The involvement of mitochondria in chronic low-grade inflammation associated with maltreatment experiences during childhood

Alexander Karabatsiakis

Clinical & Biological Psychology,

Molecular Psychotraumatology

Ulm University

MIP2017, Hradec Kralove

November 16th, 2017

Childhood maltreatment (CM) is a worldwide phenomenon present in all classes of low-and high-income countries

Child maltreatment includes all forms of physical and emotional ill-treatment, sexual abuse, neglect, and exploitation that results in actual or potential harm to the child's health, development or dignity (WHO)
-> five subtypes

- International prevalence estimates of childhood maltreatment

  - Physical abuse: 25 % of all adults

  - Sexual abuse: 20 % women and 8 % of all men

  - Emotional & physical neglect most prevalent forms of CM

- Chronic (stress) condition

 - Re/Poly-victimization

- *Childhood Trauma Questionaire* (CTQ)

Emotional neglect

Physical neglect

Sexual abuse

Emotional abuse

Physical abuse

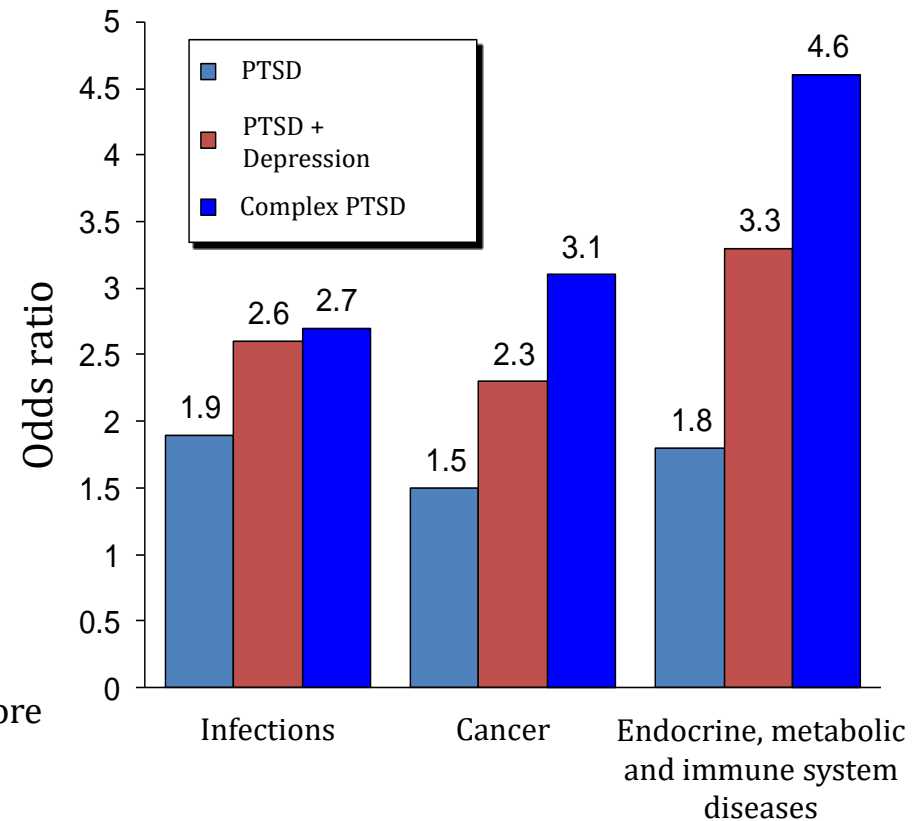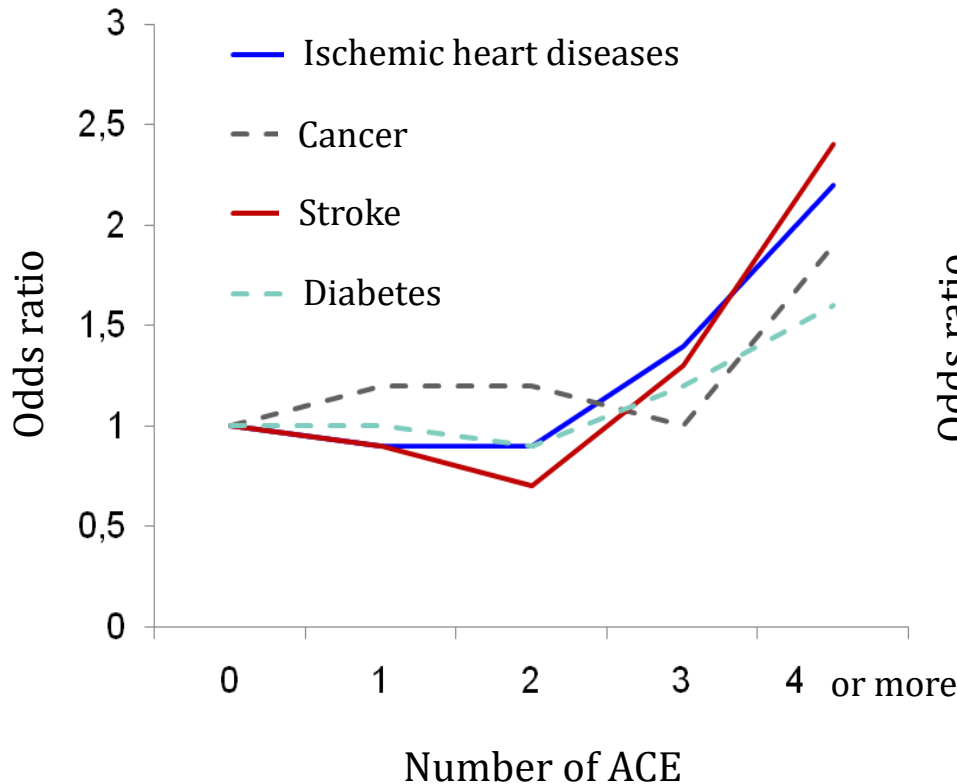[1] [2] [3]
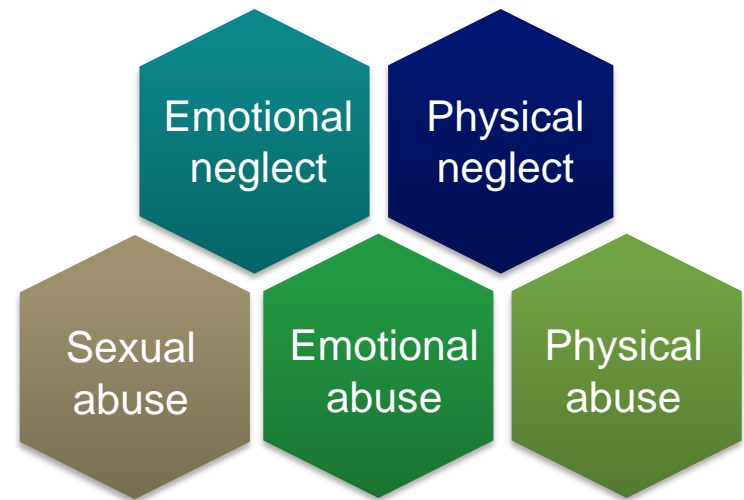
Childhood Trauma Questionaire (CTQ)

The self-report includes a 28-item test that measures the 5 subtypes of childhood maltreatment (age < 18 years) with a 5-point Likert-scale.

