

# EARLY LIFE NUTRITION

## The opportunity to influence long-term health



The views and recommendations contained in this report paper are those of a panel of expert physicians and scientists comprising:

- Professor Peter SW Davies, Queensland Children's Medical Research Institute, University of Queensland
- Professor John Funder, Prince Henry's Institute
- Associate Professor Debbie Palmer, University of Western Australia
- Associate Professor John Sinn, University of Sydney
- Associate Professor Mark Vickers, The University of Auckland
- Associate Professor Clare Wall, The University of Auckland

Danone Nutricia provided funding to support the production of this report paper but had no input to the content or recommendations contained herein.

## EARLY LIFE NUTRITION: THE OPPORTUNITY TO INFLUENCE LONG-TERM HEALTH

The rapid increase in prevalence of metabolic and allergic disease is a significant global health problem, with a growing body of evidence now linking nutrition in early life to an increased risk of disease in adulthood.

The risk of developing metabolic and allergic disease is influenced by a range of factors across an individual's lifespan. Environmental exposures during foetal development and infancy are now considered responsible for a significant part of lifetime disease risk, as they can trigger adaptations in the developing offspring.

Research has identified vulnerable time periods both prior to conception and during development where exposure to environmental factors, including nutrition, can trigger adaptations in the growing foetus.<sup>1,2</sup> While 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,<sup>3</sup> type 2 diabetes, heart disease<sup>4-7</sup> and allergy.<sup>8</sup>

Maternal and paternal behaviour are therefore important determinants of pregnancy outcomes and the longer-term health of the offspring. Identifying vulnerable periods in foetal development provides an important opportunity for parents and healthcare professionals to intervene and optimise future health outcomes.

This report provides an overview of early-life nutrition research findings and provides practical, evidence-based recommendations to maximise nutritional status before and during pregnancy, as well as during infancy and early childhood, when the foundations of future heath are created.

"Early life nutrition refers to nutritional exposures prior to conception and during pregnancy, infancy and early childhood. These exposures can leave an imprint on the foetus and young child that results in increased risks for disease in later life. For many metabolic and allergic diseases, the stage is set well before a child can reach the fridge door."

### Snapshot of metabolic and allergic disease in Australia and New Zealand

**Cardiovascular disease:** The leading cause of death in Australia and New Zealand, affecting approximately 3.7 million Australians<sup>9</sup> and responsible for 30% of deaths in New Zealand annually.<sup>10</sup>

**Type 2 diabetes:** The fastest growing chronic condition in Australia and New Zealand, with approximately 1 million Australians<sup>11</sup> and 200,000 New Zealanders diagnosed with type 2 diabetes.<sup>12</sup>

**Obesity:** In Australia, more than 65% of adults are overweight or obese (based on BMI) and 25% of children are overweight or obese.<sup>13</sup> In New Zealand, 30% of adults are obese, 20% of children are overweight and almost 10% of children are obese.<sup>14</sup>

**Asthma:** Approximately 1 in 10 adults and 1 in 9 children in Australia have asthma. <sup>15</sup> In New Zealand, 1 in 6 adults and 1 in 4 children experience asthma symptoms. <sup>16</sup>

**Eczema:** Affects approximately 1 in 5 infants under the age of 2 years.<sup>17</sup>

**Food allergy:** Affects approximately 1 in 20 children and 2 in 100 adults.<sup>17</sup> An Australian study found more than 10% of one-year-olds had challenge-proven IgE mediated food allergy.<sup>18</sup> In Australia, hospital admissions for severe allergic reactions (anaphylaxis) have doubled over the last decade, while the rise in anaphylaxis has increased fivefold in children aged 0–4 years over the same time period.<sup>17</sup> In New Zealand, an estimated 1 in 10 children will develop food allergies.<sup>19</sup>

### WHAT DOES THE RESEARCH SHOW?

Nutrition is one of the most easily modifiable environmental factors during early life, and has been shown to strongly influence foetal growth and development,<sup>20</sup> as well as the risk of metabolic and allergic disease in childhood and adult life.<sup>3-8</sup>

