

**KING'S**  
College  
LONDON  
University of London

Institute of Psychiatry  
at the Maudsley

South London and Maudsley **NHS**  
Maudsley Hospital Trust

**Biological embedding of child stress  
through inflammation**  
Andrea Danese, M.D. Ph.D.

MRC Social, Genetic, and Developmental Psychiatry (SGDP) Centre and  
Department of Child & Adolescent Psychiatry  
National & Specialist Child Traumatic Stress and Anxiety Clinic

background

biological studies

clinical implications

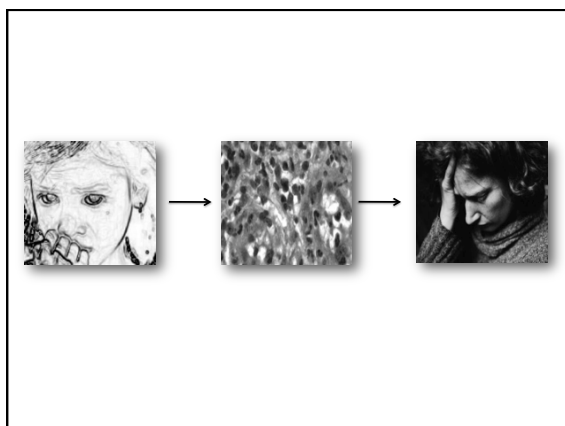
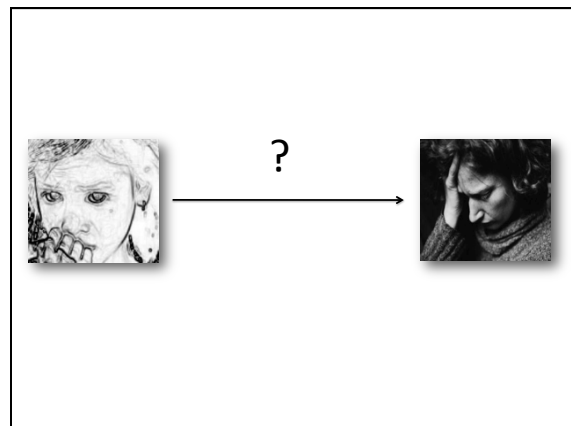
conclusion

background

biological studies

clinical implications

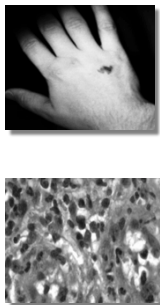
conclusion



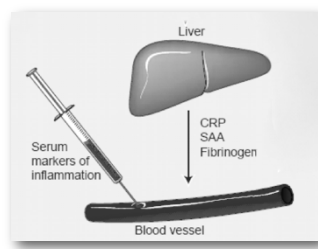
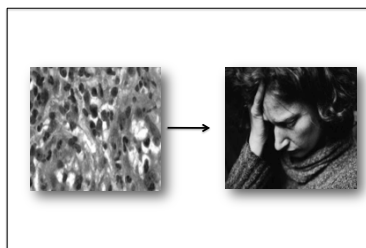
## INFLAMMATION

> Innate immunity

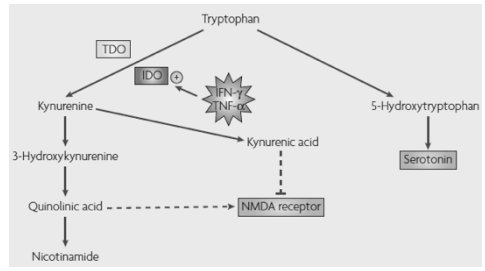
- Body physical barriers  
(e.g., skin, gastrointestinal tract)
- Non-self recognition  
(complement system, Toll-like receptors)
- Activation  
(cytokines, endothelial cells)
- Response  
(phagocytes, acute phase proteins)



## MEASURING INFLAMMATION

## INFLAMMATION & DEPRESSION



Dantzer R et al, *Nat Rev Neurosci* 2008, 9: 46-56. Miller AH et al, *Biol Psychiatry* 2009, 65: 372-41

## ELEVATED INFLAMMATION IN DEPRESSION

IN ADULTS

**CRP:**  $d=0.15$  (95%CI=0.10, 0.21),  $p=0.001$ ;

**IL-6:**  $d=0.25$  (95%CI=0.18, 0.31),  $p=0.001$ ;

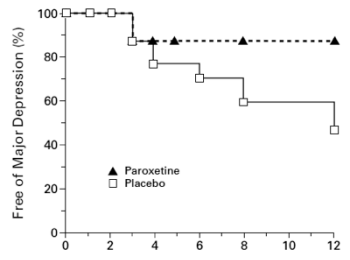
**IL-1:**  $d=0.35$  (95%CI=0.03, 0.67),  $p=0.03$ ;

