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REVIEW

Early life nutrition and the opportunity to influence long-term health: an Australasian perspective

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There are now significant data to support the hypothesis that early life nutrition in the fetus, infant and young child can have profound effects on long-term health. This review considers some of this evidence with specific reference to the current burden of disease in Australia and New Zealand. As the findings of further research become available, recommendations on optimizing early life nutrition should be formulated and made widely available as part of the preventative health policy agenda in both Australia and New Zealand.

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A growing body of evidence now links nutrition in early life to an increased risk of disease in adulthood, and the rapid increase in the prevalence of metabolic and allergic disease across the globe. Australia and New Zealand have not been immune to this major health problem.

The risk of developing metabolic and allergic disease is influenced by a range of factors across each individual's lifespan. Environmental exposures during fetal development and infancy are now considered responsible for a significant part of lifetime disease risk, as they can have long-term effects on both health and disease.

Critical time periods have been identified, both before conception and during fetal and postnatal development, where exposure to environmental factors, including altered nutrition, can cause adaptations to occur in the growing fetus and infant.[1,2] Although these effects may be adaptive in the short term, they may also be associated with adverse outcomes in childhood and later life, including a greater risk of obesity,[3] type 2 diabetes, heart disease[4–7] and allergy.[8]

Significant contributions to this literature have been made by a number of long-term studies such as the British-based Avon Longitudinal Study of Parents and Children[9,10] and the Dutch-based Generation R Study.[11,12]

Maternal and paternal nutrition may be important determinants of pregnancy outcomes and the longer term health of the offspring. Furthermore, these effects can be transmitted to subsequent generations, thus perpetuating a cycle of metabolic disorders. Identifying vulnerable periods in fetal and postnatal development provides an important opportunity for parents and healthcare professionals to intervene and optimize future health outcomes.

Nutrition is one of the most easily modifiable environmental factors during early life. It has been shown to influence both fetal and postnatal growth and development,[13] and the risk of metabolic and allergic disease in childhood and adult life.[3–8]

This review provides an overview of the importance of early life nutrition, focussing on the situation in Australia and New Zealand.

Impact of maternal and paternal nutrition before conception

It is well accepted that the health of a woman before conception has a significant impact on pregnancy outcomes and thus a lifelong impact on her child's health.[14] Obesity reduces fertility and affects the health of the human oocyte.[15] Overweight and obesity in women during their reproductive years is of increasing concern. In Australia, over 12 million men and women (~60%) are overweight or obese with that figure having increased by 5% since 1995. Over 30% more people living in outer regional and remote areas are obese than people living in major cities.[16] In New Zealand, there has been an increase in obesity in men from 17% in 1997 to 30% in 2013 and an increase in women from 21 to 32% over the same time period;

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a further 34% of adults are overweight. There are also marked ethnic disparities with adult obesity rates of 48 and 68% for Maori and Pacific Islanders, respectively.[17]

Women who are obese before becoming pregnant are also more likely to develop gestational diabetes (GDM) when pregnant, which in turn increases the risk of diabetes and overweight in the offspring.[18]

Increased paternal body mass index (BMI) has also been linked to impaired embryo and fetal development, as well as reduced pregnancy rates and pregnancy loss.[19–22] Conversely, paternal exposure to famine or undernutrition has been associated with a higher BMI in offspring compared with the offspring of fathers who were not exposed to famine.[23] An animal study involving male rats fed long-term, high-fat diets found that glucose intolerance and impaired insulin secretion developed in their adult female offspring.[24] These associations between paternal nutrition and health outcomes in the offspring appear to reflect epigenetic changes in the sperm in response to altered nutrition.[25]

Nutrition during pregnancy

Maternal undernutrition increases metabolic risk in offspring

The Dutch famine provided one of the first insights into the importance of maternal undernutrition and the development of disease in offspring in later life.[4–6,26] In the Netherlands, there were serious food shortages and a major reduction in daily food intake over a 7-month period during the winter of 1944–1945. Official daily rations for the general adult population fell to between 400 and 800 calories a day. This calorie restriction had a significant impact on the offspring of women who were pregnant at the time, and of note is that the effects differed according to the timing in gestation of the exposure to the famine.

