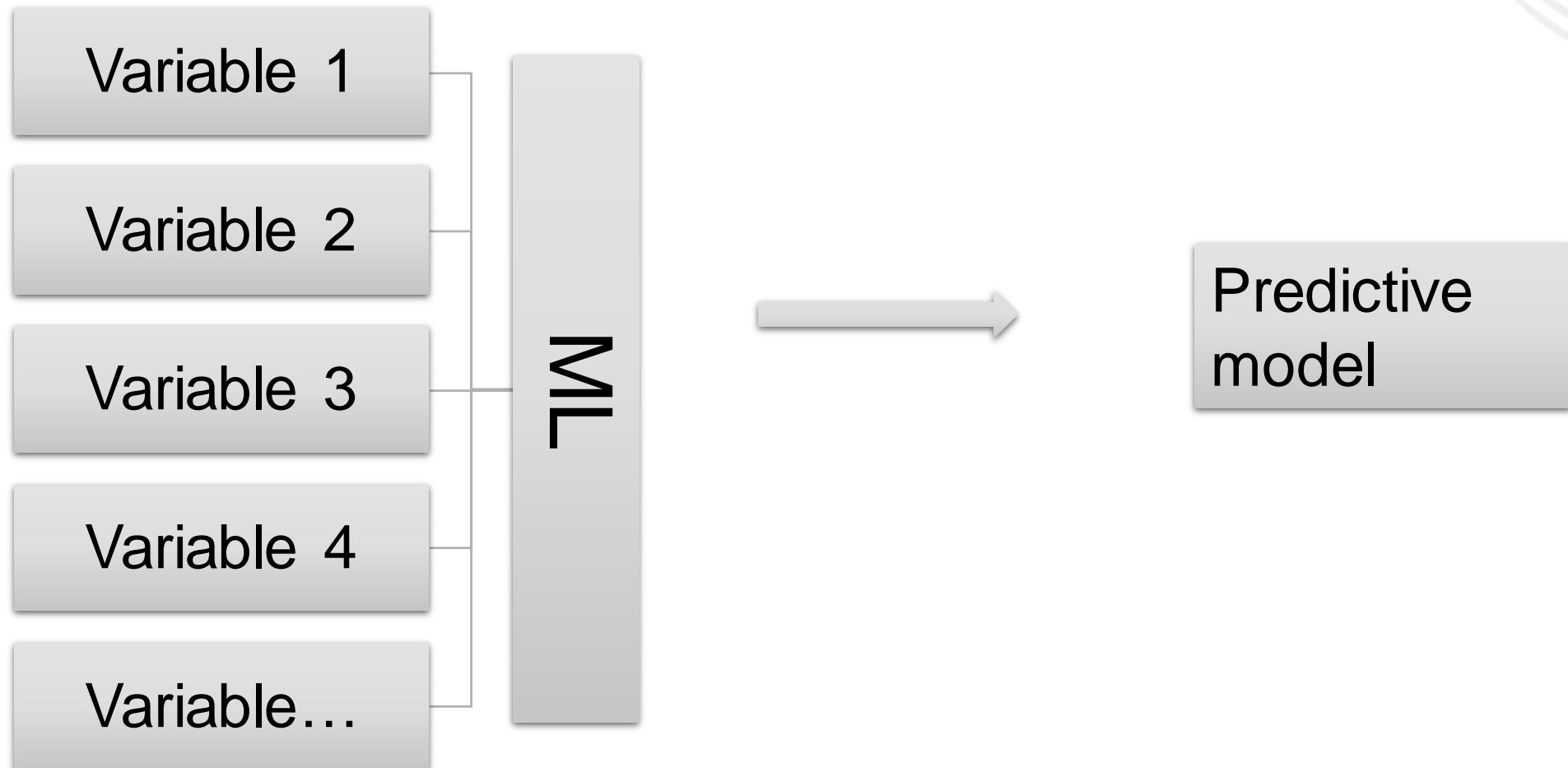


Traditionella statistiska metoder





Prediktion





	Etiology research	Prediction research
Individual risk factors	Main interest	Irrelevant
Confounding	Very important	Irrelevant
Missing data	Possible problem	Might not be a problem
Model fit of the statistical model	Not important	Crucial
Causality (cause-consequence)	Crucial	Irrelevant



