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# Pathways into Noncommunicable Diseases Start Early in Life

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## Epidemic of noncommunicable diseases

We are living in a time of unprecedented risk for noncommunicable diseases (NCDs), such as obesity, cardiovascular disease, diabetes, cancer and chronic pulmonary disease. In 2008, it was estimated by the World Health Organization that NCDs were responsible for 63% of deaths (57 million deaths) worldwide. In Australia and other developed countries, communicable (or infectious) diseases are no longer the primary cause of mortality. Instead, we are seeing unprecedented levels of NCDs. While a century ago, infectious diseases such as pneumonia, influenza, tuberculosis and gastrointestinal infection were the top causes of death in the United States (causing 53% of deaths), they only now account for 0.03% of deaths. In 2010, heart disease and cancer now account for the bulk of deaths, that is, 22.5% of deaths.[1] The patterns and figures are very similar in Australia. The current top five causes of mortality in Australia are heart disease, cancer, non-infectious airways disease, strokes and accidents.

While we may consider NCDs such as obesity, cardiovascular disease and diabetes are diseases of affluence and issues in first world countries, it is projected that in the next few decades these will dominate the health agendas in developing countries. For

example, in India, NCDs now account for 53% of deaths and are projected to increase.[2] In China, NCDs are estimated to account for over 80% of the disease burden with the leading causes of death and disability being stroke and cardiovascular disease.[3] NCDs are going to become increasingly important in populations experiencing urbanisation, demographic and socioeconomic transition. Across the entire globe, in both transitioning countries and Western countries, we are experiencing changes in environments, such as easy access to high energy foods, increasing sedentary lifestyles, decreased physical activity, cigarette smoking and alcohol consumption.

NCDs are being recognised as an urgent health priority. The United Nations has held only two meetings of heads of state on health-related issues, the first pertaining to HIV in 2001 and the second in 2011 to address NCDs.

## Children and NCDs

Children are at risk of NCDs. This was recognised by the World Health Organization at its May 2013 Geneva meeting, where it was stated at its assembly that 'children can die from treatable non communicable diseases, such as rheumatic heart disease, type 1 diabetes, asthma, and leukaemia, if health promotion, disease prevention, and comprehensive care are not provided' (Omnibus Resolution on NCDs, WHA 2013, page 8, para 2)

A great part of the risk for NCDs in children is due to marked increases in the proportions of children and young people being overweight and obese in our societies. Childhood obesity has risen two- to threefold in the last three decades, resulting in what some have called an epidemic. Currently, one in four Australian children are overweight or obese.[4] Obesity is directly causing NCDs in children and adolescents. In the Australian Raine Study (www.rainestudy.org.au), a longitudinal study of nearly 3,000 children followed from in utero to age 24–25 years, this risk is clearly observed, with 29% of 14-year-olds at high risk of future

cardiovascular and obesity related metabolic disease.[5] In another study of obese children in Western Australia, it was noted that 39% already had prediabetes, 32% had liver disease, 74% had elevated cholesterol and lipids, and the obese children suffered 18 times the rate of depression compared to their peers.[6] These and similar data show that children are not only starting to develop NCDs but are requiring treatment in childhood and adolescence.

## Overweight / obesity is central to a multiplicity of NCDs

Obesity has been estimated to cost the Australian purse in excess of $58 billion per year, attributable to both direct costs and loss of productivity. The reason for this considerable financial burden is that obesity is central to many NCDs that are reaching epidemic proportions (such as diabetes, heart disease and cancers). Being overweight in childhood leads directly to a myriad of diseases affecting many organs in the body, including the pancreas (related to diabetes), heart and blood vessels, lungs (related to obstructive sleep apnoea), joint problems and liver (related to fatty liver disease), as well as psychosocial disorders (poor self-esteem, depression and poor quality of life) and neurological conditions such as pseudotumor and a higher risk for stroke.

## Pathways into NCDs

While we often consider that diseases such as diabetes, heart disease, strokes and heart attacks are diseases of adulthood, it is clear that the development of these diseases starts in childhood, and even earlier, in the womb. As a pertinent illustration, we know that the first seeds for heart attacks and stroke begin in young life. Heart attacks and strokes are the result of thickening and development of plaques on blood vessels, also known as atherosclerosis. Evidence of atherosclerosis has been seen in young men who have died prematurely during war and in accidents.[7] This means that this first signs of atherosclerosis (which will ultimately lead to heart attacks and strokes) is present in apparently healthy young men.