### Impact of maternal and paternal nutrition prior to conception

The health of a woman prior to conception has a significant impact on pregnancy outcomes and may have a lifelong impact on her child's health.<sup>21</sup> Obesity reduces fertility and affects the health of the human oocyte.<sup>22</sup> Overweight and obesity in women during their reproductive years is of increasing concern – around 60% of women aged 20–39 years are now either overweight or obese.<sup>23</sup> Women who are obese before becoming pregnant are also more likely to develop gestational diabetes when pregnant, which in turn increases the risk of diabetes and overweight in the offspring.<sup>24</sup>

Increasing paternal body mass index (BMI) has also been linked to impaired embryo and foetal development, as well as reduced pregnancy rates and pregnancy loss. <sup>25-28</sup> Conversely, paternal exposure to famine and undernutrition has been associated with a higher BMI in their offspring compared with the offspring of fathers who were not exposed to famine. <sup>29</sup> 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. <sup>30</sup> These associations between paternal nutrition and health outcomes in the offspring appear to reflect epigenetic changes\* in the sperm that develop in response to nutrition. <sup>31</sup>

## Nutrition during pregnancy – Maternal undernutrition increases metabolic risk in offspring

The Dutch Famine cohort provided insights into the importance of maternal undernutrition and the development of disease in the offspring in later life. 4.5.6.32 In this cohort, serious food shortages and a major reduction in daily food intake over a six-month period in 1944–1945 had a significant impact on the offspring of women who were pregnant at the time. The birth cohort was shown to have a significantly greater risk of obesity, heart disease, type 2 diabetes and renal dysfunction 40–50 years later. 4.5.6.32.33 These effects were also transmitted to the second generation. These results suggest that, in the face of calorie restriction, the foetus becomes conditioned to seek out every last calorie. If the child is then born into a world where food is plentiful, they tend to over-eat because the hunger/satiety set points have been altered during development, probably via epigenetic mechanisms.

# Maternal obesity, excessive gestational weight gain, 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, e.g. hunger and satiety, adipose tissue development and metabolism:<sup>35-37</sup>

**Maternal obesity:** 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.<sup>38</sup> In addition, maternal obesity often precedes gestational diabetes.<sup>39</sup> A systematic review found that maternal pre-pregnancy BMI is directly associated with the risk of developing gestational diabetes.<sup>24</sup> Prior to conception, obesity also reduces fertility and affects the health of the human oocyte.<sup>22</sup>

**Excess gestational weight gain:** Approximately 50% of women gain excess weight during pregnancy.<sup>40</sup> 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 six years than children whose mothers' gestational weight gain was within the recommended range.<sup>40</sup> The study found that excessive weight gain in pregnancy was common, and most marked in women who were overweight or obese prior to becoming pregnant.

The timing of excess pregnancy weight gain also has an impact on the health of the offspring. A study found 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 compared to 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.<sup>41</sup>

**Maternal diabetes:** Maternal gestational diabetes mellitus has been shown to predispose male offspring to a greater BMI at 18 years of age.<sup>42</sup> In addition, animal studies have shown that macrosomic offspring of diabetic mothers exhibit many physiological disorders associated with the metabolic syndrome.<sup>43</sup>

<sup>\*</sup> Epigenetic changes are heritable changes or the stop/go signals that regulate gene expression without changes to the underlying DNA sequence. In other words, signals that change the phenotype but not the genotype.

**Maternal stress:** A study involving Danish army recruits found that those recruits who were born to mothers bereaved during pregnancy had an overall higher risk of overweight in early adult life than those whose mothers did not experience bereavement. There was also an increased risk of overweight when the mother was bereaved in the six months prior to conception.<sup>44</sup>

The mechanisms that link maternal obesity, excessive gestational weight gain, diabetes and stress during pregnancy to later disease risk in the offspring involve a range of factors. These include epigenetic changes that reset foetal energy metabolism, appetite and adipose tissue development, an abnormal intrauterine environment and poor or restricted placental development. These factors may subsequently alter the likelihood of developing obesity later in life, the with the effects of a sedentary lifestyle and modern energy-dense diets exacerbated 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.<sup>36,47-51</sup>