Machine learning

- Artificiell intelligens
- Classical ML vs Deep Learning
- Deep Neural Networks (DNN)
- Bestämma den bästa modellen för att förutsäga risken för depression på olika tidpunkter
- Tidigare studier: små urvalsstorlekar, begränsade till självrapporter/register, endast traditionella maskininlärningsmetoder, begränsade metoder

MÅL:

Vi syftar till att

förutsäga kvinnor med risk för
depressiva symtom 6 veckor efter
förlossningen,
baserat på

kliniska, demografiska och
psykometriska frågeformulärsdata

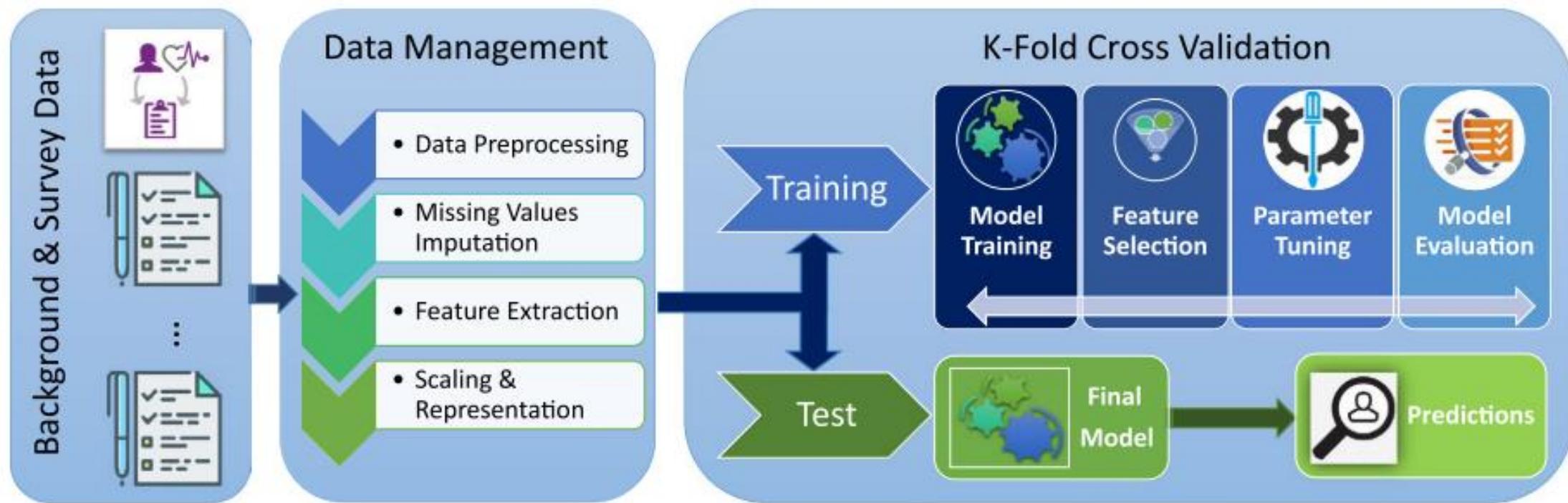
tillgängliga efter förlossningen,

med hjälp av
maskininlärningsmetoder.



