



University Children's Hospital Zurich

Dysregulated immune system & impaired quality of life in maltreated children

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Inappropriate activation of T cells

Gender impact

Ongoing impaired Quality of Life

Mismatch of perception

Lymphocyte correlate with Quality of Life



Paradigm

„Health is a state of complete physical, mental and social well-being, and not merely the absence of disease or infirmity.“

World Health Organization, 1948



Outline of study

- Background
- Design
- Immune System
- Health Related Quality of Life (HRQoL)
- Synthesis
- Conclusion



Maltreatment in children...

- Compromised cognitive, psychosocial and somatic development
- Risk of PTSD, depression, ... disease burden in public health!
- Mixed results on impact on HPA-axis & MRI
- (Epi)genetics: many non-replicated findings
- Lack of research on outcome of immunology & beyond behavioral issues or mental health



Design

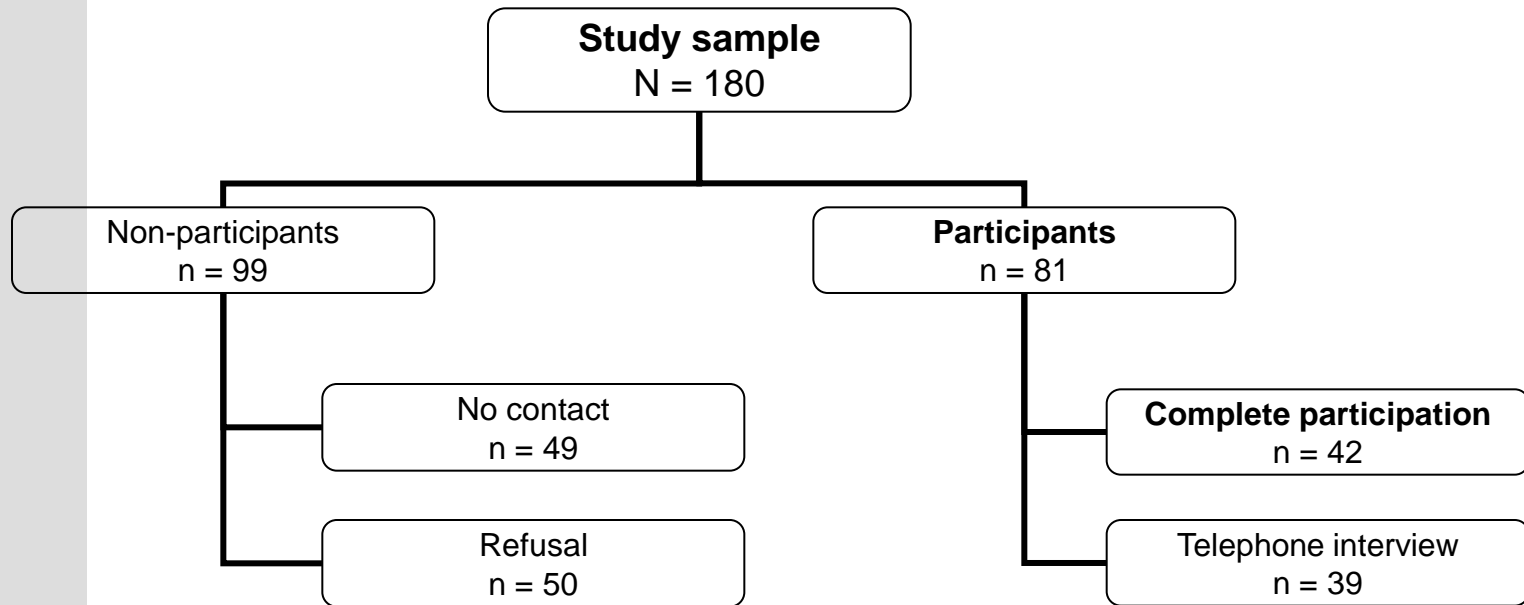


How we measure outcome

- 1-3 years later
- Interview
- Ratings / Questionnaires
- Tests
- Health status
- Blood sample



Child protection team 2005/6 - revisited





Group similarities

- **M (n = 42)**
 - 55% Swiss
 - 18 , 24
 - mean age 8.0 (SD 3.7, range 2.6-16.5)
 - Maltreatment: 15 (36%) sexual, 11 (26%) physical
- **C (n = 42)**
 - Matched for age, gender, incomplete for nationality
 - Exclusion of illnesses & PTSD
 - Higher SES



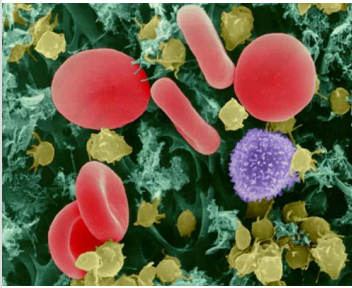
Dysregulated immune system in maltreated children



Background I



Immune response	Innate	Adaptive
Time	Hours	Days
Specificity	Limited and fixed	Diverse and improves
To repeat infection	Identical	More rapid
Major components	Barriers (skin) Pattern recognition Molecules (complement) Phagocytes (monocytes, NK cells)	Lymphocytes (B, T) Antigen specific -receptors -antibodies