**IL-1ra:**  $d=0.25$  (95% CI 0.04, 0.46),  $p=0.02$

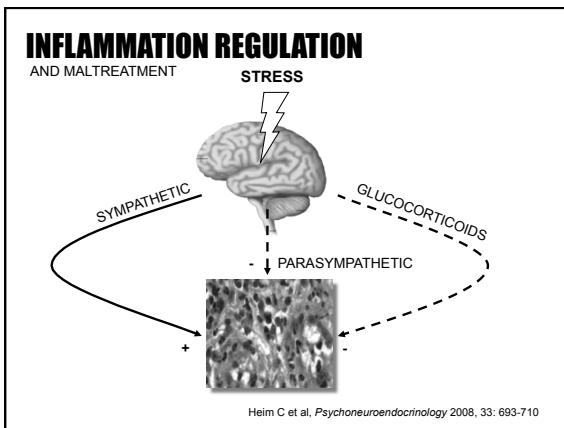
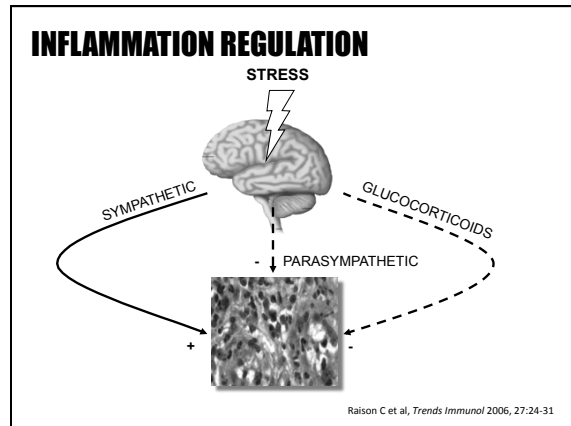
Howren M et al, *Psychosom Med* 2009, 71: 171-86

