Stress - asthma relationship in children

Seija Sandberg

University College London
Why concern about stress?

Growing evidence that **psychosocial stress**
- contributes to development of wheezing illnesses and **asthma** especially in early childhood
- predicts greater illness severidity in children who already have asthma

Presentation outline

Childhood asthma – characteristics
Childhood stress – characteristics
Biology of atopy / allergy / asthma
Biological stress mechanisms
Contribution of stress on
- development of atopy/allergy phenotype
- manifestation of asthma
- course of existing asthma
(Differential effects of stress on children with asthma compared with healthy children)
Early life stress and risk of asthma
Summary/conclusions

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Asthma

Is a complex, coordinated, multi system, multi cellular, inflammatory disorder

Manifests with repeated, variable, episodic attacks of breathlessness, cough & wheeze, occurring secondary to broncho-constriction in the setting of airway hyper responsiveness & mucous hyper secretion

Its development requires interaction between environment & genetic susceptibility

Murphy DM & O'Byrne PM (2010), Chest, 137; 1417-1426
Asthma

- Commonest chronic disease in childhood
  11-14% of school-age children in W Europe affected

- Remains a serious health problem, despite effective pharmacological therapies

- Almost 30-fold between-country variation in prevalence, urbanised & more westernised countries with highest rates UK, Ireland, NZ, Australia, USA, Canada, some L-A countries

- Exposure to urbanised way of life does not explain all between & within country differences

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2 Asher et al (2006), Lancet, 368: 733-743
Atopic vs. Non-atopic Asthma

Most children with asthma have history of atopy/allergy\(^1\)

**Atopic/allergic asthma**

the dominant form of childhood asthma in affluent communities, but far less common in poor communities\(^2\)

**Non-atopic/non-allergic (intrinsic) asthma**

predominant form of childhood asthma in poor communities of the tropics (S-Am, Africa)\(^3\)

& rural China\(^4\)

(often associated with helminth infections & bronchiolitis)

- Helminth infestations inversely associated with both allergies & asthma in low income populations

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\(^1\) Robinson (2009), *Clin Exper Allergy*, 39, 1314-1323
\(^3\) Leonardi-Bee et al (2006), *Am J Respir Crit Care Med*, 174, 514-23
\(^4\) Palmer et al (2002), *Am j Respir Crit Care Med*, 165, 1489-93

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<table>
<thead>
<tr>
<th><strong>Stress, stressor, stress reaction</strong></th>
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<td><strong>Stressor</strong></td>
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Types of child stress

- Acute stress (negative life events)
- Chronic stress
- Episodic stress (e.g. exams)
Life events to children

Majority
involve important social relationships
family
friends
and relate to the child’s immediate environment
home
school

Fewer
Can be seen as unpredictable ‘acts of fate’
major traumatic incidents
sudden loss of a close person
The concept of contextual threat

The term **Contextual Threat** refers to the level of threat caused or implied by a life event to an average child/adolescent of the same age, sex & biographical characteristics as those of the young person in question.

It is simultaneously an **objective** & **personalised** measure.

‘**Contextual positive impact**’ is defined along similar principles.

Sandberg et al, (1993), *JCPP*, 34: 879-897
Sources of contextual threat

**Real life change:** major alteration in life circumstances
e.g., death of parent; move to another city or country

**Threat mainly cognitive**
Event drastically changes child’s perception of themselves/
Of other people in a way that presents threat to child’s
Self-esteem, or reduces perceived sense of security

**Combination of real life change & cognitive threat**
e.g., parents’ marital separation

Sandberg et al, (1993), *JCPP*, 34: 879-897
Chronic stress in children usually stems from enduring adverse circumstances such as unsafe environment and socio-economic deprivation, parental unemployment or illness, and family discord or criminality.
Acute life events & chronic adversity

Negative life events more common in children who also suffer from chronic psychosocial adversities

Parental illness / personality disorder / parental discord
Poverty / deprived life circumstances
Neighbourhood violence / disorganisation

Negative life events → Chronic psychosocial adversity

Atopic (allergic) asthma chronic inflammatory disorder, characterised by T-helper type 2 (Th2) immune response, results from their inappropriate responses to common environmental proteins termed allergens.

