Stress - asthma relationship in children

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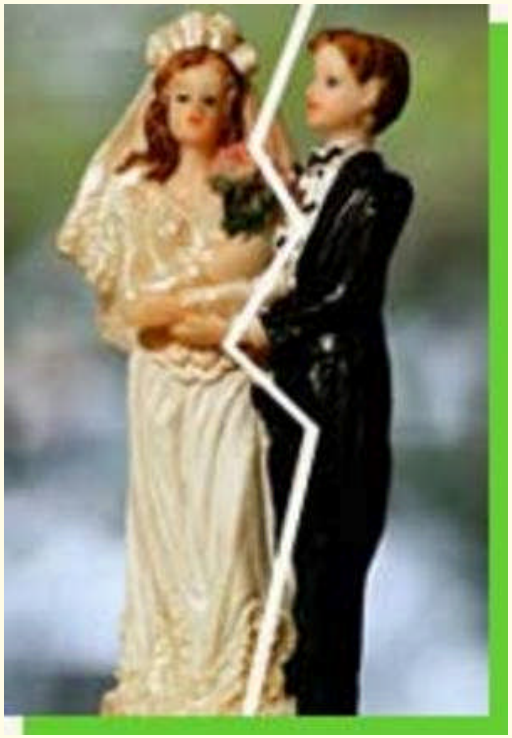


Why concern about stress?

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**

Bloomberg & Chen (2005), *Immunol Allergy Clin N Amer, 25: 83-105*
Chen et al (2006), *J Allergy Clin Immunol, 117: 1014 – 20*
Chida et al (2008), *Psychosom Med, 70: 102 -16*
Kozyrskyj et al (2008), *Am J Respir Crit Care Med, 177: 142-7*
Turyk et al (2008), *Pediatr Allergy Immunol, 19: 255-63*

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

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 [1]

- **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 [2]**

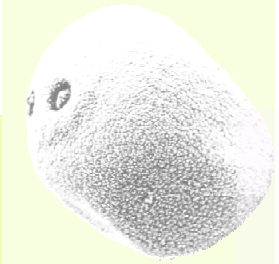
- **Exposure to urbanised way of life does not explain all between & within country differences**

[1] Pearce et al (2007), *Thorax, 62*: 758-766
[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



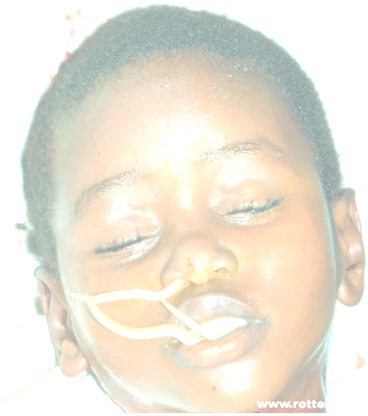
the dominant form of childhood asthma in affluent communities, but far less common in poor communities[2]

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 populatons**



[1] Robinson (2009), *Clin Exper Allergy, 39, 1314-1323*
[2] Weinmayr et al (2007), *Am J Respir Crit Care Med, 176: 565-74*
[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*

Definition of child stress

Stress, stressor, stress reaction

Stressor

Any intrusion into child's
normal physical / psychosocial life experiences

Stress

that acutely or chronically unbalances
physiological or psychological equilibrium,
threatens security or distorts
physical / psychological growth & development

and

Stress reaction

the psychophysiological consequences
of such intrusion / distortion

Types of child stress

Acute stress (negative life events)

Chronic stress

Episodic stress (e.g. exams)

Life events to children

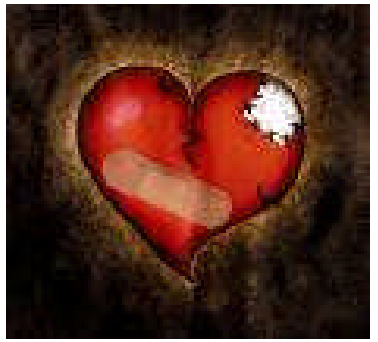
Majority

involve important social relationships

- **family**
- **friends**

and relate to the child's immediate environment

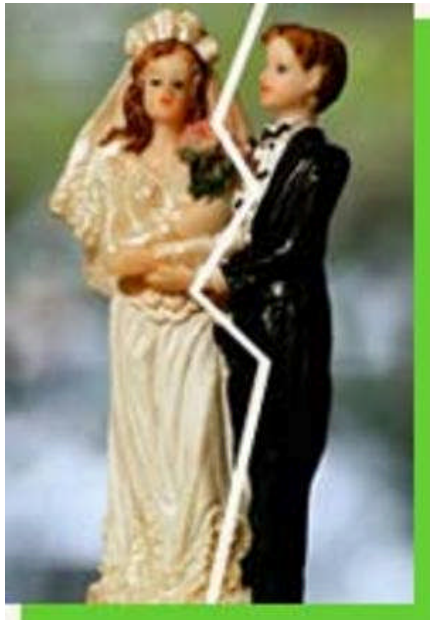
- **home**
- **school**



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*

Sources of chronic stress

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

Seija Sandberg/ IASA2010

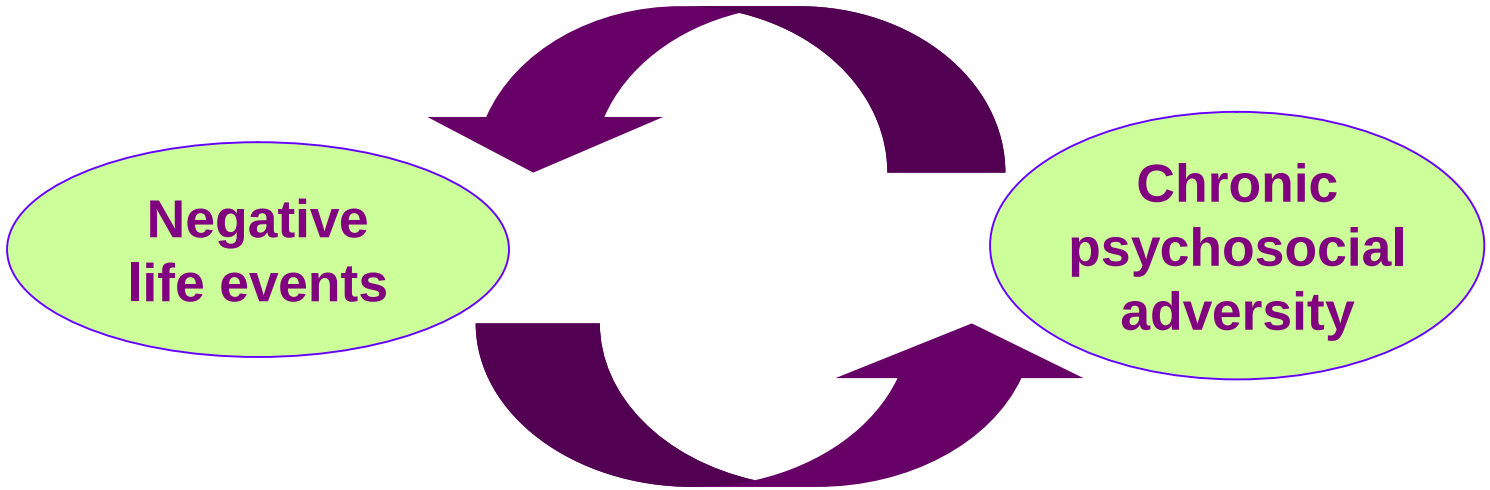
Acute life events & chronic adversity

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



Sandberg et al, *JCPP 1993, 34: 879-97; Lancet 2000, 356:982-87*

Biology of atopic asthma

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 results from deficiency of regulatory T cells (Treg) that suppress potentially harmful immune responses[1]

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

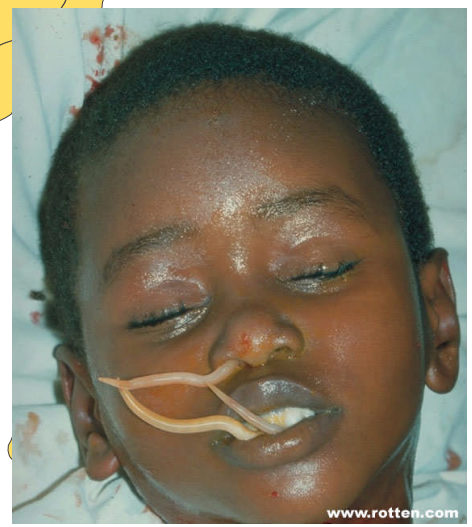
and

acute stress response

Have they joined together and begun to work against us?

From Parasites to Allergy

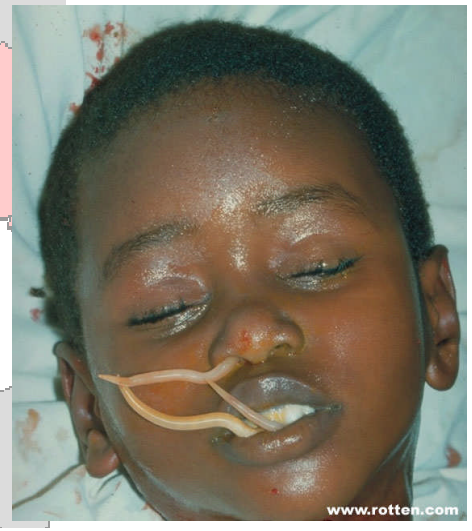
Modern man arose in tropical Africa where helminths thrived. They had to develop methods to fight them.



Le Souef et al (2006), Eur Respir J, 28,1258-63

From Parasites to Allergy

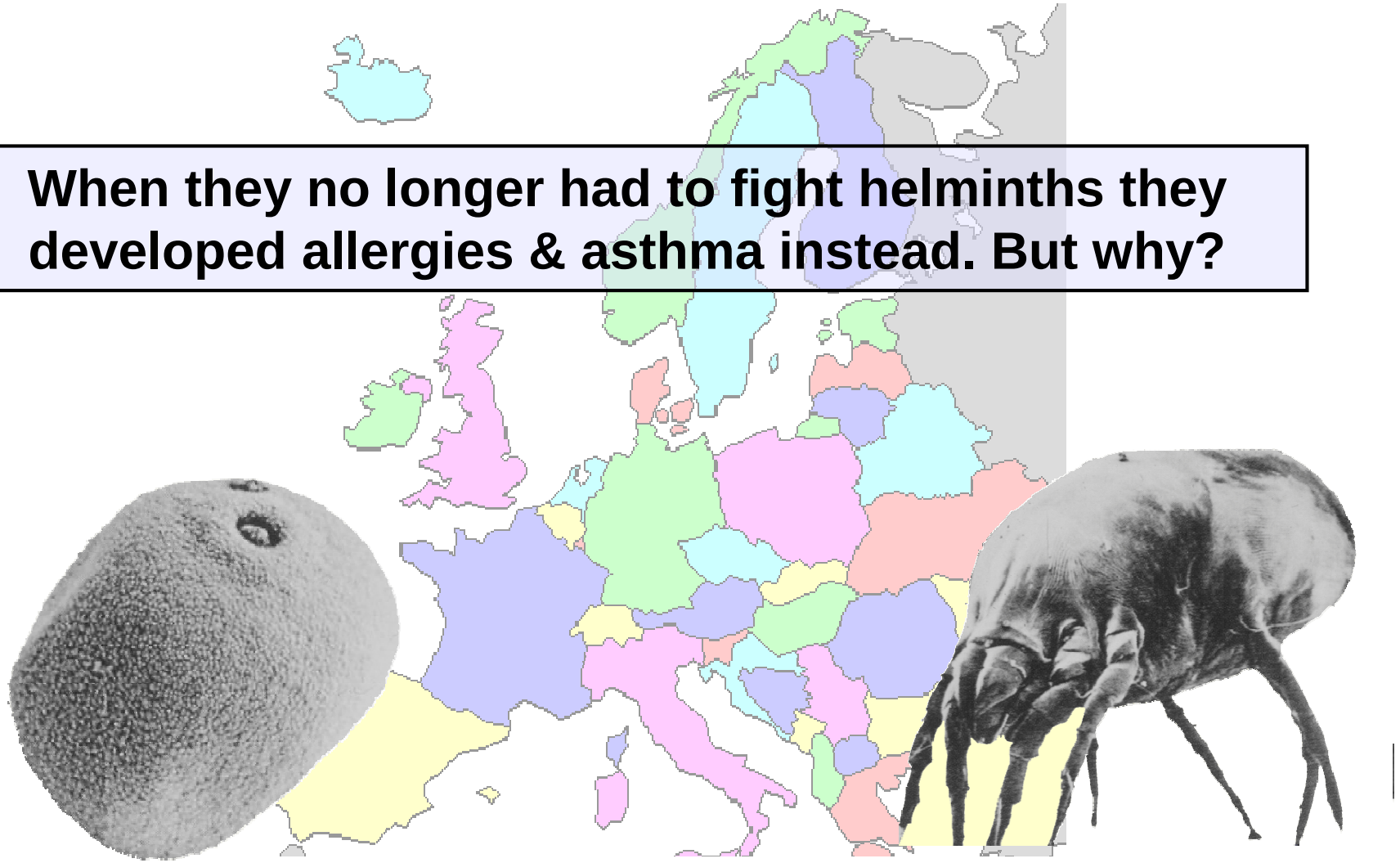
Relatively recently, humans migrated to cooler and drier climates where helminths struggle to survive



Le Souef et al (2006), Eur Respir J, 28,1258-63

From Parasites to Allergy

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**

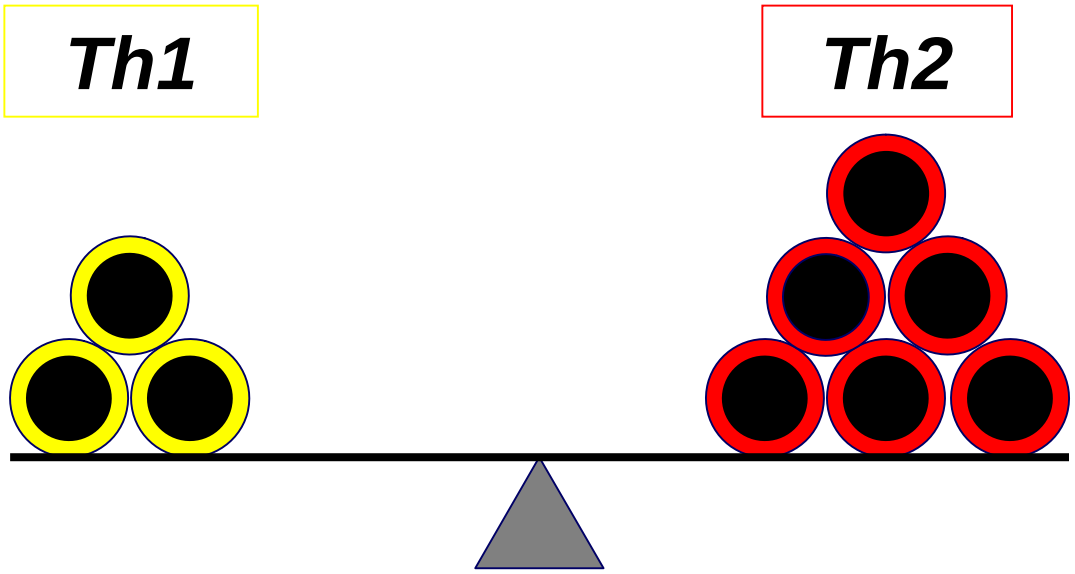
and

- **increased prevalence of allergic disease**

Th2 responses are thought to have evolved in mammals to resist infection by parasites, particularly helminths