## INFLAMMATION CAUSES DEPRESSION

IN ADULTS



Musselman D et al, *N Engl J Med* 2001, 344: 961-6

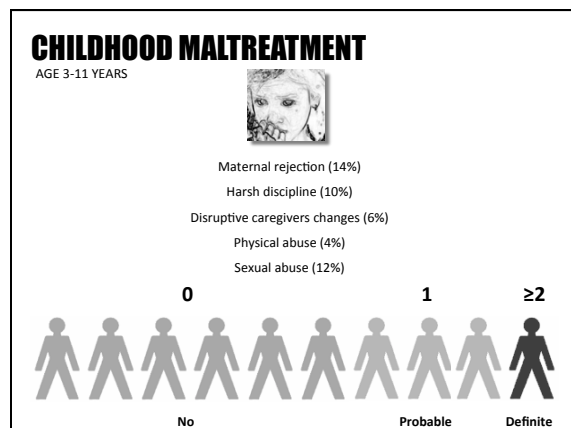


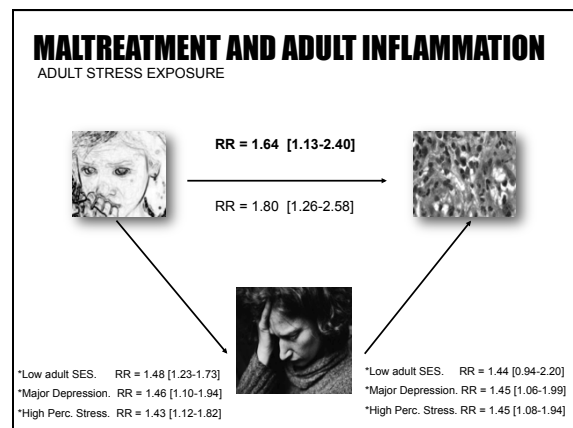
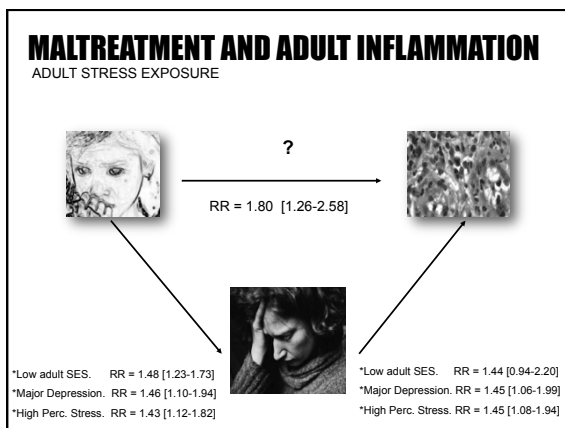
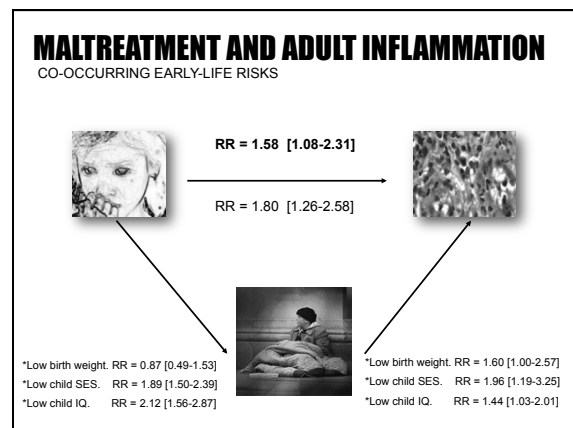
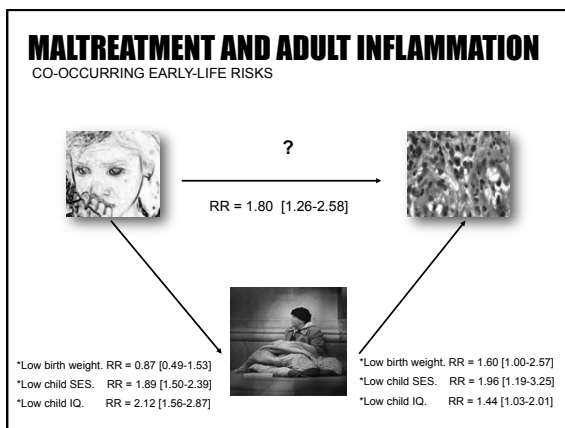
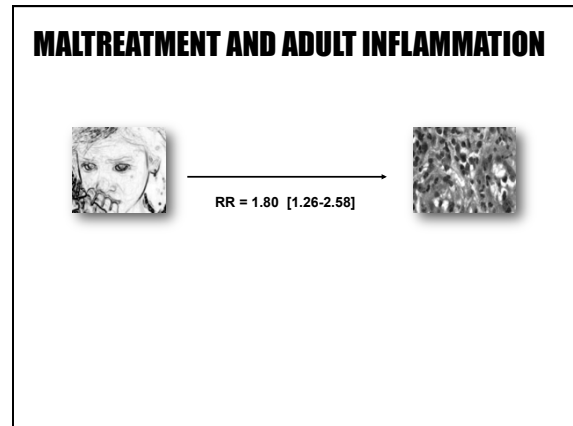
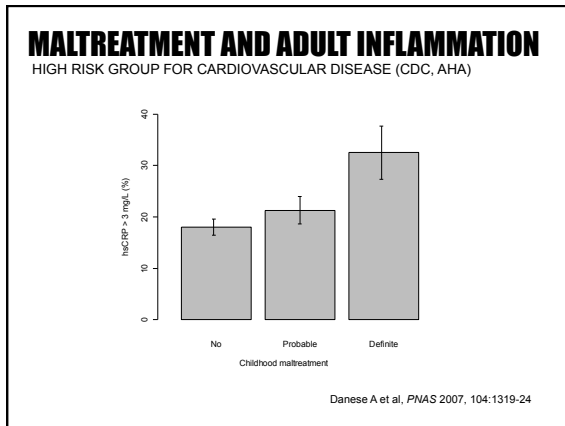
- background
- biological studies
- clinical implications
- conclusion