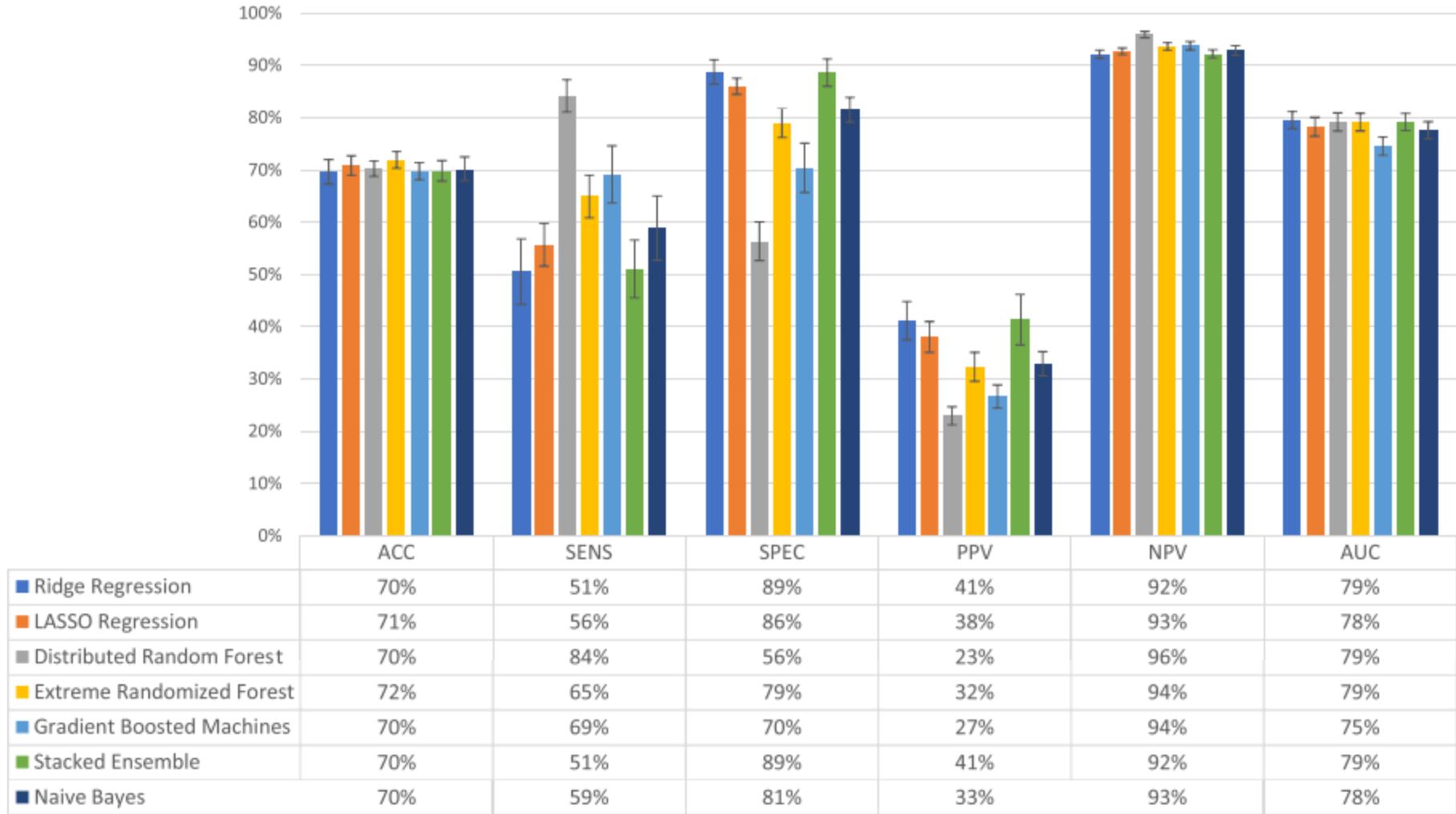
UPPSALA
UNIVERSITET

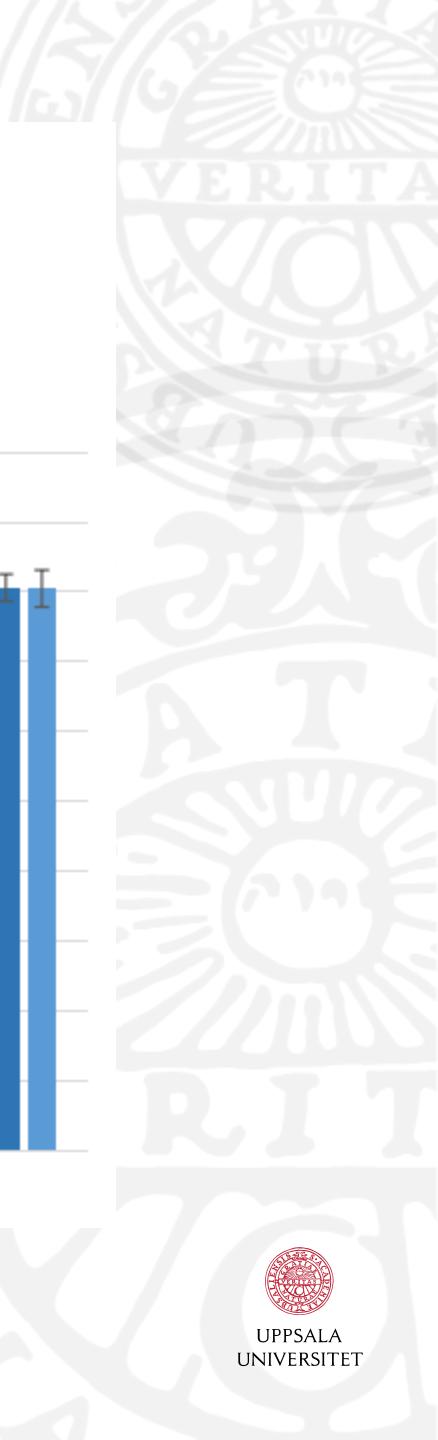