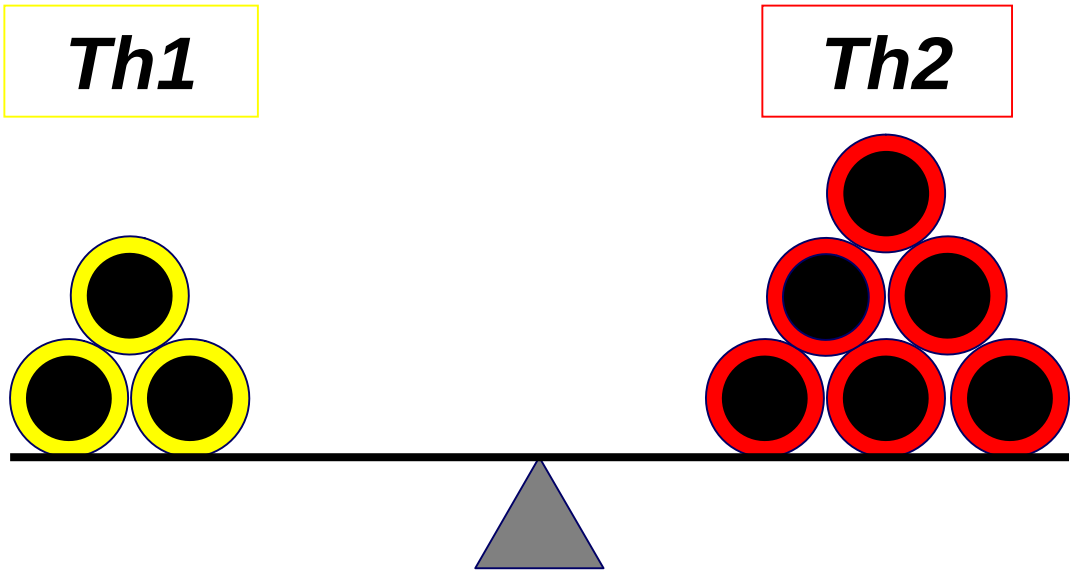
From Parasites to Allergy

The genetic tendency to mount strong Th2 responses may have become a liability causing allergy rather than defending against parasites



From parasites to allergy & asthma

The genetic tendency to mount strong Th2 responses may have become a liability causing allergy rather than defending against parasites



The Acute Stress Response

SAM
(Sympathetic Adrenal Medullary axis)

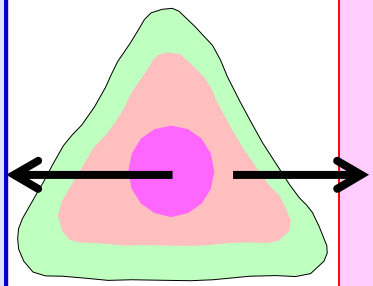
Adrenal Medulla
(Sympathetic Nervous System)

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



Adrenal Gland

HPA
(Hypothalamic-Pituitary-Adrenal axis)

Adrenal Cortex
(Zona Fasiculata)

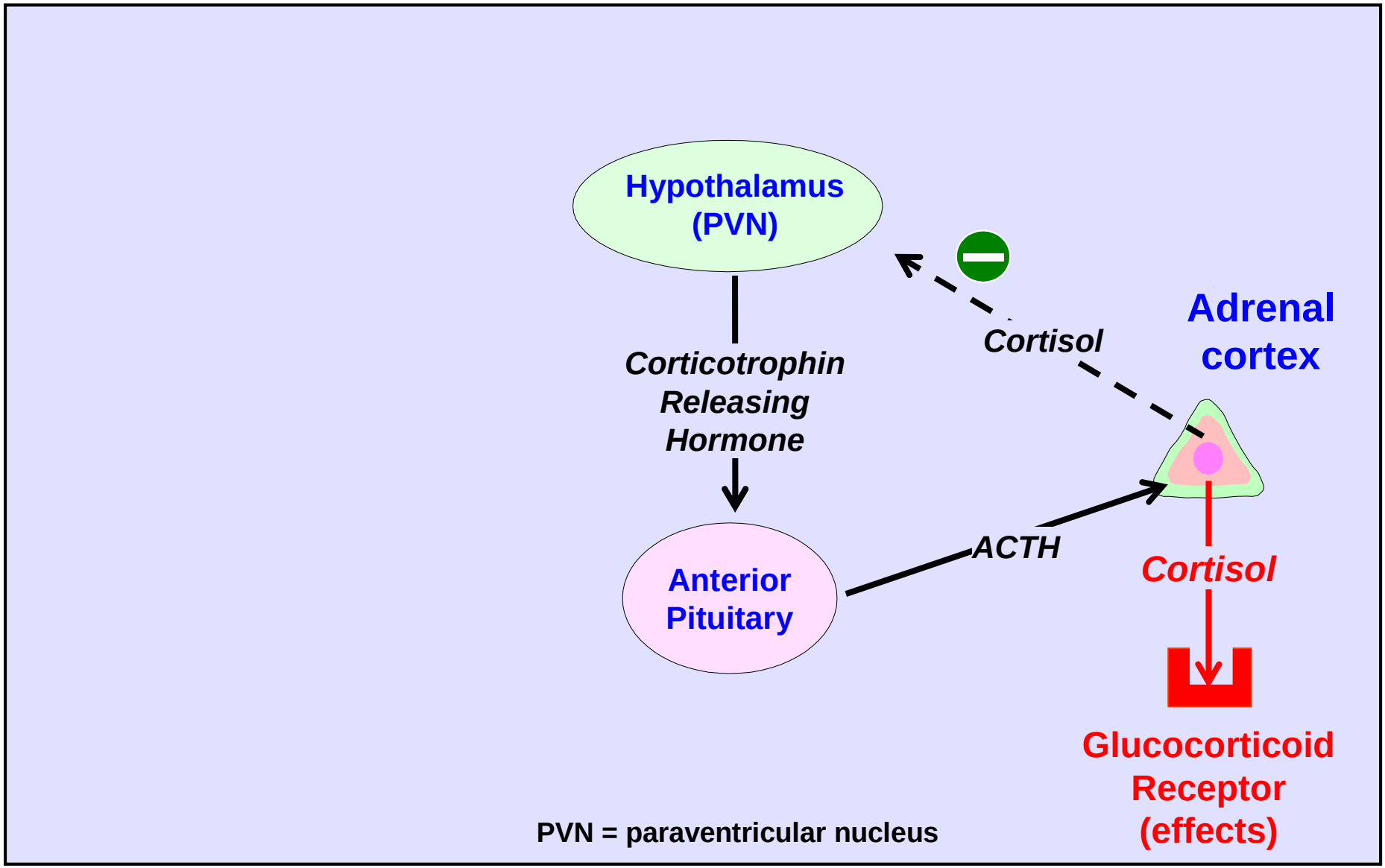
Cortisol

Slow activation

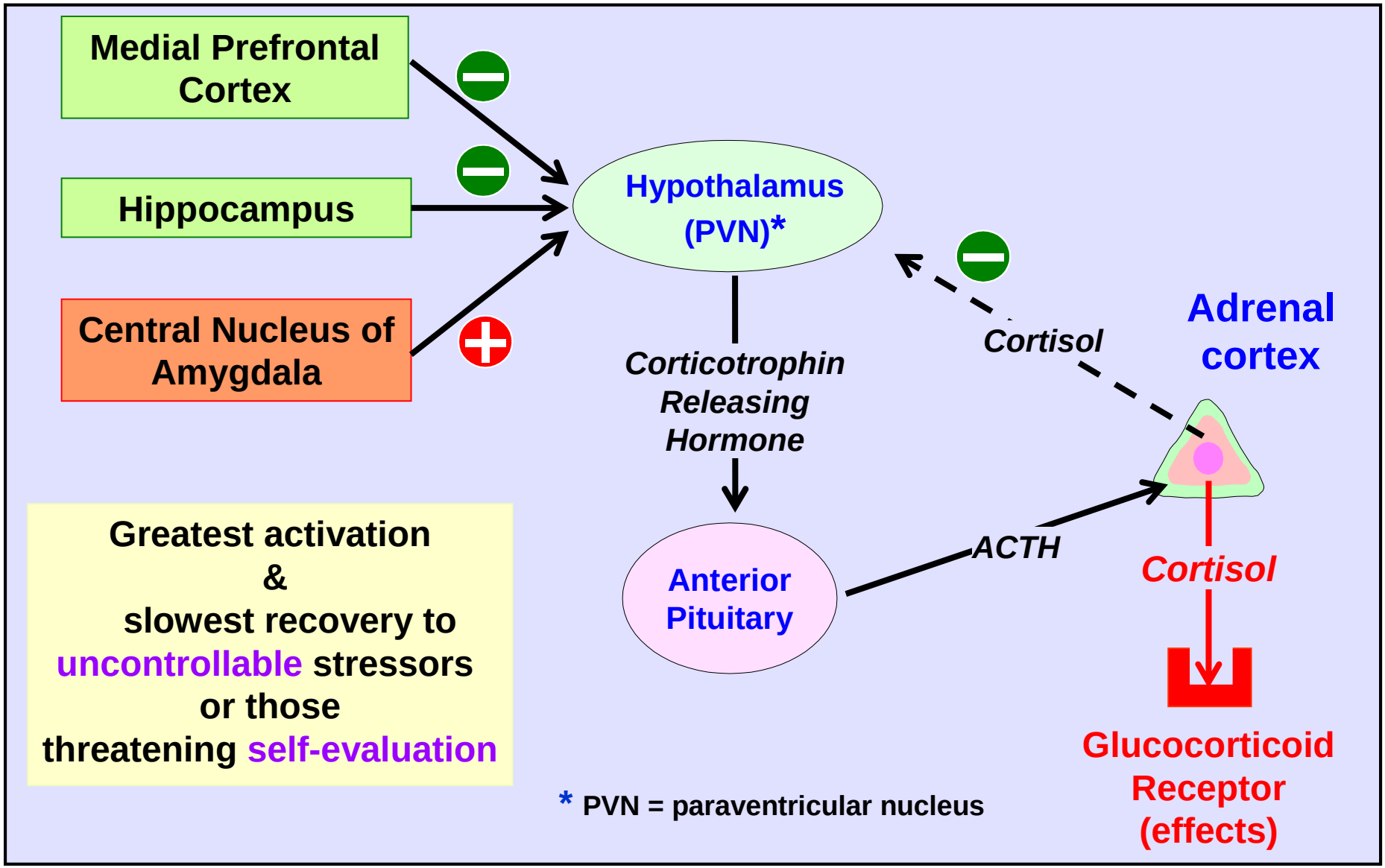
Restores homeostasis after severe physical trauma or stress

Regulate innate & adaptive immune systems through binding to glucocorticoid receptors on leukocytes

The hypothalamic-pituitary-adrenal (HPA) axis



Acute Stress on the HPA Axis



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 & **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

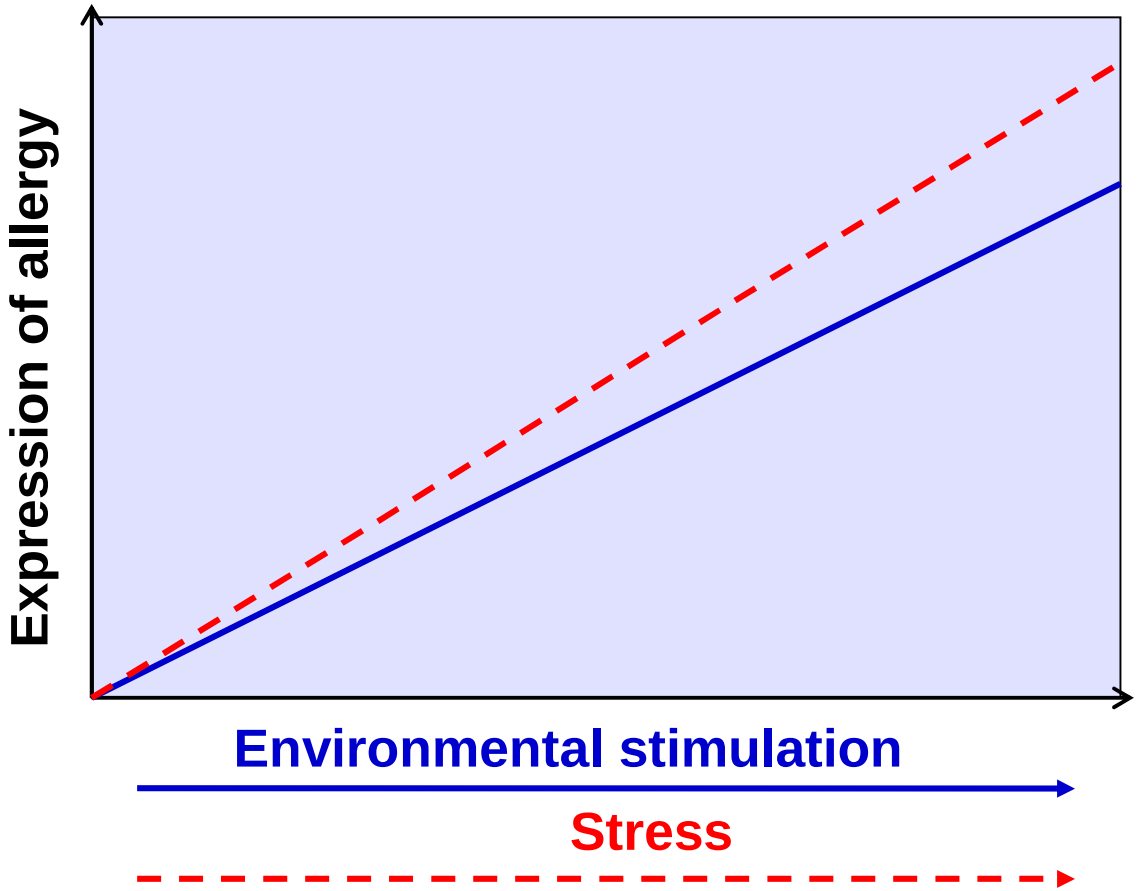
and

Acute Stress Response

Have they joined together and begun to work against us?