When I was growing up...	Never True	Rarely True	Sometimes True	Often True	Very Often True
1. I didn't have enough to eat.					
2. I knew that there was someone to take care of me and protect me.					
3. People in my family called me things like "stupid," "lazy," or "ugly".					
4. My parents were too drunk or high to take care of the family.					
5. There was someone in my family who helped me feel that I was important or special.					
6. I had to wear dirty clothes.					
7. I felt loved.					
8. I thought that my parents wished I had never been born					
9. I got hit so hard by someone in my family that I had to see a doctor or go to the hospital.					
10. There was nothing I wanted to change about my family					
11. People in my family hit me so hard that it left me with bruises or marks.					
12. I was punished with a belt, a board, a cord, or some other hard object.					

Aversive childhood experiences have long-life negative consequences on the risk for somatic as well as mental health conditions.

Daskalakis et al. 2013; Gilbert et al. 2009
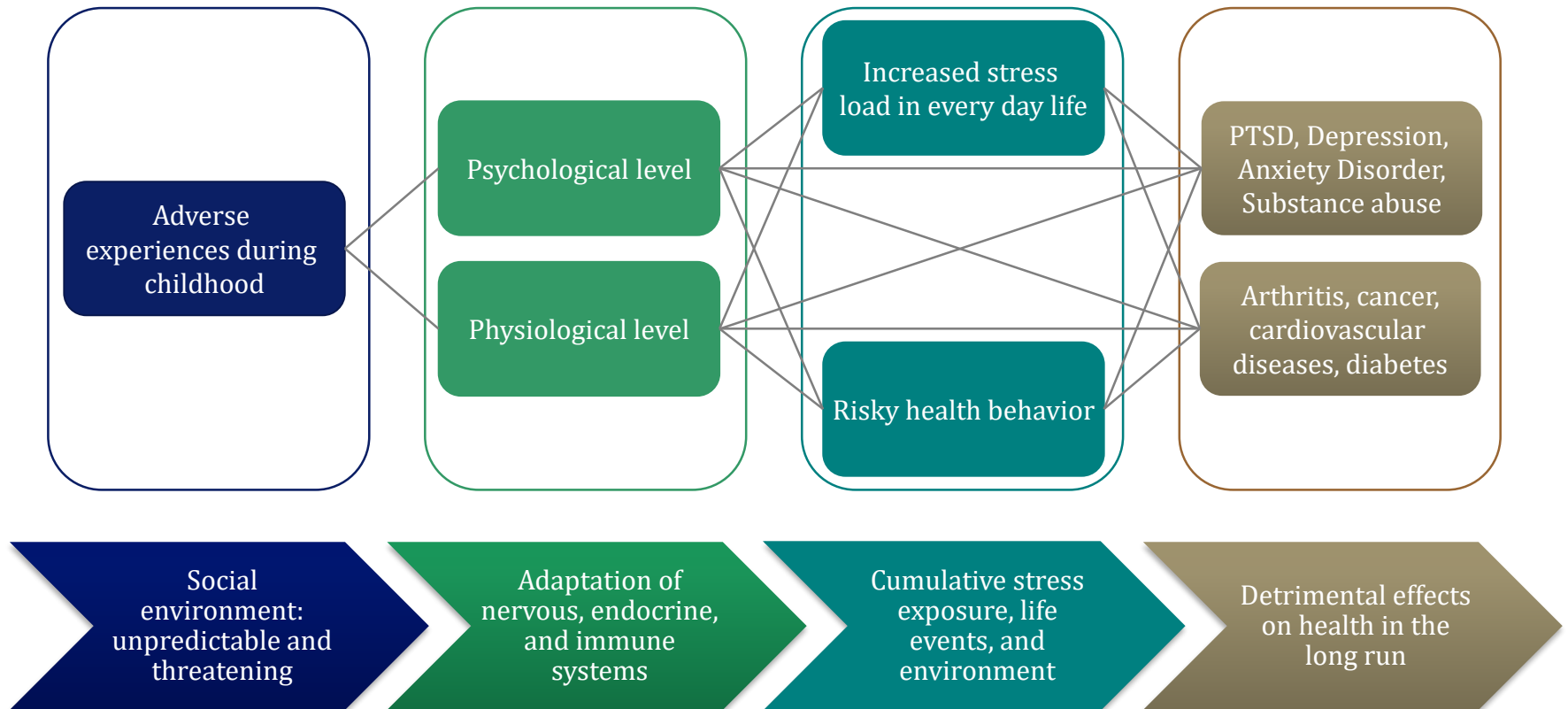
Chronic and traumatic stress, including adverse childhood experiences (ACE), increase the risk for various physical diseases and diminishes life quality.
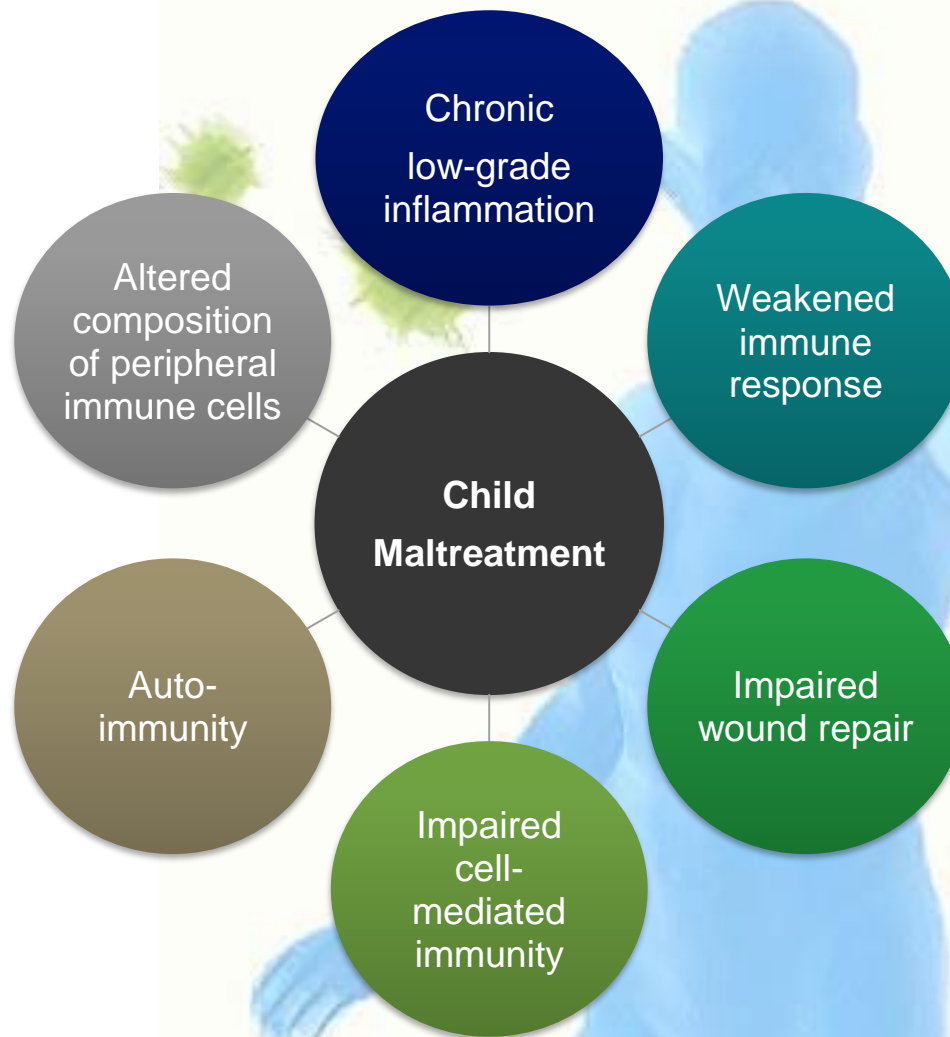
Seng et al. (2006), *Journal of Traumatic Stress*
Felitti et al. (1998), *American Journal of Preventive Medicine*

ACEs show a dose-response effect on the risk for mental pathology, especially major depression and anxiety disorder.