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, while an increased risk of obesity was associated with high birth weight.<sup>52</sup> In birth cohorts from Finland, mortality from stroke and heart disease was greater in people born at a low birth weight.<sup>50,51</sup> A British study involving more than 15,000 people found that death rates from heart disease fell with increasing birth weight.<sup>47,53</sup>

While overweight and obesity, excessive gestational weight gain and gestational diabetes all are associated with large for gestational age infants,<sup>39</sup> maternal obesity can also lead to low birth weight infants. A New Zealand retrospective analysis involving more than 26,000 pregnancies found that maternal obesity was an independent risk factor for small-for-gestational age infants.<sup>54</sup> Several mechanisms may account for these findings, including a reduced likelihood that intrauterine growth restriction is detected and acted upon in obese mothers.<sup>46</sup>

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

Programming of appetite and food preferences may occur during foetal 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 post-natal paternal and maternal intake, suggesting that some programming of appetite in the offspring may occur during foetal development.<sup>55</sup>

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.<sup>56</sup> Experimental models have also shown that altered maternal protein intake can result in a preference for high-fat foods in the offspring.<sup>57</sup>

### 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. While many immune system disorders are inherited, genetic factors alone cannot explain the dramatic rise in many immune diseases in recent years. These changes, particularly the rise in food allergy, highlight the vulnerability of the immune system to early environmental exposure.<sup>8,20</sup>

Allergic disease may 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 foetal development. 8,58,59 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.<sup>8</sup> Women with a history of allergy appear to have altered immune interactions with their foetus, so that the foetal immune response to environmental cues may be modified.<sup>8</sup> In addition, maternal allergy is a stronger predictor of allergic risk in offspring than paternal allergy.<sup>8</sup>

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.<sup>20</sup> The LISA PLUS study, a prospective study involving more than 3,000 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.<sup>60</sup>

Gut colonisation and microbial diversity in the offspring differs between vaginal and Caesarian delivery,<sup>61</sup> and this may have an impact on the later development of allergic disease.<sup>62</sup> Breastfeeding also influences the establishment of the gut microbiota. Low gut microbial diversity and disturbances in gut colonisation patterns during infancy and childhood have been associated with later onset of allergic disease.<sup>63,64</sup>

The rate of foetal growth may affect allergy risk. In the UK Southampton birth cohort, rapid foetal abdominal growth between 11 and 19 weeks' gestation followed by slowing of abdominal growth was associated with later atopy.<sup>65</sup>

## 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 and pre- and probiotics have been linked to multiple health outcomes, including asthma and allergic disease and obesity.

#### **Antioxidants**

In vitro human studies have shown that antioxidants can favourably improve immune function.<sup>66</sup> Observational studies suggest that higher dietary intakes of antioxidant-rich foods (such as fresh fruits and vegetables) or higher antioxidant levels measured in pregnancy may reduce the risk of wheezing, asthma and/or eczema in the offspring.<sup>67,68</sup>

#### Long chain polyunsaturated fatty acids (LCPUFA)

Dietary omega-3 LCPUFA have been shown to have multisystem anti-inflammatory benefits in terms of immune and metabolic outcomes. Several randomised controlled trials investigating maternal fish oil supplementation during pregnancy have found beneficial immunomodulatory effects in terms of reduced allergen sensitisation and allergic disease outcomes in the offspring. Studies have also shown beneficial effects on metabolic programming and cardiovascular risk with higher dietary intakes of omega-3 LCPUFA in early life. Pa-74

#### Vitamin D

There is consistent geographical variation in the prevalence of vitamin D status and this 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), while a higher prevalence of allergic disease is noted with increasing distance from the equator (where vitamin D levels are typically lower).<sup>75</sup> This association is reported for food allergy, eczema and asthma.<sup>76-78</sup> 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.<sup>79</sup>

#### Prebiotics and probiotics

Modern diets typically contain more processed, low-fibre foods and less fruit, vegetables, unprocessed grains, nuts and seeds.<sup>80,81</sup> This dietary pattern is associated with changes in gut microbial biodiversity, another common risk factor now strongly linked with both allergy and obesity.<sup>82</sup>