Children born to women exposed to the famine early in the gestation period have been shown to have a significantly greater risk of obesity, heart disease, type 2 diabetes and renal dysfunction 40–50 years later.[4–6,26,27] These effects were also transmitted to the second generation.[28] This suggests that in the face of energy restriction the fetus becomes conditioned to become highly energy efficient, known as a predictive adaptive response.[29] A child born into a world where food is plentiful, they tend to consume excessive energy because the hunger/satiety set-points have been altered during development, possibly via epigenetic mechanisms.[30]

Maternal obesity, excessive gestational weight gain (GWG), diabetes and stress during pregnancy increase the risk of obesity in the offspring

Several other environmental circumstances have been found to drive obesity in the offspring. These primarily define the 'set-points' or sensitivity for obesity and associated risk factors, for example, hunger and satiety, adipose tissue development and metabolism.[31–33]

Table 1. *Recommended weight gain during pregnancy*[37]

Pre-pregnancy body mass index	Recommended total weight gain
<18.5 kg/m^2	12.5–18 kg
18.5–24.9 kg/m^2	11.5–16 kg
25–29.9 kg/m^2	7–11.5 kg
>30 kg/m^2	5–9 kg

Maternal obesity

A 2015 study from Auckland showed that the risk of having an obese mother was double in Maori and Pacific infants compared with New Zealand European infants (OR 2.23 95% CI 1.23–4.04).[34] Overweight or obese mothers are significantly more likely to have overweight children, with evidence showing that a woman's BMI at the start of pregnancy is a strong predictor of her offspring's risk for obesity in adult life.[35] In addition, maternal obesity often precedes GDM.[35] A systematic review found that maternal pre-pregnancy BMI is directly associated with the risk of developing GDM.[18]

Excess GWG

A recently published Australian study[36] reported that in a cohort of over 2000 women 42% had a GWG above international guidelines,[37] figures similar to previously published smaller studies. In one such study, 38% of Australian women gained more weight during their pregnancy than recommended[38] and in another, 54% of Australian women gained more than recommended (see Table 1).[39]

Recent data from New Zealand are more disturbing still. Over 74% of women in a multicentre study that included Auckland gained more weight during pregnancy than recommended in the international guidelines. Further, 70% of New Zealand woman surveyed were unaware of how much weight gain was appropriate during pregnancy.[40] Clearly excessive GWG is an important issue to address in Australasia.

The Southampton Women's Survey found that children born to mothers who gained excessive weight during pregnancy had a greater fat mass at birth and at 6 years than children whose mothers' GWG was within the recommended range.[41] This study also reported that excessive weight gain in pregnancy was common, and most marked in women who were overweight or obese before becoming pregnant.

The timing of excess weight gain in pregnancy can also affect the health of the offspring. Davenport *et al.*[42] reported that women following guidelines for healthy living during pregnancy who gained excessive weight during the first half of pregnancy had offspring with a greater heel-crown length, higher birth weight and higher body fat at birth than women who did not gain excessive weight during this time (including those who gained excessive weight during the second half of pregnancy). Excessive weight during the first half of pregnancy was found to be a stronger predictor of excessive body fat in the offspring at birth than total excessive maternal weight gain.[42]

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Maternal diabetes

Gestational or maternal diabetes mellitus in Australasia is of significant concern. In Australia, analysis of the Midwives Perinatal Data Collection from 2000 to 2009 in over 120,000 indigenous women and nearly 3.5 million non-indigenous women showed a crude prevalence of 5.1 and 4.5%, respectively, a small but highly significant difference ($P < 0.0001$). Moreover, in older (35+ years) indigenous women the crude prevalence of GDM was about 14%.[43] Prevalence rates in New Zealand are also around 5% but appear to have risen from around 3% between 2008 and 2012.[44]

Maternal GDM has been shown to result in a number of both short- and long-term complications in offspring,[45] including a greater BMI at 18 years of age.[46] Recent work by Leng *et al.*[47] examined the association between pre-pregnancy BMI, GWG and anthropometry in the offspring of mothers with GDM. Offspring born to GDM mothers with pre-pregnant overweight or obesity or excessive GWG were associated with increased risks of large for gestational age and macrosomia at birth, and childhood overweight at 1–5 years old, compared with those born to GDM mothers with pre-pregnancy normal weight and adequate GWG.