Work-flow



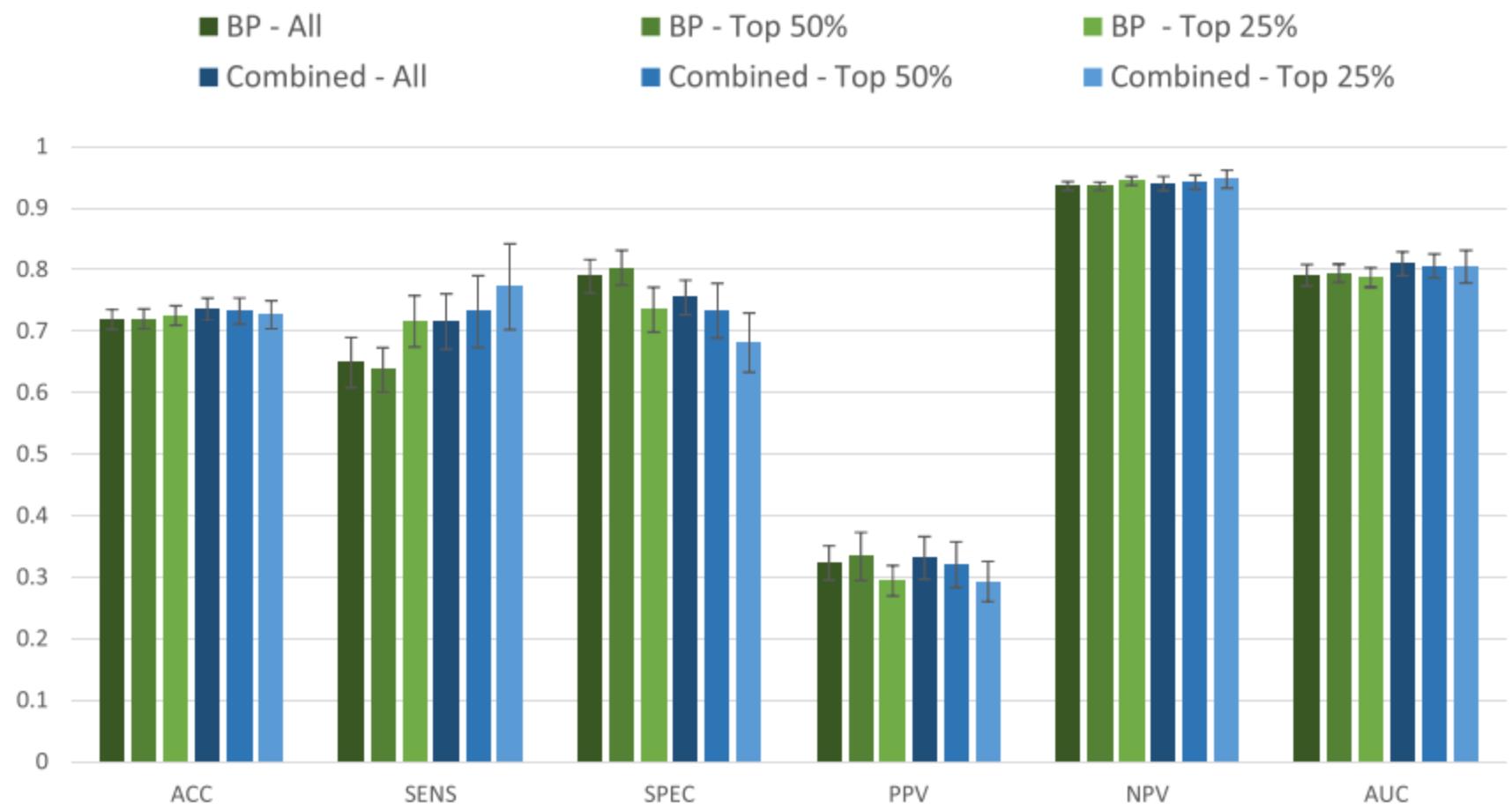
Resultat- Klassiska