Allergy, the Environment and Stress

Expression of allergy in a person with a genetic predisposition to allergy



Th2-bias and Immune Dysregulation

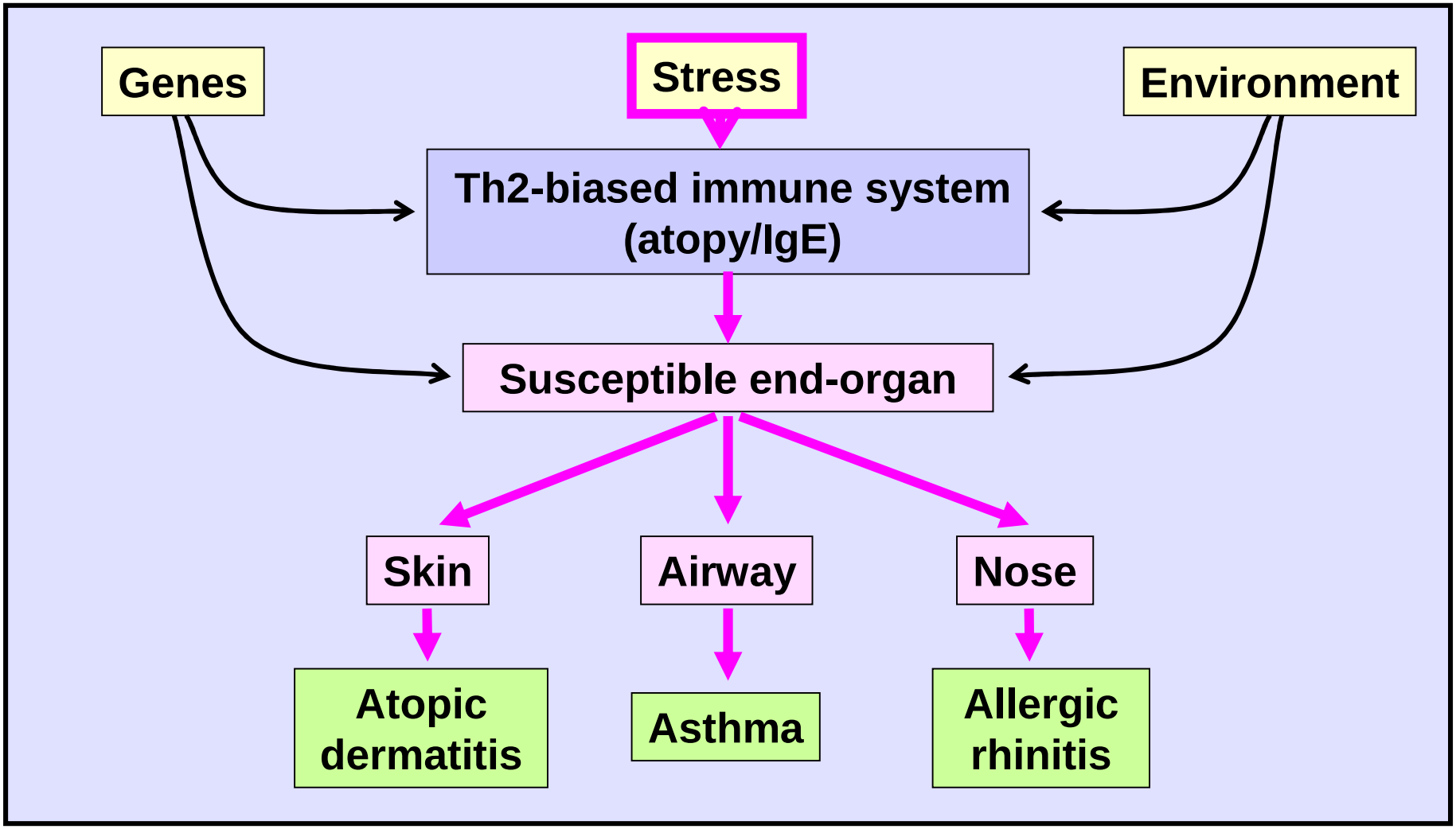


Diagram re-drawn according to Georas et al (2005), Eur Respir J, 26:1119-37

Contribution of stress to manifestation of asthma

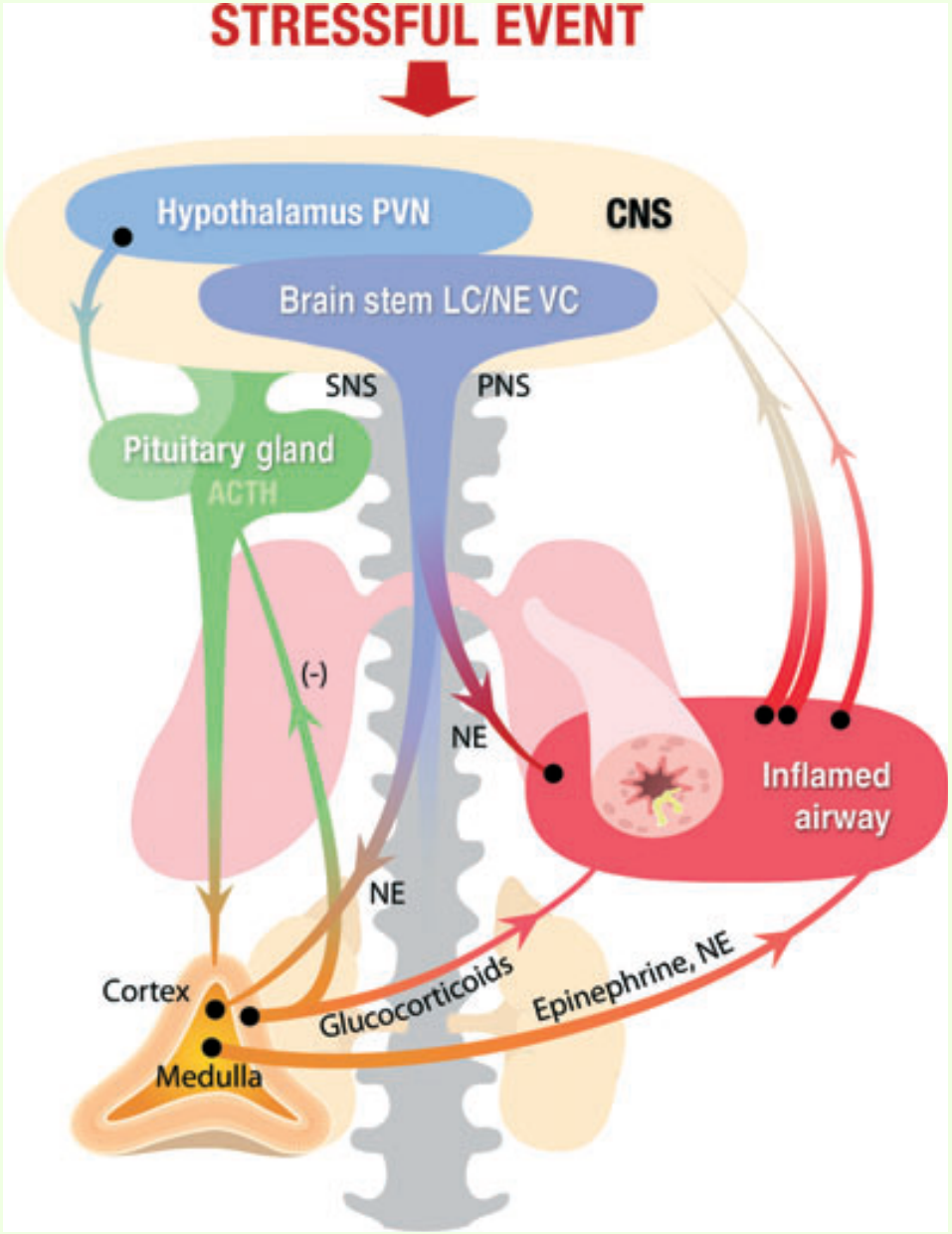
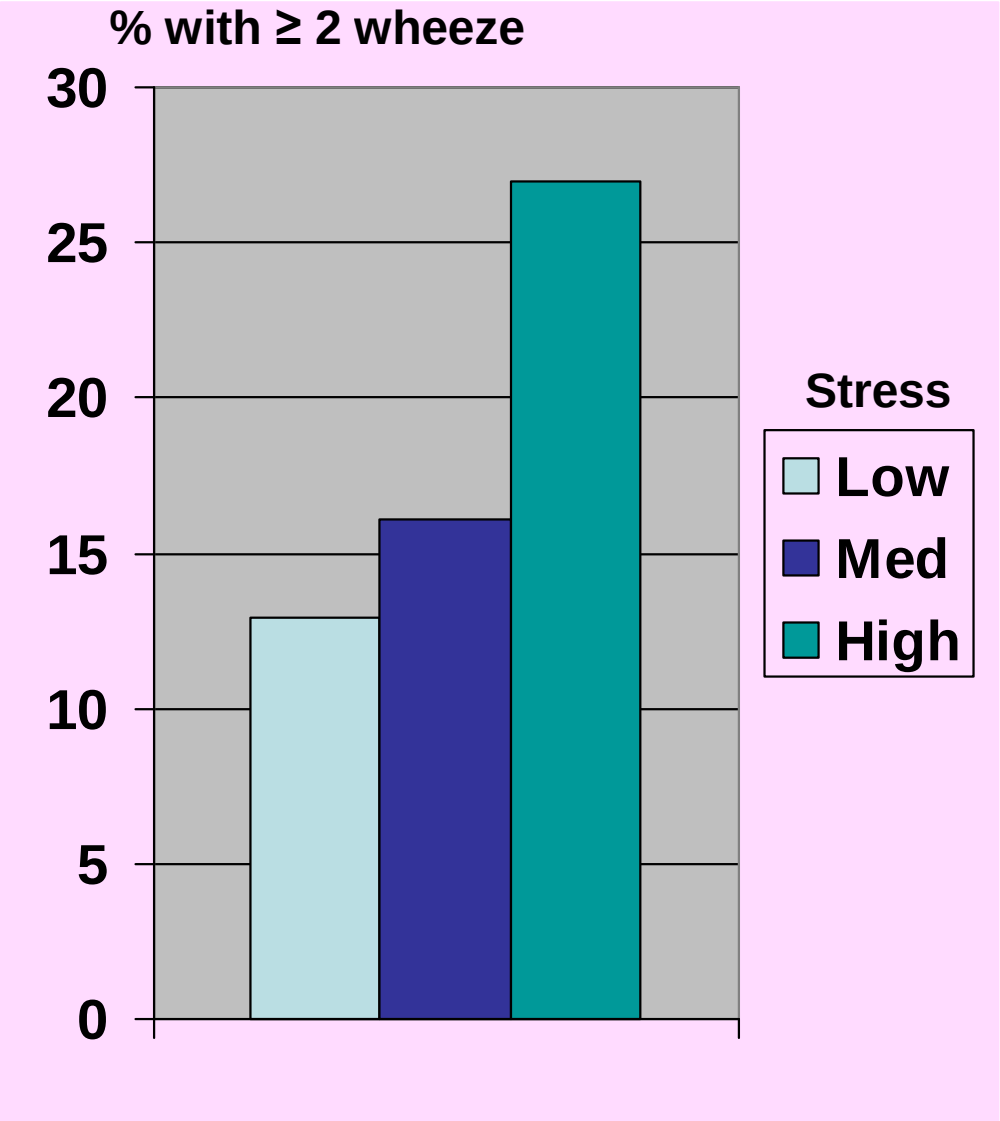


Diagram by Priftis KN et al (2009) Allergy, 64, 18-31

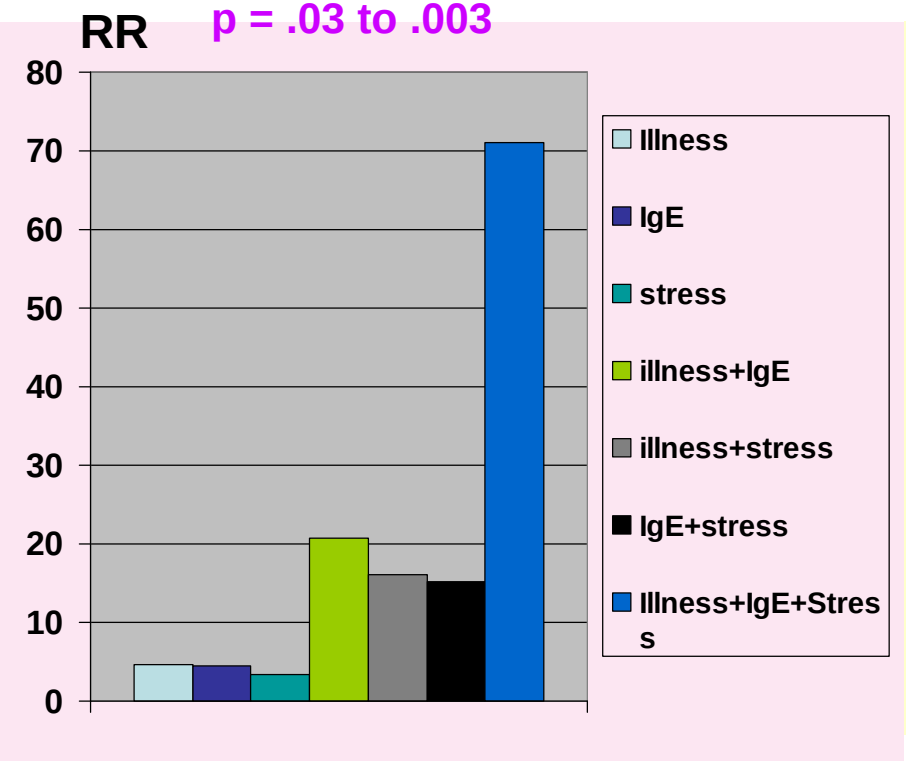
Early caregiver stress – wheeze in 1st yr