Child abuse and neglect increase the risk for:

▸ **Reduced healt-related life quality**

▸ **Unsecure or desorganized psychosocial attachment**

▸ **Depression**

▸ Anxiety disorders

▸ Alcohol abuse /-dependency

▸ Drug abuse /-dependency

▸ Eating disorders

▸ **Posttraumatic stress disorder**

▸ Dissociative disorder

▸ Personality disorder

▸ Suicide attempts

Chapman et al. (2004), *Journal of Affective Disorders*
Li et al. (2016), *Psychological Medicine*
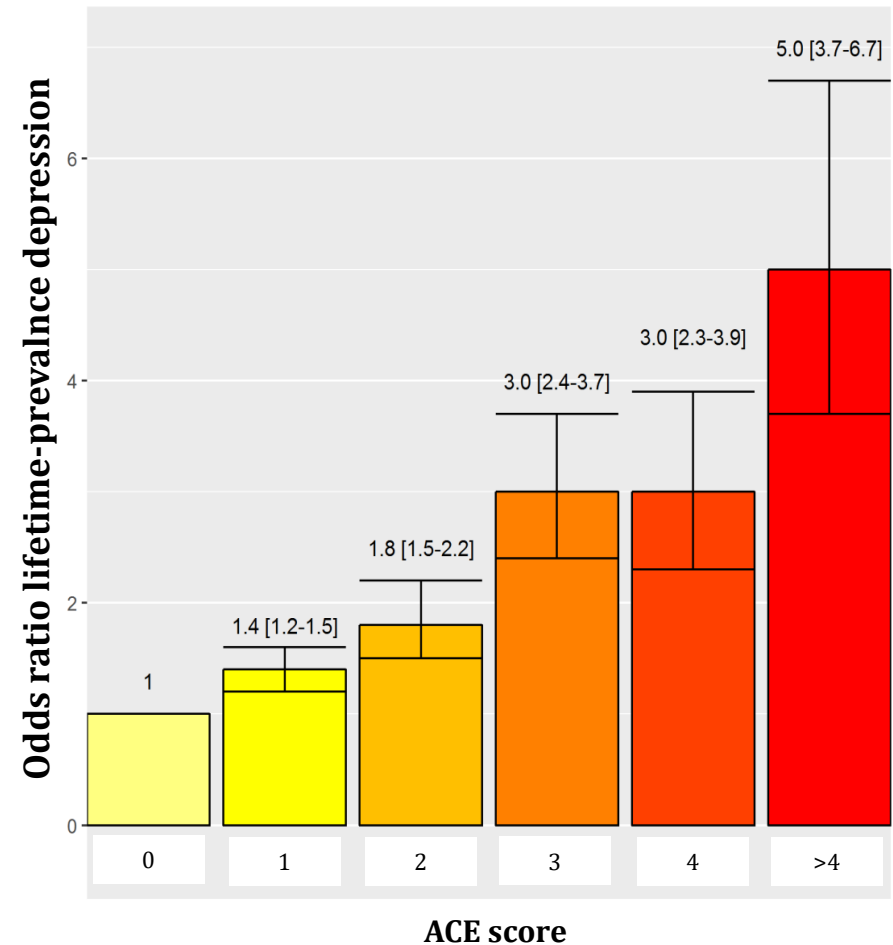
A history of childhood maltreatment is associated with a higher risk for immunological impairments.