Tracing this back even earlier in life, we see that the first signs of atherosclerosis may start even earlier, in childhood. Studies that use an ultrasound technique called aortic or carotid intima medial thickness (IMT) measure the thickness of the blood vessel wall. Using aortic IMT, scientists are showing that there are signs of atherosclerosis or thickened blood vessels in children and babies with high cholesterol and diabetes.[8] Interestingly, overweight[9] and weight gain from birth up to 18 months of age were associated with thickening of blood vessels in children.[10] Therefore, we are detecting subtle evidence that blood vessels of children are starting to thicken in response to known cardiovascular risk factors such as elevated cholesterol.

In fact, the first seeds of obesity and related NCDs starts even earlier in life, in the womb. It was observed by Professor Barker in the Hertfordshire population in the United Kingdom born in the 1920s that low birth weight was associated with increased risk of death due to heart disease.[11] Birth weight, in this case, is an indicator of growth and health of the baby while in the womb. Therefore, it seemed that your risk of dying from heart disease was being determined to some extent by factors in the womb. These observations were repeated in other populations around the world. For example, in Western Australia, the same Raine study mentioned earlier, which recruited pregnant women in 1989–1991, has followed up the children up to current times. By doing so, it was also observed that low birth weight babies went on to have higher risk of obesity and related prediabetes risk.[12]

Of relevance to the Australian population and other modern day populations, it is not only the low birth weight babies, but those who were also of high birth weight who subsequently have a higher obesity and prediabetes risk. The optimal birthweight for babies falls in the percentage of expected birth weight (PEBW) range 98–104. Those in the lowest quintile and highest two quintiles had a significantly higher cardiometabolic risk. In any case, the relationships that have been repeatedly observed between

birth size and later obesity and diabetes risk suggest that environmental conditions of the baby, prior to birth (in the womb) plays a role in 'programming' later life risk. This has led to a rapidly expanding international field of research now referred to Developmental Origins of Health and Disease (DOHaD).

## Environmental factors in the womb

What are these environmental factors that seem to be 'programming' later life risk? They are many and varied. Some we know and have heard a lot about, such as diet and smoking during pregnancy. Others are perhaps less well known and understood, such as maternal stress and exposure to toxins and pollution. And obviously, genetic risks are likely to be important as well — genes that influence fetal growth, being overweight and influencing the risk of developing heart disease or diabetes. But genetic risks need environments to switch them on (see comments below).

Maternal diet is likely to have some effect on the developing baby in terms of future risk for NCDs. This can clearly be demonstrated in animal experiments, which test two groups of animals, one with a 'normal diet' and another with an altered diet. These experiments show that animals (usually mice) with the altered diet during pregnancy have babies with a different risk for obesity, diabetes and growth compared to the group with the 'normal' diet.

In humans, this effect has been observed in special historical and geographical cases. One example is the Dutch Hunger Winter, which occurred at the end of World War II. In the winter and spring of 1944, the German occupation limited rations such that acute starvation occurred in parts of the Netherlands. The timing of the limited rations was very accurately defined in relation to the stages of pregnancy. Women who were pregnant during this time have had offspring who have subsequently gone on to greater rates of obesity, hypertension and diabetes as adults.[13,14]

There is other indirect evidence in humans that maternal diet affects the risk of NCDs developing in the offspring. On the other end of the spectrum, maternal obesity and excessive weight gain is associated in many populations with increased risk of obesity in the offspring. It is difficult in observational studies of humans to determine how much of this is due to shared environment (diet and lifestyle factors), shared genetics and direct DOHaD 'programming' effects that occur during pregnancy.

Maternal smoking during pregnancy is also likely to have some effects upon risk for NCDs in the offspring. Indirect evidence of this has been seen in humans. In an Australian longitudinal study, maternal smoking during pregnancy increased the risk of cardiometabolic risk for a child at age 8 years, with an odds ratio of 1.82.[15]

Maternal stress and anxiety/depression in pregnancy can also have marked effects on the child, probably due to interactions between cortisol and the social and emotional environments controlled by a depressed mother/parents.[16] While this is important, and parental mental health problems are increasing,[17] this is a huge area of research and will not be covered further here. Suffice to say that parental mental health problems do influence NCDs in their children.