ML metoder

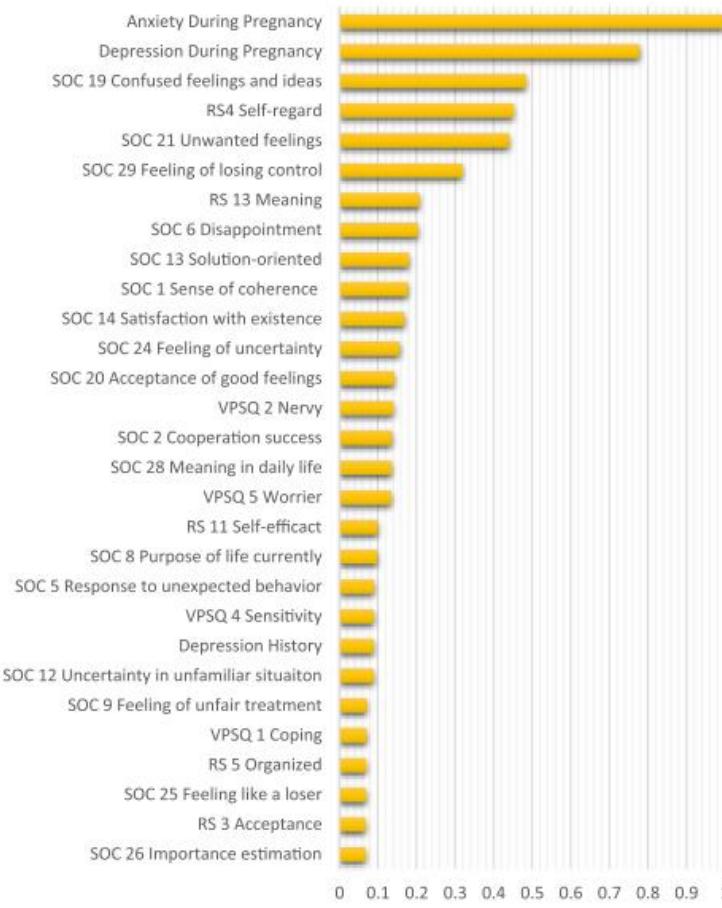
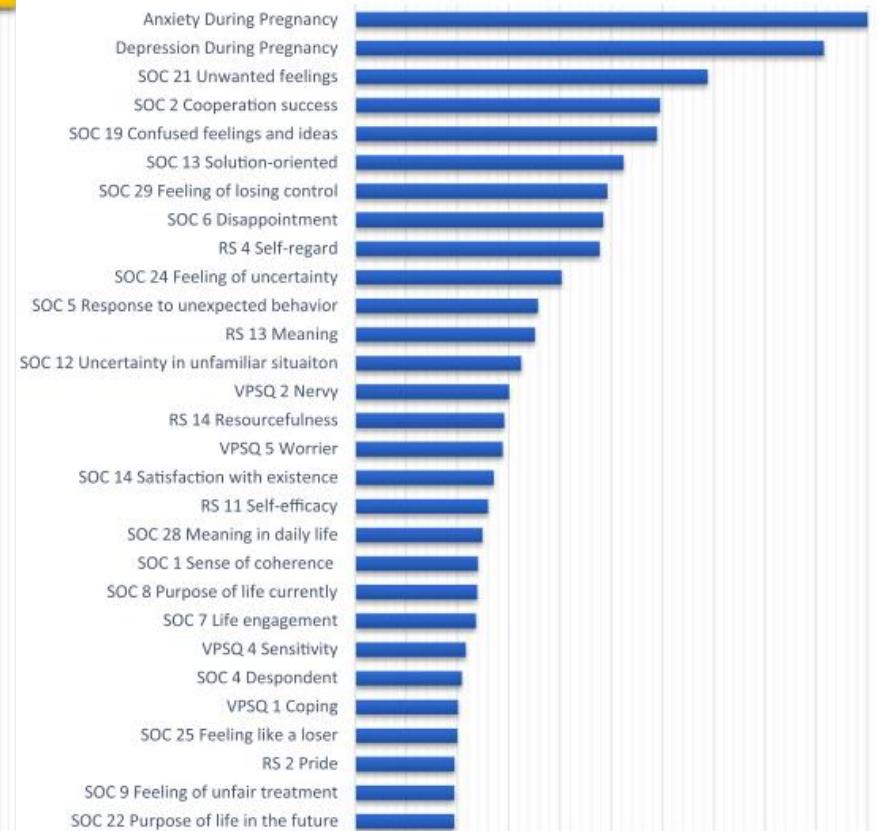