The maternal gut microbial environment is also emerging as potential risk/protective factor for allergy in the offspring, with maternal microbial transfer to the foetus likely to begin during pregnancy. This early exposure may help to prepare the foetus for a extensive microbial exposure during vaginal delivery and after birth.<sup>83</sup> A healthy balance of specific micro-organisms in the gut is essential for healthy immune system development; infants who develop allergic disease have an altered balance of gut micro-organisms in early life.<sup>84,85</sup>

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. Similarly, the use of soluble 'prebiotic' fibre (oligosaccharides) has been shown to have beneficial effects on both immune and metabolic homeostasis. 9,90

#### 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 up to three years of age 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 if 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,<sup>91</sup> a reduced risk of obesity<sup>92</sup> as well as positive effects on cognitive function.<sup>93,94</sup> Breast-fed 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.

While infant feeding guidelines have typically recommended exclusive breastfeeding until six months of age, there is emerging evidence that introducing solids after 17 weeks and before six months of age (while continuing breastfeeding) has potential benefits in terms of reducing the risk of some food allergies. P5-97 Researchers believe that there may be a time window for the child to develop appropriate immunological gut tolerance, and this begins from approximately four months of age. In line with these findings, the Australasian Society of Clinical Immunology and Allergy (ASCIA) has advised relaxing recommendations to avoid certain food groups and allow the introduction of solid foods after 17 weeks, while continuing breastfeeding. However, it is important that the introduction of solids does not occur before 17 weeks of age; a systematic review found that introducing solid foods any earlier may increase the risk of childhood overweight.

The composition and quality of milk and early solid foods may also influence changes in BMI and lead to obesity. <sup>100</sup> 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. <sup>100</sup> The study found that infants fed the higher protein content formula had a significantly higher BMI at six years of age and a greater risk of obesity. While 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. <sup>101</sup>

### 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. 102-104
Rapid growth during the first year of life has also been associated with an increased risk of heart disease in later life; a study of more than 3,000 women born in Finland demonstrated a relationship between low birth weight, rapid weight gain during infancy and later heart disease. 105

### Importance of early eating patterns and behaviours

The first two to three years after birth are critical times for programming of long-term energy regulation, especially establishing patterns of healthy nutrition and physical activity. <sup>106</sup> 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.<sup>106</sup>

"The body of evidence that supports good nutrition as a way to maximise foetal growth and development, as well as to reduce the risk of disease in later life, continues to grow. Planning, expectant and current parents should be informed of the significant role of good early life nutrition in ensuring the long-term health of their offspring."

### RECOMMENDATIONS

Pre-pregnancy, pregnancy, infancy and early childhood represent key windows of opportunity for parents to adopt lifestyle and nutritional strategies that can improve foetal and childhood development and lower the risks of their children developing allergic and metabolic disease in later life.

Practical, evidence-based recommendations can support parents and healthcare professionals to maximise foetal and childhood development during the period in which the key foundations of future heath are created.

### Pre-conception and pregnancy

#### Reduce excess weight prior to conception

- Obesity is now one of the most common and important risk factors for infertility and adverse pregnancy outcomes.<sup>21</sup> It reduces the likelihood of becoming pregnant, increases maternal complications during pregnancy<sup>107</sup> and is also associated with an increased risk of obesity in the offspring in later life.<sup>3,38</sup>
- Women should aim to achieve and maintain a healthy body weight prior to becoming pregnant.<sup>107,108</sup>
- Women who are obese (BMI of 30 kg/m2 or more) should be advised and encouraged to safely reduce their weight before becoming pregnant. This may require specific education about nutrition and physical activity strategies from appropriate specialists. 107,108
- Losing 5–10% of body weight can have significant health benefits for the woman and may also increase the chances of becoming pregnant.<sup>108</sup>
- Women should be supported in their weight control endeavours by their partner.