## Environmental factors in childhood predispose to adult obesity and cardiovascular disease

The first 1,000 days of life (from a woman's pregnancy to a child's second birthday) have been identified as a critical time when environment, especially diet, can affect a child's future health. This was recognised in 2010 with the launch of the 1,000 Days Partnership (www.thousanddays.org) in September 2010 by the U.S. Secretary of State Hillary Clinton and other global leaders. How rapidly you grow in the first two years of life has been associated in some studies with future risk for cardiovascular disease. Many studies have observed that infants who gain excessive

amounts of weight in the first 6 to 12 months, up to 2 years of age are at increased risk of subsequent childhood obesity and related metabolic disease.[18,19] In Australian children, we see that trajectories of rapid weight gain are associated with higher fasting insulin and blood pressure levels in adolescents.[20] Children with stable-to-high, rising-to-high, and rising-to-moderate trajectories accelerate in fatness in early childhood and concurrently have higher levels of blood pressure and insulin (a sentinel of type 2 diabetes risk).

Infant feeding practices will affect the velocity of early infant weight gain. Breast feeding has been observed to protect against later obesity, compared to formula feeding. Australian statistics show that breast feeding for more than 4 months protected the children from obesity-related metabolic risk at 8 years of age.[21] A European group undertook a randomised controlled trial to test breastfeeding with low versus high protein infant formulae. This study showed that the breastfed and low protein formula-fed babies had a lower body mass index and body weight during childhood compared to the high protein formula fed babies.[22] The recommendations regarding infant feeding is that breast-feeding is ideal for up to 6 months of life in terms of prevention of adverse growth trajectories (and other outcomes as well). Breast-feeding is, however, not always possible or practical, so nutrition companies need to optimise the amount of protein and other nutrients in their baby formulae.

By middle childhood, the trajectory for noncommunicable disease is becoming established. It has been observed in many studies that risk factors for cardiovascular disease are stable and track from middle childhood into adult life.[23,24,25] Factors such as childhood obesity, elevated cholesterol and lipids in the blood and prediabetes are a harbinger for these same issues in adult life. Therefore, minimising these risks needs to begin as early as possible. While it is still beneficial to manage these risk factors in adult life, it is in a sense intervening after the horse has bolted. Modifying lifestyle (diet, physical activity, time spent on comput-

ers and in front of the television) ideally should begin in childhood to have greater effect. In Australia and in other developed countries with colonised indigenous populations who are more recently hunter-gatherers, these risks (and intergenerational risks) are much higher. Thus, we see much higher rates of both poor lifestyles, early risk factors for NCDs and rates of NCDs in Aboriginal and Torres Strait Islander populations in Australia than in the non-Aboriginal populations.[26,27] NCDs are the main reason for the gap between Aboriginal and non-Aboriginal life expectancy in Australia.

Achieving a healthier lifestyle in our children, compared with what is currently practiced across much of Australian society, is clearly beneficial. The reality is that changing habits that are entrenched in our societal norms is difficult. It is clear that preventing children from becoming overweight and obese must be the major aim as reviews of studies show that only a modest effect is achievable in treating children and youth once they are overweight.[28] Achieving meaningful changes in childhood lifestyle will require a concerted effort on the part of local, state and federal governments, dialogue with food companies, urban planners, public health physicians, the medical profession and schools. It will need systemic changes in community attitudes. It cannot rely simply on the willpower of the individual child or adult. There needs to be awareness that the childhood obesity epidemic is being driven by powerful and subtle forces pushing the entire population towards increasing obesity.

## Epigenetics

Epigenetics can be defined as the study of changes in our DNA that can be inherited but occur without altering the genetic code. It can be imagined as akin to the punctuation within a text, which gives meaning. Without changing the actual words in a sentence, the punctuation can change the meaning of a sentence dramatically. For example the comma in the sentence, ‘Let’s eat,

Grandmother' can greatly alter the meaning to the more macabre 'Let's eat Grandmother'.

DNA is made up of base pairs (called cytosine, guanine, adenine and thymine) that appear in a particular order. What is increasingly being understood is that there are ways to change the shape or conformation of DNA without changing the actual code. This leads to the DNA being more open or closed at a particular point. Being more open allows more protein to be expressed or produced from that part of the DNA. Therefore, without changing the code and order of the base pairs, different effects (or phenotype) can be seen. This is what is referred to as epigenetics and is a very exciting new area of medical research of particular relevance to NCDs. To illustrate this, think of cells from your eye, your hair, your heart. They all have exactly the same genetic code, but are manifestly different in appearance and function.