May result from deficiency of regulatory T cells (Treg) that suppress potentially harmful immune responses.

Amongst the various environmental factors, psychosocial stress proposed as an important agent contributing to the function of regulatory T cells.

1 Robinson DS (2009), Clin Exper Allergy, 39, 1314-23
The Two Survival Mechanisms of Humans

T-helper 2 (Th2) immune response and acute stress response

Have they joined together and begun to work against us?
Modern man arose in tropical Africa where helminths thrived. They had to develop methods to fight them.


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From Parasites to Allergy

Relatively recently, humans migrated to cooler and drier climates where helminths struggle to survive.

When they no longer had to fight helminths they developed allergies & asthma instead. But why?
Genes and the Th2 Pathway

The same genes are involved in both the immunology of:

- increased host protection from parasites
- increased prevalence of allergic disease

Th2 responses are thought to have evolved in mammals to resist infection by parasites, particularly helminths.
The genetic tendency to mount strong Th2 responses may have become a liability causing allergy rather than defending against parasites.
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The Acute Stress Response

SAM (Sympathetic Adrenal Medullary axis)
- Adrenal Medulla (Sympathetic Nervous System)
  - Epinephrine & Norepinephrine
  - Rapid activation
  - Prepares the body for sudden response (fight or flight)
  - Regulate innate & adaptive immune systems through binding to beta-adrenergic receptors on leukocytes

HPA (Hypothalamic-Pituitary-Adrenal axis)
- Adrenal Cortex (Zona Fasiculata)
  - Cortisol
  - Slow activation
  - Restores homeostasis after severe physical trauma or stress
  - Regulate innate & adaptive immune systems through binding to glucocorticoid receptors on leukocytes

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The hypothalamic-pituitary-adrenal (HPA) axis

Hypothalamus (PVN) 

Corticotrophin Releasing Hormone 

Anterior Pituitary

ACTH 

Adrenal cortex 

Cortisol 

Glucocorticoid Receptor (effects)

PVN = paraventricular nucleus
Acute Stress on the HPA Axis

- Medial Prefrontal Cortex
- Hippocampus
- Central Nucleus of Amygdala

Greatest activation & slowest recovery to uncontrollable stressors or those threatening self-evaluation

Hypothalamus (PVN)*

Corticotrophin Releasing Hormone

Anterior Pituitary

ACTH

Cortisol

Adrenal cortex

Glucocorticoid Receptor (effects)

* PVN = paraventricular nucleus
Chronic Stress

Involves the activation of SAM & HPA axes
Immune, metabolic and neural defensive biological responses, important for short-term response to stress, produce long-term damage if not eventually terminated

Allostatic Load
Potential detrimental cost to such accommodation – wear & tear from chronic underactivity/overactivity of the allostatic system

McEwen BS (1998), NEJM 38:171-179
Effects of chronic stress on immunity

Enhances Th2 cytokine production
(Th2 activate humoral immunity & \textbf{exacerbate} allergy)

Suppresses Th1 cytokine production
(Th1 activate cellular immunity to provide defence against infections & neoplastic diseases)

Schmidt et al (2010), Brain Beh Immun, in press
Contribution of stress to development of atopy/allergy phenotype
The Two Survival Mechanisms of Humans

T-helper 2 (Th2) Immune Response

and

Acute Stress Response

Have they joined together and begun to work against us?
Expression of allergy in a person with a genetic predisposition to allergy

Expression of allergy

Environmental stimulation

Stress

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Th2-bias and Immune Dysregulation

Diagram re-drawn according to Georas et al (2005), Eur Respir J, 26:1119-37
Contribution of stress to manifestation of asthma

Diagram by Priftis KN et al (2009) Allergy, 64, 18-31
Caregiver stress in first few months predicted multiple wheeze in 1st year in predisposed children RR=1.4 (95% CI 1.1-1.9)

Parental stress together with early parenting difficulties predict onset of asthma in those genetically at risk. The asthma risk greatly increased in the context of frequent infections in 1st year & elevated serum IgE at 6 months.