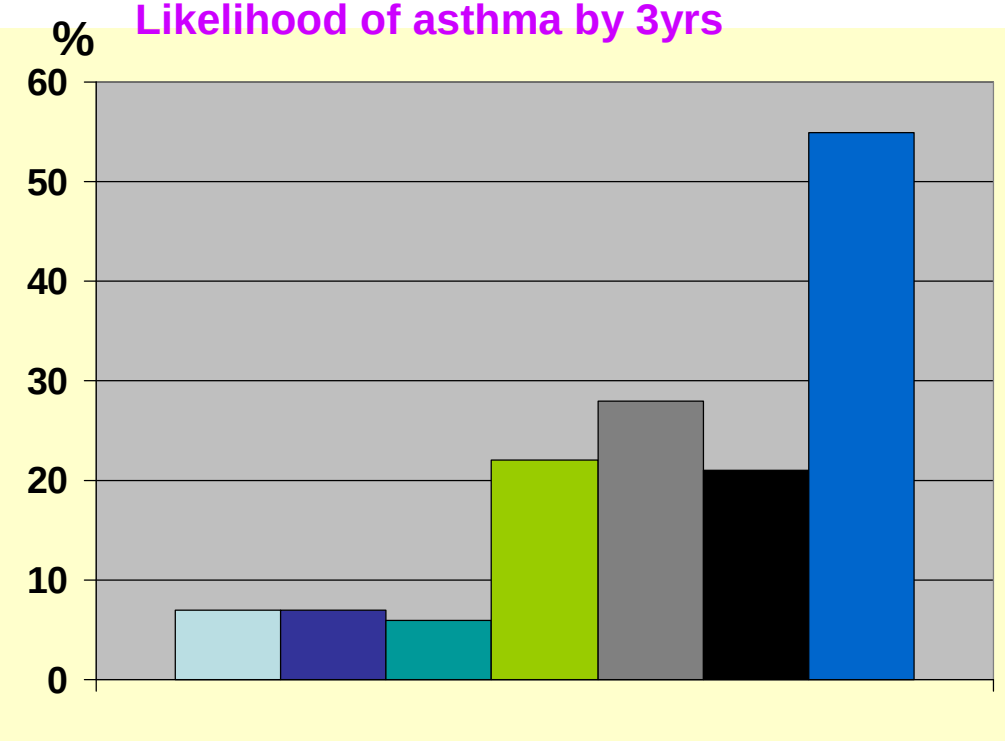
Caregiver stress in first few months predicted multiple wheeze in 1st year in predisposed children
RR=1.4 (95% CI 1.1-1.9)



Wright et al (2002), *Am J Respir Crit Care Med, 165: 358-65*

Early stress, onset of asthma by 3 yrs

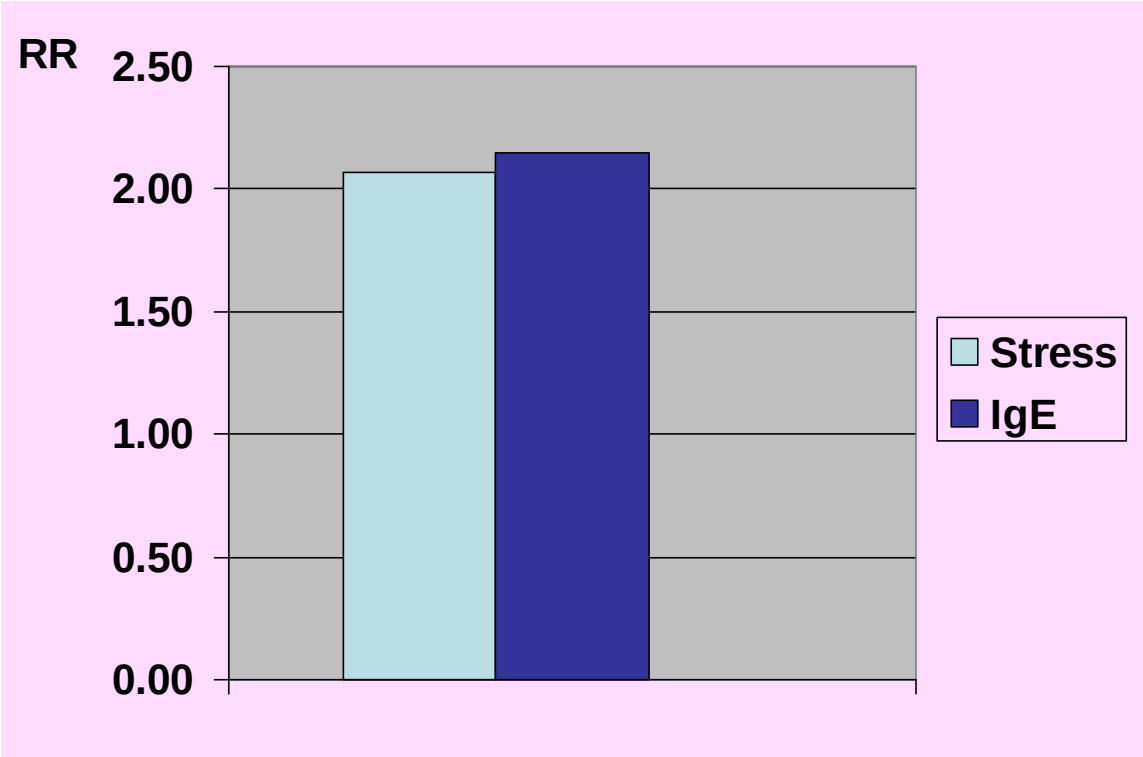




Parental stress together with early parenting difficulties predict onset of asthma in those genetically at risk. The asthma risk greatly increased in the context of frequent infections in 1st year & elevated serum IgE at 6 months.

Mrazek et al (1999), *Pediatr Pulmonol, 27: 85-94*

Early parental stress – asthma at 6-8 yrs

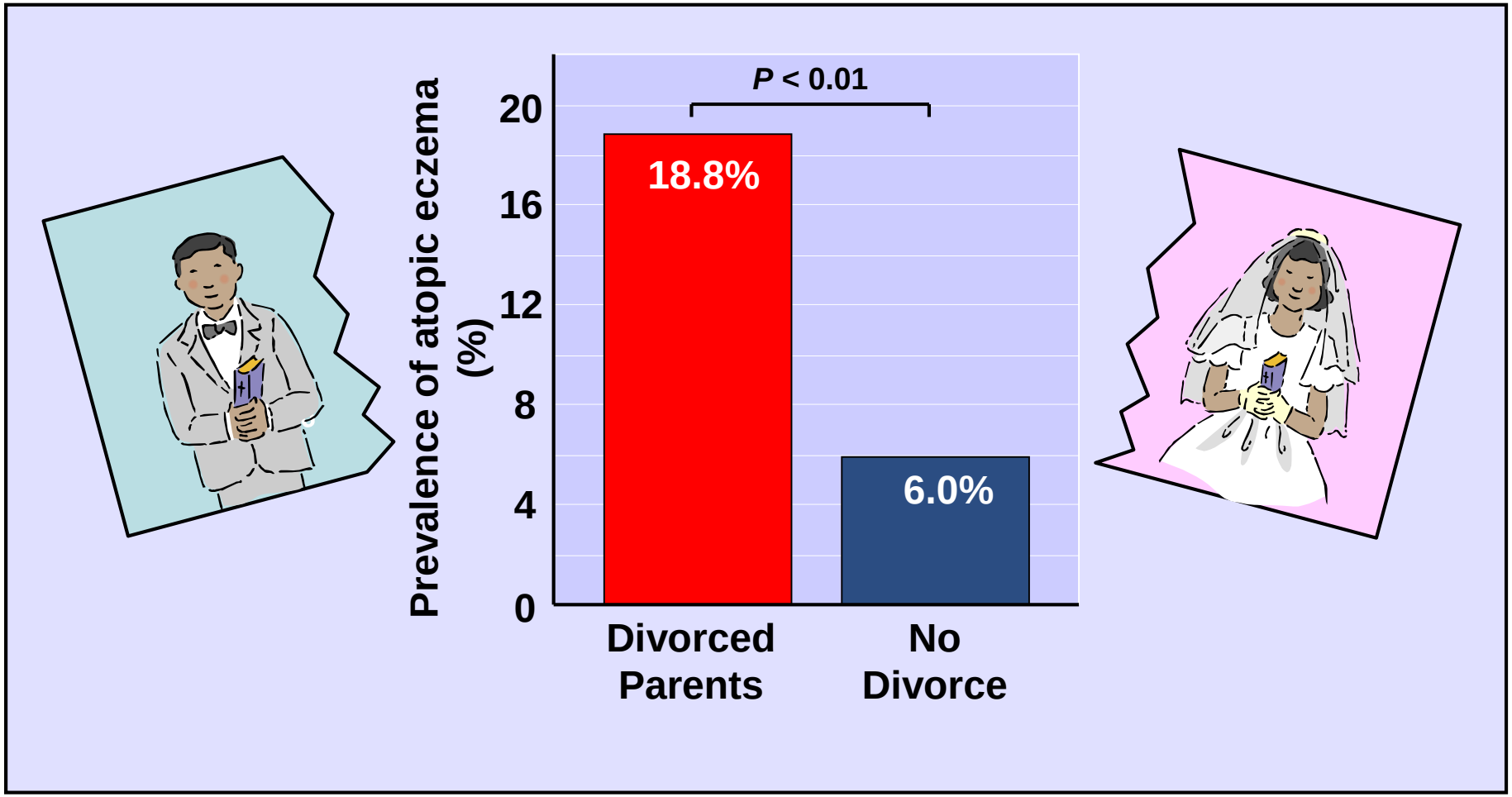


Early parental stress and parenting difficulties doubled the risk of asthma by age 6-8 yrs

Klinnert et al (2001), *Pediatrics, 108: 69-76*

Evidence: Stress and risk of atopic eczema

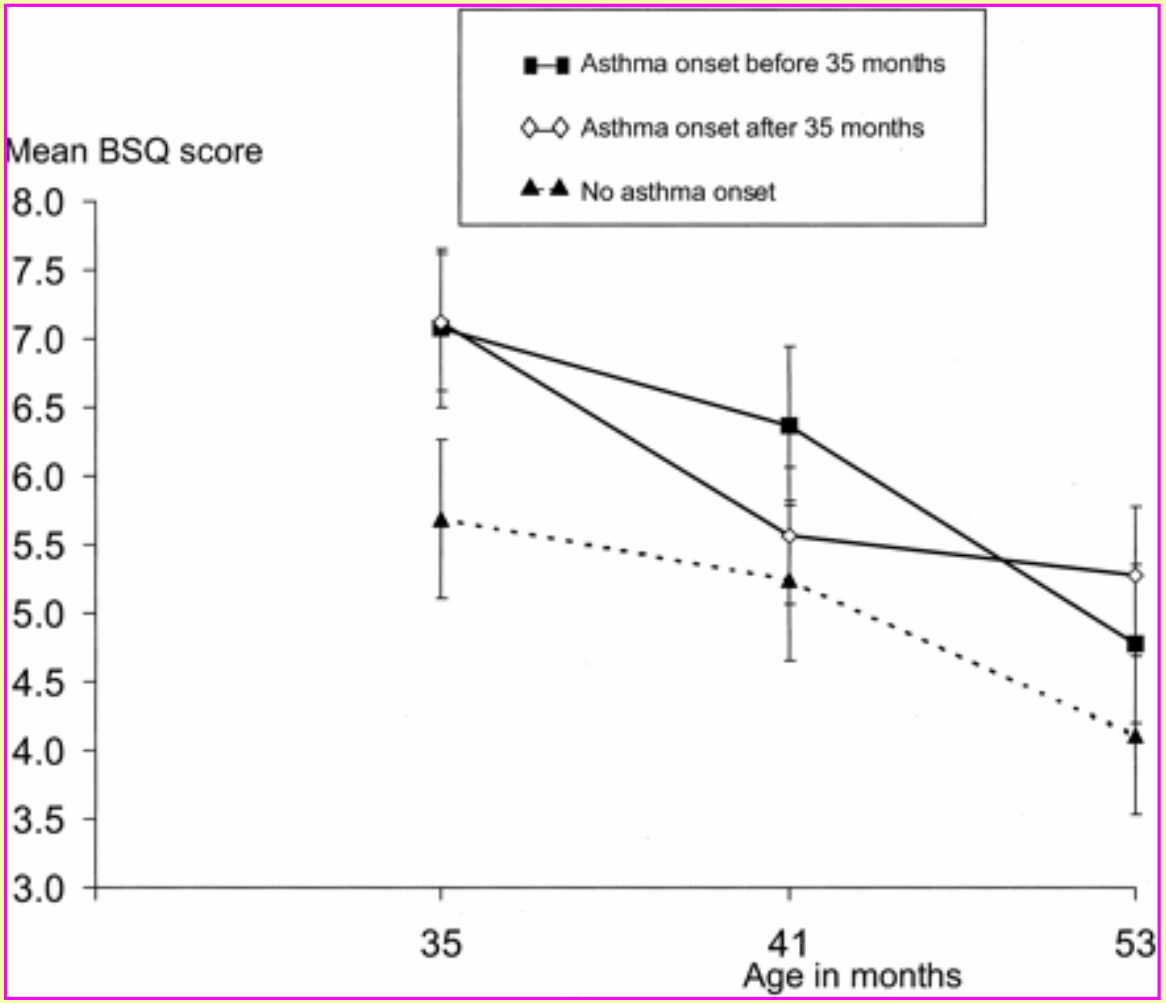
Prevalence of atopic eczema in children aged 4 years