Epigenetics can be modified by environmental influences, particularly in early life. An example from nature is that of the honey bee. If a larval bee is bathed and fed royal jelly it will develop into a queen bee, which is fertile and 2.5 times larger than a worker and lives a staggering 200 times longer. If precisely this same bee is not exposed to royal jelly, it will develop into a worker bee with none of these attributes. Therefore, while both the worker bee and queen bee have the same DNA code, their early environment exposure alters both their epigenetic profile and adult appearance.

In a similar manner, in humans, epigenetics may mediate the effects that are established within the womb. For example, it has been observed that individuals whose mothers were exposed to the Dutch Hunger Winter when pregnant had altered epigenetic marks as adults around the age of 60 years.[29] At the same time these individuals were also at increased risk of obesity.

A second example of altered epigenetics according to diet in pregnancy in humans has been observed in Gambia. In Gambia there is a very strong seasonal variation in dietary availability. This

seasonal variability has been exploited by scientists to observe if there are differences in epigenetic profiles between those who are in the womb during the season of plenty and those in the womb during the time of relative scarcity.[30] Indeed, this appears to be the case.

This area of research is still in its infancy. In part, many of the future discoveries in this field will be facilitated by our increasing ability to analyse large datasets through supercomputers and bioinformatics. Technology is allowing us to perform studies of thousands (potentially millions) of sites across the whole genome to look for changes in both the genetics and epigenetics of our DNA.

## Pathways into NCDs might start from exposures in your grandparents

In fact, the first seeds of predisposition to NCDs may begin even earlier than in the womb. There are early suggestions, that a grandparent's exposures could affect his or her grandchild. There are two ways that this could happen. First, the egg that eventually is fertilised to produce you is actually present in your mother when she is a foetus inside her mother or your grandmother. Therefore, exposures that occur when your grandmother is pregnant with your mother might affect you. Another way that this might occur is through direct inheritance of epigenetic changes. These ideas are still open to debate, and there is currently insufficient evidence to conclude to what extent and how this occurs in humans.

In studies of mice, however, there is emerging evidence that direct inheritance of epigenetic changes can occur. In these studies, two groups of animals are compared. In one group a change is made to the diet of the pregnant mother and then several generations of mice are followed up, without further changes in subsequent generations. These mice are compared to the other group where no changes are made to the diet at any point. The mice three to four generations down the line are showing persist-

ent epigenetic changes following a dietary modification only in the first generation.

## What can we do about diabetes and cardiovascular disease?

Certainly, there are both lifestyle and medical treatments for diabetes and cardiovascular disease. There are medical and some surgical treatments that can be administered once the disease is established.

Arguably, more attention should be given to preventing these and other NCDs from occurring in the first place. By identifying early drivers of obesity that occur to the baby in the womb and in the early years of life ('the First 1,000 Days'), it may be possible to prevent obesity and related diseases. Therefore there may be opportunities to prevent these diseases in the children of the next generation. To achieve this will require concerted efforts on the part of governments, food and baby formulae companies, urban planners, the education department, medical fraternity and public health advocates.

## Endnotes

1 DJ Hunter and KS Reddy, 'Noncommunicable diseases', *New England Journal of Medicine*, vol. 369, no. 14, pp. 1336–1343, 2013.

2 K. Sharma, 'Burden of non communicable diseases in India: setting priority for action', *International Journal of Medical Science and Public Health*, vol. 2, no. 1, pp. 7–11, 2013.

3 G Yang et al., 'Rapid health transition in China, 1990-2010: findings from the Global Burden of Disease Study 2010', *Lancet*, vol. 381, no. 9882, pp. 1987–2015, 2013.

4 Australian Bureau of Statistics (ABS), 'Australian Health Survey: updated results, 2011–2012', 2013.

5 RC Huang et al., 'Synergy between adiposity, insulin resistance, metabolic risk factors, and inflammation in adolescents', *Diabetes Care*, vol. 32, no. 4, pp. 695–701, 2009.

6 LM Bell et al., 'High incidence of obesity co-morbidities in young children: a cross-sectional study', *Journal of Paediatrics and Child Health*, vol. 47, no. 12, pp. 911–917, 2011.

7 HC McGill, 'Relationship of atherosclerosis in young men to serum-lipoprotein cholesterol concentrations and smoking — a preliminary report from the pathobiological determinants of atherosclerosis in youth (PDay) research group', *Journal of the American Medical Association*, vol. 264, no. 23, pp. 3018–3024, 1990.