Early parental stress and parenting difficulties doubled the risk of asthma by age 6-8 yrs

Evidence: Stress and risk of atopic eczea

Prevalence of atopic eczea in children aged 4 years

<table>
<thead>
<tr>
<th>Divorced Parents</th>
<th>No Divorce</th>
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<tr>
<td>18.8%</td>
<td>6.0%</td>
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P < 0.01

Bockelbrink et al (2006), Allergy, 61: 1397-1402
Early behaviour problems precede asthma in children with atopy

Age 3 behaviour problems (markers of stress) more common in children with atopic dermatitis who developed asthma by age 4½ years, and often preceded onset of asthma

Stevenson (2003), Psychosom Med, 65: 971-5
Behaviour problems, family functioning, late onset (by age 5) wheeze

Behaviour problems age 3 & poor family functioning
- low expressiveness
- low cohesion,
- high conflict predict wheeze by age 5

A model of how Stress may influence Asthma

Stress

- Sympathetic nervous system
- Hypothalamic-Pituitary-Adrenal axis (HPA)

Immune imbalance (Th1 ↔ Th2)

Asthma / Allergic disease

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Mechanisms of effects

**Caregiver stress** early in life associated with atopic immune profile in young children genetically predisposed to atopy / asthma*

**Early ‘behaviour’ problems** markers of emotional dysregulation, and of stress**

Emotional dysregulation reflects wider physiological dysregulation indicating a common genetic vulnerability with asthma***

* Bockelbrink et al (2006), *Allergy*, 61, 1397-1402
** Stevenson (2003), *Psychosom Med*, 65, 971-5
Contribution of stress to the course of existing asthma
Glasgow study

Design & Methods

- Prospective follow-up 18/12
- Clinical sample
- N= 90
- Age 6 -13 yr
- Chronic asthma
- moderate to severe
- preventative & rescue medication

Outcome measures

- Repeat measurement of
  - life events
  - chronic stress
    by Child & Parent interviews (PACE) ¹

- Asthma monitoring
  - independent
  - continuous
  - daily diaries
  - peak flows

¹ Sandberg et al, (1993), JCPP, 34: 879-897
Risk of asthma attacks following severe events –
effect of ongoing chronic stress

Severe event
↑ risk of new attack in coming weeks

Risk influenced by chronic stress (dynamic logistic regression)

Severe Event
- In Previous 2 Weeks
- 2-4 Weeks Earlier
- 4-6 Weeks Earlier

Low / Medium Chronic Stress
(N=70)

High Chronic Stress
(N=20)

OR

p<.05

3.6

7.4

3.5

3

2.5

2

1.5

1

0.5

0

p<.01

p<.05

Use of statistical methods capable of examining short time lags showed that severe life events increase immediate risk of new asthma attack also in the low-medium chronic stress group, with a another rise 5-7 weeks later (Cox’ regression).

Emotional problems & stress-asthma relationship

Anxiety/depression further increased risk of new asthma attack following severe life event – but only in the absence of chronic stress

In conditions of high chronic stress, oppositional/rebellious behaviour protected against new asthma attack following severe life event.

Severe event
- In Previous 2 Weeks
- 3-6 weeks earlier

Sandberg et al (2003), Eur Child Adol Psychiatry, 12, S2: 230
Summary: Glasgow study

- Severely **negative life events** increase the risk of children’s asthma attacks immediately and over the coming weeks
- **High chronic stress** magnifies the risk associated with severe events
- **Emotional problems** further increase the risk
- **Minor rebelliousness** is protective when chronic stress is high
- In the absence of high chronic stress, **positive life event** occurring in close proximity to severe event protects against the increased risk*

*(data not shown in this presentation)
Mean number of chronic adversities per child

Possible explanation: **Stress is not evenly shared**

90 children with asthma:

- **High chronic stress:** 20 children, 105 stressors
  - Mean = 5.25
- **Low/moderate chronic stress:** 70 children
  - 74 stressors
  - Mean = 1.06

Depressed children with asthma

- Children with asthma and depressive symptoms manifest vagal bias when emotionally stressed.
- Those with depressive symptoms and poorer lung function ($\text{FEV}_1<80\%$) manifest greater airway resistance.