### Maintain healthy weight and monitor weight gain during pregnancy

- Excessive weight gain and obesity during pregnancy can have an adverse impact on a woman's health and the longterm health of her child, in particular an increased risk of obesity, coronary heart disease and type 2 diabetes in later life.<sup>3,6,7</sup>
- Steady weight gain during pregnancy is normal and important for the health of the mother and baby. However, it is important that women who are pregnant do not gain too much weight.
   Weight gain should be discussed by healthcare professionals and monitored regularly during antenatal care.<sup>107</sup>
- Women should be advised about the appropriate amount of weight to gain during each stage of pregnancy.
   Recommendations are outlined in Table 1.<sup>107</sup>

- Just as overconsumption can be damaging to the developing foetus, a lack of nutrients is also problematic. As such, dieting or weight loss programs during pregnancy are not recommended as they may compromise the health of the unborn child.<sup>108</sup>
- Women may notice changes in appetite and taste preferences during pregnancy, and these generally settle down over time.
   Women should satisfy their appetite but continue to eat a healthy diet and monitor weight gain so that it is not excessive (Refer Table 1).

Table 1. Recommended weight gain during pregnancy<sup>109</sup>

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

### Maintain a healthy diet and lifestyle prior to and during pregnancy

- Couples planning a pregnancy should implement and maintain a pattern of healthy eating and physical activity in order to increase the likelihood of pregnancy and, in the case of the male, improve sperm quality.
- It may be appropriate to assess the presence of any nutritional deficiencies in women planning a pregnancy. Both Australia and New Zealand have evidence-based healthy eating guidelines about the type and amount of foods that are recommended.
- Physical activity is also important for maintaining a healthy
  lifestyle prior to and during pregnancy.<sup>21</sup> Women should be
  encouraged to do at least 30 minutes of moderate intensity
  physical activity on most if not all days of the week (i.e. target
  of at least 150 minutes per week).
- A woman should stop smoking before attempting to become pregnant. Paternal smoking prior to conception should also be discontinued as it has been associated with damage to sperm DNA and an increased risk of malignancy in offspring.<sup>21</sup>

### Stop smoking and alcohol use during pregnancy

- Cigarette smoking (including passive smoking) and alcohol consumption during pregnancy can have serious health consequences for the women and her unborn child and should be avoided.
- Cigarette smoking increases the risk of ectopic pregnancy,

- miscarriage, premature labour, low birth weight and sudden unexpected death in infancy.<sup>110</sup>
- Drinking alcohol during pregnancy has been associated with miscarriage, low birth weight and intellectual impairment (known as foetal alcohol syndrome). Women should be advised that there is no safe level of alcohol consumption during a pregnancy.<sup>21</sup>

### Optimise control of existing health conditions

- Existing health conditions should be controlled prior to and during pregnancy in order to reduce the risk of complications during pregnancy.
- Women with chronic diseases such as asthma, diabetes and chronic kidney disease have an increased risk of complications during pregnancy.
- Women with diabetes who are planning a pregnancy should be informed that establishing good glycaemic control before conception and maintaining good glycaemic control during pregnancy has important health benefits, including a reduced risk of miscarriage, congenital malformation, stillbirth and neonatal death.<sup>111</sup>

#### Take folic acid supplementation

- Maternal folic acid deficiency has been linked to the development of neural tube defects (NTD) such as spina bifida in the offspring.
- It is recommended that folic acid supplementation is taken for a minimum of one month before conception to assist the prevention of NTD.<sup>112</sup>
- Folic acid supplementation should be continued for the first trimester of pregnancy.<sup>112</sup> There is no evidence that continued folic acid supplementation after the first trimester is beneficial.
- The recommended dose of folic acid supplementation during pre-conception is at least 0.4 mg daily. Where there is an increased risk of NTD (e.g. in women who are obese, those using anticonvulsant medication, those with existing type 2 diabetes, those with a previous history of a child with NTD or a family history of NTD) a 5mg daily dose of folic acid is recommended.<sup>112</sup>

#### Take iodine supplementation

 Severe maternal iodine deficiency has been linked to pregnancy loss and impaired mental and physical development in the foetus. Mild-to-moderate iodine deficiency during pregnancy adversely affects infant thyroid function and may affect mental development.

- lodine supplementation (150mcg daily) is recommended before a woman becomes pregnant to help optimise foetal development and pregnancy, as well as for the duration of pregnancy and during breastfeeding.<sup>94</sup>
- Women with diagnosed pre-existing thyroid conditions should seek advice from their doctor before taking any iodine supplements.<sup>94</sup>
- In addition, women who consume daily seaweed soup should seek advice before taking iodine supplementation, as it may lead to an excess of iodine and subsequently impact on thyroid function.

