Early life adversity, biological risk factors, and later health

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introduction

enduring effects of child stress

timing matters

biological embedding

conclusions
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conclusions
Foam cells  Fatty steak  Intermediate lesion  Atheroma  Fibrous plaque  Complicated lesion / Rupture

From First Decade  From Third Decade  From Fourth Decade

## Child Maltreatment and Disease Risk

<table>
<thead>
<tr>
<th>Disease</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic lung disease</td>
<td>3.9</td>
<td>[2.6-5.8]</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>2.2</td>
<td>[1.3-3.7]</td>
</tr>
<tr>
<td>Cancer</td>
<td>1.9</td>
<td>[1.3-2.7]</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.6</td>
<td>[1.0-2.5]</td>
</tr>
</tbody>
</table>

> 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)
INFLAMMATION & AGE-RELATED DISEASE

INFLAMMATION REGULATION

STRESS

SYMPATHETIC

GLUCOCORTICOID

PARASYMPATHETIC

INFLAMMATION REGULATION
INFLAMMATION REGULATION AND CHILD MALTREATMENT

Heim C et al, Psychoneuroendocrinology 2008, 33: 693-710
introduction

> enduring effects of child stress

timing matters

biological embedding

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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
CHILDHOOD MALTREATMENT
AGE 3-11 YEARS

Maternal rejection (14%)
Harsh discipline (10%)
Disruptive caregivers changes (6%)
Physical abuse (4%)
Sexual abuse (12%)

No
Probable
Definite
MAL'TREATMENT AND ADULT INFLAMMATION

HIGH RISK GROUP FOR CARDIOVASCULAR DISEASE (CDC, AHA)

Danese A et al, PNAS 2007, 104:1319-24
MALTREATMENT AND ADULT INFLAMMATION

RR = 1.80  [1.26-2.58]
MALTREATMENT AND ADULT INFLAMMATION
CO-OCCURRING EARLY-LIFE RISKS

Low birth weight. RR = 0.87 [0.49-1.53]
*Low child SES. RR = 1.89 [1.50-2.39]
*Low child IQ. RR = 2.12 [1.56-2.87]

*Low birth weight. RR = 1.60 [1.00-2.57]
*Low child SES. RR = 1.96 [1.19-3.25]
*Low child IQ. RR = 1.44 [1.03-2.01]

RR = 1.80 [1.26-2.58]
MALTREATMENT AND ADULT INFLAMMATION
CO-OCCURRING EARLY-LIFE RISKS

RR = 1.58 [1.08-2.31]

Low birth weight. RR = 0.87 [0.49-1.53]
*Low child SES. RR = 1.89 [1.50-2.39]
*Low child IQ. RR = 2.12 [1.56-2.87]

RR = 1.80 [1.26-2.58]

*Low birth weight. RR = 1.60 [1.00-2.57]
*Low child SES. RR = 1.96 [1.19-3.25]
*Low child IQ. RR = 1.44 [1.03-2.01]
MALTREATMENT AND ADULT INFLAMMATION

ADULT STRESS EXPOSURE

*Low adult SES.  RR = 1.48 [1.23-1.73]
*Major Depression.  RR = 1.46 [1.10-1.94]
*High Perc. Stress.  RR = 1.43 [1.12-1.82]

Low adult SES.  RR = 1.44 [0.94-2.20]
*Major Depression.  RR = 1.45 [1.06-1.99]
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MALTREATMENT AND ADULT INFLAMMATION

ADULT STRESS EXPOSURE

*Low adult SES.     RR = 1.44 [0.94-2.20]
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*High Perc. Stress. RR = 1.43 [1.12-1.82]

RR = 1.64 [1.13-2.40]

RR = 1.80 [1.26-2.58]

Low adult SES.   RR = 1.44 [0.94-2.20]
*Major Depression. RR = 1.45 [1.06-1.99]
*High Perc. Stress. RR = 1.45 [1.08-1.94]
MALTREATMENT AND ADULT INFLAMMATION
ADULT HEALTH & HEALTH BEHAVIOURS

*CV risk cluster. RR = 2.38 [1.84-3.10]
*Smoking. RR = 1.18 [0.69-2.03]
*Physical inactivity. RR = 1.57 [1.05-2.34]
Diet. RR = 1.01 [0.68-1.48]
MALTREATMENT AND ADULT INFLAMMATION
ADULT HEALTH & HEALTH BEHAVIOURS

RR = 1.76 [1.23-2.51]
RR = 1.80 [1.26-2.58]

*CV risk cluster. RR = 1.48 [1.10-2.00]
Smoking. RR = 1.91 [1.13-3.23]
Physical inactivity. RR = 0.87 [0.69-1.11]
Diet. RR = 0.98 [0.78-1.23]