In addition, animal studies have shown that macrosomic offspring of diabetic mothers exhibit many disorders associated with the metabolic syndrome.[48,49]

Maternal stress

A study involving Danish army recruits found that those recruits born to mothers bereaved during pregnancy had an overall higher risk of overweight in early adult life than those whose mothers did not. There was also an increased risk of overweight when the mother was bereaved in the 6 months before conception.[50]

The mechanisms that link maternal obesity, excessive GWG, diabetes and stress during pregnancy to later disease risk in the offspring involve a range of factors. These include epigenetic changes that reset fetal energy metabolism, appetite and adipose tissue development, an abnormal intrauterine environment and poor or restricted placental development.[51,52] These factors, although currently largely associative in nature, may subsequently provide a causal link to the likelihood of developing obesity later in life,[50] with the effects of a sedentary lifestyle and modern energy-dense diets exacerbating these effects in affected offspring.

Birth weight is associated with later disease risk

There are clear links between birth weight and subsequent disease risk. While not a causal factor, many studies use birth weight as a proxy measure or clinical marker of the impact of developmental factors on later disease risk. Both low and high birth weights have been associated with an increased risk of childhood and adult obesity, as well as heart disease, stroke and type 2 diabetes later in life.[31,53–57]

The United States Nurses' Health Study involving more than 70,000 women found that in full-term offspring an increased risk of hypertension was associated with low birth weight, whereas an increased risk of obesity was associated with high birth weight.[58] In birth cohorts from Finland, mortality from stroke and heart disease was greater in people born at a low birth weight.[56,57] A British study involving more than 15,000 people found that death rates from heart disease fell with increasing birth weight.[53,59]

Although overweight and obesity, excessive GWG and GDM are all associated with large for gestational age infants,[35] maternal obesity can also lead to low birth weight infants. A New Zealand retrospective analysis of more than 26,000 pregnancies found that maternal obesity was an independent risk factor for small-for-gestational age infants.[60] Several mechanisms may account for these counter intuitive findings, including a reduced likelihood that intrauterine growth restriction is detected and acted upon in obese mothers.[52] Further, animal studies suggest that a maternal high-fat diet may lead to fetal growth restriction due to placental insufficiency and reduced nutrient transport.[61]

Influence of maternal macronutrient intake on appetite and food preferences in the offspring

Programming of appetite and food preferences may occur during fetal development. A study comparing maternal nutrient intake of protein, fat and carbohydrate during pregnancy with the maternal, paternal and child dietary intake of the same nutrients following birth found that the maternal diet during pregnancy was most strongly associated with later childhood intake (assessed at 10 years of age) of the same nutrients, particularly protein and fat. This association was greater than those observed for postnatal paternal and maternal intake, suggesting that some programming of appetite in the offspring may occur during fetal development.[62]

Maternal carbohydrate intake has also been associated with alterations in epigenetic markers at birth and later childhood.[51]

A study involving the Dutch famine cohort found that the offspring of mothers exposed to famine in early gestation were twice as likely to consume a high-fat diet in later life.[63] Experimental models have also shown that alterations in the maternal nutritional environment can programme altered appetite and food preferences in offspring.[64] For example, a reduction in maternal protein intake can result in a preference for high-fat foods in offspring[65] and maternal undernutrition can lead to persistent hyperphagia in offspring in later life.[66]

Early life nutrition affects the developing immune system and risk of allergic disease

Early life nutrition has a substantial impact on the developing immune system, which is highly sensitive to environmental changes. Although many immune system disorders are inherited, genetic factors alone cannot explain the dramatic rise in many

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immune diseases in recent years. For example, Australia has one of the highest rates of food allergy in the world[67] and there have been reports that there has been a 10-fold increase in specialist referrals for food allergy and a five-fold increase hospitalization for food-related anaphylaxis in recent years.[68]

Surprisingly, there are few if any good data on the prevalence of food allergy in New Zealand. It has been suggested, however, that based on the similar rates of asthma in New Zealand, Australia, the United Kingdom and the United States that the prevalence of food allergy might also be similar to that in Australia.[69] These changes, particularly the rise in food allergy, highlight the vulnerability of the developing immune system to early environmental exposure.[12,13]

Allergic disease may be manifest very early in life, often in the first few months after birth. There are demonstrated differences in the immune function of newborns that develop allergic disease compared with those who do not, suggesting that alterations in immune system function begin during fetal development.[8,70,71] A range of environmental cues have been shown to influence immune development and function, including maternal nutrition, microbial burden and pollutants such as cigarette smoke.