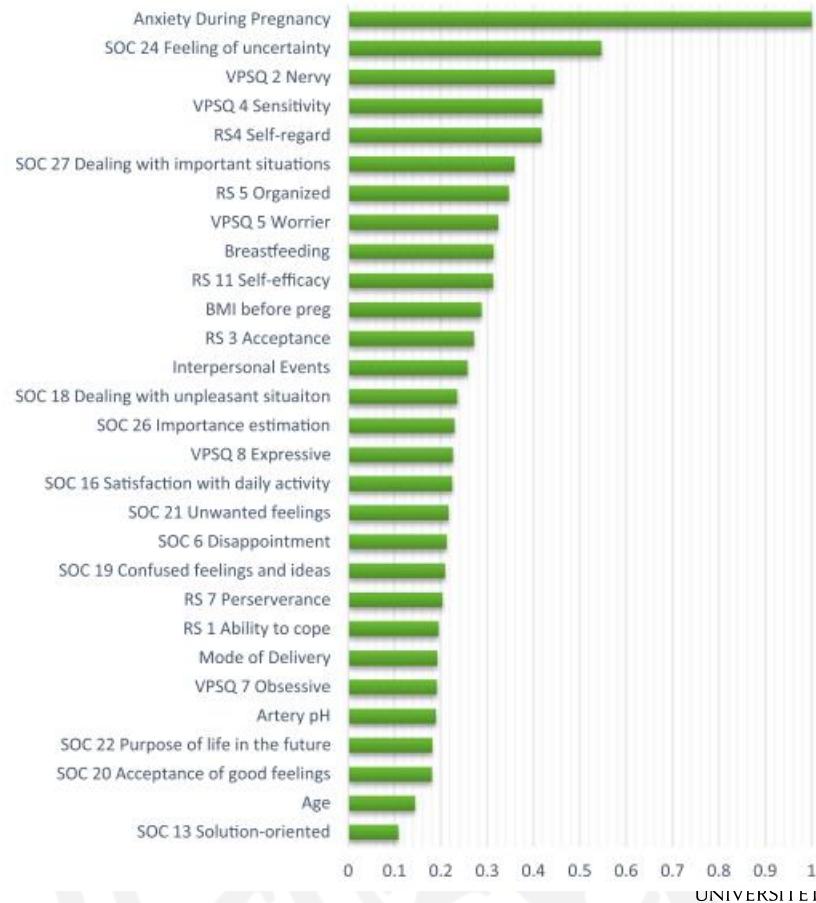
Andersson S,
Sci Rep 2021