*CV risk cluster. RR = 2.38 [1.84-3.10]
Smoking. RR = 1.18 [0.69-2.03]
*Physical inactivity. RR = 1.57 [1.05-2.34]
Diet. RR = 1.01 [0.68-1.48]
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MALTREATMENT AND ADULT INFLAMMATION

Danese A et al, PNAS 2007, 104:1319-24

A

B

C

D

hsCRP (log-transformed)

Fibrinogen (g/L)

WBC (x10^9)

Inflammation factor

No
Probable
Definite

No
Probable
Definite

No
Probable
Definite

No
Probable
Definite

Childhood maltreatment

Childhood maltreatment

Childhood maltreatment
CHILD MALTREATMENT AND ADULT INFLAMMATION

CHILD SOCIO-ECONOMIC DISADVANTAGE AND ADULT INFLAMMATION

CHILD SOCIAL ISOLATION
AND ADULT INFLAMMATION

SUMMARY (1)

> Children who experienced maltreatment, socio-economic disadvantage and social isolation show a significant and graded elevation in inflammation levels 20 years later, in adulthood.

> The effects of adverse childhood experiences on adult inflammation are independent of the influence of co-occurring risk factors.

> 10% of the cases of inflammation in the population may be attributable to childhood maltreatment.
introduction

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conclusions
EARLY EXPERIENCE & HEALTH
THE EPIGENETIC LANDSCAPE

TIME (age)

ADULT DISEASE RISK

E1 (t1)
E1 (t2)
E2 (t3)

Waddington CH (1975)
CHILD STRESS vs ADULT STRESS

Danese A et al, Arch Gen Psychiatry 2008, 65: 409-15
CHILDS STRESS vs ADULT STRESS

Danese A et al, Arch Gen Psychiatry 2008, 65: 409-15
CHILD STRESS vs ADULT STRESS

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CHILD STRESS vs ADULT STRESS

Danese et al, Arch Gen Psychiatry 2008, 65: 409-15
## CHILD STRESS vs ADULT STRESS

### STRESS PHYSIOLOGY

<table>
<thead>
<tr>
<th></th>
<th>Adult stress</th>
<th>Child stress</th>
<th>Adult+Child stress</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BRAIN IMAGING</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hippocampus volume</td>
<td>=</td>
<td>?</td>
<td>↓</td>
</tr>
<tr>
<td><strong>TSST</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACTH</td>
<td>=</td>
<td>↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>Cortisol</td>
<td>=</td>
<td>=</td>
<td>↑</td>
</tr>
<tr>
<td><strong>DEX SUPPRESSION TEST</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACTH</td>
<td>=</td>
<td>=</td>
<td>↓</td>
</tr>
<tr>
<td>Cortisol</td>
<td>=</td>
<td>=</td>
<td>↓</td>
</tr>
<tr>
<td><strong>INFLAMMATION</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hsCRP &gt;3 mg/L</td>
<td>=</td>
<td>↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>Inflammation factor</td>
<td>=</td>
<td>↑</td>
<td>↑↑</td>
</tr>
</tbody>
</table>

Danese A et al, *Arch Gen Psychiatry* 2008, 65: 409-15
SUMMARY (2)

> Stress in childhood may modify developmental trajectories and have long-term effect on disease risk.

> If stress does modify developmental trajectories, more favourable conditions later in life may have little effect on disease risk.

> Stress later in life may have a smaller effect on disease risk, because it acts on a more developed system.
introduction

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STRESS BIOLOGY IN YOUNG PEOPLE

DRIED BLOOD SPOTS
BIOLOGICAL EMBEDDING
OF CHILD STRESS THROUGH INFLAMMATION PROCESSES

Danese A et al, Mol Psychiatry (in press)
BIOLOGICAL EMBEDDING
OF CHILD STRESS THROUGH INFLAMMATION PROCESSES

$r(CRP_{dbs}, WHR) = .22, p = 0.005$

Danese A et al, *Mol Psychiatry (in press)*
BIOLOGICAL EMBEDDING
OF CHILD STRESS THROUGH INFLAMMATION PROCESSES

$r(CRP_{dbs},T^\circ)=.18, \ p=0.020$

Danese A et al, *Mol Psychiatry (in press)*
> Stress-related elevation in inflammation biomarkers can already be observed in childhood.

> Childhood elevation in inflammation levels has been linked to the presence of key preclinical indicators of adult disease risk in children, such as advanced atherosclerosis progression.

> Interventions targeting stress in children could prevent the translation of psychosocial risks into enduring biological risks.
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during effects of child stress

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> conclusions
CONCLUSIONS

> Inflammation could be an important biological mediator of the effect of adverse childhood experiences on adult health.

CONCLUSIONS

> Effective preventive strategies for adult disease should start from an early age.

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