### Maintain recommended dietary intake of omega-3 fatty acids

- Omega-3 fatty acids are important for foetal development, including brain development.<sup>113</sup>
- Australian and New Zealand dietary guidelines recommend 2–3 servings of oily fish (e.g. salmon, tuna) per week to provide adequate amounts of omega-3 fatty acids.<sup>114</sup>
- Most fish in Australia and New Zealand are low in mercury, but this varies depending on the type of fish. The higher up the food chain, the more mercury the fish is likely to contain.
- Too much mercury can harm the developing nervous system,<sup>114</sup> so it is recommended that pregnant women are aware of the mercury levels of different types of fish and how often to eat each type.<sup>113,114</sup>

### Consume appropriate levels of other vitamins and minerals

- Maternal micronutrient status plays an important role in pregnancy and birth outcomes. Maternal deficiencies in certain micronutrients may have an impact on foetal development and the subsequent health of the offspring.
- Above and beyond the intake of folic acid, iodine and omega-3 fatty acids, pregnant women should maintain adequate levels of vitamins and minerals including:

**Calcium:** Calcium is required for the normal development and maintenance of the skeleton. 113

- Calcium supplementation is recommended for women who avoid dairy in their usual diet and do not consume alternative high calcium food (e.g. calcium-enriched soy milk).
- The recommended dietary intake of calcium for pregnant women is 1300mg per day for those aged under 18 years and 1000mg for those aged 19–50 years.<sup>112</sup>

**Iron:** Requirements increase during pregnancy in order to provide for the growing foetus and increased maternal blood volume.

- Maternal iron deficiency anaemia has been shown to adversely affect foetal brain development, increasing the risk of poor cognitive, as well as poor motor and behavioural development in the offspring.<sup>113</sup> Children of iron-deficient mothers are also more likely to have low iron stores and be susceptible to iron deficiency.<sup>113</sup>
- Iron status in pregnant women should be monitored, and iron deficiency treated with iron medications. All women should receive advice on dietary sources of iron and factors affecting iron absorption.<sup>113</sup>

**Zinc:** Essential for growth and neurobehavioural development of the foetus and its requirements increase during pregnancy.

 Maternal zinc deficiency has been associated with growth retardation and congenital abnormalities (including neural tube defects), low birth weight and premature delivery, as well as problems with neurobehavioural and immunological development in the foetus.<sup>113</sup>

**Vitamin B12:** Essential for cell function and neurological function, including neural tube development.

- Maternal deficiency has been associated with impaired neurodevelopment in infants.
- Low plasma vitamin B12 status in early pregnancy has been associated with a significant elevation in insulin resistance in the offspring.<sup>115</sup>
- The recommended daily intake of vitamin B12 is 6 mcg/day.
   Vegetarians and vegans should be advised to eat foods that contain vitamin B12, such as milk and milk products, eggs and foods fortified with B12 (e.g. soy milk). They should also receive vitamin B12 supplementation during pregnancy and breastfeeding.
- It is important to note that vitamin B12 in plant sources, such as seaweed and spirulina, does not translate to vitamin B12 activity in the human body. 113

**Vitamin D:** Severe maternal deficiency has been associated with rickets in the offspring. Maternal vitamin D deficiency has also been associated with decreased foetal growth through its effect on maternal calcium homeostasis<sup>116</sup>, and may also affect bone mineralisation in adulthood at the time of peak bone mass.<sup>117</sup>

 Women who are at risk of vitamin D deficiency should be identified and advised about methods to increase vitamin D levels. This includes women with reduced sunlight skin exposure (e.g. women who wear a veil), those who use sunscreen on a regular basis, dark-skinned women and obese women.<sup>112,113</sup>  For women who are at increased risk of vitamin D deficiency, testing should be considered and supplementation instituted where needed.