Feature Selection (XRT)



A**All Women****B****With previous/pregnancy depressed****C****Without previous depression**

Blir det bättre med genetiska data?

Data	Samples	Features	Mean
	(n = common)	(f = ALL)	AUC
Background	4254	64	0.77 ± 0.02
Questionnaires	2386	52	0.74 ± 0.02
Background + Questionnaires	2381	116	0.79 ± 0.02
Background + Questionnaires + GWAS	1213	3626	0.71 ± 0.09



Sammanfattning

- **Extremely randomized trees** method gav robust prestanda med högsta noggrannhet och välbalanserad sensitivitet och specificitet (noggrannhet 73%, sensitivitet 72%, specificitet 75%, area under kurvan 81%).
- Bland kvinnor utan tidigare psykiska problem var noggrannheten lägre, 64%.
- Variablerna som satte kvinnor med högst risk för PPD var **depression och ångest under graviditeten**, liksom variabler relaterade till **motståndskraft och personlighet**.
- Med hjälp av DNN fann vi att GWAS-data inte gav någon ytterligare information för att förbättra PPD -förutsägbarhetsnoggrannheten utöver bakgrunds- och frågeformulärsinformation.





Mom2B studien

Syftet med Mom2B mobil app studien är att med AI
metoder predicera förlossningsdepression

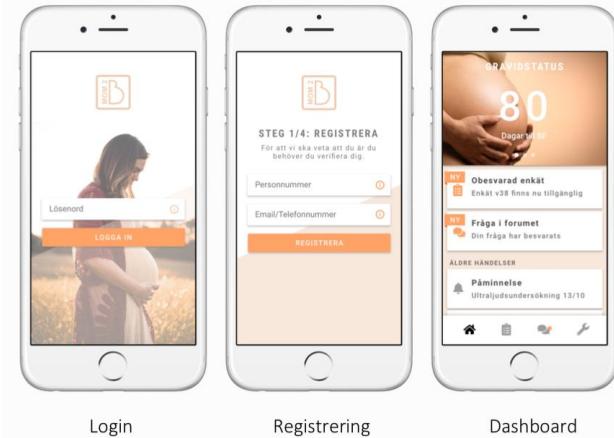
Digital fenotyping

- The process of using digital devices (eg. smartphones) to capture moment-by-moment, objective data, regarding the user's experiences and functions in the real world.
- **active data** and **passive data**





App innehåll



- Självskattningsfrågor (t.ex. angående depressiva symptom och välmående)
- Digitala beteendedata (t.ex. allmän mobilanvändning, geografiskt rörelsemönster och sociomedial aktivitet).
- Inspelning av korta texter.
- Graviditets- och förlossningsrelaterad information från nationella hälsoregister (t.ex. PTB).



UPPSALA
UNIVERSITET



Mom2B kohorten

- Swedish-speaking women above 18 years owning a smartphone
- Pregnant – 3 months postpartum
- Register to Mom2B mobile app
- Goal: 20,000 women
- 3600+ women registered, ~1800 actively using app
- Average 31 years, 92% Swedish, 80% received higher education,