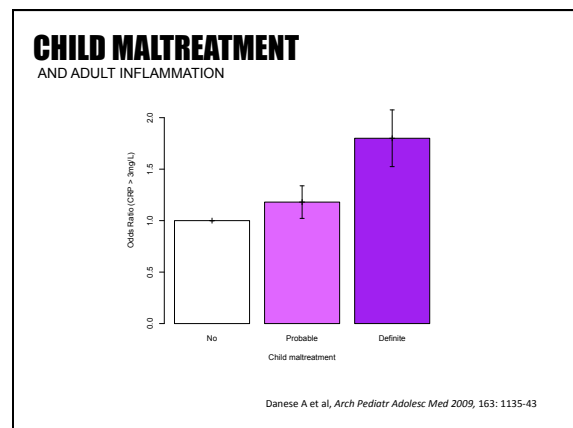
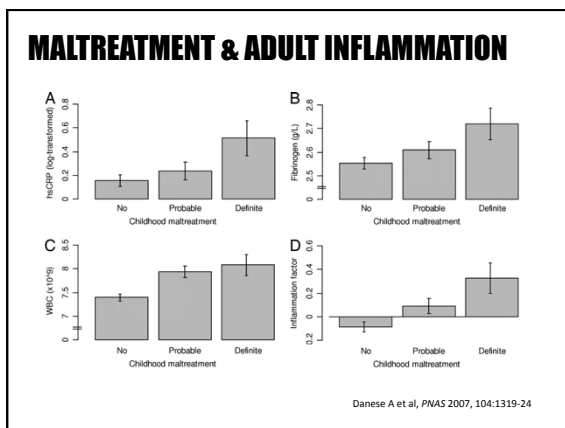
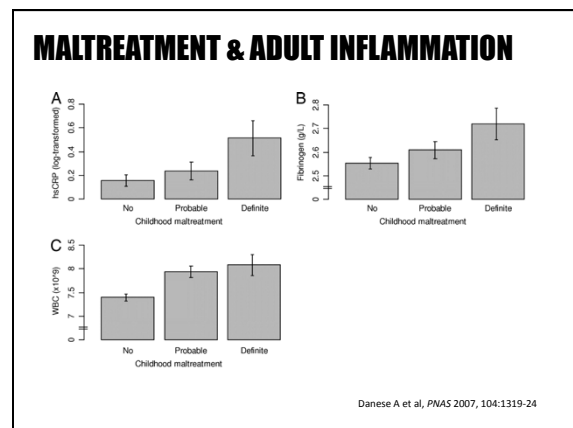
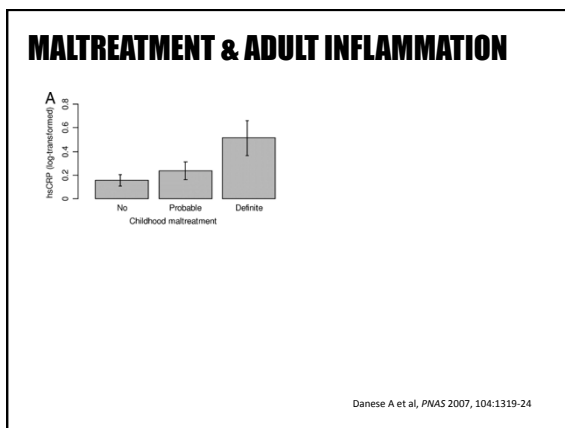
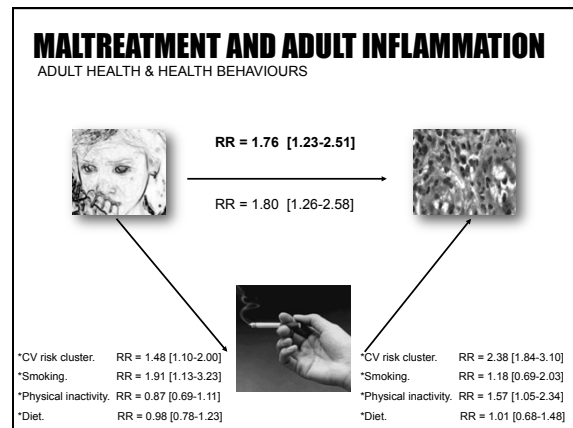
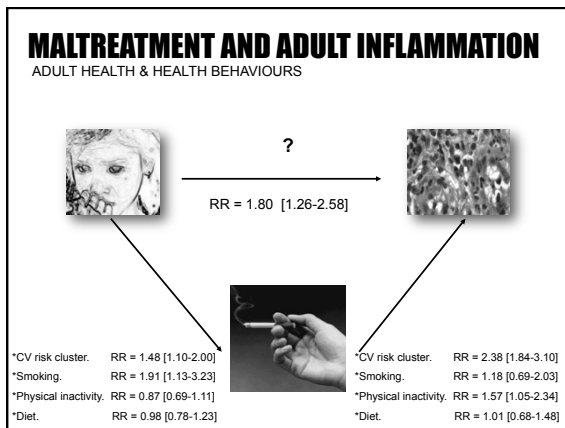
### THE DUNEDIN STUDY

