‘Origins’ (DOHaD)
Early life solutions to the modern health crisis

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Overview

• The NCD Pandemic
  - Shared risk factors with other NCDs
  - Need for an interdisciplinary approach

• Inflammation
  - As a common element of most NCDs
  - Evidence of early programming

• Early life factors that influence propensity for inflammation in later life:
  as strategies for disease prevention

The wider context:
the NCD pandemic

In the 20th Century: dramatic increase in life expectancy

Role of improved conditions in early life under-estimated

Early life conditions remain a significant factor in disparities in life expectancy

Major factor in ‘closing the gap’ of social disadvantage

The 21st Century: a new set of problems

New epidemics of ‘early’ onset NCDs

- Allergy and immune disease
- Childhood obesity and associated NCDs
- Mental ill-health; young people

Consequence of rapid environmental change on human health

Inflammation and immune dysregulation are major elements of these conditions

Disclosures

• President – DOHaD Society (ANZ)
• Chair - WUF in-FLAME network
• Director - World Allergy Organisation
• Co-Director ORIGINS Project
• Advisory Boards
  - NNI, Danone
  - Speakers fees (ALK Abello, NNI, Danone)
• Author: ‘Allergy Epidemic’, ‘The Calling’ and ‘Origins’

‘Getting the early life origins message out’

All author proceeds donated to research

Author: ‘Allergy Epidemic’, ‘The Calling’ and ‘Origins’

Inflammation and immune dysregulation are major elements of these conditions
While the world has focused on fighting infectious diseases…

...a pandemic of NCDs has been emerging, in all regions of the globe.

By 2030:
52 million deaths/yr from NCDs (surpassing infectious deaths, even in Africa)

Non-communicable diseases (NCDs):

Chronic inflammatory diseases of virtually all organ systems:
All dramatically increasing in modern societies

A significant component of NCD programmed early in life

Our children predicted to have shorter life expectancy....simply because of obesity and the NCDs that result

Inflammation and accelerated aging process
(oxidative stress, DNA and telomere damage)

Increases risk of all NCDs

A substantive element of risk programmed in very early life

Examples of diseases that are developmentally programmed

Food allergy, eczema
Allergic rhinitis
Obesity and metabolic disease (diabetes)
Autism, learning and behavioural disorders
Depression and anxiety
Infertility
Breast cancer
Cardiovascular disease
Cancer

Risk of later disease (NCDs)
(heart disease, obesity, dementia, diabetes, allergy, asthma)

The effects of the early exposures can last a lifetime

Early environment (diet, microbes, toxins, stress)

Early conditions influence the development and function of all organ systems with both early and latent long term effects

Inflammation and the modern world

The basis of 'DOHaD' a new health discipline
(Developmental Origins of Health and Disease)
Living in a ‘new age’ of chronic inflammation

Modern challenges
Human and environmental health

Inflammation implicated in virtually all NCDs

Characterised by immune dysregulation and low-grade systemic inflammation

A central role of the immune system

The immune system

Inflammation implicated in virtually all NCDs

Characterised by immune dysregulation and low-grade systemic inflammation

A central role of the immune system

Factors that influence early immune development, will influence susceptibility of many systems to NCDs

Many risk factors also modulate early immune gene expression to increase the risk of NCDs

The immune system influences development and function of many systems:

Influences the development and function of many systems

Local and systemic interplay between metabolism and immunity – begins in utero

Factors that influence early immune development, will influence susceptibility of many systems to NCDs

The nexus between metabolism and immune function occurs at many levels:

- Gut microbiota
- Nutrient sensing
- Hormonal interactions

‘The two faces of leptin’

(important for optimal metabolic and immune function)

No coincidence that we are increasingly prone to both immune diseases and obesity-associated NCDs

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Inflammation (elevated ‘CRP’) is a risk factor for many NCDs

Low grade inflammation ‘C-reactive protein’: Increases risk of CVD, diabetes and ‘all cause’ mortality

IL-6
TNF-α
IL-1β
CRP
Baseline CRP > 3 mg/L predicts risk of CVD

2. Pradhan et al., JAMA 2001; 286:327-34.

Low grade inflammation: ‘C-reactive protein’: Increases risk of CVD, diabetes and ‘all cause’ mortality

1. Around 1/3 of adults in high income countries have CRP >3mg/L

Inflammation and NCDs: Is this a cause or consequence?