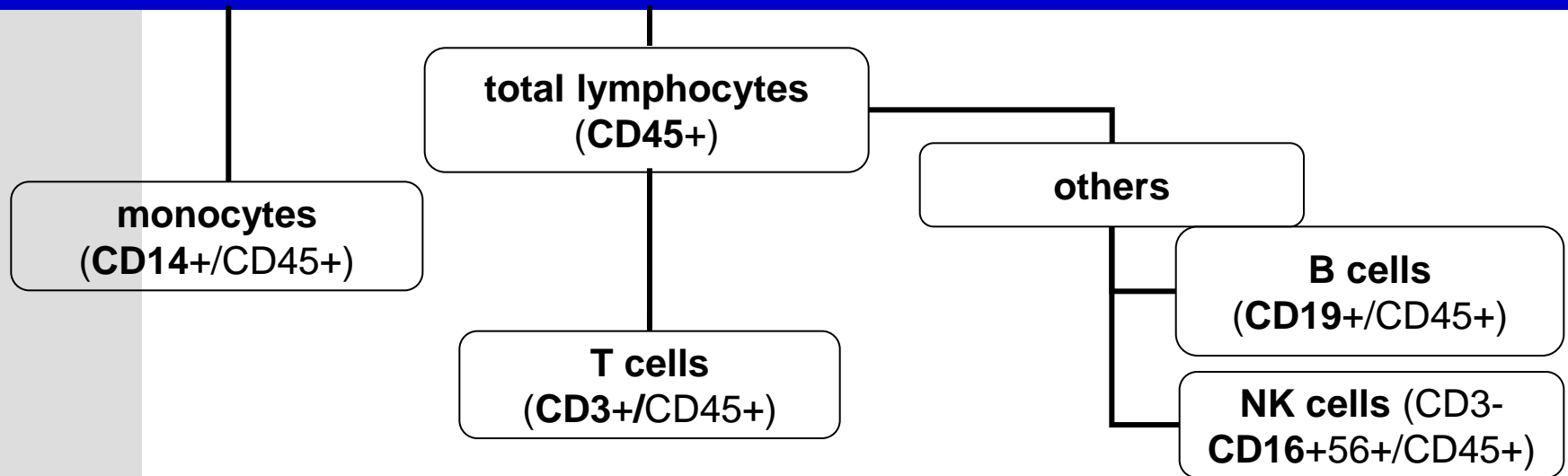


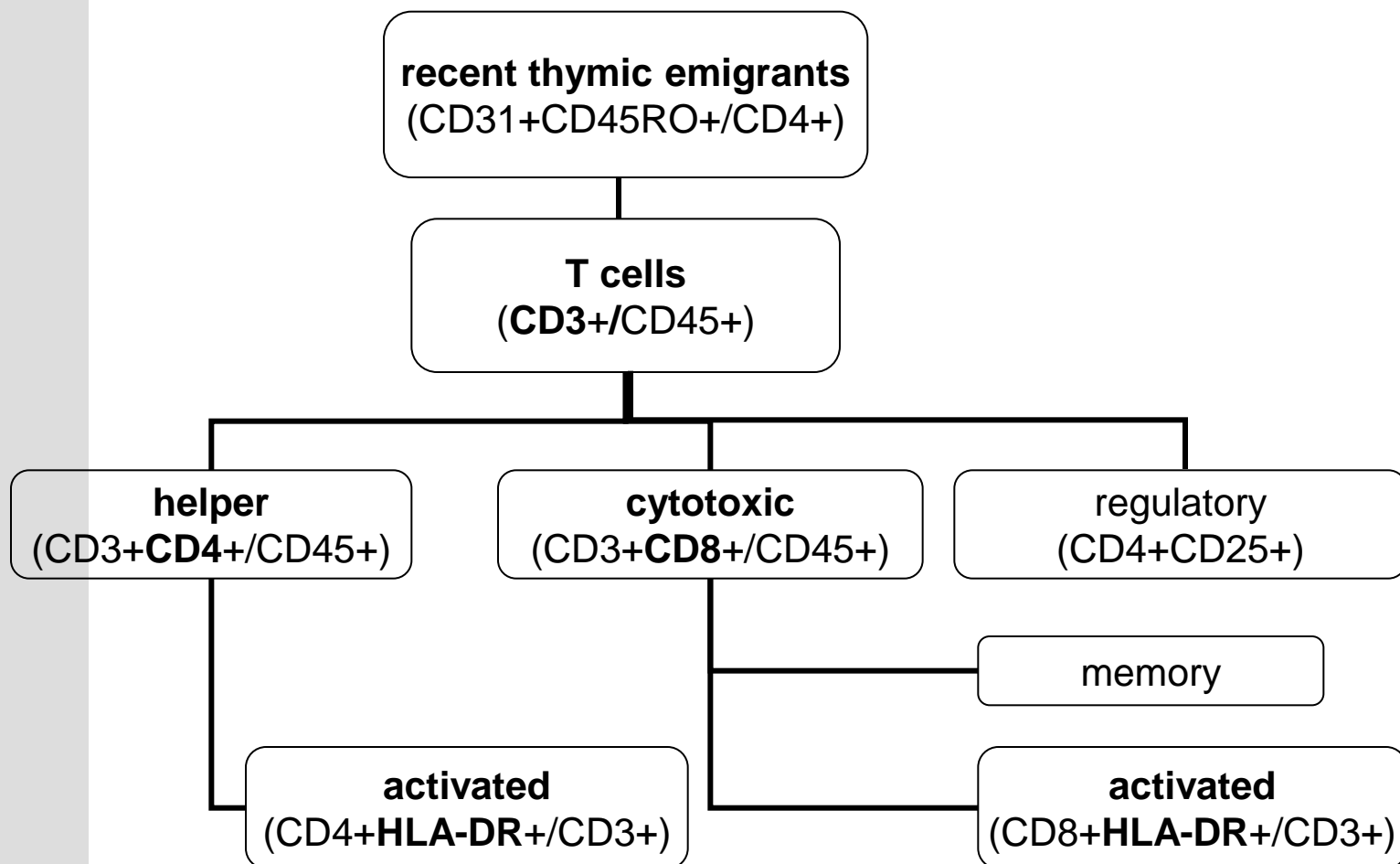
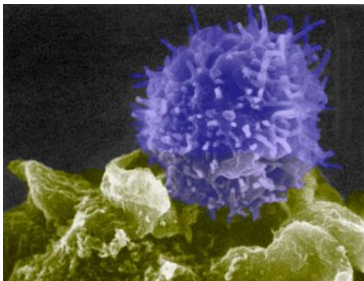
- Cell counts in children adapt to adult set:
- Red blood cells
- Platelets
- Leukocytes (7.3×10^3 cells/mm³)
 - Neutrophile (50-70%)
 - **Lymphocyte** (30-40%)
 - **Monocyte** (1-6%)
 - Eosinophile (1-3%)
 - Basophile (<1%)





Haematopoiesis in bone marrow







Pilot study



Dysregulated immunity in maltreated child?

- No studies in children
- Adults:
 - autoimmune diseases associate with cumulative stress in childhood
 - mixed results on lymphocyte deviation after childhood abuse
- MHC-II(HLA-DR)-expression
 - Kuby: on T cells is “inappropriate”
 - Associated with autoimmune diseases (e.g. MS)



Methods I



Group similarities

- **M (n = 27)**
 - 48% Swiss
 - 11 , 16
 - mean age 8.7 (SD 3.7, range 2.6-16.5)
- **C (n = 19)**
 - 46% Swiss
 - 8 , 11
 - mean age 9.3 (SD 3.3, range 4.6-15.7)

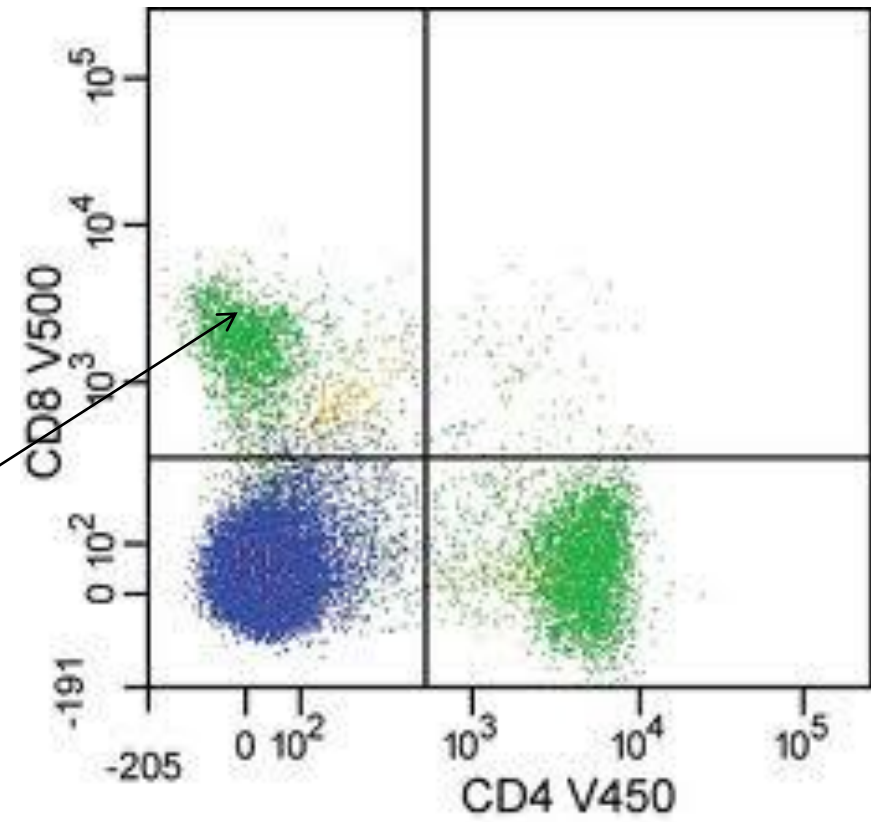
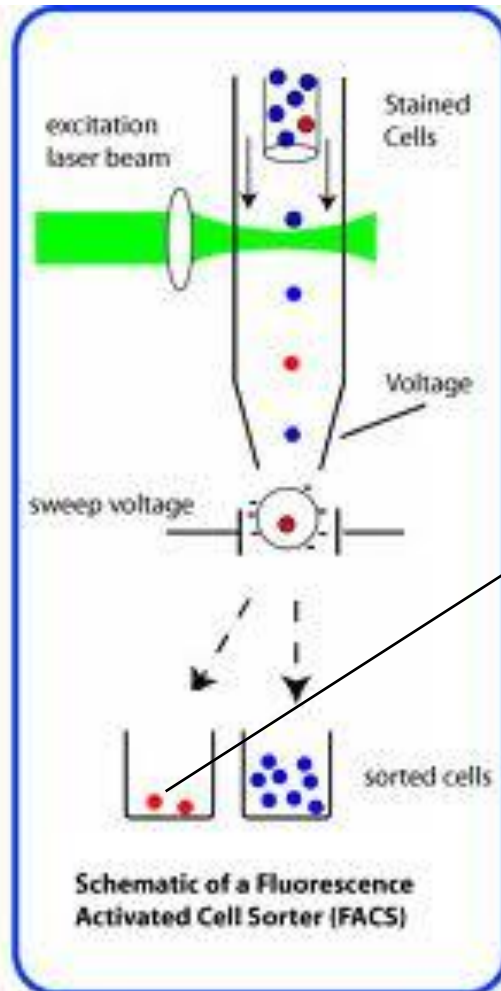


Group differences

- M
 - Social economic status (SES, n = 23: 13 low, 7 medium, 3 high)
 - Posttraumatic stress disorder (PTSD: n = 8 vs. No: n = 12)
 - 4 with lymphocytes above age-limits
- C
 - SES (n = 19: 3 low, 9 medium, 7 high)
 - No PTSD (n = 15)