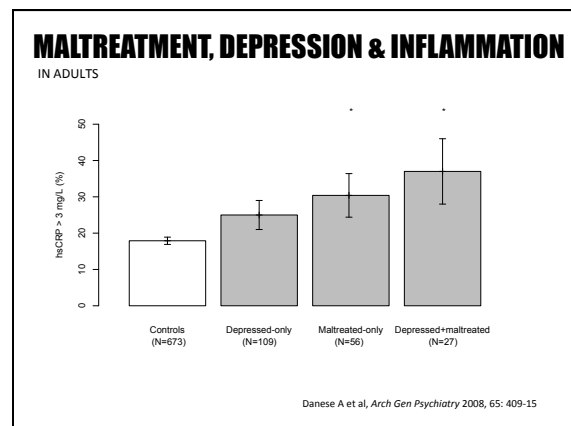
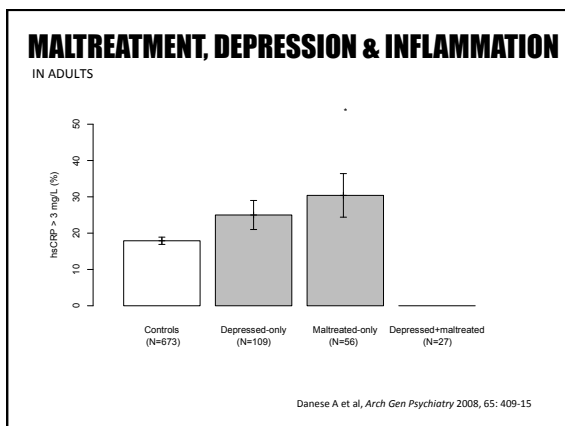
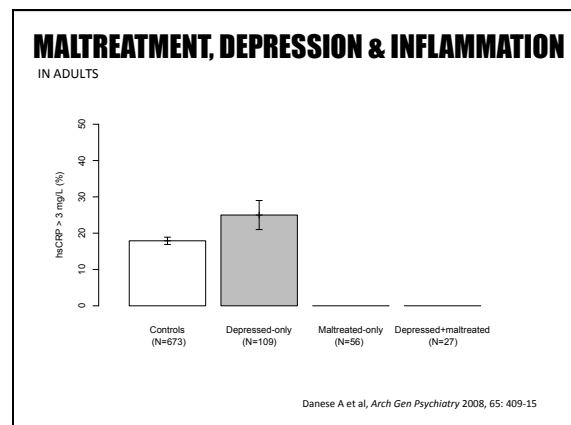
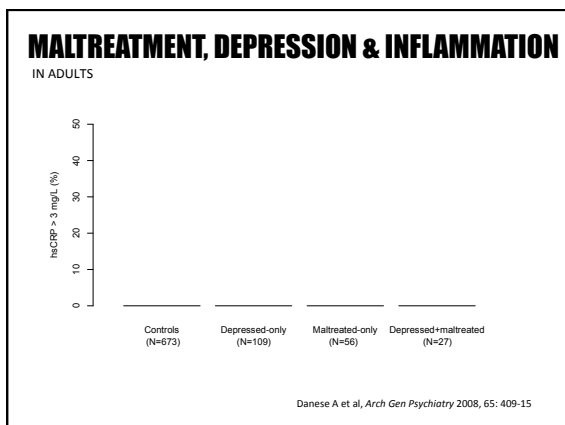
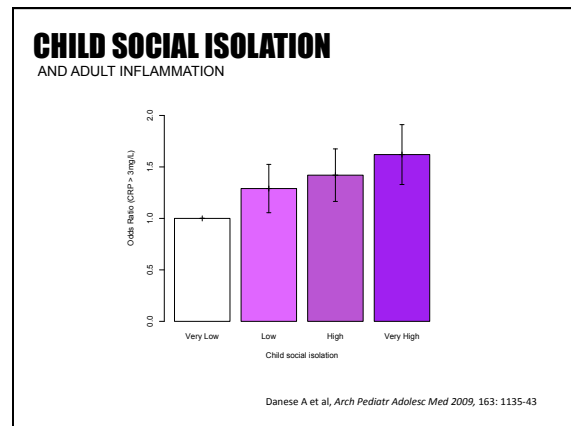
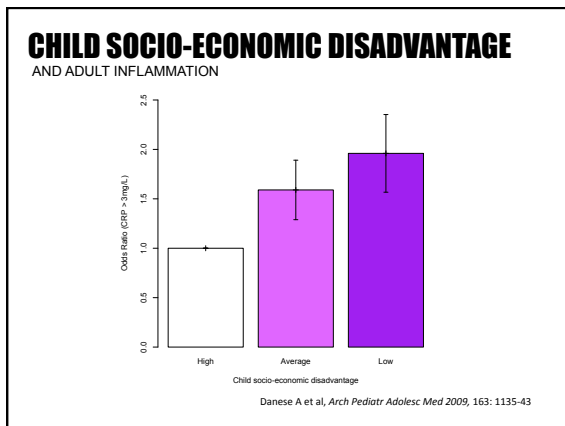
Representative birth cohort followed up from birth to age 32y  
 N=972 (at age 32 years)