Inflammation predates disease: evident in childhood

By 14 yrs:
Many Australian children have inflammatory markers* that predict cardiometabolic disease:

• Higher BP, waist circumference, dyslipidaemia, abnormal insulin,
• UFTs, inflammatory markers (recognised predictors of adult CVD)

Indicates initiating events occur very early in life


Maternal obesity

Pre-pregnant BMI predicts inflammatory NCDs in offspring:

• Higher CRP in offspring (12 years)
• Obesity, CVD, diabetes
• Autism, asthma and lung disease

Adding to the NCD burden of the next generation


Maternal obesity: Obesity, a chronic inflammatory state with effects on fetal programming

Higher pro-inflammatory mediators in the maternal circulation* and the placenta


Obesity: a chronic inflammatory state with effects on fetal programming

Early onset NCDs: evidence of very early immune dysregulation


Around 1/3 of adults in high income countries have CRP >3mg/L

Early life conditions affect baseline CRP as an adult (nutrition, poverty, stress, breastfeeding, pollutants, microbial exposure)
Allergic disease the most common NCDs of childhood

Immune diseases are ‘early onset’ NCDs

1. White Book on Allergy, 2011, WAO
2. Osburne et al. JACI 2011; 127: 668-678

Allergic disease the most common NCDs of childhood

Early onset: typically in 1st months of life

Food allergies and eczema
- >25% infants have eczema
- >30% infants have food allergy

Respiratory allergies
- >25% children have ‘asthma’
- >30% adults: history of hayfever

1. Osborne et al. JACI 2011; 127: 668-678
2. Osburne et al. JACI 2011; 127: 668-678

Increasing burden of eczema and food allergy

Earlier and more severe disease in infancy

Earlier vulnerability of the immune system to modern environmental changes

1. Mullins, MJA 2007; 186: 618 - 621 (Australian data)

More than 20% of Australian infants have food ‘sensitisation’

Melbourne study: 5000 infants attending 1yr health checks

Rate of ‘sensitisation’ (positive allergy tests):
- Children with allergic antibodies to foods

- egg: 16%
- peanut: 9%
- cows milk: 6%
- TOTAL: >20%

1. Mullins, MJA 2007; 186: 618 - 621 (Australian data)

Over 10% with challenge-proven clinical food allergy

All children with positive allergy test: food challenges

Reactions on challenge:
- (hives, swelling, noisy breathing, choking, vomiting, pallor, floppiness)

- egg: 9%
- peanut: 3%
- other: 2%
- TOTAL: >10%

1. Mullins, MJA 2007; 186: 618 - 621 (Australian data)

Over 10% with challenge-proven clinical food allergy

More than 1 in 10 of all 1 year olds in Australia have clinical food allergy
The significance of allergy should not be under-estimated

Very early measure of impact of modern environmental change
Specific vulnerability of the immune system
Early propensity for inflammation and immune dysregulation

Very early environmental effects on developing immune system

Presymptomatic differences in immune function at birth

Infants who go on to develop allergic disease in the first years of life:
Differences in immune function already evident in cord blood

Indicates the importance of in utero events in immune programming

Variation in immune function driven by non-heritable factors

In every category, non-heritable influences dominantly influence immune function
>80% of variance (in 58% measurements)
>50% of variance (in 77% measurements)

More variable with age, suggesting the cumulative influence of environment.