In addition, the rising rates of maternal allergy – itself a risk factor for the development of allergic disease in the offspring – may further amplify the effects of environmental exposures on the developing immune system.[8] Women with a history of allergy appear to have altered immune interactions with their fetus, so that the fetal immune response to environmental cues may be modified.[8] In addition, maternal allergy is a stronger predictor of allergic risk in offspring than paternal allergy.[8]

Some maternal nutritional changes have been associated with altered immune programming. These include a reduced intake of omega 3 polyunsaturated fatty acids, folate and zinc.[13] The recently released Australian Bureau of Statistics/Food Standards Australia New Zealand Australian Health Survey: Usual Nutrient Intakes, 2011–12,[72] reveals that about 10% of women aged 19–50 years have an inadequate intake of folate and between 10 and 15% of women in the same age range have an inadequate intake of zinc.

The LISA PLUS study, a prospective study involving more than 3000 infants, found that a high maternal intake of margarine, vegetable oils and some fruits and vegetables (celery, citrus fruit, sweet peppers) during pregnancy may be associated with an increased risk of allergies, especially eczema.[73]

Gut colonization and microbial diversity in the offspring differs between vaginal and caesarean delivery,[74] which may have an impact on the later development of allergic disease;[75] breastfeeding also influences the establishment of the gut microbiota. Low gut microbial diversity and disturbances in gut colonization patterns during infancy and childhood have been associated with later onset of allergic disease.[76,77]

The rate of fetal growth may affect allergy risk. In the UK Southampton birth cohort, rapid fetal abdominal growth between 11 and 19 weeks' gestation followed by slowing of abdominal growth was associated with later atopy.[78]

Other key maternal nutritional factors that alter the risk of allergic disease and obesity in the offspring

Several other key nutrients, including antioxidants (selenium, zinc, vitamins A, C, D and E), long-chain polyunsaturated fatty acids (LCPUFA) and pre- and probiotics have been linked to multiple health outcomes, including asthma and allergic disease and obesity. The recent Australia New Zealand Australian Health Survey: Usual Nutrient Intakes, 2011–12[72] shows that vitamin A deficiency is around 26% in 14–18-year-old women but falls to around 15–20% in women aged 19–50 years. The number of women with an inadequate intake of vitamin C and selenium is low, being around 5%. Data for vitamin D and vitamin E were not reported.

Antioxidants

In vitro studies in human macrophages have shown that antioxidants can favourably improve immune function.[79] Observational studies suggest that higher dietary intakes of antioxidant-rich foods, such as fresh fruit and vegetables, or higher antioxidant levels measured in pregnancy may reduce the risk of wheezing, asthma and/or eczema in the offspring,[80] although there is inconsistency in the evidence.[81]

LCPUFA

Dietary omega 3 LCPUFA have been shown to have multi-system anti-inflammatory benefits in terms of immune and metabolic outcomes. Several randomized control trials of maternal fish oil supplementation during pregnancy have found beneficial immunomodulatory effects in terms of reduced allergen sensitization and allergic disease outcomes in the offspring.[82–84] Other studies have shown beneficial effects on metabolic programming and cardiovascular risk with higher dietary intakes of omega 3 LCPUFA in early life.[85–87]

Vitamin D

There is consistent geographical variation in the prevalence of vitamin D status, which has been associated with the incidence of allergic disease. Specifically, a low prevalence of allergic disease is seen in equatorial regions (where vitamin D levels are generally higher), and a higher prevalence of allergic disease with increasing distance from the equator (where vitamin D levels are typically lower).[88] This association is reported for food allergy, eczema and asthma.[89–91] A systematic review and meta-analysis[92] concluded that vitamin D insufficiency during pregnancy is associated with an increased risk of GDM, pre-eclampsia and small-for-gestational age infants. A recent Australian cohort study of infants with a parental history of allergic disease found that lower cord blood vitamin D concentrations were significantly associated with eczema at 1 year of age.[93] Vitamin D deficiency in pregnancy had been called a potential 'threat' to the child, an indication of the perceived importance of vitamin D status during this time.[94] Moreover, a 2014 publication from South Australia revealed that

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an inadequate vitamin D status (<50 nmol/l) was present in about 21% of women aged 24–34 years and in about 27% of women aged 35–44 years.[95]