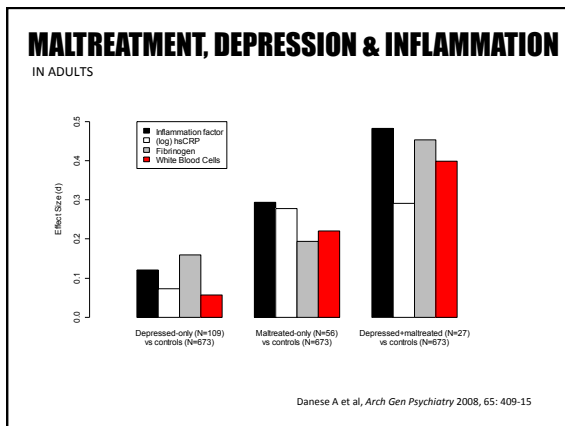
Childhood maltreatment (multiple informants, multiple time points)  
 High-sensitivity CRP (>3mg/dL, cont), fibrinogen, white blood cell count





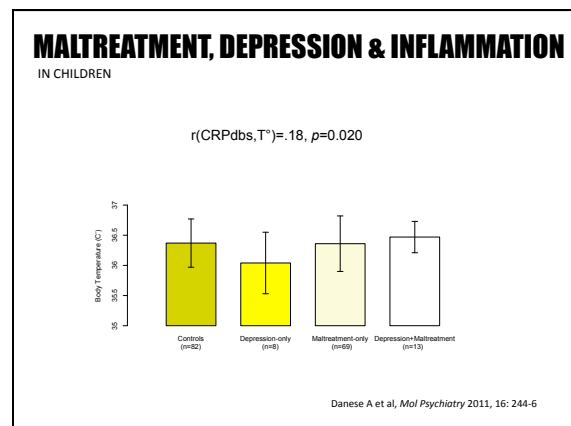
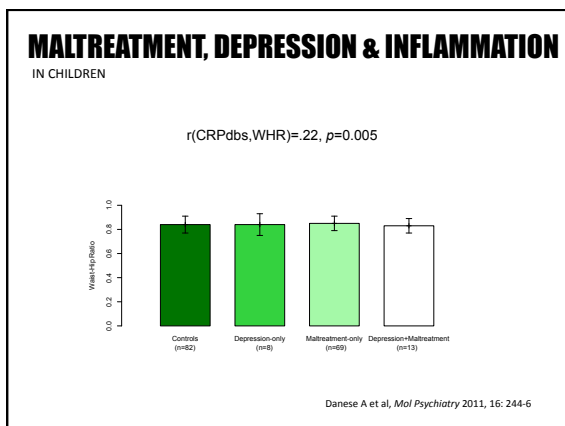
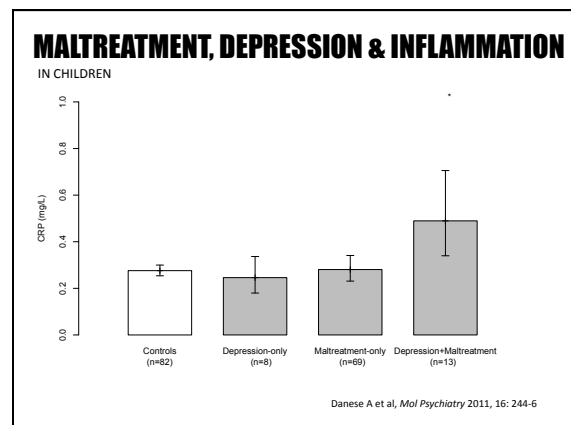
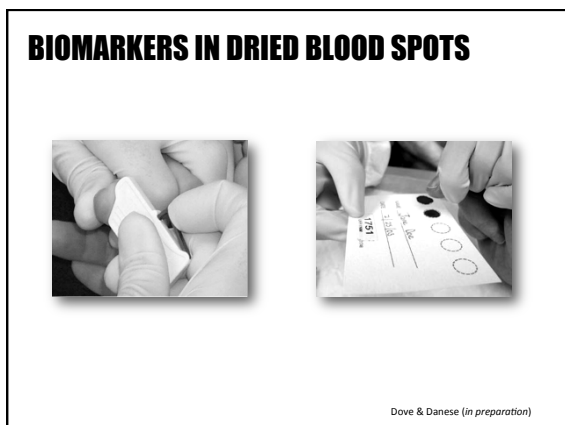