Chronic low-grade inflammation

Weakened immune response

Altered composition of peripheral immune cells

Child Maltreatment

Impaired wound repair

Auto-immunity

Impaired cell-mediated immunity

Besides they bioenergetic functioning, mitochondria play a key role in immunity and inflammation. So far, they role in CM has not been investigated on a functional level.
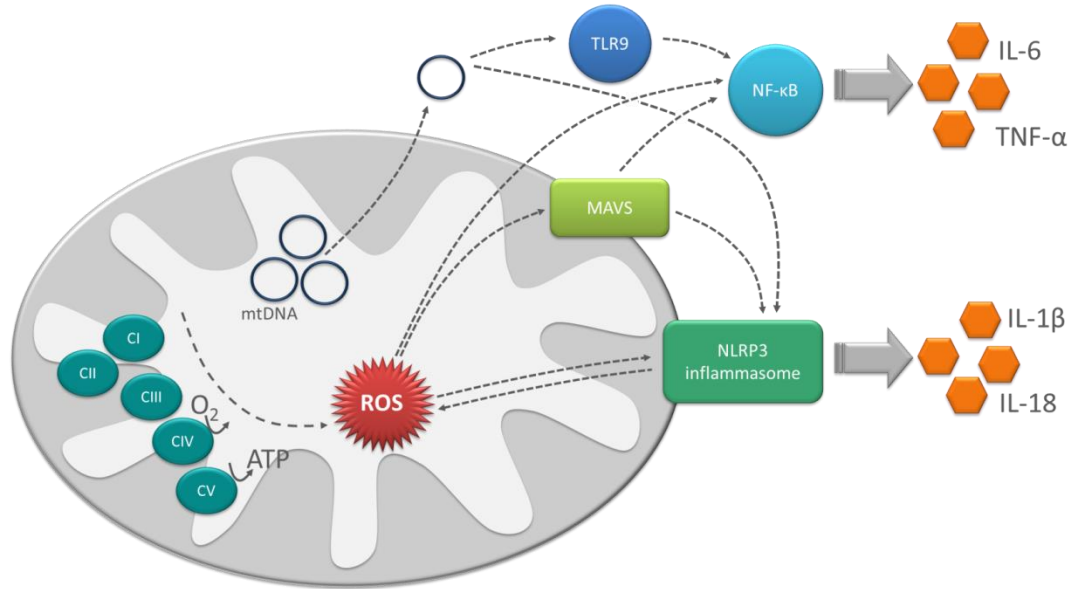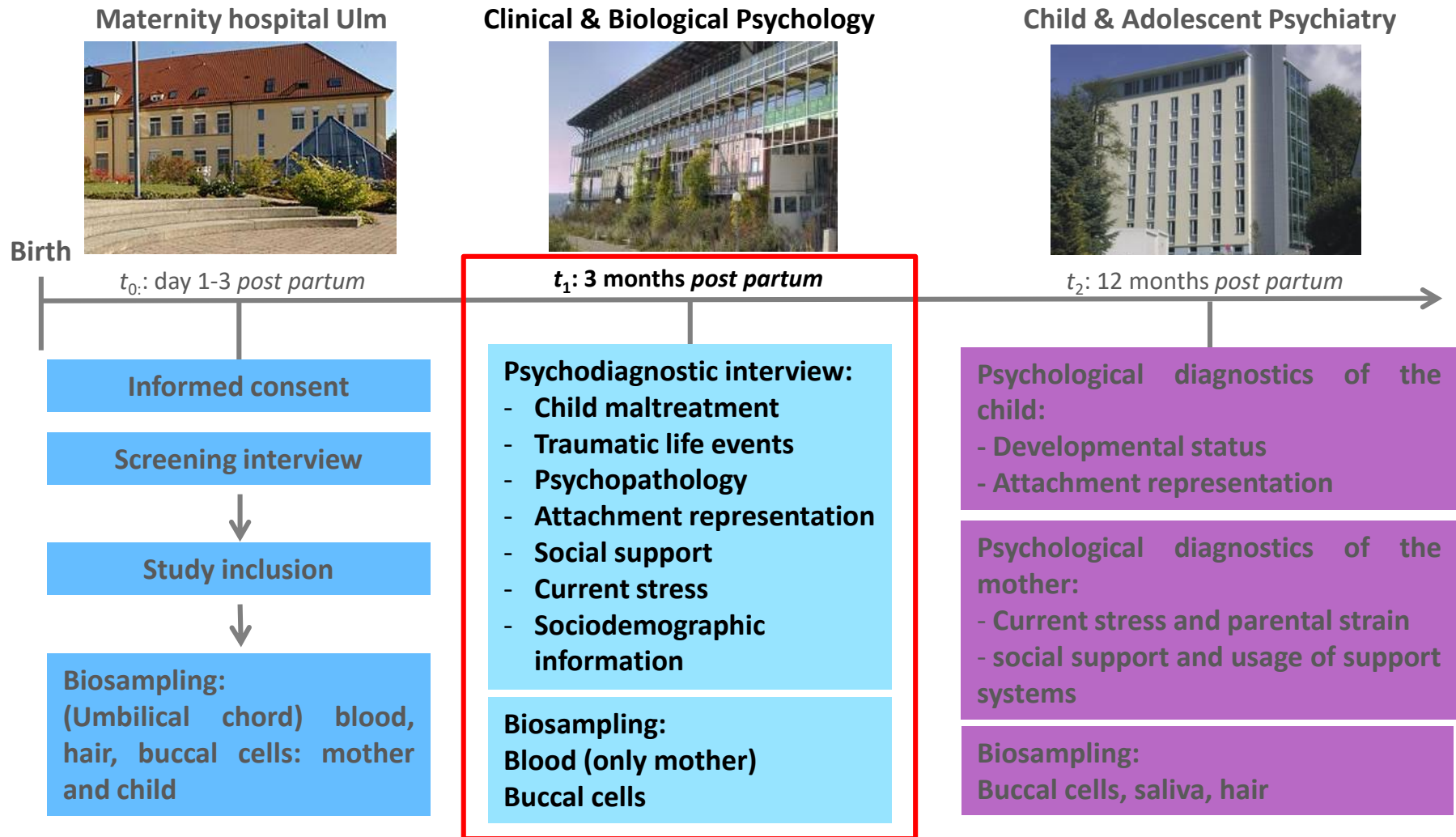

Are mitochondrial alterations involved in the establishment of the pro-inflammatory phenotype with child maltreatment experiences?
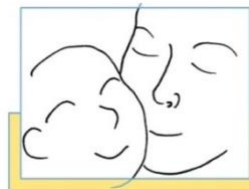
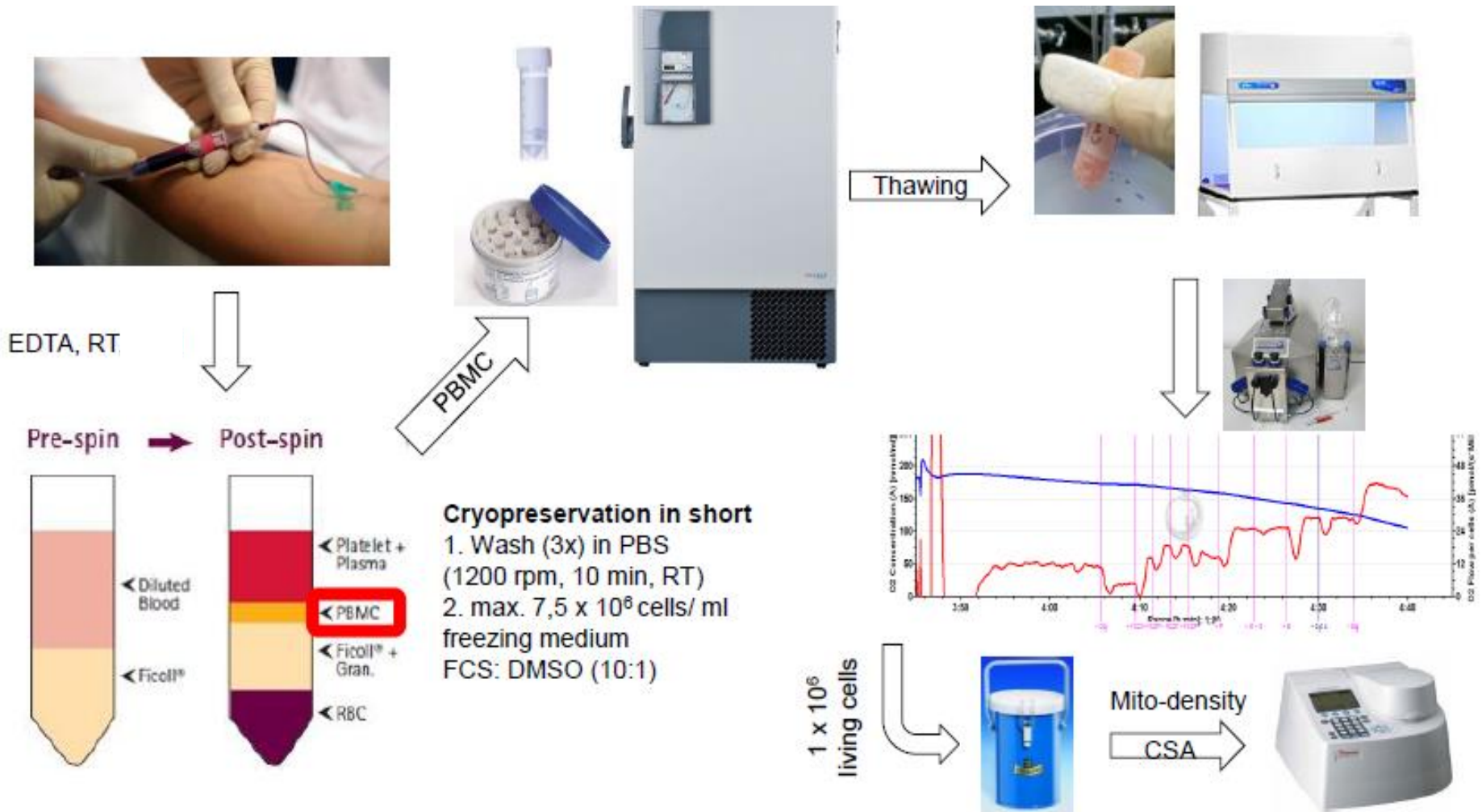# "My Childhood – Your Childhood": The influence of childhood experiences on mothers and their infants in a transgenerational context.