Measure

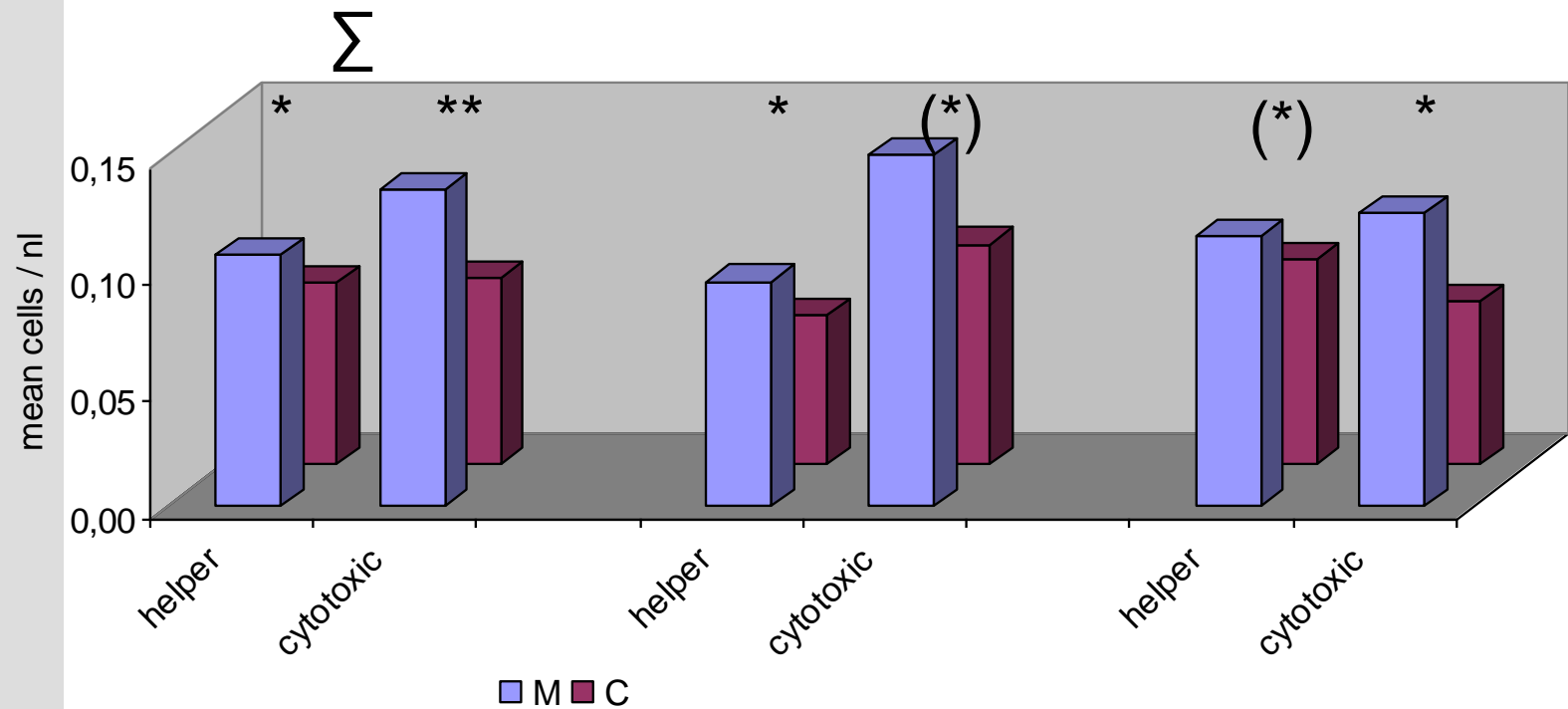




Results I

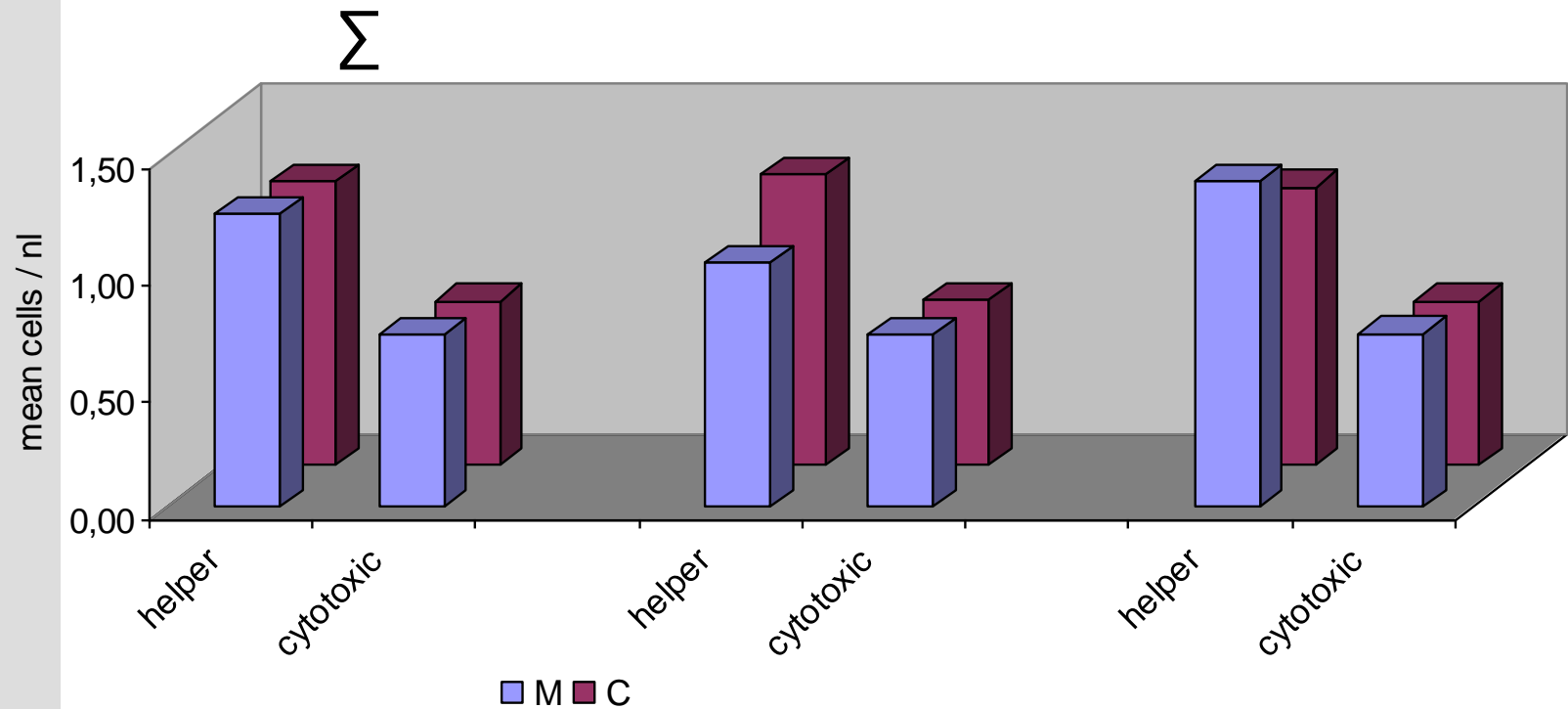


Increased activated T cells in M





Unchanged T cell populations



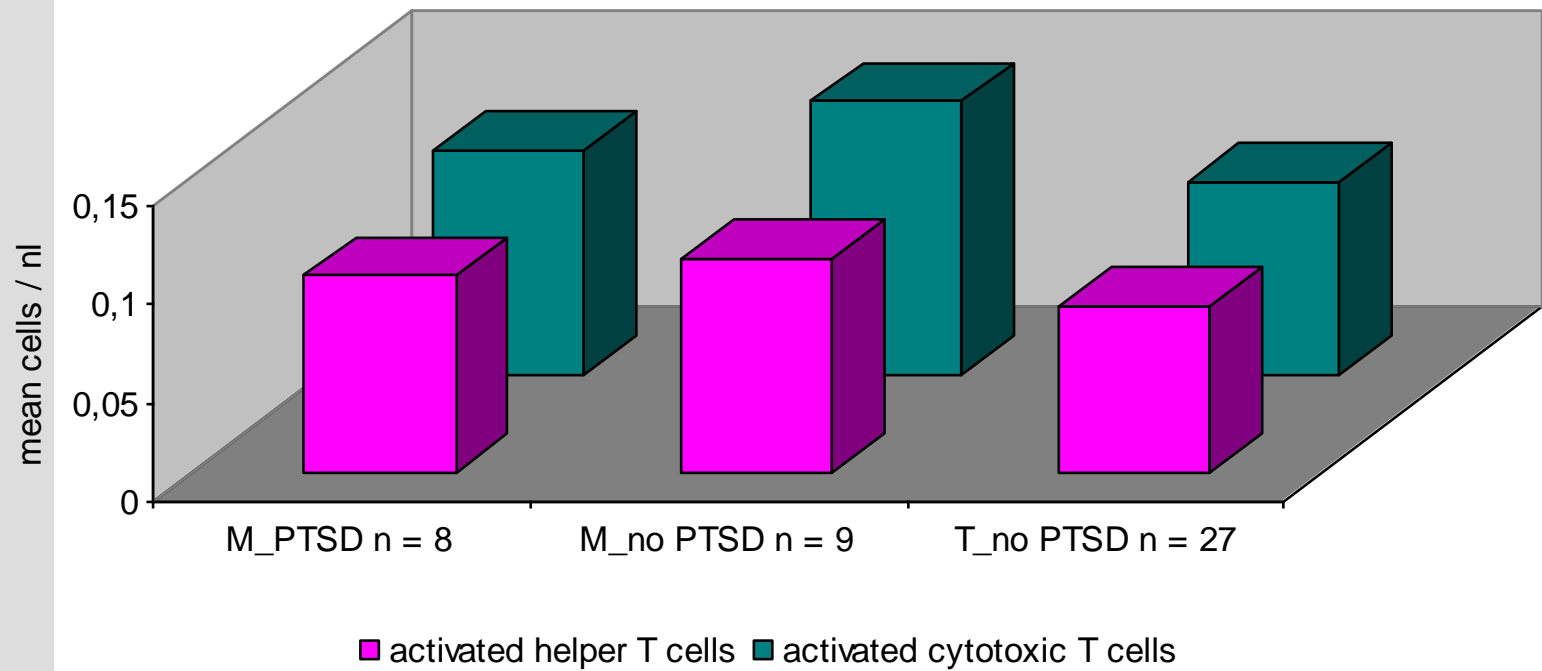


Consistency of increased activation

- Higher percentage of activated/whole T cell population in M
- Deviation from mean-values of C is
 - 40% for activated helper T cells
 - 70% for activated cytotoxic T cells
- M, , : No other cell line with significant differences, except:
 - * decreased recent thymic emigrants in male
- Differences between groups are irrelevant (psychological, economical, medical - ?)