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

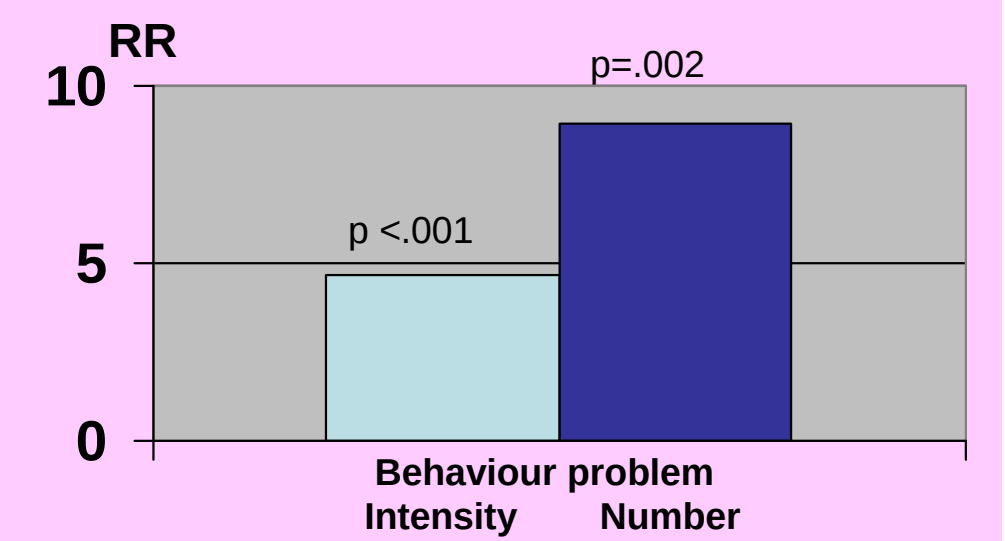


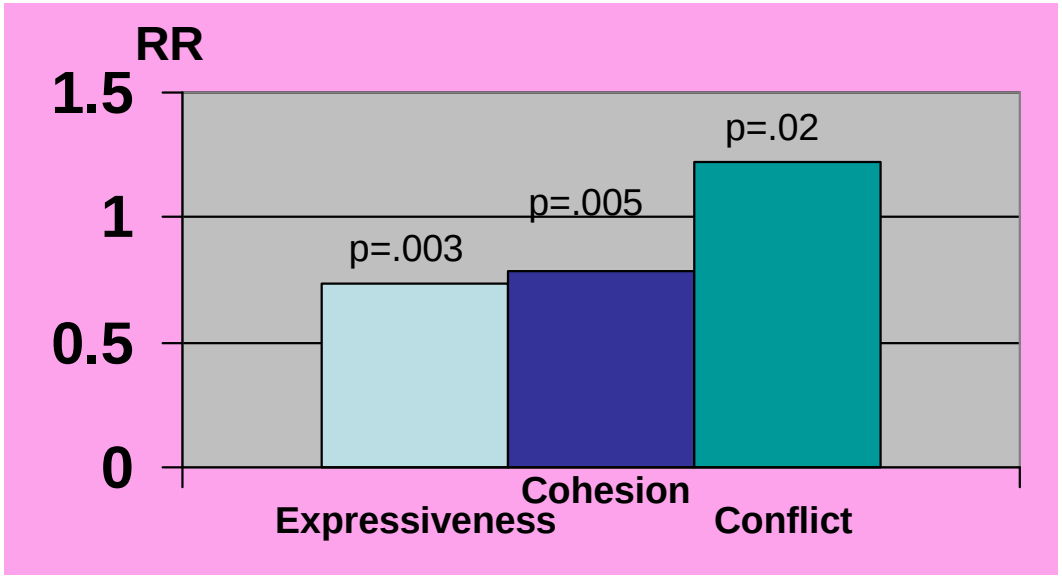
Stevenson (2003), *Psychosom Med, 65: 971-5*

Behaviour problems, family functioning, late onset (by age 5) wheeze

Behaviour problems age 3
&
poor family functioning
- **low expressiveness**
- **low cohesion,**
- **high conflict**

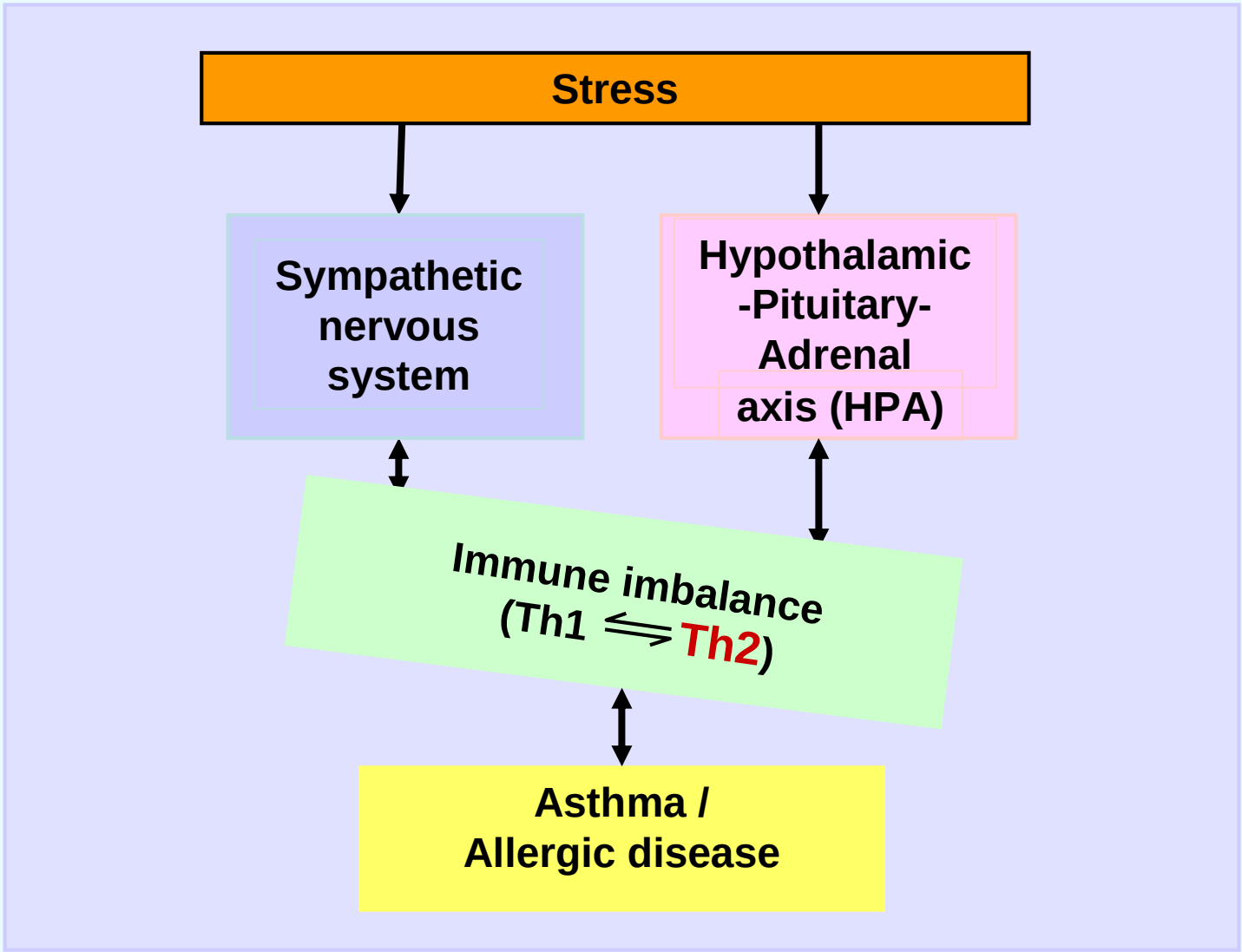
predict wheeze by age 5





Calam et al (2005), *Am J Resp Crit Care Med, 171: 323-7*

A model of how Stress may influence Asthma



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***

* Wright et al (2004), *J Allergy Clin Immunol, 113, 1051-7*

* Bockelbrink et al (2006), Allergy, 61, 1397-1402

** Stevenson (2003), *Psychosom Med, 65, 971-5*

*** Mrazek (2003). *Child Adol Clin N Am, 12, 459-71*

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]

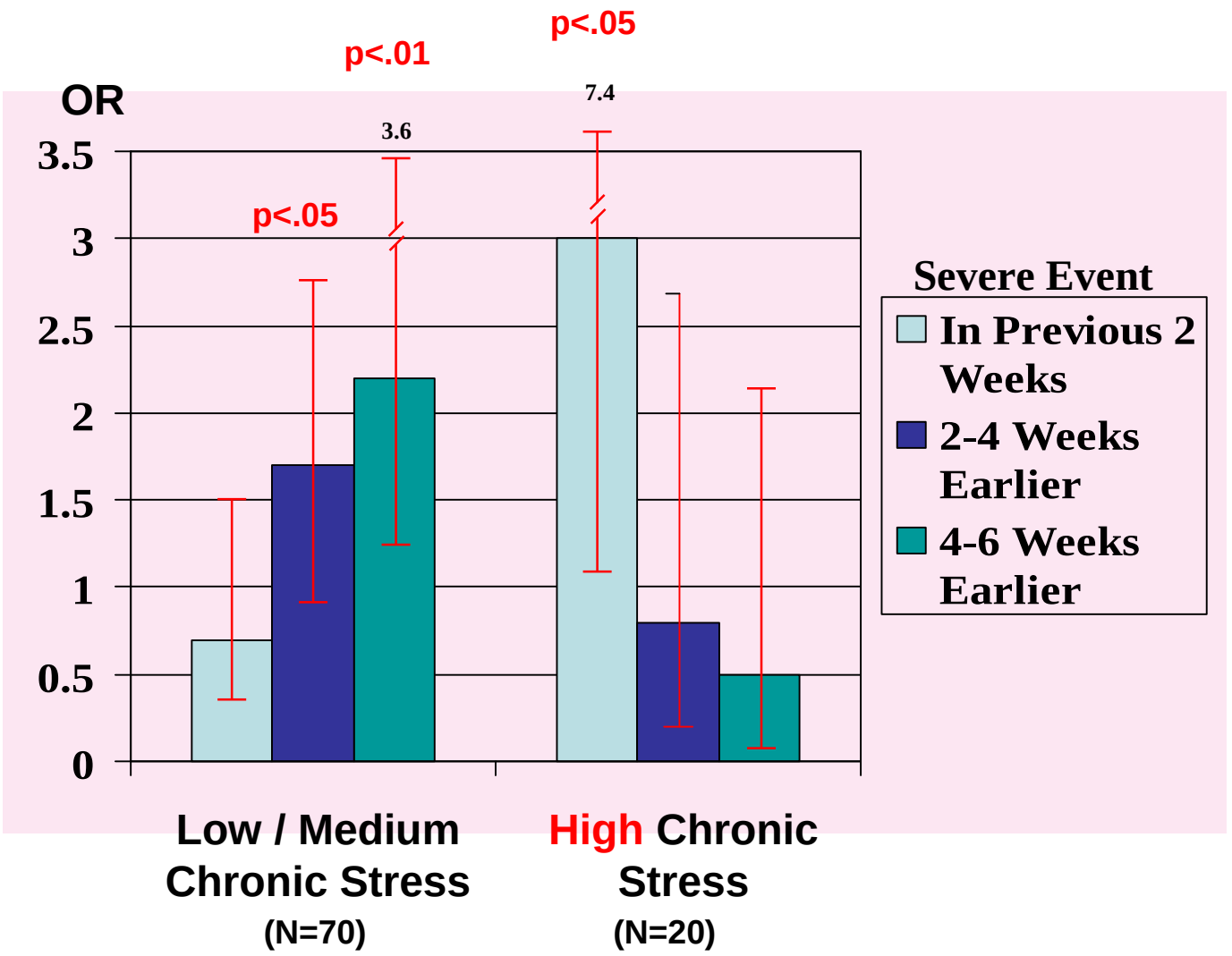
- **Asthma monitoring**
  - independent
  - continuous
  - **daily diaries**
  - **peak flows**

[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

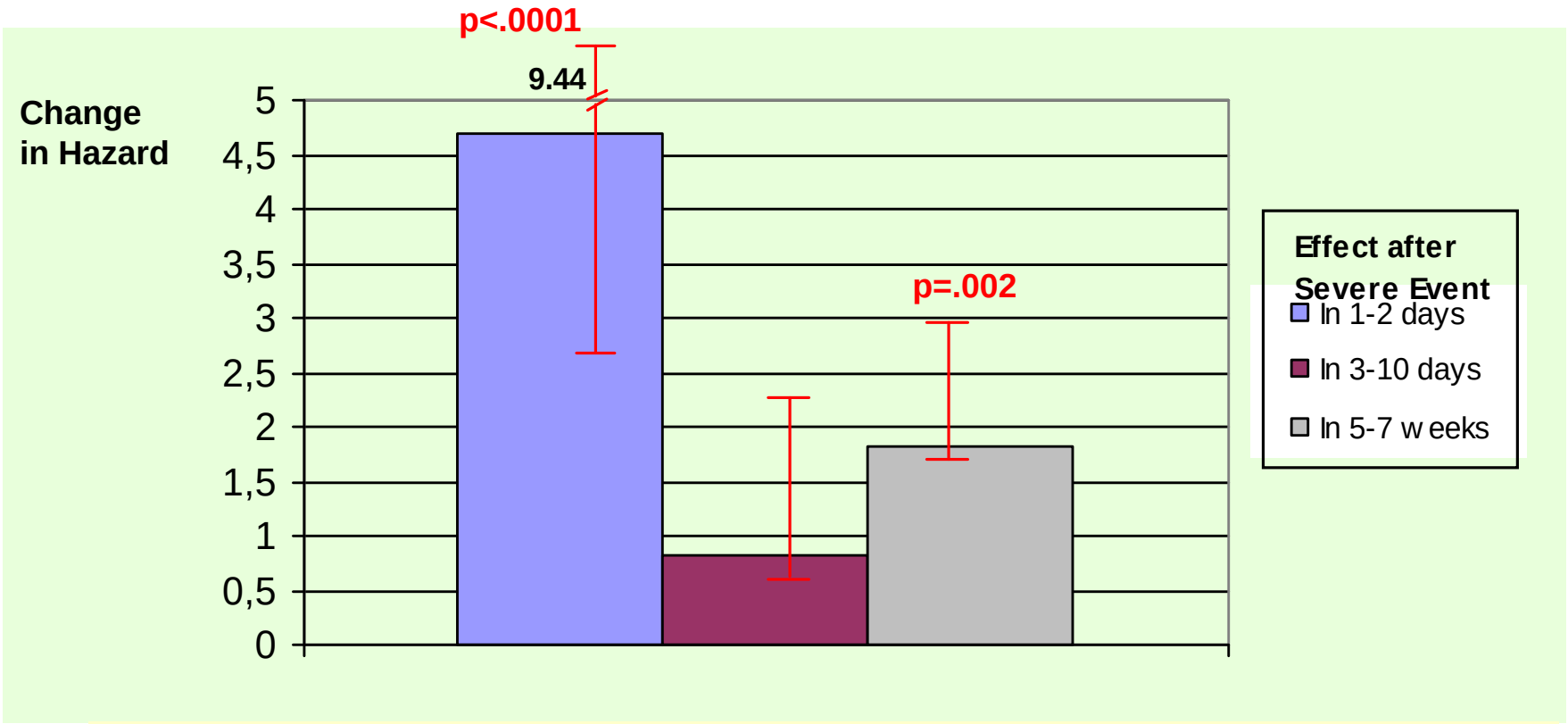
Risk influenced by chronic stress (dynamic logistic regression)