Maternity hospital Ulm
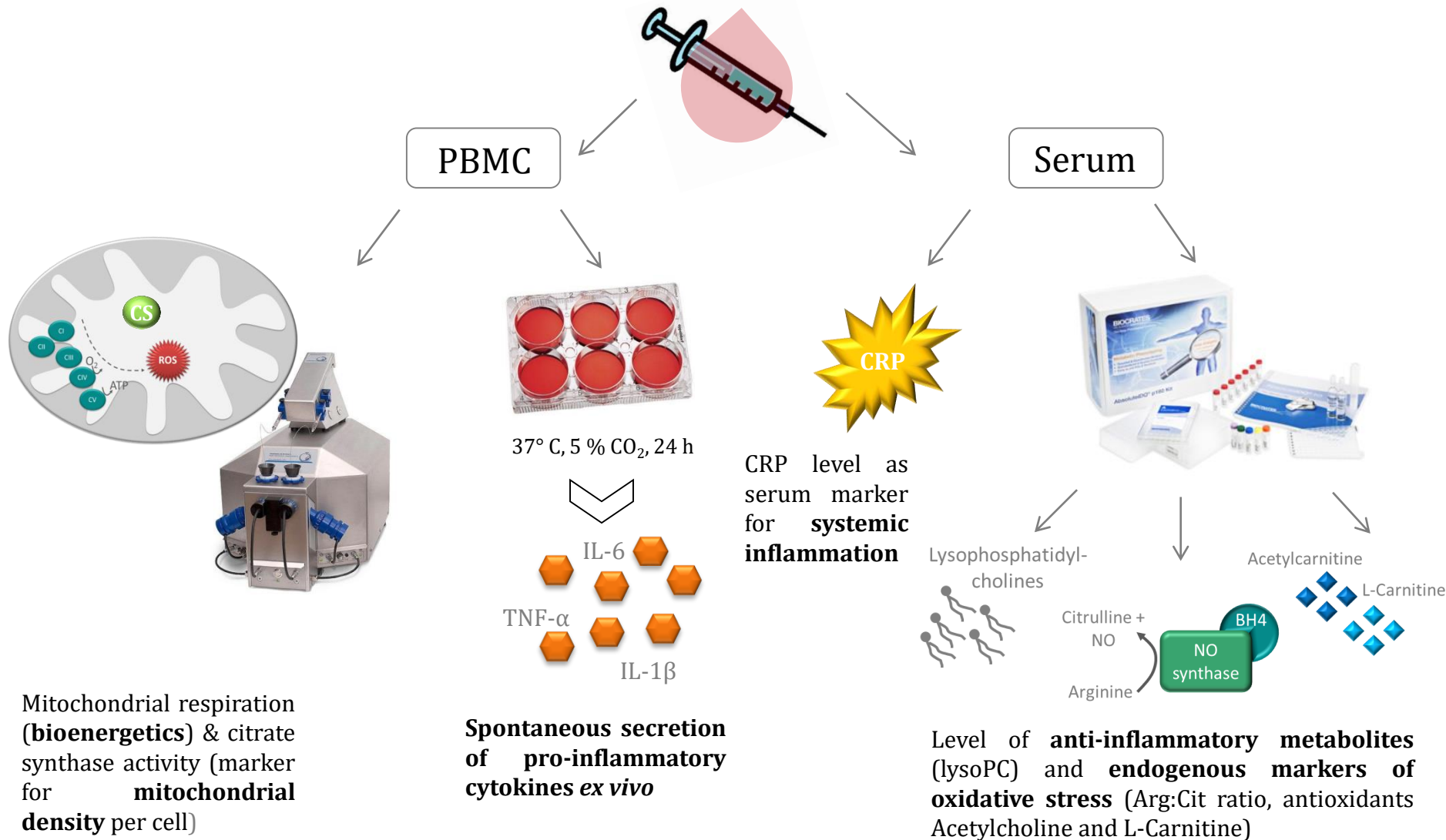
Clinical & Biological Psychology

Child & Adolescent Psychiatry

Birth

t_0: day 1-3 *post partum*

t_1: **3 months *post partum***

t_2: 12 months *post partum*

Informed consent

Screening interview

Study inclusion

Biosampling:
(Umbilical chord) blood, hair, buccal cells: mother and child

Psychodiagnostic interview:
- Child maltreatment
- Traumatic life events
- Psychopathology
- Attachment representation
- Social support
- Current stress
- Sociodemographic information

Biosampling:
Blood (only mother)
Buccal cells

Psychological diagnostics of the child:
- Developmental status
- Attachment representation

Psychological diagnostics of the mother:
- Current stress and parental strain
- social support and usage of support systems

Biosampling:
Buccal cells, saliva, hair

Demographical and psychological data: "My Childhood – Your Childhood"

	Total	CTQ classification			p^a
		None	Low/moderate	Severe	
Demographics	$(N = 30)$	$(N = 8)$	$(N = 11)$	$(N = 11)$	
Age (years)	31.6 ± 6.0	32.5 ± 4.5	33.6 ± 6.7	29.0 ± 5.7	0.19
BMI (kg/m^2)	25.3 ± 6.4	26.6 ± 7.7	26.3 ± 8.0	23.3 ± 2.5	0.43
Smoking status (yes, n (%))[b]	8 (26.7%)	1 (12.5%)	3 (27.3%)	4 (36.4%)	0.22
Alcohol consumption (yes, n (%))[b]	10 (33.3%)	3 (37.5%)	3 (27.3%)	4 (36.4%)	0.36
Physical activity (yes,n (%))[b]	8 (26.7%)	3 (37.5%)	3 (27.3%)	2 (18.2%)	0.64
Ethnicity (Caucasian, n (%))	29 (96.8%)	8 (100.0%)	11 (100.0%)	10 (90.9%)[c]	0.41
Adversity and psychiatric symptom load					
CTQ sum score	42.8 ± 14.2	28.3 ± 1.7	37.7 ± 4.5^d	$58.6 \pm 9.7^{d,e}$	<0.001
Emotional abuse sum score	9.8 ± 5.3	5.6 ± 0.9	7.6 ± 2.1	$15.0 \pm 5.1^{d,e}$	<0.001
Physical abuse sum score	7.1 ± 3.8	5.3 ± 0.5	5.7 ± 1.6	$9.9 \pm 5.0^{d,e}$	0.005
Sexual abuse sum score	6.7 ± 4.1	5.0 ± 0	5.8 ± 2.1	8.8 ± 6.1	0.09
Emotional neglect sum score	12.3 ± 4.8	7.4 ± 1.7	12.6 ± 2.6^d	15.6 ± 5.1^d	<0.001
Physical neglect sum score	6.9 ± 2.9	5.0 ± 0	6.0 ± 1.1	$9.2 \pm 3.8^{d,e}$	0.002
PSS sum score	4.1 ± 2.8	3.5 ± 2.4	3.0 ± 2.4	6.2 ± 2.4	0.06
HADS depression sum score	3.8 ± 3.2	2.8 ± 2.1	3.6 ± 2.5	4.9 ± 4.3	0.34
HADS anxiety sum score[f]	6.3 ± 3.5	5.1 ± 2.6	4.5 ± 2.8	8.9 ± 3.2	0.004

Short workflow for cryopreservation of PBMC and sample processing for high-resolution respirometry using O2K-Oxygraphs.