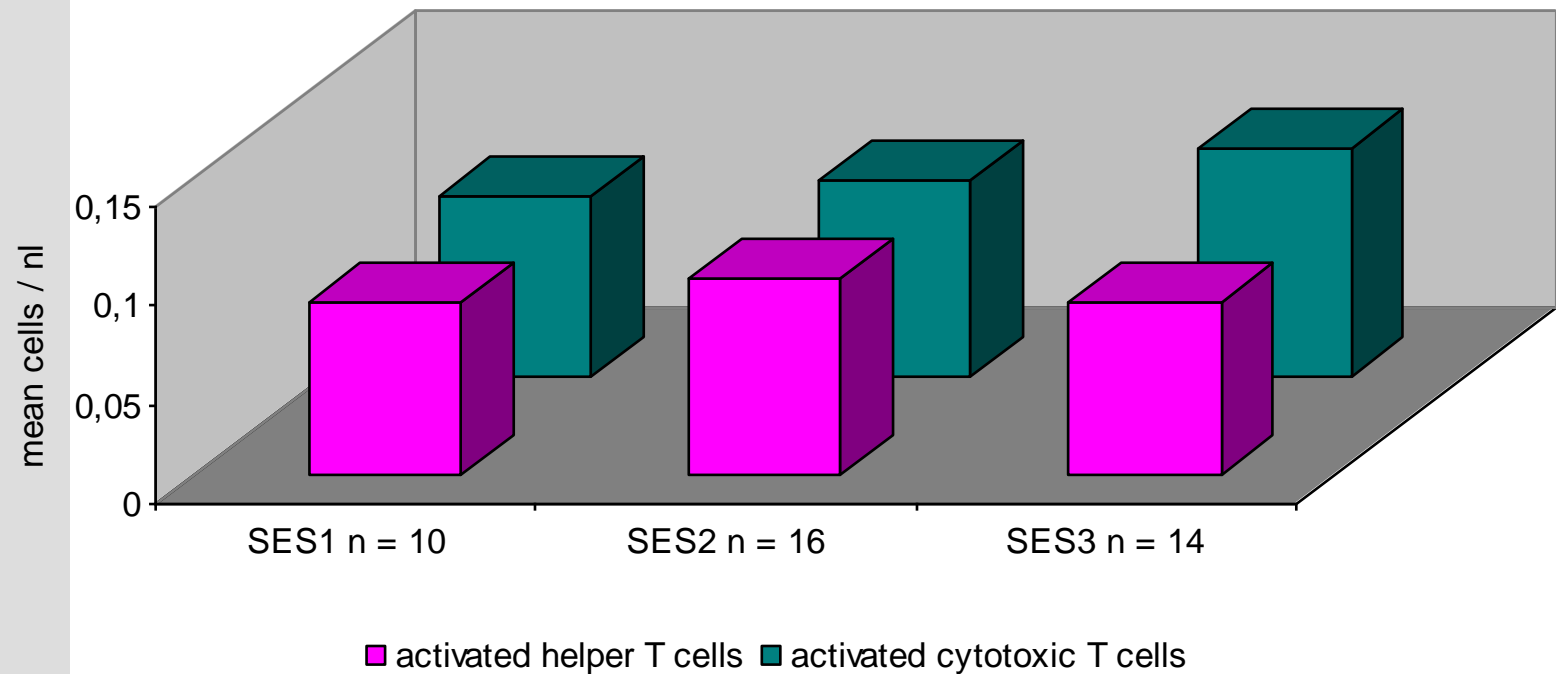


Mean cell concentration in PTSD



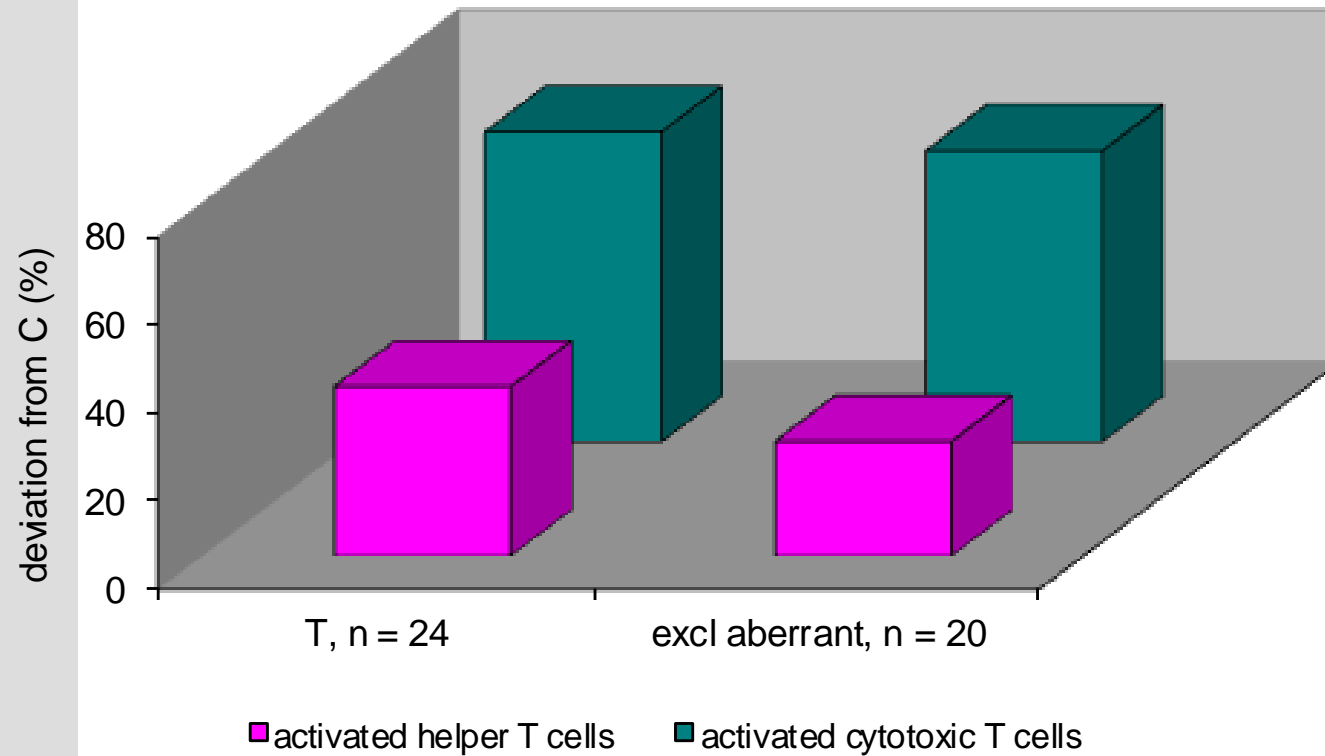


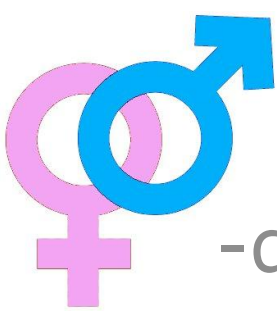
Social economic status (SES)



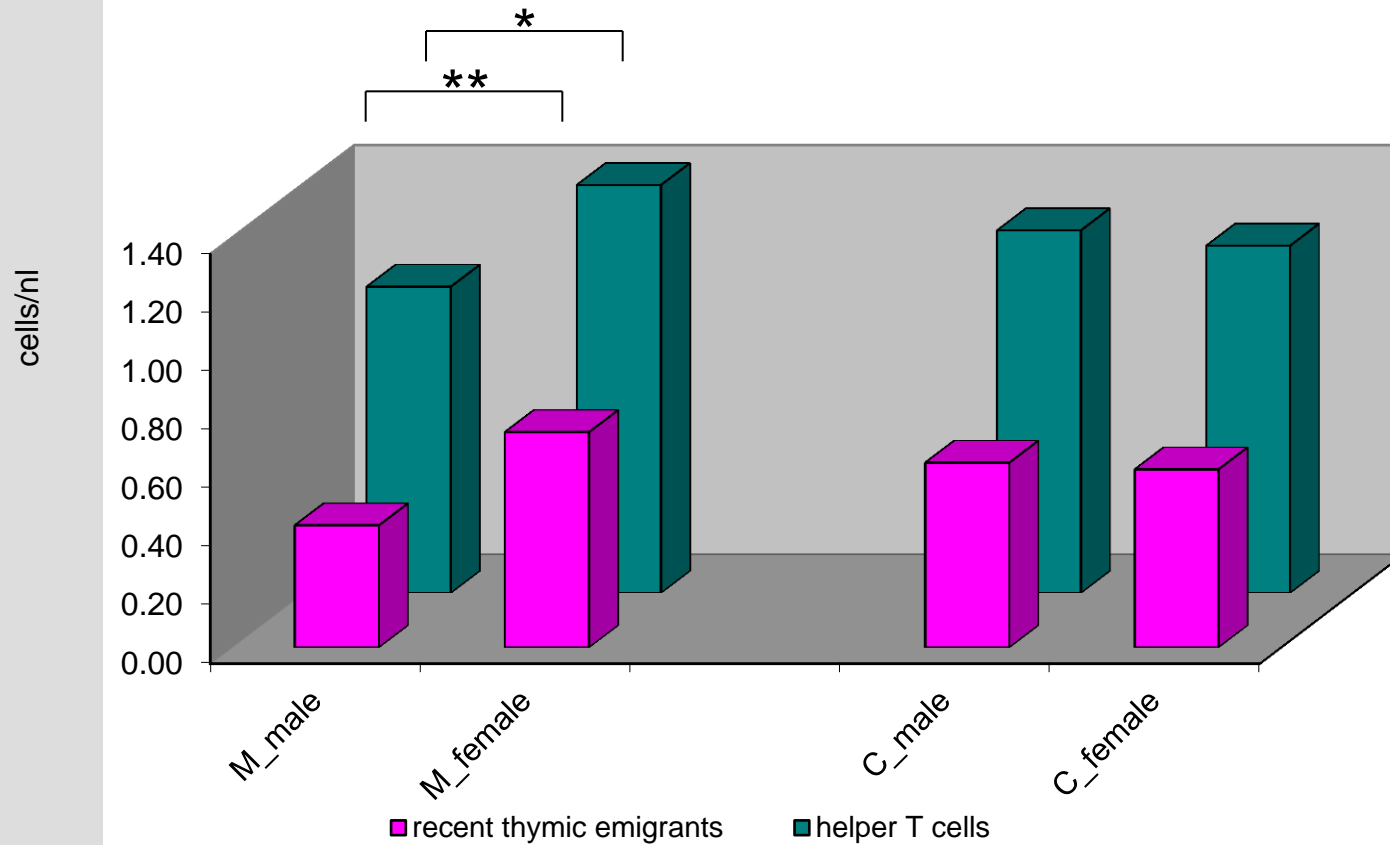


with high lymphocytes excluded



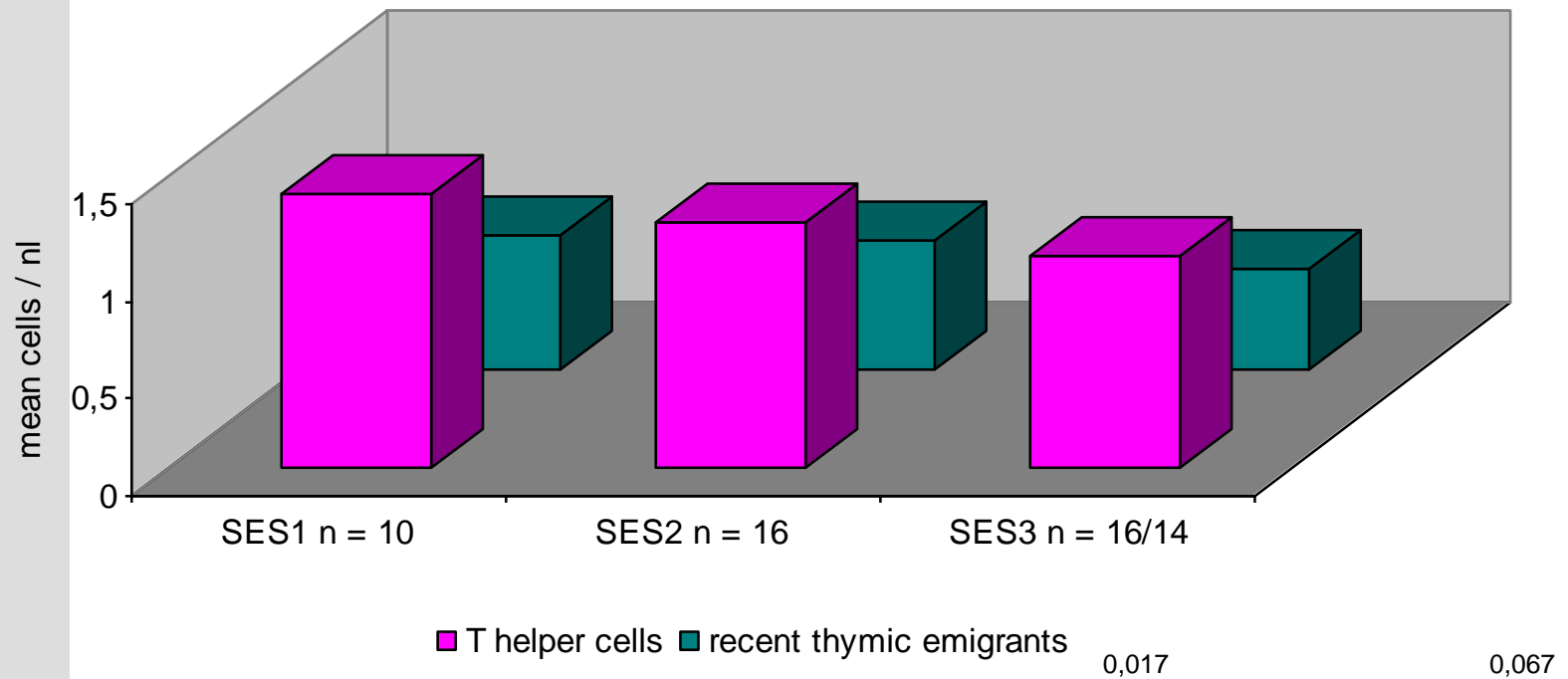


-differences in T cells





Gender-differences independent from SES





Discussion I



Summary I

- M vs C: overall increased activated T cells, independent from gender
- Only in M: counts of recent thymic emigrants & helper T cells differ between gender
- Findings are not explained by differences between sub-groups of possible confounders