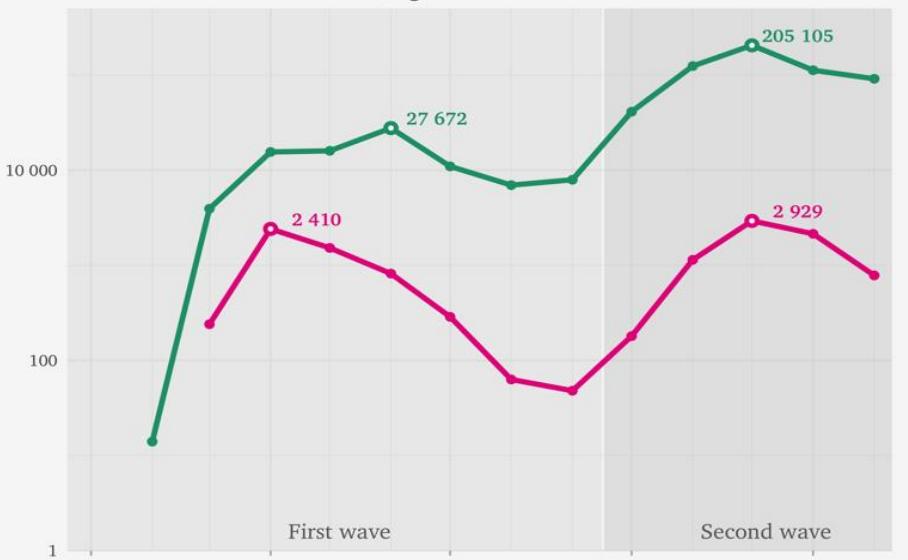


Hur har Mom2B deltagare mått under pandemins två frösta vågorna?



UPPSALA
UNIVERSITET

Covid cases and deaths (log)



Depression



Anxiety



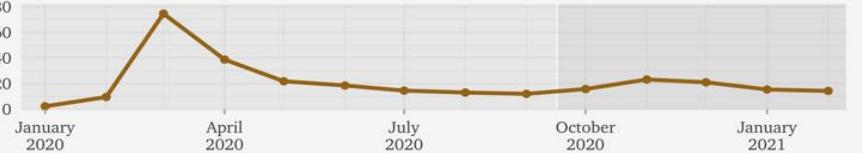
WHO-5 Well-Being Index



Mobility



Google searches



UPPSALA
UNIVERSITET

"Due to restrictions about physical appointments, I am not sure that my diagnosis is the right one"

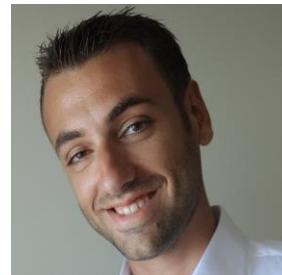
"I was advised not to seek care"

"All my appointments have been completed"

"I don't feel safe with my health care"

"Very frustrated and worried about the restriction policy, which I experience as arbitrary and incomprehensible"





UPPSALA
UNIVERSITET

UPPSALA UNIVERSITY

Dept of Neuroscience, Psychiatry

- Lisa Ekselius, Fotios Papadopoulos, Mia Ramklint, Mimmie Willebrand

Dept Physical and Analytical Chemistry (SciLife lab)

- Jonas Bergqvist

Dept of Immunology, Genetics and Pathology (SciLife lab)

- Masood Kamali-Moghaddam

Dept of Information Technology

- Ginevra Castellano

Dept of Psychology

- Gustaf Gredebäck

National and International collaboration

Prof. Hasse Karlsson, **Turku University, Finland**

Prof. Georgios Chrouzos, **Athens University, Greece**

Prof. Maria Klapa, **Patras University, Greece**

Prof. Lars Engstrand and Dr. Emma Frasson, **CTMR, Karolinska Institute, Sweden**

Dr. Richard White, **Institute of Public Health, Norway**

Dr. Deepti Bathula, **University of Ropar, India**

Medarbetare



Anslag

- Marianne och Marcus Wallenberg Stiftelse
- Vetenskapsrådet
- Göran Gustafsson Stiftelse
- Hjärnfonden
- Svenska Läkarsällskapet
- Söderström-Köningska Stiftelse
- Brottsoffermyndigheten
- Systembolagets forskningsråd



*“Wisdom
begins
in wonder”*

Socrates



UPPSALA
UNIVERSITET