Overview – Biological analyses

PBMC

Serum

$37°$ C, 5% CO_2, 24 h

IL-6

TNF-α

IL-1β

CRP

CRP level as serum marker for **systemic inflammation**

Lysophosphatidyl-cholines

Acetylcarnitine

L-Carnitine

Citrulline + NO

BH4

NO synthase

Arginine

Mitochondrial respiration (**bioenergetics**) & citrate synthase activity (marker for **mitochondrial density** per cell)

Spontaneous secretion of pro-inflammatory cytokines *ex vivo*

Level of **anti-inflammatory metabolites** (lysoPC) and **endogenous markers of oxidative stress** (Arg:Cit ratio, antioxidants Acetylcholine and L-Carnitine)

Inflammatory markers are positively associated with maltreatment load, *while* anti-inflammatory markers show a negative association with CM.

Serum CRP levels
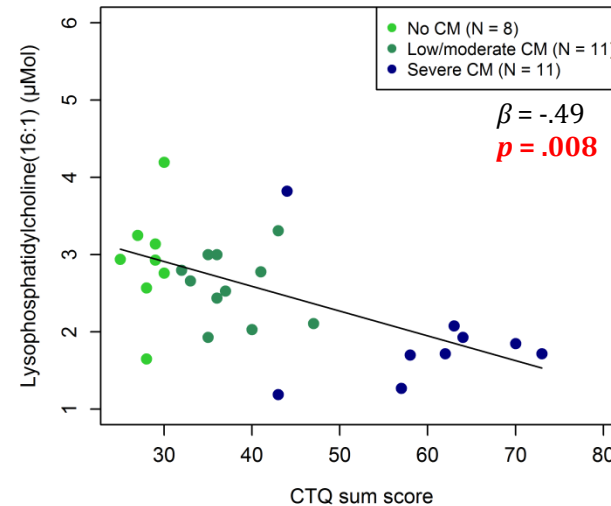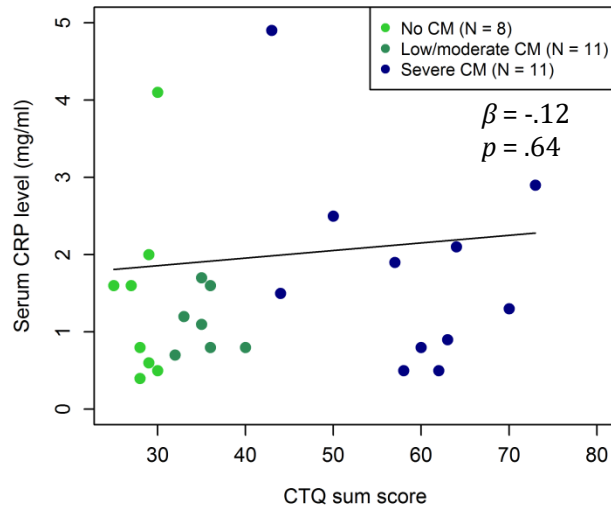
Serum level of lysoPC

Spontaneous IL-6 secretion (supernatant)
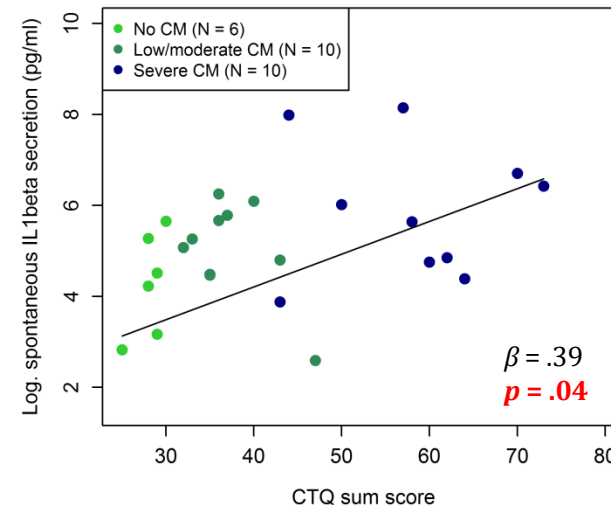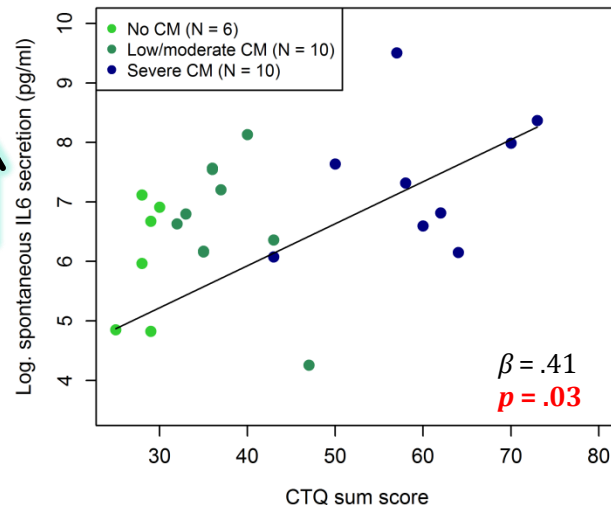
Spontaneous IL-1β secretion (supernatant)

Mitochondrial activity of PBMC increases with higher severity of CM experiences in a dose-dependent manner