Conclusion I

- Random activity leading to a unspecific over-reactive immune response that may lead to:
 - Autoimmune diseases?
 - Increased allergic reactivity?
- Lack of information
 - Different time points
 - Functionality in vitro
 - Cytokines, hormones ... (HPA-axis)



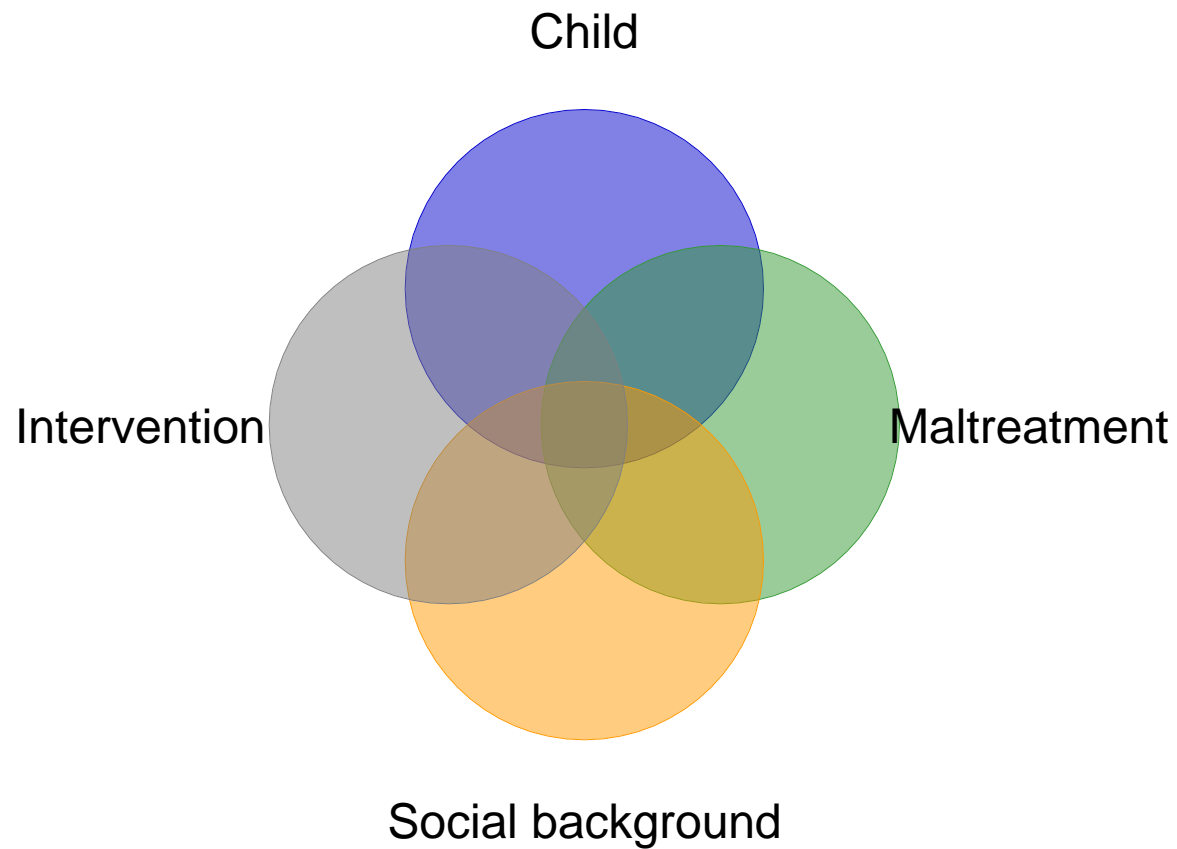
Impaired health related quality of life in maltreated children