### THE E-RISK STUDY

Longitudinal twin study of children born in 1994-95 in England and Wales  
 Target sample N=172, age 12 years  
 Childhood physical abuse: K Dodge's interview with mothers (prospectively collected)  
 Matched for family SES, gender, zygosity  
 Depression: Children's Depression Inventory (CDI≥20)  
 Inflammation: minimally-invasive collection of CRP through dried blood spots



### SUMMARY (1)

> Since childhood, maltreated children show stress-related elevation in inflammation levels.

> What is the clinical relevance of the observed biological abnormalities?

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### DEPRESSION COURSE

12-month prevalence: 7%

Lifetime prevalence: 16%

60% of remitted patients will have recurrence in 5 years

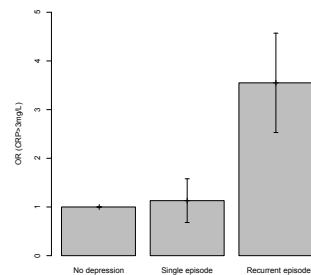
Each new episode increases risk of recurrence

Each new episode reduces time to recurrence

> Depression is a *recurrent* and possibly *progressive* illness

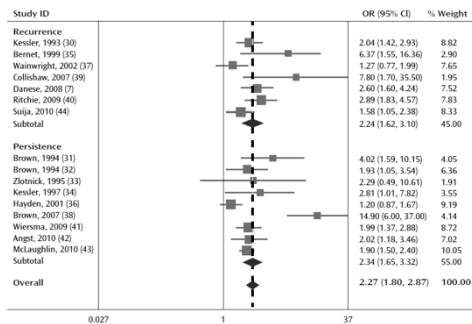
Kessler et al, JAMA 2003, 289:3095-105. Solomon D et al, Am J Psychiatry 2000, 157:229-33

### INFLAMMATION & DEPRESSION COURSE



Ford D et al, Arch Intern Med 2004, 164: 1010-4

### MALTREATMENT & DEPRESSION COURSE



### TREATING DEPRESSION

NICE GUIDELINES

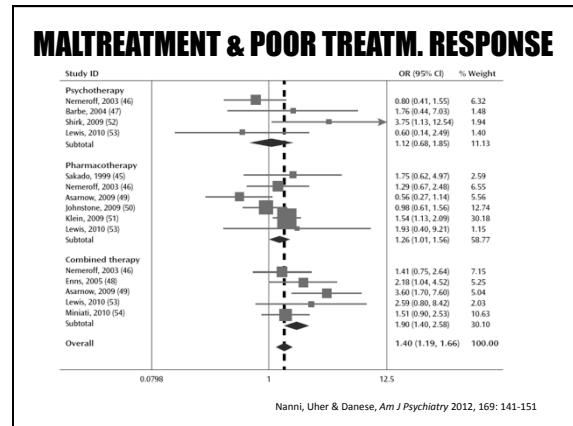
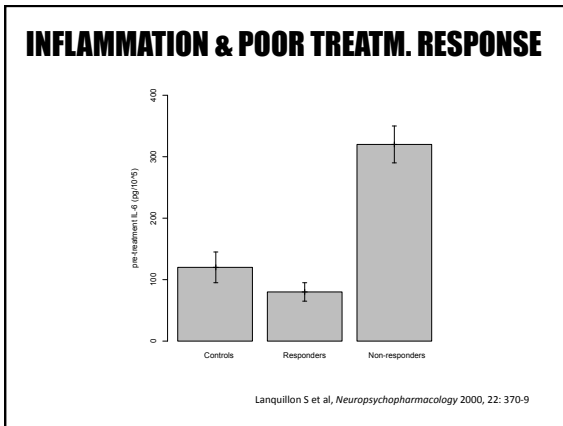
ADULTS

*Psychotherapy* (CBT, IPT) should be used to treat mild depression.  
*Pharmacotherapy* should be used in addition to psychotherapy to treat moderate and severe depression (*combined therapy*).