Basal ("routine") respiration of intact PBMC
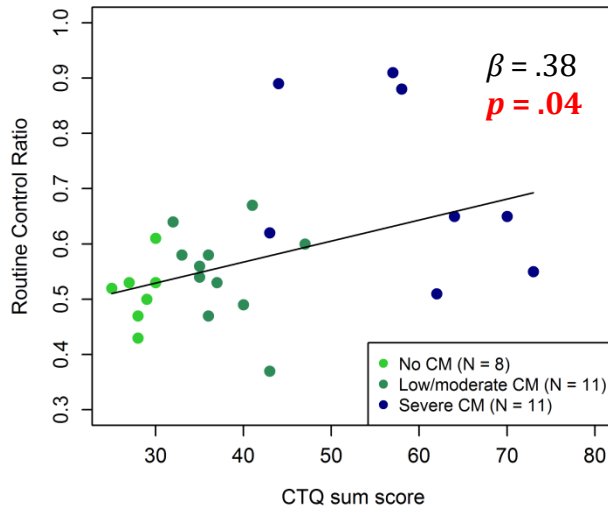
Oxygen consumption related to ATP-turnover
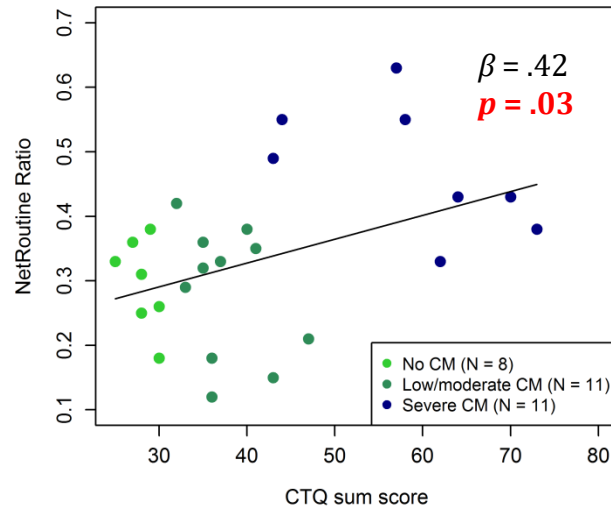
Oxygen consumption attributable to proton leak
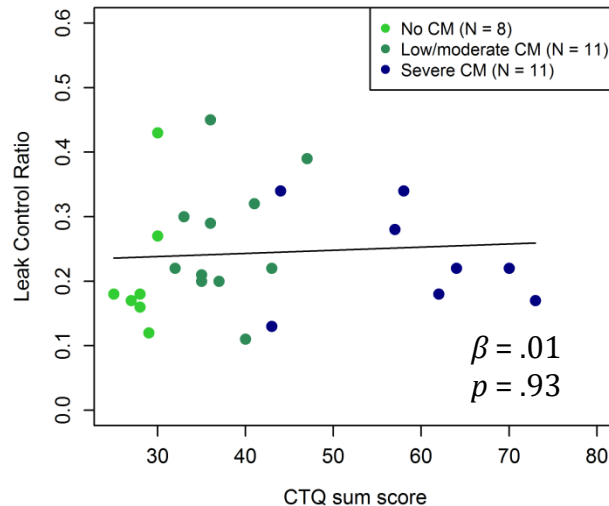
Citrate synthase activity (mitochondrial density)
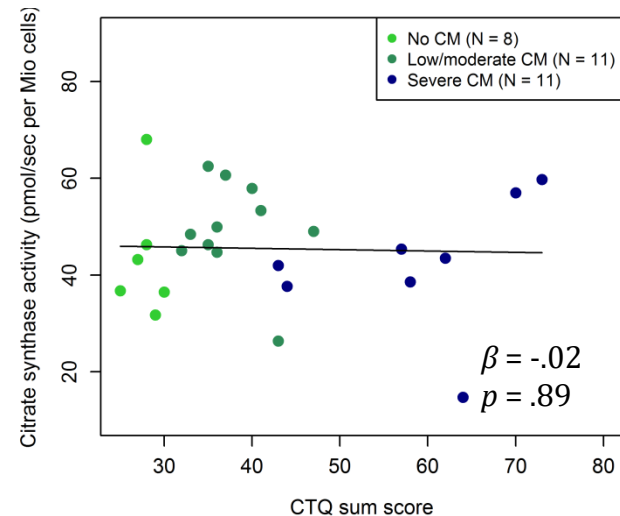
More severe CM experiences are dose-dependently associated with higher levels of biovariables related to oxidative stress
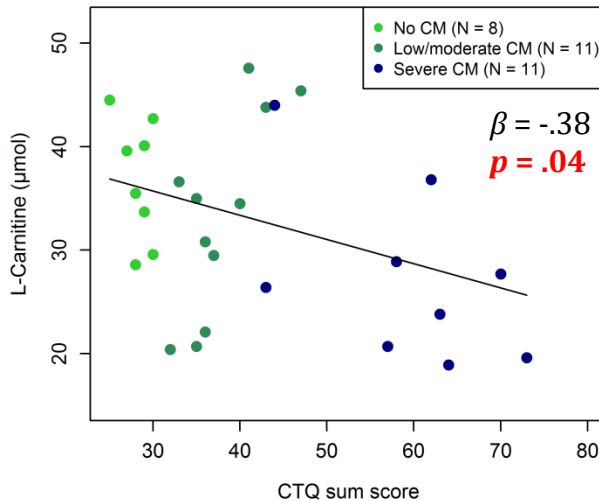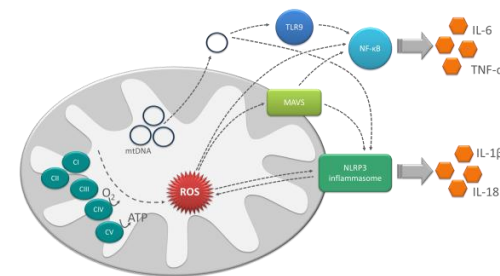
Non-OXPHOS oxygen consumption of intact PBMC

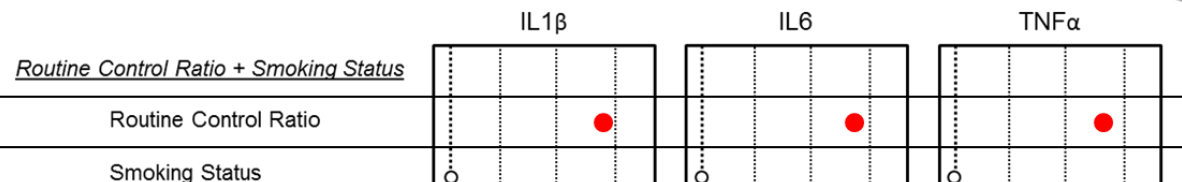**Serum L-carnitine level**
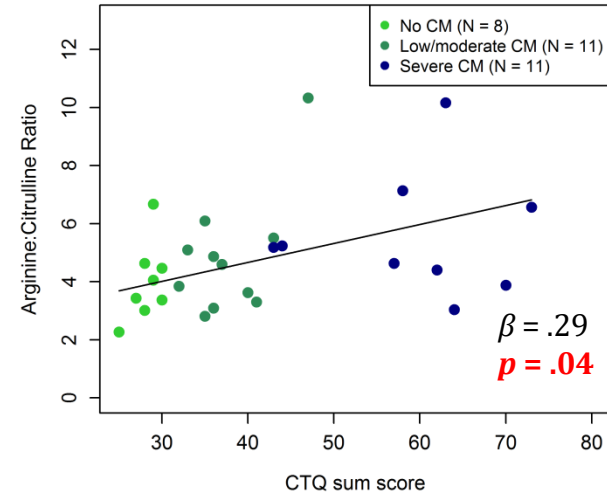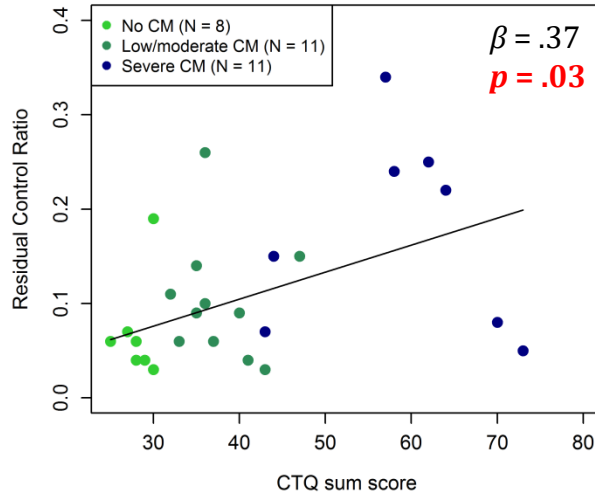
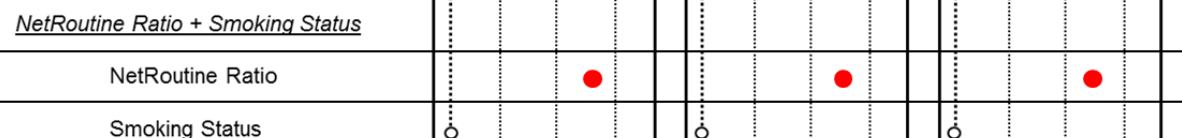**Arginine:citrulline ratio**
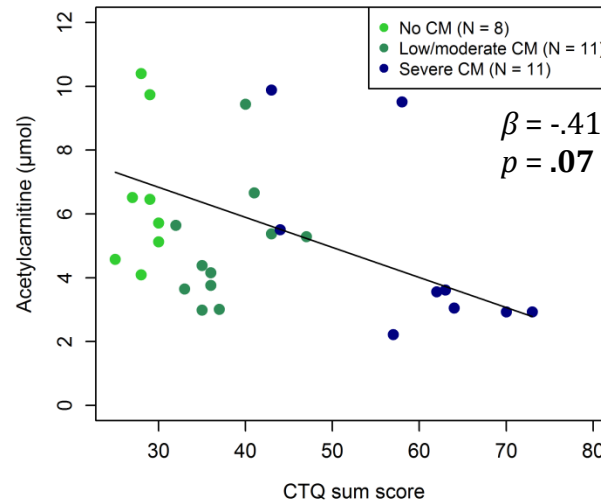
Serum acetylcarnitine level