Background II

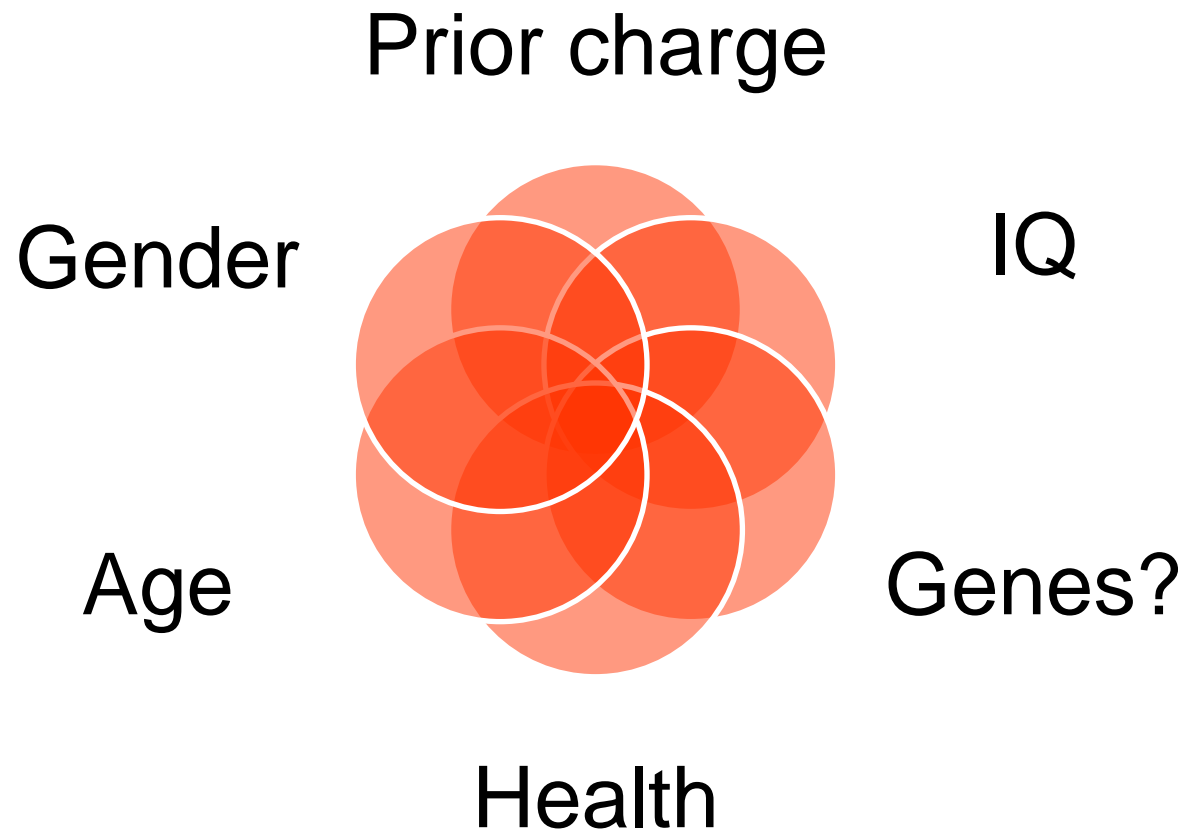


Quality of Life in maltreated children



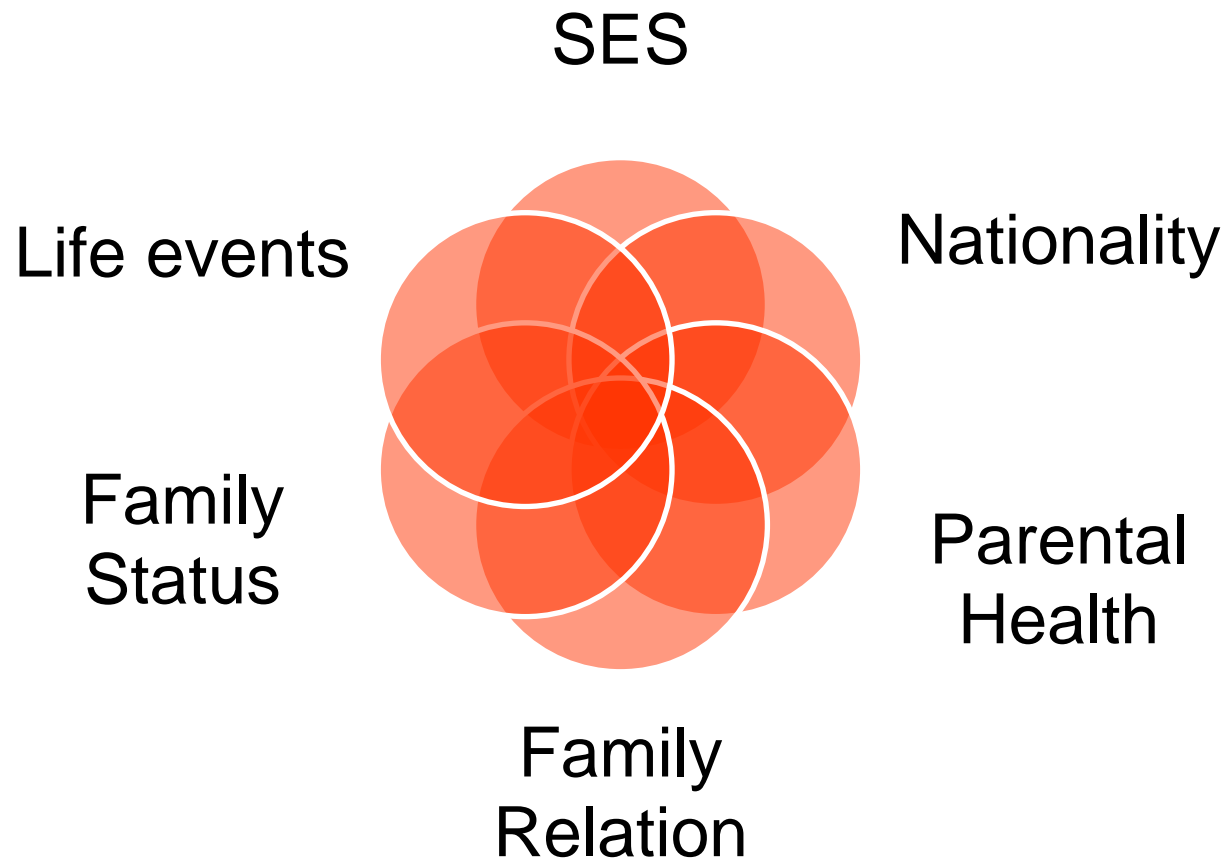


Variables of child



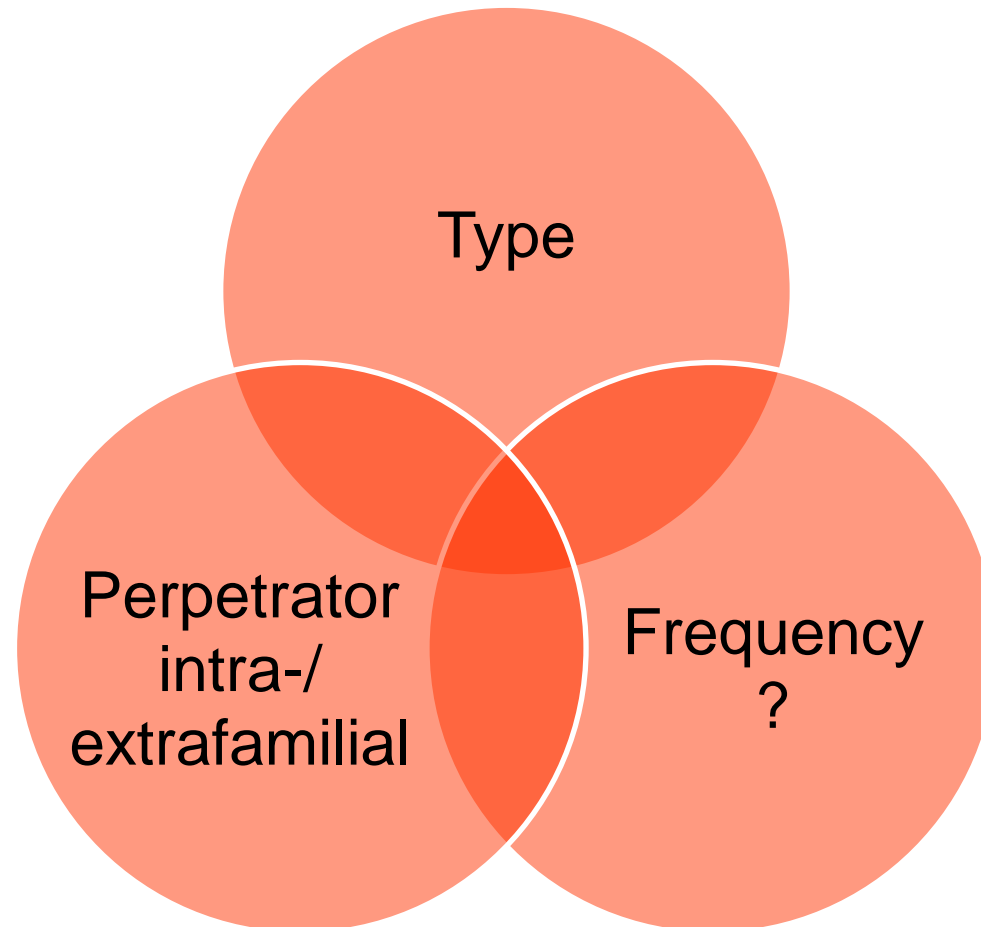


Variables of social background



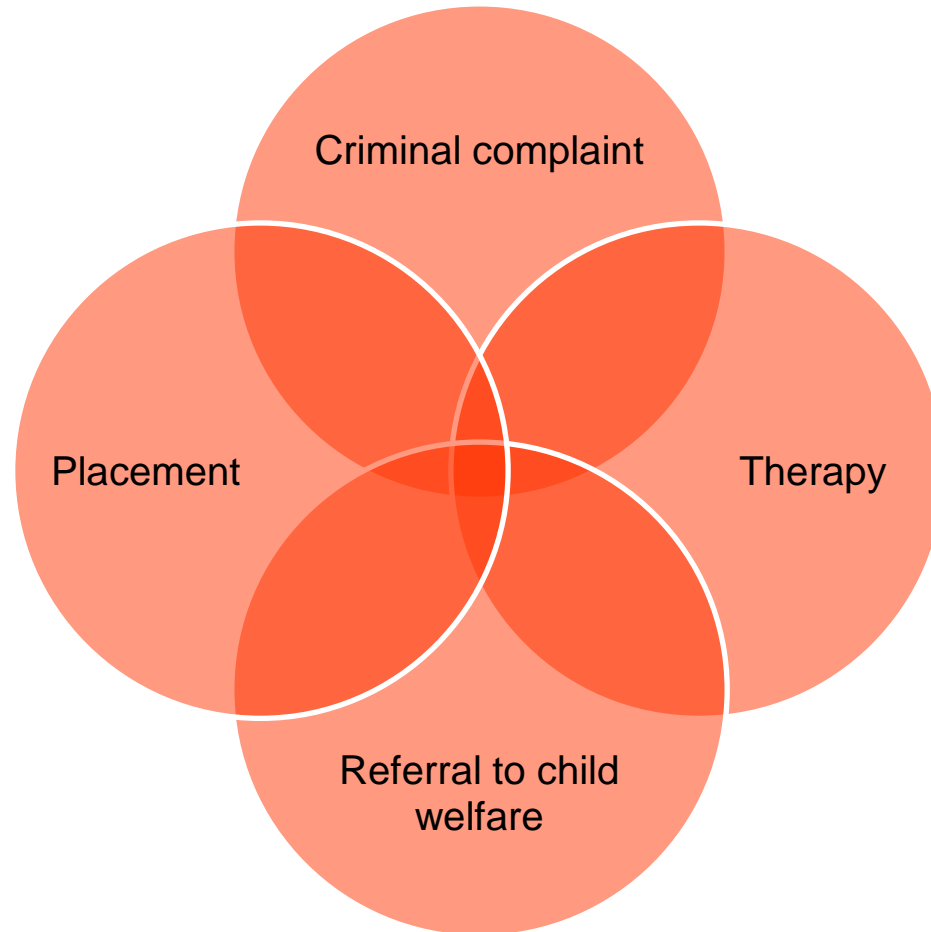


Variables of maltreatment





Variables of intervention





Methods II



Additional testing/rating/questionnaires

- Burden: Life events, SES
- Quality of Life: TNO-AZL (TAPQOL, <6y) & KIDSCREEN-27
- Depression: DIKJ (\approx Children's Depression Inventory)
- Mental health: Child behavior checklist (CBCL)
- Parental health: Brief symptom inventory (BSI)
- Family relationship Index