An alternative hypothesis linking stress, neuroendocrine and immune function with allergic disease

Asthma patients show variable response to treatment because of acquired steroid resistance induced by chronic inflammation or immune activation

Possible reason: prolonged activation of SAM & HPA axes caused by chronic stress results in down regulation of Glucocorticoid Receptor expression or function
Why does early life stress increase risk of asthma?
How does stress increase risk of asthma?

When and how does it start?

Problems with HPA function and its consequences on the immune system start *in utero* and continue to develop in early life.

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Neuroendocrine Axis in Pregnancy

Mother

Hypothalamus

\[ CRH \]

Anterior Pituitary

\[ ACTH \]

Cortisol

Placenta

Hypothalamus

\[ CRH \]

Corticotrophin Releasing Hormone (CRH)

Anterior Pituitary

\[ ACTH \]

Foetus

Hypothalamus

\[ CRH \]

Anterior Pituitary

\[ ACTH \]

Cortisol

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Polarisation of the immune system into atopic phenotype occurring *in utero* and in early childhood

From early stress to allergy

- Development of immune response
- Altered modulation of GR-responsive genes
- Varying cortisol levels
- Altered HPA function in infancy
- Prenatal/neonatal stress

*Allergic phenotype*
Your Childhood Determines Your Adulthood

Early life interactions between allergens and Th-cells determine whether a Th2-biased response emerges.

Epidemiological evidence: The critical time period for establishment of allergy and asthma is between conception and 3 years of age.

In genetically predisposed individuals, environmental factors and stress may interact resulting in more severe asthma phenotypes which last into adulthood.

Turner SW & Devereux G (2007), Clin Exper Allergy; 37:163-165
Heritable changes in gene expression that occur without directly altering DNA sequence

Most commonly regulated by direct methylation or by post-translational modifications of histones

Transcription factor binds to Cytosine residues in the DNA to stimulate or suppress transcription.
A mutation of CG to TA prevents binding of the transcription factor to DNA and inhibits transcription.

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Epigenetic methylation of the Cytosine residues prevents binding of the transcription factor to DNA and inhibits transcription.

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Epigenetic gene transcription in stress & asthma

Epigenetic changes:

• heritable changes in gene expression that occur without directly altering DNA sequence\(^1,2,5\)

• cytokine gene regulation via methylation & acetylation of histones (resulting in silencing the Th1 gene)\(^2\)

• may occur prenatally or neonatally and influence the phenotype throughout life span\(^1,4,5\)

• enable trans-generational inheritance of allergy to offspring or offspring’s offspring\(^3,4\)

E.g., a grandmother smoking while pregnant may increase the risk of asthma in her grandchild\(^3\)

1 Roth et al (2009), *Biol Psychiatry*, 65: 760-769
  3 Li et al (2005), *Chest*, 127: 1232-1241
I love my granny but she could be to blame for my allergy!
In children genetically at risk

- early caregiver stress and
- parenting difficulties
- predict multiple wheeze in 1st year
- onset of asthma by age 3
- occurrence of asthma at early school age
Early ’behaviour’ problems

- precede onset of asthma in young children with atopy
- together with family problems predict late-onset wheeze
- are possibly expressions of stress
- reflect wider physiological dysregulation interacting with genetic vulnerability
In children with chronic asthma

- severely negative life events increase risk of new exacerbations immediately afterwards and in coming weeks
- simultaneous chronic stress magnifies the risk
In children with asthma, high chronic stress associated with:
- heightened production of TH2 cytokines
- higher eosinophil counts
- but has opposite effect in healthy children
Chronic stress

- alters the properties of genes responsible for fighting infection and keeping airways open
- makes usual asthma medications less effective
- may affect other biological systems, e.g. contribute to hypoactive HPA-axis
Gene-environment interactions

- may explain why stress affects the immune system differently in children with asthma compared with healthy children

Epigenetic inheritance

- likely to apply to atopy & asthma
- as well as to stress
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