Sandberg et al (2000), *Lancet, 356: 982-987*

Severe events: Immediate & delayed effects

*** low / medium chronic stress (N=60)**

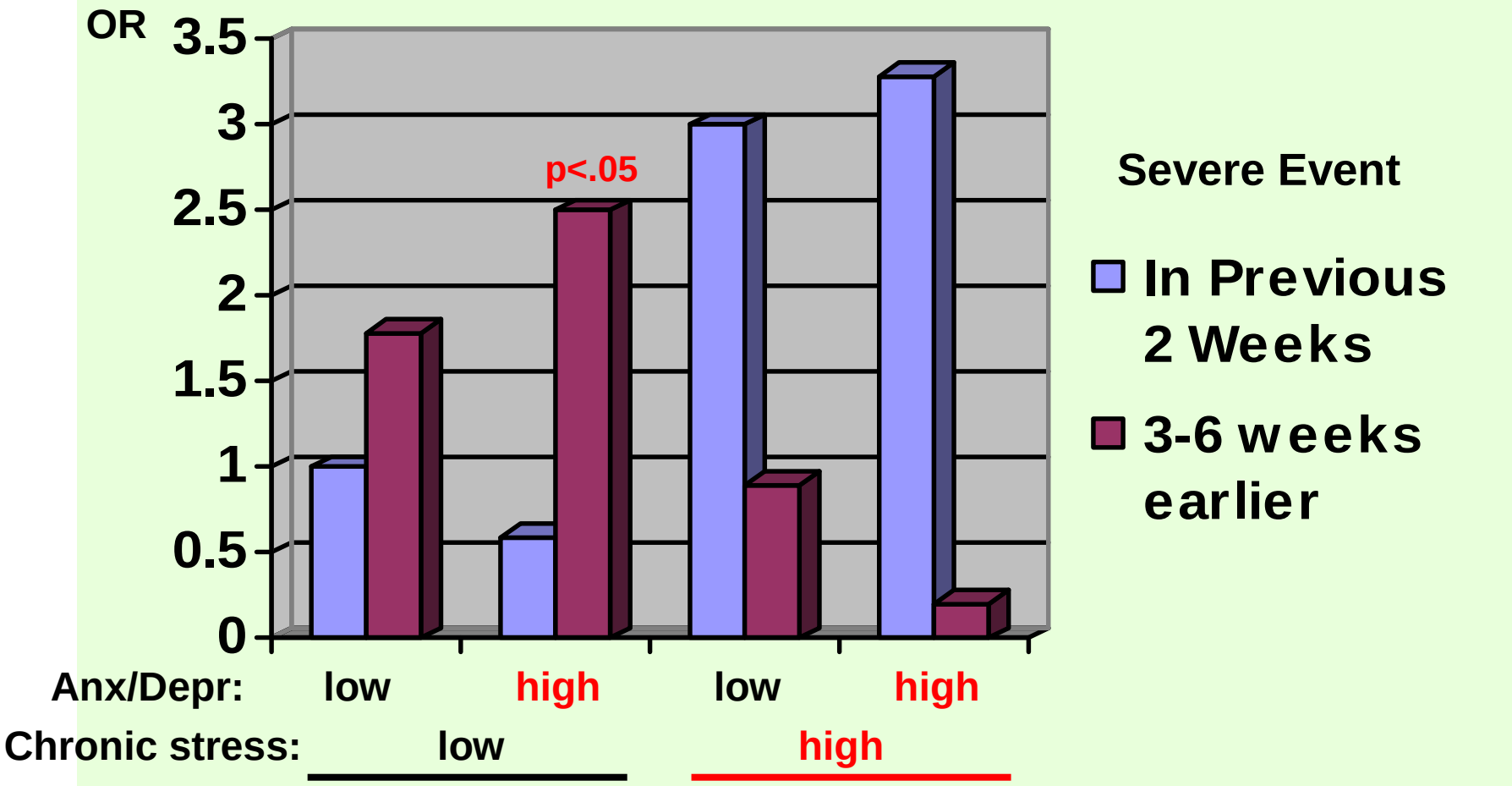


Use of statistical methods capable of examining short time lags showed that severe life events increase immediate risk of new asthma attack also in the low-medium chronic stress group, with a another rise 5-7 weeks later (Cox' regression)

Sandberg et al (2004), *Thorax, 59: 1046-1051*

Emotional problems & stress-asthma relationship

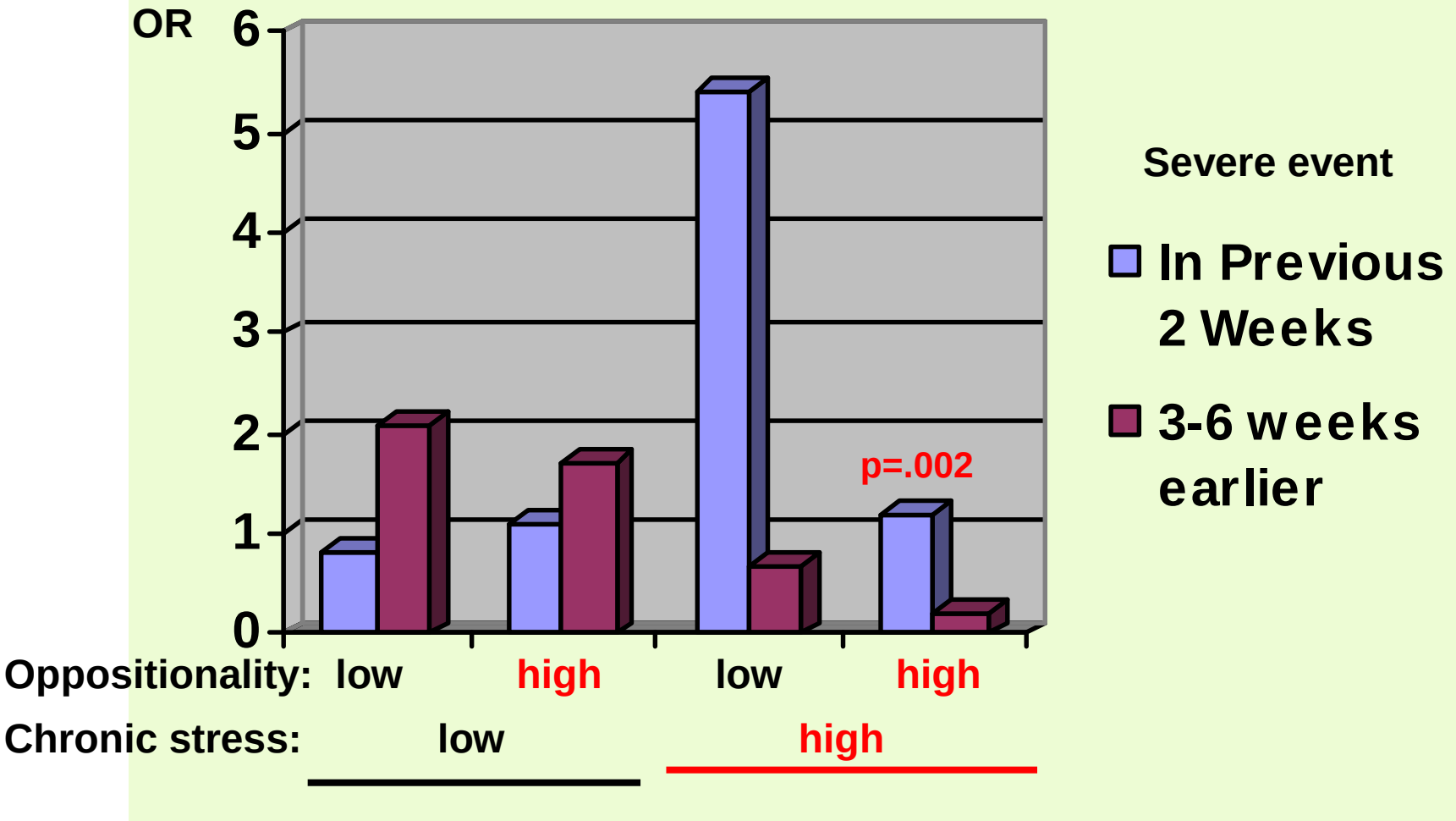
Anxiety/depression further increased risk of new asthma attack following severe life event – but only in the absence of chronic stress



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

Oppositional behaviour and stress-asthma relationship

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



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

Summary: Glasgow study

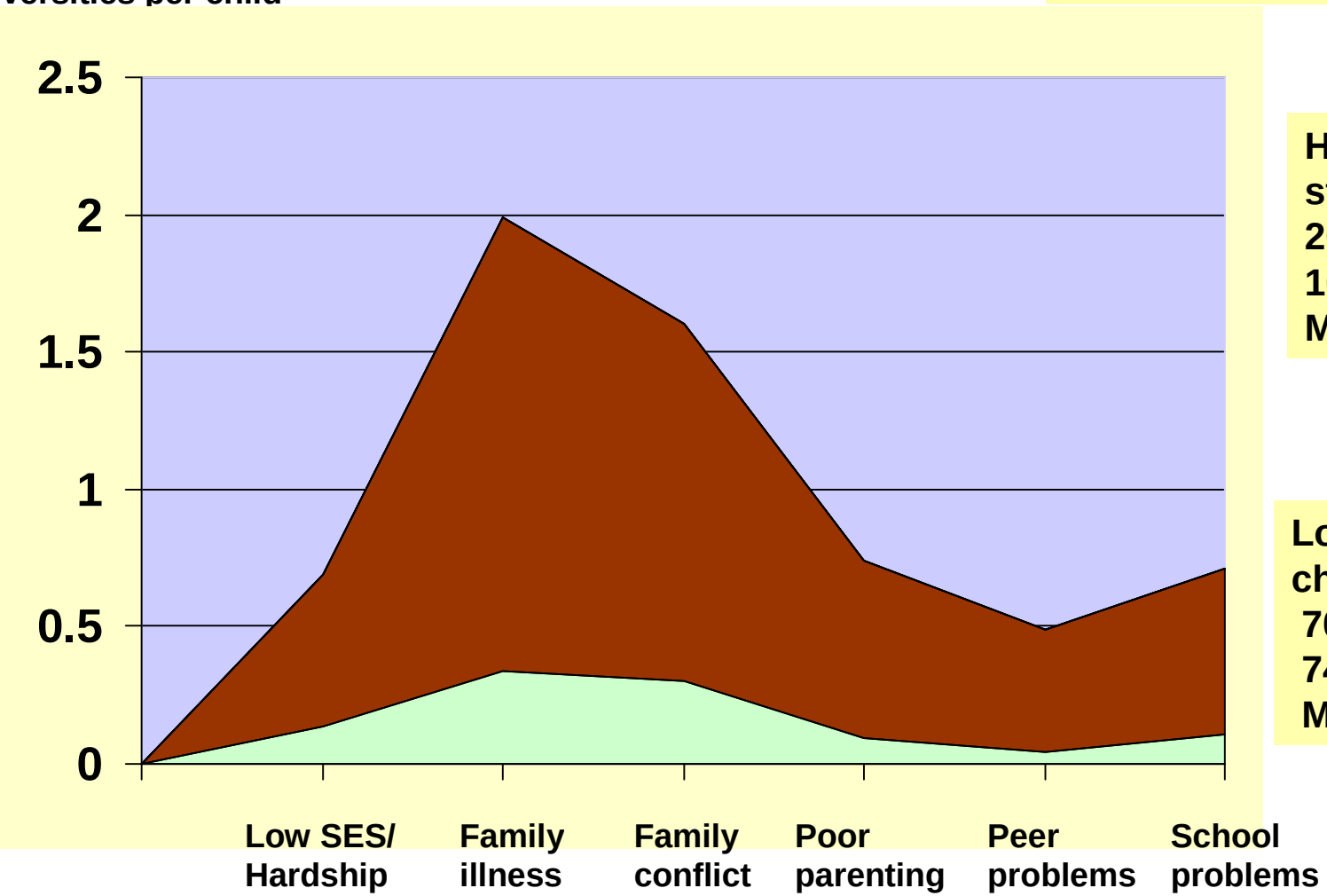
- Severely **negative life events** increase the risk of children's asthma attacks immediately and over the coming weeks
- **High chronic stress** magnifies the risk associated with severe events
- **Emotional problems** further increase the risk
- **Minor rebelliousness** is protective when chronic 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*

Sandberg et al, *Lancet, 2000, 356: 982-7; Thorax, 2004, 59: 1046-51; Acta Paed, 2002: 91, 152-158; Eur Child Adol Psych, 2003: 12 S2, 230*

*(data not shown in this presentation)

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

Mean number of chronic adversities per child



90 children with asthma:

High chronic stress:
20 children,
105 stressors
Mean= 5.25

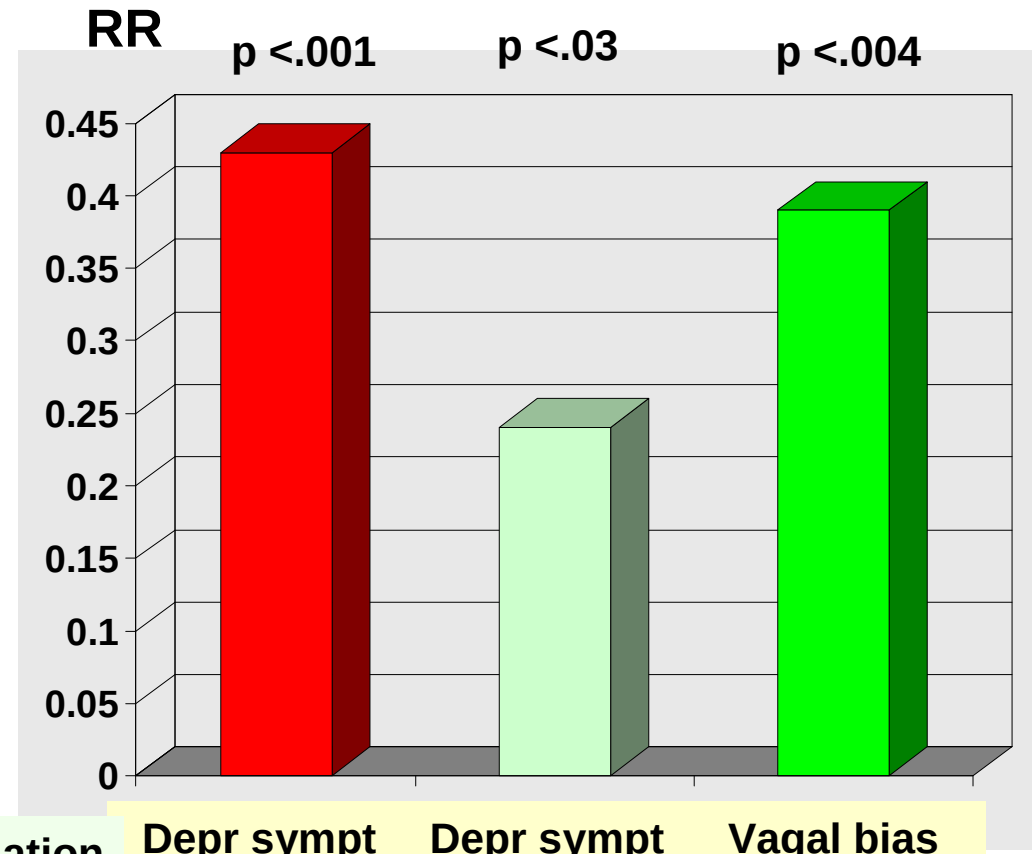
Low/moderate chronic stress:
70 children
74 stressors
Mean = 1.06

Sandberg et al (2000), Lancet, 356: 982-7

Depressed children with asthma

- **Children with asthma and depressive symptoms manifest vagal bias when emotionally stressed**

- **Those with depressive symptoms and poorer lung function (FEV_1<80%) manifest greater airway resistance**



Miller et al (2009), *J Allergy Clin Immunol, 124*:66-73

Stress and Glucocorticoid Resistance

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

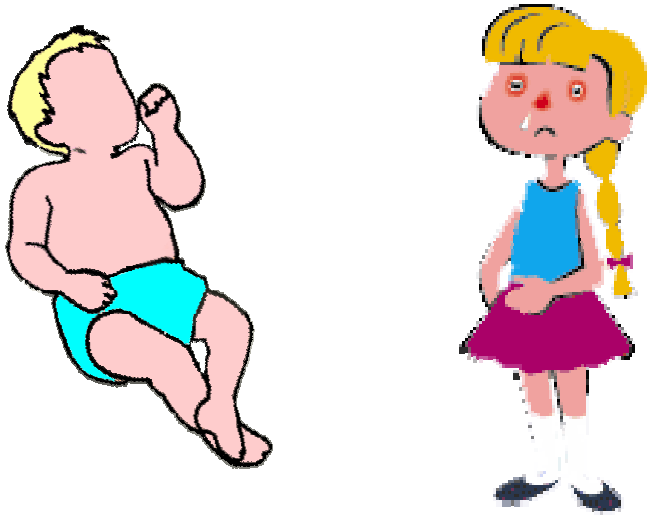
Asthma patients show variable response to treatment because of **acquired steroid resistance** induced by chronic inflammation or immune activation

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?