Heritability estimated in MZ and DZ Twins

Largely shaped by the environment (microbial and nutritional factors outweigh heritable influences)

Network interactions also driven by non-heritable influences

The environment: the main determinant of patterns of immune response

- All network hubs dominated by non-heritable influences
- Heritable factors are buffered by connected nonheritable ones

Heritability estimated in MZ and DZ Twins

The antenatal environment also important in subsequent pattern of immune response

Genetic predisposition plays a role in allergy risk
BUT
the early environment is driving allergic epidemic

The maternal environment is a major factor in variations in neonatal immune responses
A range of in utero exposures influence immune maturation

Maternal exposures shown to influence fetal immune development:

- Nutrition (PUFA), toxins and smoking, probiotics and microbial diversity
- Effects on cord blood immune responses

Implications for all developing organ systems

Many lifestyle risk factors for NCDs promote inflammation

Many have direct metabolic and immune effects

All of these factors have effects on the developing fetus

Early intervention for prevention: multisystem benefits

Need for a more integrated multi-disciplinary approach

- To move beyond medical 'specialty' silos
- More integrated approach:
  - to health and disease,
  - risk factors and solutions
- From the first moments of life

Strategies to promote early 'immune' and 'metabolic' health will have multisystem benefits

Common risk factors

For many modern diseases

- Microbial diversity
- Dietary profile
- Saturated fat
- Dietary fibre
- n3/n-6 PUFA
- Fresh foods
- Sunlight
- Stress
- Physical activity
- Pollutants
- Smoking
- Toxins & POPs
- EM radiation?

Means common solutions and interdisciplinary collaboration

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The role of early microbial diversity?
Declining biodiversity: Major implications for both environmental and human health

- Allergy, diabetes, obesity, mental health, and many other inflammatory diseases
- Loss of the macrobiome (flora and fauna)
- Impact on the microbiome (less 'visible', but just as significant for human health)

Microbiota: integral in homeostasis of multiple interconnected systems

Result of co-evolution and mutualism

Central role in evolution, development and function of these systems

A critical role in immune maturation

Normal colonisation and microbial exposure

Changing cytokine milieu with age (thymus & periphery)

Allergen

Th2 skewed responses (initial regulatory responses)

Th1/Th2 maturation (mature regulatory responses)

Variations and delay in maturation may predispose to Th2 responses

gene-environmental interactions

In utero microbial products protect against inflammation

Prenatal microbial exposure
- Prevents allergy/asthma in offspring
- Prevents preterm labour

Allergy protection mediated by epigenetic changes (histone deacetylation of IFN)

Germ free animals: abnormal immune development

With multisystem effects:
- Inflammation, allergy and auto-immune disease
- Abnormal stress responses
- Altered gene expression (BDNF) in the brain

Antibiotics, even in low doses:
- Affects behaviour and BDNF in the brain
- Increase weight gain, diabetes and heart disease
The effects of declining biodiversity begin in utero

Effects on immune and metabolic regulation

Obesity
Metabolic disease
Type 2 diabetes
Cardiovascular disease
Neurodevelopmental disorders
Allergic disease
Autoimmune diseases

Low grade systemic inflammation

Modern diet
Unhealthy high fat low fibre diet

Intestinal microbiota

‘Cleaner’ built environment

[antibiotics, lifestyle, agriculture, pollutants]

With multisystem effects – on all organ systems

Diet is a major determinant of our changing microbiome

Metabolic and immune effects

Fibre, fat, protein and micronutrients determine species relative abundance

May be more important than cleaner environment

Many effects of dietary patterns mediated through changes in the microbiome

Who is there is important, but what they are doing may matter more!

Increasing focus on the metabolic activity of the gut microbiome

Metabolic diversity may exist even microbial diversity

Diet contributes to both ‘who’ and ‘what’

Overwhelming evidence of positive health benefits high dietary fibre

...and emerging evidence that this may be mediated through the microbiome and associated SCFAs released fermentation processes

SCFA metabolites

From microbial digestion of dietary fibre

Dietary fibre and ingestible starch

Local and systemic anti-inflammatory effects

Metabolic and immune effects

Park et al. Arch Intern Med 2011; 171:1061-8

This may explain consistent protective effects:

Large studies show very clear health benefits of dietary fibre

n = 1,567,385

9 years follow-up (USA), 20,126 deaths in men, 11,310 deaths in women

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR (95% CI)</th>
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<tbody>
<tr>
<td>Dietary fibre (g/d)</td>
<td>0.79 (0.75 - 0.83)</td>
</tr>
<tr>
<td>Total death</td>
<td>0.79 (0.75 - 0.83)</td>
</tr>
<tr>
<td>Cancer death</td>
<td>0.80 (0.77 - 0.83)</td>
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<tr>
<td>Infectious disease death</td>
<td>0.83 (0.71 - 0.97)</td>
</tr>
<tr>
<td>Respiratory disease death</td>
<td>0.74 (0.62 - 0.88)</td>
</tr>
<tr>
<td>High fibre intakes (g)</td>
<td>0.79 (0.75 - 0.83)</td>
</tr>
<tr>
<td>Total death</td>
<td>0.81 (0.77 - 0.85)</td>
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Metabolites cross the placenta and into breast milk, to influence gene expression in offspring.

Diet and bacterial metabolites have multisystem effects. Effects in both mother and fetus.


The effects of the early exposures can last a lifetime.

Risk of later disease (NCDs) (heart disease, obesity, dementia, diabetes, allergy, asthma)

Early environment (diet, microbes, toxins, stress)

The impact of early immune dysregulation often overlooked

Influence development and function of all organ systems and risk of both early and late onset NCDs

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Health is a state of complete physical, mental, and social well-being. A NCD is a major cause of death, disability, and impaired quality of life.

The significance of allergy should not be under-estimated.

Major implications for rising risk many other inflammatory diseases (NCDs)

Specific vulnerability of the immune system

An early measure of broader impact of modern environmental change on our immune health

Promoting early ‘immune health’ is a vital part of preventing all inflammatory NCDs

We must target environmental factors driving inflammation

Many factors disturbing ancient host-environment equilibrium

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The solutions: in lie in redressing the balance for all aspects of human health and the natural environment

This will be the greatest challenge of the 21st century

The health of tomorrow depends on the choices we make together today

The health of tomorrow will depend on what we do today

Taking responsibility at every level

Many of today’s problems are the consequences of yesterday’s decisions

Advocates for the importance of early life

Need for long-range vision and long term commitments

Social, cultural and economic determinants of health

<table>
<thead>
<tr>
<th>Individuals</th>
<th>Society</th>
</tr>
</thead>
<tbody>
<tr>
<td>What we eat</td>
<td>Natural environment</td>
</tr>
<tr>
<td>Our physical activity</td>
<td>Built environment →</td>
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<tr>
<td>Social behaviour</td>
<td>Food, Water and Air quality</td>
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<tr>
<td>Stress</td>
<td></td>
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<tr>
<td>How we cope</td>
<td>Cultural systems</td>
</tr>
<tr>
<td>Substance abuse</td>
<td>Social structures →</td>
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<tr>
<td>Education Equity</td>
<td>Collective behaviour</td>
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</tbody>
</table>

We can’t prevent NCD without addressing the social, cultural and economic determinants of health

...and stop ‘blaming’ individuals

Individual choice → "taking responsibility" → Social structures and policies

"We believe fervently that improving nutrition for pregnant women and children under two is one of the smallest investments we or anyone can make." —September 30, 2012

Current decisions will impact the the many generations that follow

"Many of today’s problems are the consequences of yesterday’s decisions."
Our role: in biology and beyond

‘Humanity will rise or fall as one
We share the same origins
and the same destiny.
Our future depends on the choices
we make together today.

Our profession has an important role in influencing those choices
- Evidence
- Advocacy

We hope you will join us in the ‘long view’

The DOHaD Society of ANZ welcomes new members!

A healthy start to the human race

Timing is everything
A healthier start to life will mean a healthier future for individuals and our communities.

Where to get my books:

WEB orders http://uwap.uwa.edu.au
EMAIL to order marketing@uwa.edu.au

Getting the message out to the public domain

All author proceeds go to research