YOUNG PEOPLE

*Psychotherapy* (CBT, IPT, family therapy) should be used as first-line treatment of depression of any severity.  
*Pharmacotherapy* (SSRIs) should be used in addition to psychotherapy for young people who do not respond to treatment with psychotherapy alone (*combined therapy*).





### SUMMARY (2)

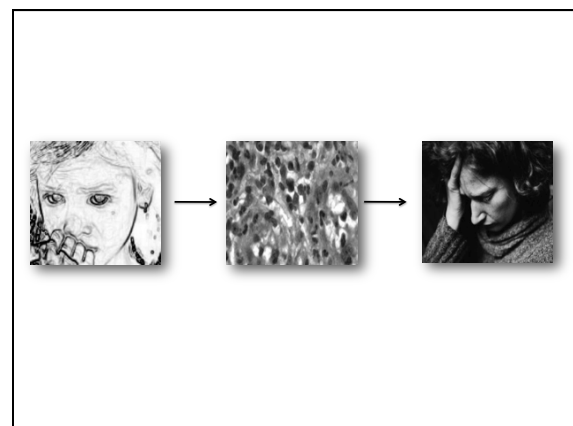
- > Maltreated children are at elevated risk of developing recurrent and progressive episodes of depression throughout the life-course.
- > Depressed individuals with a history of childhood maltreatment are at elevated risk of poor response to antidepressant treatment.

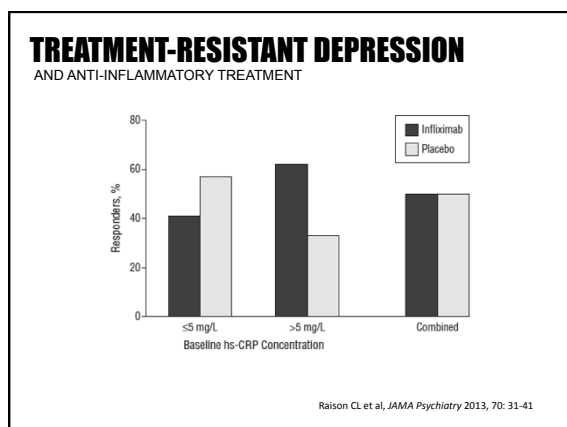
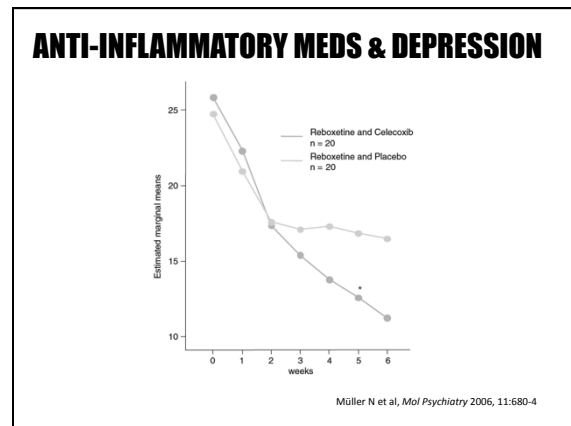
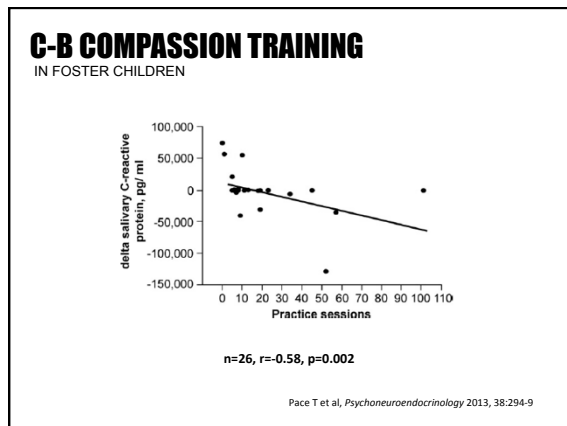
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### ACKNOWLEDGEMENTS

**STRESS & DEVELOPMENT LAB**

@stressdev

Rosamund Dove, PhD

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National Heart Lung and Blood Institute

**NARSAD**