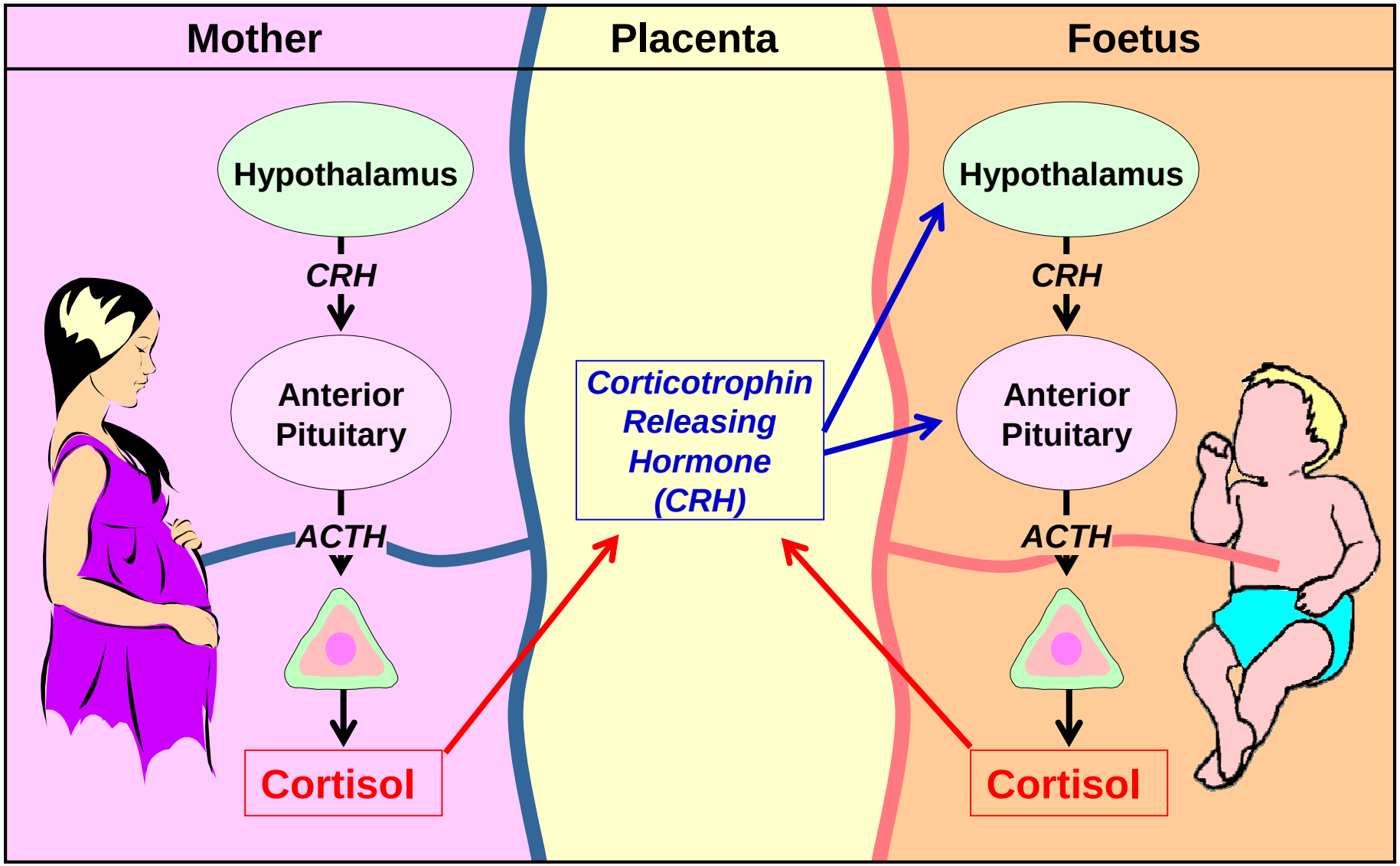
How does stress increase risk of asthma?

When and how does it start?

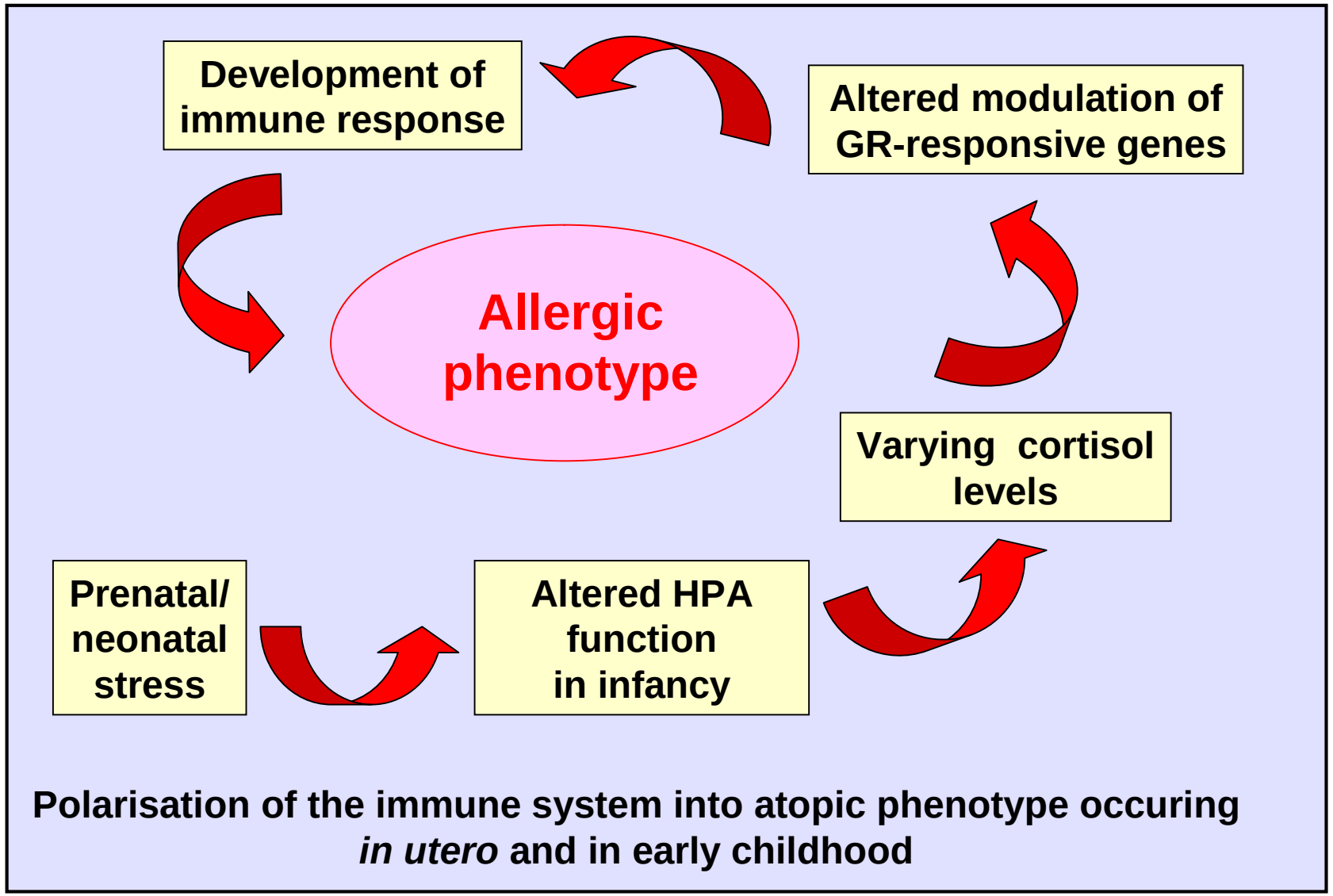


Problems with HPA function and its consequences on the immune system start *in utero* and continue to develop in early life

Neuroendocrine Axis in Pregnancy



From early stress to allergy



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

Your Childhood Determines Your Adulthood

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

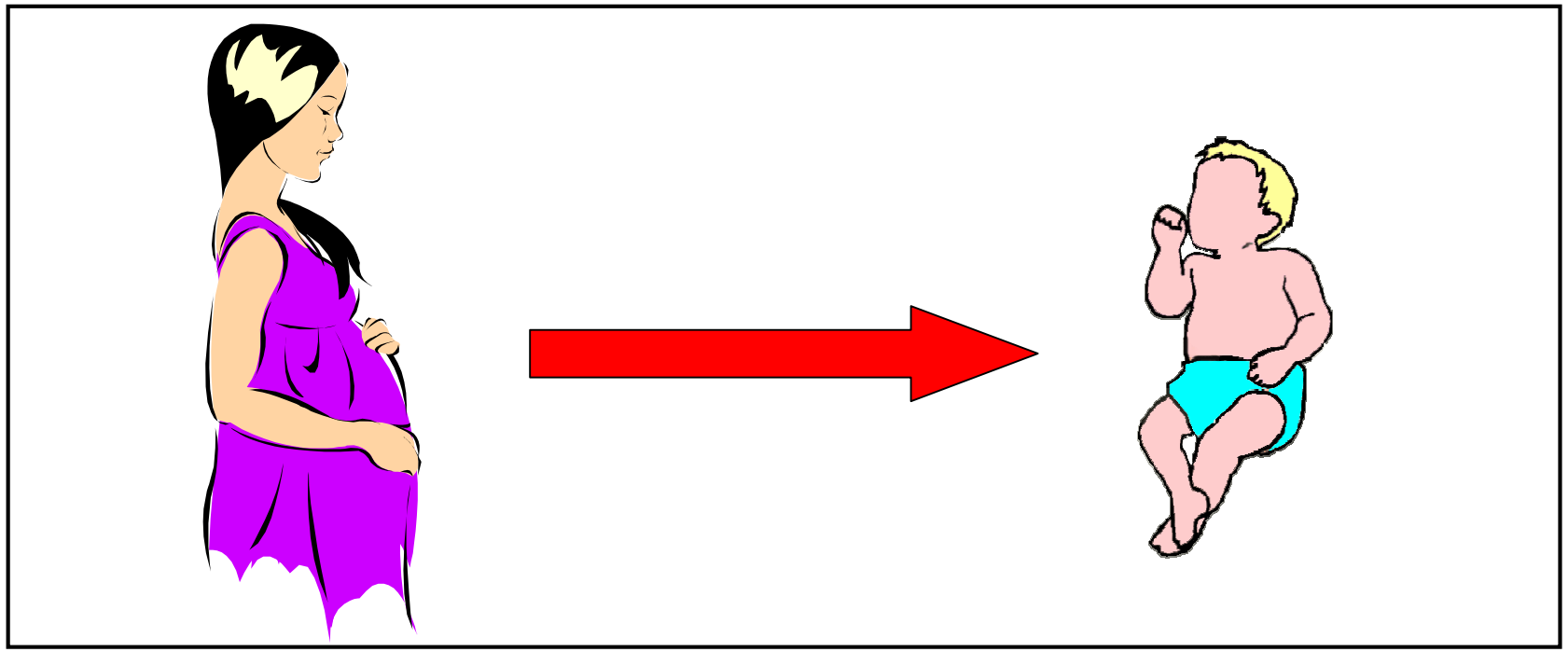
Epidemiological evidence: The **critical time period** for establishment of allergy and asthma is between **conception and 3 years** of age

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

Epigenetic Effects

Heritable changes in gene expression that occur without directly altering DNA sequence