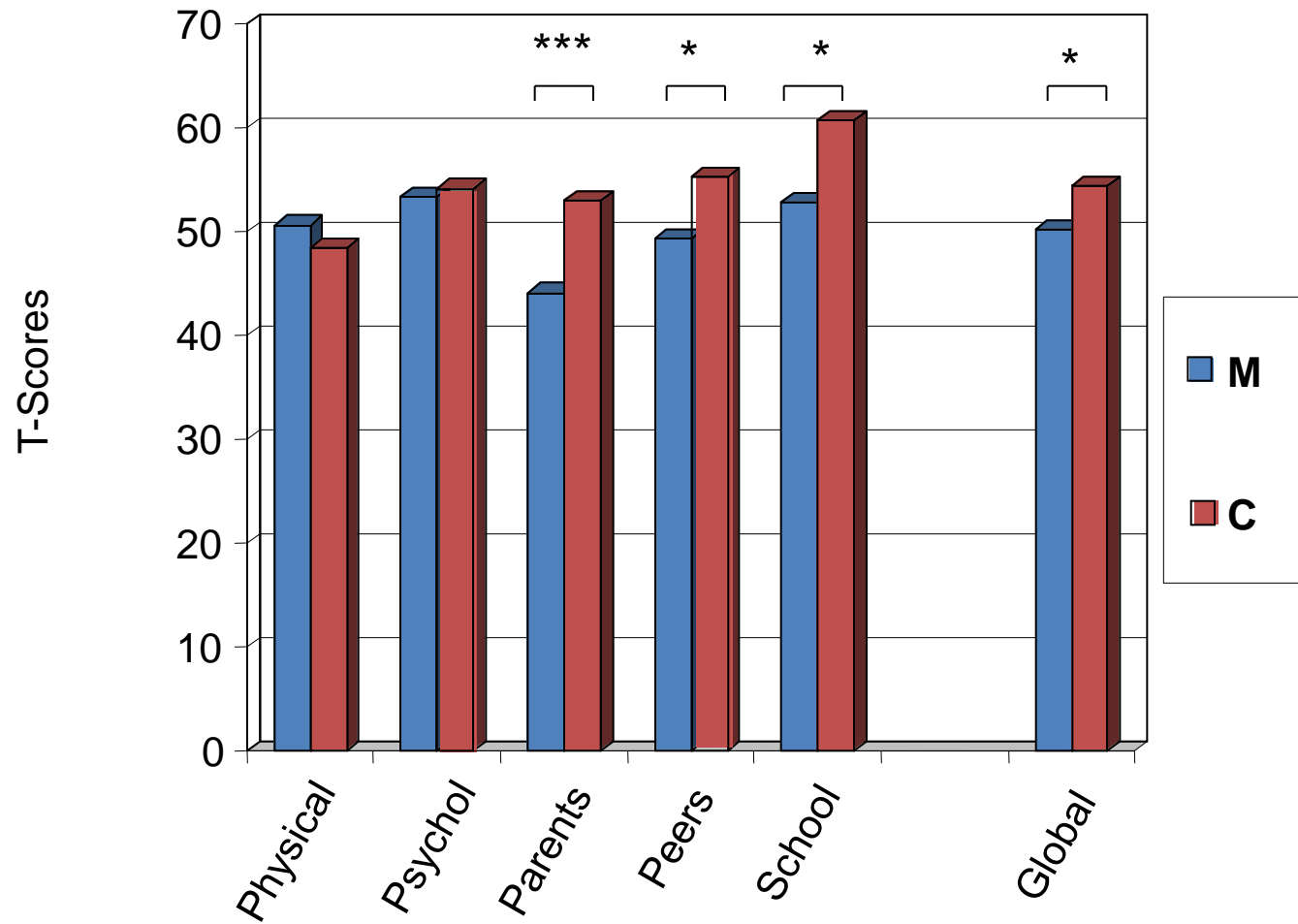




Results II



Reduced self-reported HRQoL (>6y)





Mismatch with proxy reported HRQoL

- Parental responses: no differences between M vs C
- ... for any domain
- ... including data of age < 6 years



Significant disadvantages of M

- Lower SES (continous version, Largo et al.) **
- More life events (despite maltreatment) in the last year *
- Parents with higher load BSI *
- Not for FRI



Predictors of poorer HRQoL

- Poorer FRI *
- Lower SES (continuous version, Largo et al.) *
- More Life events (despite maltreatment) **
- ? Familial perpetrator *



Discussion II



Summary II

- **persisting negative social conditions** (after intervention of CPT)
- Known discordance between child and caregiver report of HRQoL (Upton, Lawford, & Eiser, 2008; Verhey et al., 2009)
- **Lack of parental attunement** to children's experiences and beliefs (Upton et al., 2008)



Conclusion II

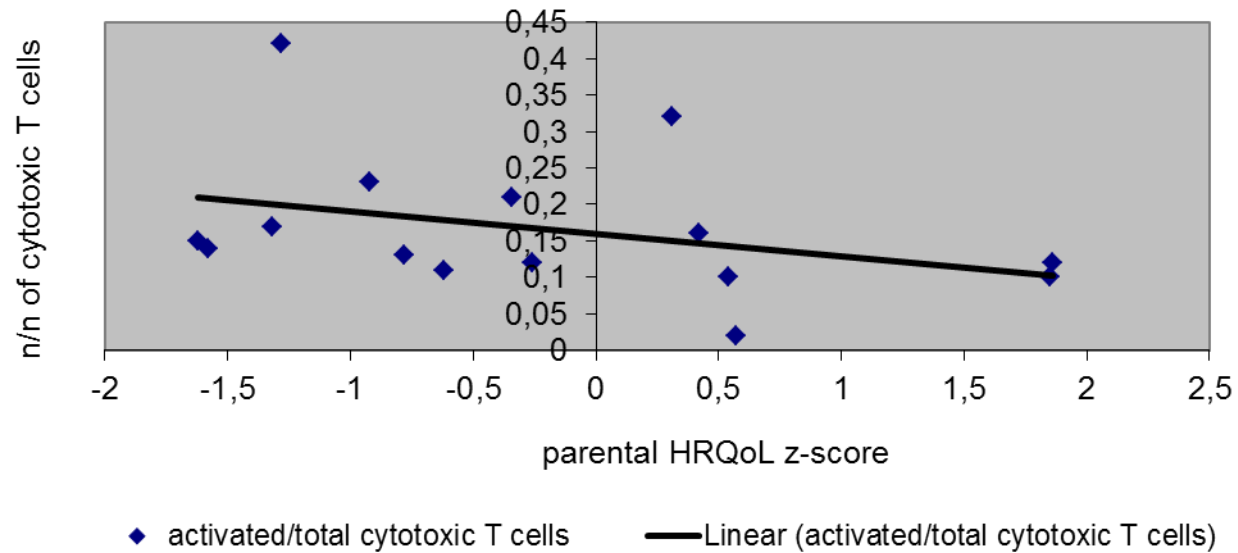
- Self-assessment of child
- Multiple domains/subscores in HRQoL are relevant
- Multidisciplinary and systemic approach
- Additional support to address socioeconomic inequity



Synthesis



Activated cytotoxic T cells & QoL correlate* in maltreated group





Activated helper T cells correlate with depression score (DIKJ)

- Positive
 - : **activated helper T cells**, B cells
- Negative
 - : **activated helper T cells**
 - All participants: recent thymic emigrants
 - M: monocytes
 - C: none



Lymphocytes & psychopathology (CBCL)

- **No** correlations between **any** T cells & T-scores for
 - both age groups (<6; 6-18y)
 - all (sub)scales
 - all participants & when separately studied for M, C, ,
 - : **only activated helper T** cells and internalizing correlate*



Discussion III



Limitations

- Cross-sectional
- Retrospective
- Small sample size
- No cytokines ...
- One time point analysis



Summary III

- Activated T cells correlate with T-scores of:
 - Proxy-HRQoL
 - Clinical descriptive scales
- Poor/no correlations with psychopathology
- Correlations with other lymphocyte-cell-lines are diverse



??? And more!



Outlook



Acknowledgement

- **Jud A¹, Lips U², Reichenbach J³ & Landolt MA^{1,4}**
 - ¹ Department of Psychosomatics and Psychiatry
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 - ³ Division of Immunology/Haematology/BMT
 - ⁴ Children's Research Center
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Thank you!