8 MJ Jarvisalo et al., 'Increased aortic intima-media thickness: a marker of preclinical atherosclerosis in high-risk children', *Circulation*, vol. 104, no. 24, pp. 2943–2947, 2001.

9 KS Woo et al., 'Overweight in children is associated with arterial endothelial dysfunction and intima-media thickening', *International Journal of Obesity and Related Metabolic Disorders*, vol. 28, no. 7, pp. 852–857, 2004.

10 MR Skilton et al., 'Weight gain in infancy and vascular risk factors in later childhood', *Pediatrics*, vol. 131, no. 6, pp. e1821–1828, 2013.

11 DJ Barker et al., 'Fetal nutrition and cardiovascular disease in adult life', *Lancet*, vol. 341, no. 8850, pp. 938–941, 1993.

12 RC Huang et al., 'Perinatal and childhood origins of cardiovascular disease', *International Journal of Obesity* (London), vol. 31, no. 2, pp. 236–244, 2007.

13 ACJ Ravelli et al., 'Obesity at the age of 50 y in men and women exposed to famine prenatally', *American Journal of Clinical Nutrition*, vol. 70, no. 5, pp. 811–816, 1999.

14 TJ Roseboom et al., 'Blood pressure in adults after prenatal exposure to famine', *Journal of Hypertension*, vol. 17, no. 3, pp. 325–330, 1999.

15 Huang et al., see note 12.

16 BR Van den Bergh et al., 'Antenatal maternal anxiety is related to HPA-axis dysregulation and self-reported depressive symptoms in adolescence: a prospective study on the fetal origins of depressed mood', *Neuropsychopharmacology*, vol. 33, no. 3, pp. 536–545, 2008.

17 M O'Donnell et al., 'Western Australian emergency department presentations related to child maltreatment and intentional injury: population level study utilising linked health and child protection data', *Journal of Paediatrics and Child Health*, vol. 48, no. 1, pp. 57–65, 2012.

18 KKL Ong et al., 'Association between postnatal catch-up growth and obesity in childhood: prospective cohort study', *British Medical Journal*, vol. 320, no. 7240, pp. 967–971, 2000.

19 N Stettler et al., 'Infant weight gain and childhood overweight status in a multicenter, cohort study', *Pediatrics*, vol. 109, no. 2, pp. 194–199, 2002.

20 RC Huang et al., 'Lifecourse childhood adiposity trajectories associated with adolescent insulin resistance', *Diabetes Care*, vol. 34, no. 4, pp. 1019–1025, 2011.

21 Ibid.

22 B Koletzko et al., 'Can infant feeding choices modulate later obesity risk?', *American Journal of Clinical Nutrition*, vol. 89, no. 5, pp. 1502S–1508S, 2009.

23 W Bao et al., 'Persistence of multiple cardiovascular risk clustering related to syndrome X from childhood to young adulthood. The Bogalusa Heart Study', *Archives of Internal Medicine*, vol. 154, no. 16, pp. 1842–1847, 1994.

24 DS Freedman et al., 'Relationship of childhood obesity to coronary heart disease risk factors in adulthood: the Bogalusa Heart Study', *Pediatrics*, vol. 108, no. 3, pp. 712–718, 2001.

25 LS Webber et al., 'Tracking of serum lipids and lipoproteins from childhood to adulthood. The Bogalusa Heart Study', *American Journal of Epidemiology*, vol. 133, no. 9, pp. 884–899, 1991.

26 K Odea et al., 'Obesity, diabetes and hyperlipidemia in a central Australian Aboriginal community with a long history of acculturation', *Diabetes Care*, vol. 16, no. 7, pp. 1004–1010, 1993.

27 Retrieved 26 June 2015 from http://www.aihw.gov.au/australias-health/2014/indigenous-health/

28 HO Luttikhuis et al., 'Interventions for treating obesity in children', *Sao Paulo Medical Journal*, vol. 127, no. 5, p. 321, 2009.

29 BT Heijmans et al., 'Persistent epigenetic differences associated with prenatal exposure to famine in humans', *PNAS*, vol. 105, no. 44, pp. 17046–17049, 2008.

30 P Dominguez-Salas et al., 'Maternal nutrition at conception modulates DNA methylation of human metastable epialleles', *Nature Communications*, vol. 5, p. 3746, 2014.