Prebiotics and probiotics

Modern diets typically contain more processed, low-fibre foods and less fruit, vegetables, unprocessed grains, nuts and seeds.[96,97] This dietary pattern is associated with changes in gut microbial biodiversity, another common risk factor now strongly linked with both allergy and obesity.[98] The maternal gut microbial environment is also emerging as a potential risk/protective factor for allergy in the offspring, with maternal microbial transfer to the fetus likely to begin during pregnancy. This early exposure may help to prepare the fetus for extensive microbial exposure during vaginal delivery and after birth.[99] A healthy balance of specific microorganisms in the gut is essential for healthy immune system development; infants who develop allergic disease have an altered balance of gut microorganisms in early life.[100,101] Animal models have shown that gut microbiota modulate immune programming and can reduce the risk of allergic disease as well as the risk of obesity, cardiovascular disease and other metabolic disease.[102–104] Similarly, the use of soluble 'prebiotic' fibre (oligosaccharides) has been shown to have beneficial effects on both immune status and metabolic homoeostasis.[105,106]

Nutrition during the first years of the life

It is not just health and nutrition during pre-conception and pregnancy that can impact on later disease risk. Exposures during infancy and as toddlers can also affect the risks of developing allergic and metabolic disease in later life.

During the early months after birth, nutrition is provided in the form of milk – either human milk via breastfeeding or formula milk via bottle feeding when breastfeeding is not possible. There are long-term health benefits in infants who are breastfed for any length of time, including protection against some immune-mediated disorders,[107] a reduced risk of obesity[108] as well as positive effects on cognitive function.[109] Breastfed babies may also gain weight at a slower rate than formula-fed babies, which has implications for the subsequent reduced risk of overweight and obesity.

Although infant-feeding guidelines have typically recommended exclusive breastfeeding until around 6 months of age,[110] there is emerging evidence that introducing solids after 17 weeks (~4 months) and before 6 months of age (while continuing breastfeeding) has potential benefits in terms of reducing the risk of some food allergies.[111–113] There may be a time window for the child to develop appropriate immunological gut tolerance beginning at around 4 months of age.[112] In line with these findings, the Australasian Society of Clinical Immunology and Allergy[114] has advised relaxing recommendations to avoid certain food groups and allow the introduction of solid foods after 17 weeks, while continuing breastfeeding. The ideal time to introduce solids is a topic of significant debate, and it may be too soon to draw definite conclusions, although most recommendations state that it is important that the introduction of solids does not occur before 17 weeks of age, before which the infant may not be developmentally ready to be able to consume solids. Moreover, two recent reviews found that introducing solid foods any earlier may increase the risk of childhood overweight or obesity, although the evidence is not strong.[115,116] A recent contemporary Australian study based in Queensland reported that in a group of first-time mothers, 21% had given their infant non-milk foods before 17 weeks of age.[117]

The composition and quality of milk and early solid foods may also influence changes in BMI and lead to obesity.[118] For example, a high intake of protein during infancy has been linked to obesity in childhood. The Childhood Obesity Project compared lower protein and higher protein content formula (both levels within recommended ranges) during the first year of life.[118] The study found that infants fed the higher protein content formula had a significantly higher BMI at 6 years of age and a greater risk of obesity. Although the optimal upper limit of dietary protein intake has not been firmly established, a systematic review found that a higher protein intake (i.e. comprising 15–20% of energy intake) in infancy and early childhood was associated with increased growth and an increased risk of being overweight in later childhood.[119]

The rate of growth during infancy influences metabolic risk in later life

Weight gain during the first year of life, often in the form of rapid 'catch-up' growth, is a strong predictor of later obesity risk.[120,121] Moreover, in premature infants at least, the rate of early growth in infancy has been related to long-term cardiovascular health.[122]

This, however, has to be considered in the light of evidence that rapid growth and 'aggressive' nutrition in such infants is associated with improved cognitive function in childhood.[123]

Importance of early eating patterns and behaviours

The first 2–3 years after birth are critical times for programming of long-term energy regulation, especially establishing patterns of healthy nutrition and physical activity.[124] It is also a key time during which a child's taste patterns and food preferences are set. Importantly, children's eating and lifestyle behaviours are heavily influenced by parenting practices. Young children may be at greater risk of becoming overweight or obese due to parental modelling of behaviours that predispose children to weight gain.[124]

Conclusion

Nutrition and lifestyle factors throughout pre-conception, pregnancy, infancy and early childhood have a profound influence on a child's development and long-term health.

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The evidence contained in this publication is designed to assist healthcare professionals in their efforts to maximize this critical window of opportunity when the foundations of future health are created.

As the findings of further research become available, recommendations for optimizing early life nutrition should be formulated and made widely available as part of the preventative health policy agenda in both Australia and New Zealand.

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Conflicts of Interest

None.

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