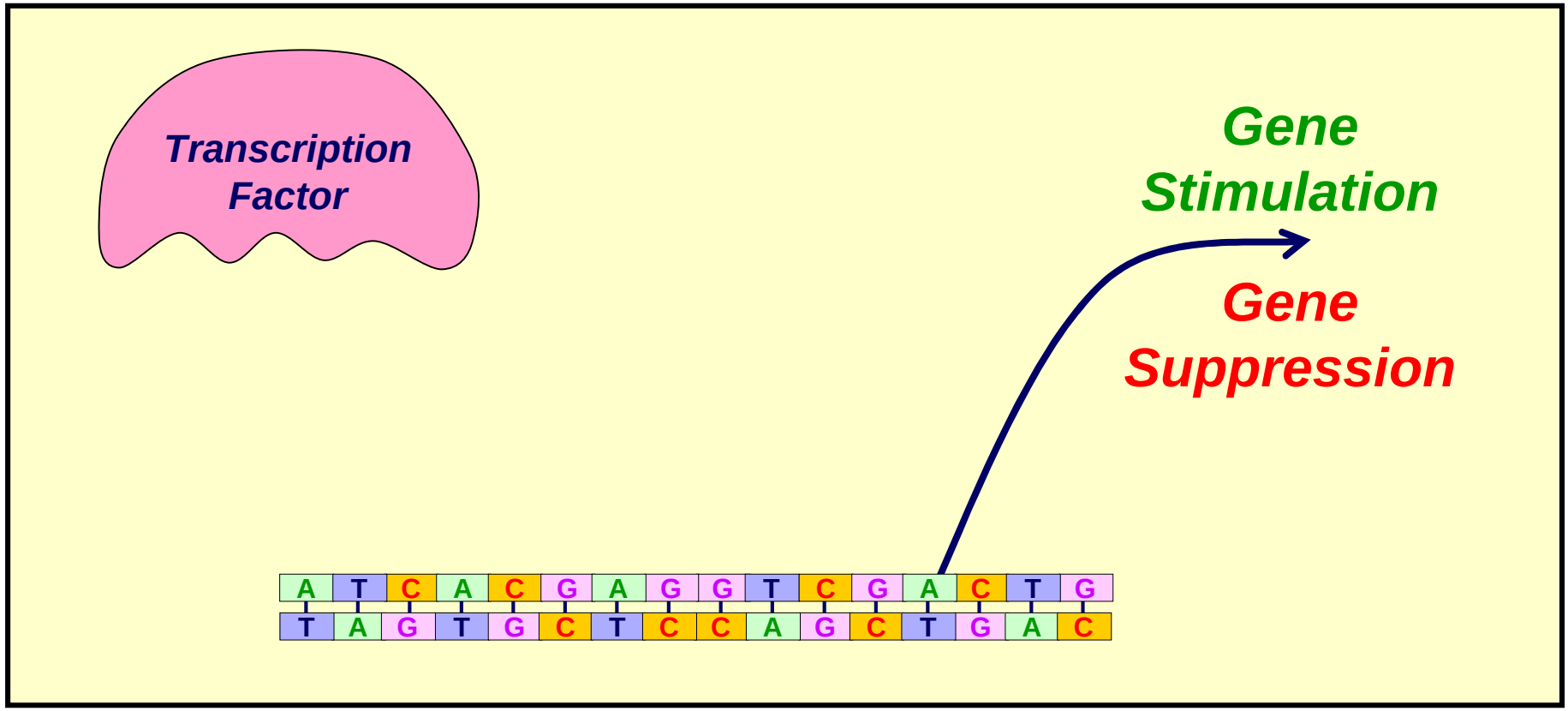


Most commonly regulated by direct methylation or by post-translational modifications of histones

Prescott SL & Clifton V (2009), Curr Opin Clin Immunol, 9. 417-425

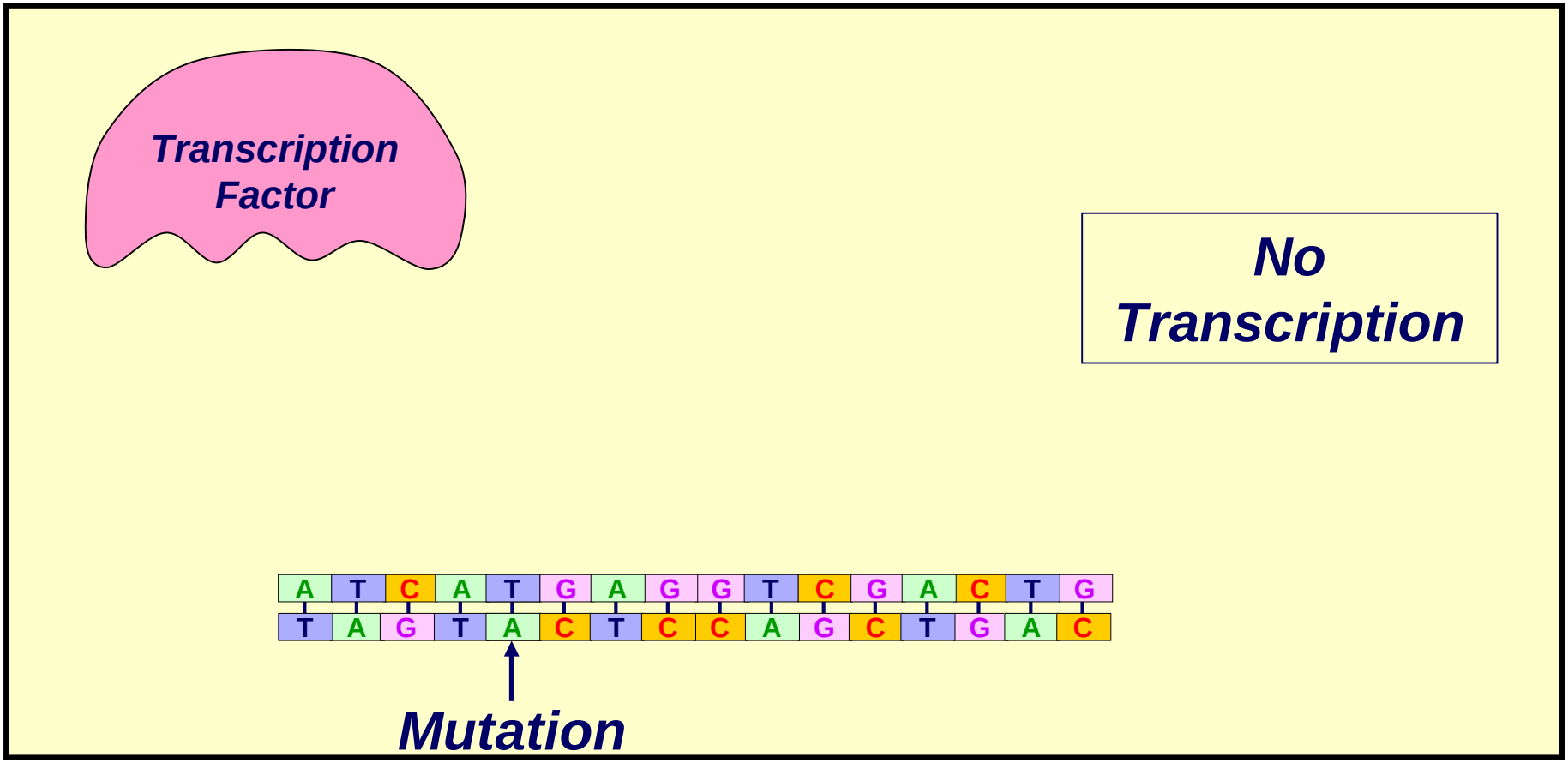
Normal Gene Transcription

Transcription factor binds to Cytosine residues in the DNA to stimulate or suppress transcription



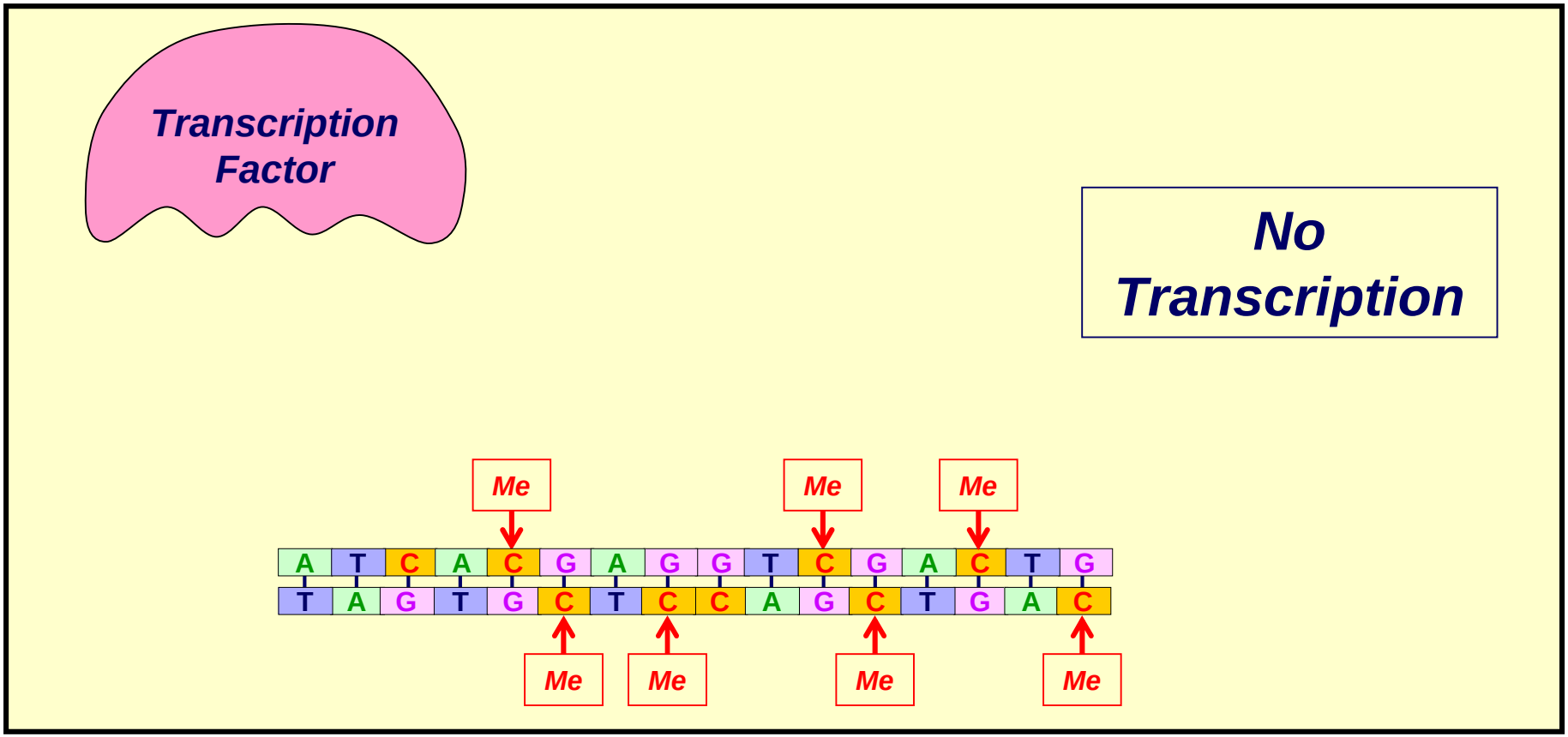
Gene Silencing – Mutation

A mutation of CG to TA prevents binding of the transcription factor to DNA and inhibits transcription



Gene Silencing – DNA Methylation

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



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]

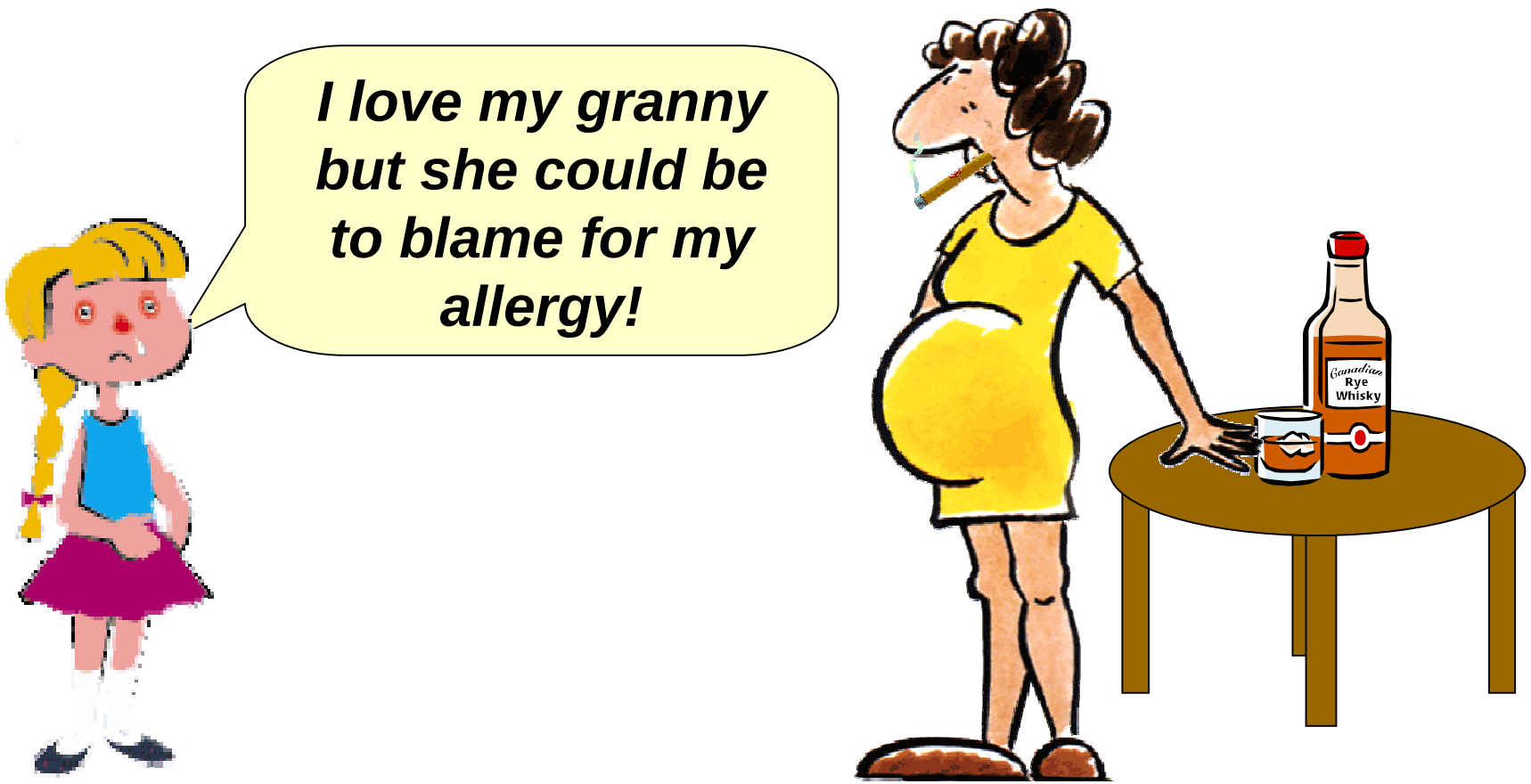
- may occur prenatally or neonatally and influence the phenotype throughout life span[1,4,5]

- 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]

1Roth et al (2009), *Biol Psychiatry*, *65*: 760-769
2 Ansel et al (2003), Nature Immunol, 4: 616-623
3 Li et al (2005), *Chest, 127*: 1232-`1241
[4]Prescott SL & Clifton V (2009), Curr OpinClin Immunol, 9, 417-26
[5]Breton et al (2009), Am J Crit Care Med, 180, 462-467

Epigenetics and Inheritance



Summary 1

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

Summary 2

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

Summary 3

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

Summary 4

In children with asthma,

high chronic stress associated with

- heightened production of TH2 cytokines
- higher eosinophil counts
- but has opposite effect in healthy children

Summary 5

UCL

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

Summary 6

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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