Mitochondrial basal respiration, ATP-turnover related respiration and the residual oxygen consumption significantly correlate with the release of pro-inflammatory cytokines *in vitro*
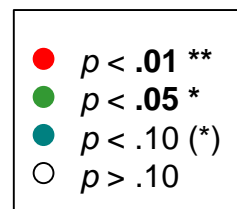
Summary
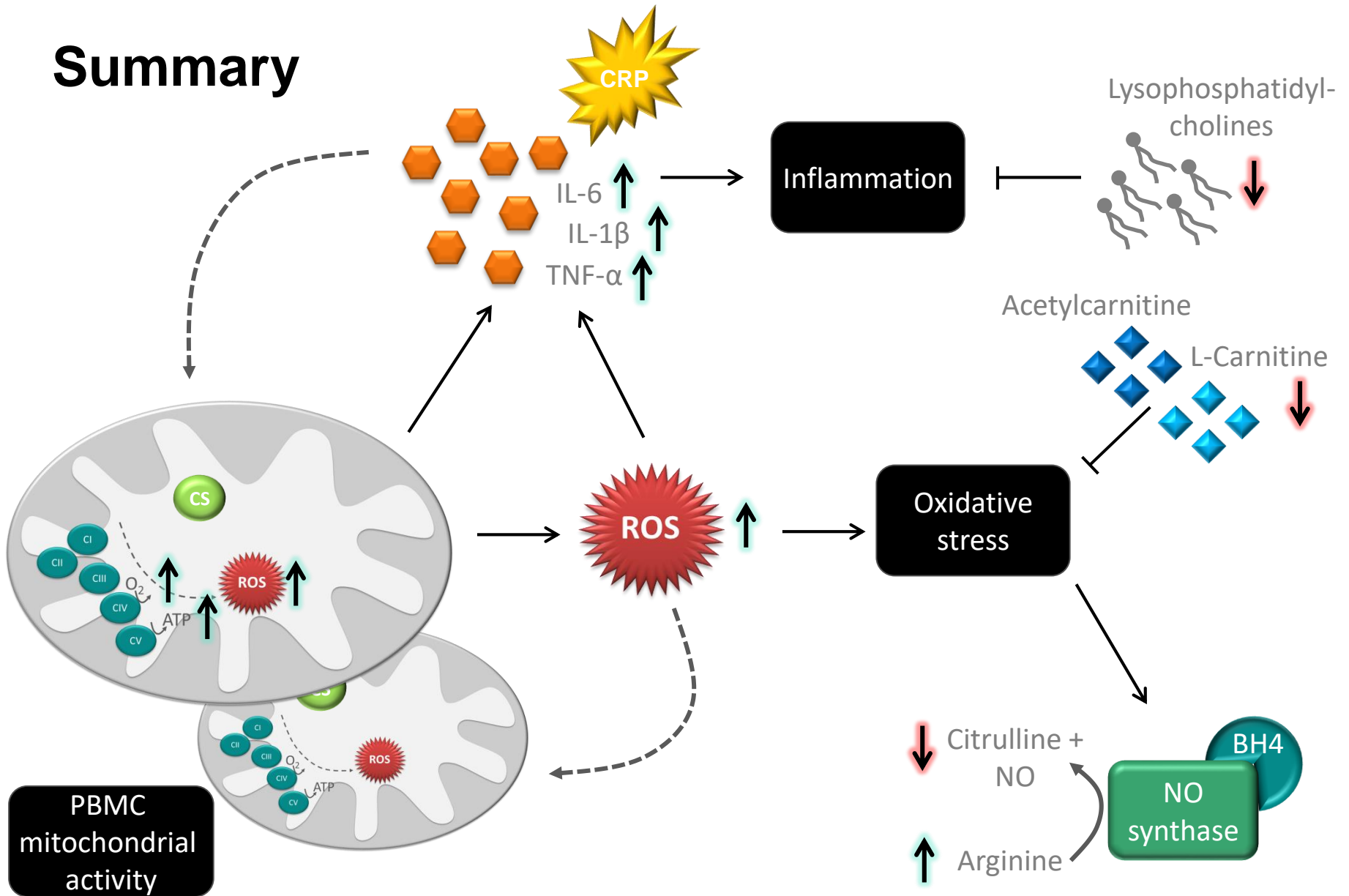
Thank you for your attention!

Clinical & Biological Psychology, Ulm University

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Dr. Alexander Karabatsiakis	Patrick Fissler
Christina Boeck	Anna Schneider
Dr. Sarah Wilker	Olivia Küster
Alexandra König	Daniela Conrad
Martha Geiger	Verena Nold
Daria Laptinskaya	Barbara Schorr
Laura Ramo Fernandez	Traudl Hiller
Manuela Rappel	Margit Zeller

Department of Psychosomatic Medicine and Psychotherapy, University Hospital Ulm
Prof. Dr. Christiane Waller
Prof. Dr. Harald Gündel

Department of Child and Adolescent Psychiatry and Psychotherapy, University Hospital Ulm
Prof. Dr. Jörg Fegert

Institute of Anesthesiological Pathophysiology and Process Engineering, University Hospital Ulm
Prof. Dr. Enrico Calzia
Peter Radermacher