### Increase protein and carbohydrate consumption and moderate fat intake

- Increased consumption of protein and carbohydrate is required during pregnancy to promote foetal growth and development; however fat intake – especially saturated fat – may need to be reduced.
- **Protein:** The requirement for protein increases during pregnancy to support foetal growth, especially in the third trimester. However, high protein diets (over 20% of total energy) should be avoided as they may lead to increased birth weight.<sup>113</sup>
- Carbohydrate: Increased intake of carbohydrates is important
  in pregnancy to ensure adequate glucose supply for maternal
  brain metabolism, as well as for foetal development.<sup>113</sup> Pregnant
  women should aim for 8.5 serves of breads and cereals
  (preferably wholegrain) each day.<sup>118</sup>
- **Fat:** Pregnant and breastfeeding women should aim to reach the recommended fat intake level of 20–35% of energy intake. This may mean a reduction in fat intake, especially saturated fat.<sup>113</sup>

### Consumption of allergenic foods

- The developing foetus and newborn infant benefit from exposure to a wide range of nutritious foods consumed by the mother during pregnancy and breastfeeding.
- Avoiding allergenic foods such as peanuts, peanut products and tree nuts during pregnancy and breastfeeding with the aim of reducing allergy risk in the offspring is not necessary.<sup>98</sup>
  However, if a pregnant or breastfeeding woman has a food allergy, she should continue to avoid those foods for her own safety.

#### Prebiotics and probiotics

- A healthy balance of micro-organisms in the gut is essential for healthy immune system development and metabolic regulation.<sup>84,85</sup>
- The use of probiotic bacteria, commonly found in yoghurt, yeast and supplements, during pregnancy has been shown to have metabolic and immune system benefits.<sup>20</sup> A study found that combined dietary counselling and probiotics improved insulin sensitivity and glucose metabolism in healthy women.<sup>119</sup>

• There is emerging evidence that the use of prebiotics (naturally occurring dietary fibre which acts as food for probiotics) during pregnancy may protect against allergy in the offspring long term. Changing the gut flora of the mother can change the microbiota of the infant. A systematic review found that prebiotic use in late pregnancy and early infancy was associated with a significant reduction in the development of eczema.<sup>120</sup> Further studies are required to determine the effects off prebiotics in pregnancy.

#### Women with additional needs

Pregnant women with the following conditions, or in the following situations, should talk with their doctor about nutrition during pregnancy and breastfeeding:

- Morning sickness
- Low gestational weight gain
- Pre-existing diabetes or gestational diabetes
- Smokers, illicit drug users, women who continue to consume alcohol
- Teenage mothers

### Newborn and infant – first six months

#### Breastfeed for as long as reasonably possible

- Human milk contains an ideal balance of nutrients to promote optimal growth and healthy development.
   Breastfeeding conveys significant short- and long-term health benefits for the infant, promotes mother-infant bonding and provides economic benefits.<sup>94</sup>
- Exclusive breastfeeding is recommended for around six months.
   It should be continued until at least 12 months of age and beyond or for as long as the mother and child desire.<sup>94</sup>

#### **Pre-term Infants**

- Breastfeeding reduces the risk or severity of a number of conditions in infancy and later life, including necrotising enterocolitis in preterm infants.<sup>94</sup>
- Breastfeeding also has significant cognitive benefits, which appear to be more pronounced in preterm infants.<sup>94</sup>
- In addition to breastfeeding for as long as possible, preterm breastfed infants require iron supplements from 4-8 weeks of age.<sup>94</sup>
- Those born at less than 32 weeks' gestation usually require

- fortification of breast milk with protein and calories in the pre-term period, in order to promote adequate growth.<sup>94</sup>
- If a mother is unable to provide enough breast milk, breast milk bank products are available in Australia for pre-term infants or those with serious medical conditions.<sup>94</sup>

#### Full-term Infants

- Exclusive breastfeeding is recommended for around six months.
   It should be continued until at least 12 months of age and beyond or for as long as the mother and child desire.<sup>94</sup>
- It is important to note that feeding with expressed breast milk is both practical and safe, provided the expressed milk is appropriately stored to prevent the risk of bacterial growth.
- It is recommended that breastfed infants receive vitamin D supplements (10 mcg/day) if their mothers are dark-skinned or wear a veil because of the potential for vitamin D deficiency in these women.<sup>94</sup>

#### Breastfeeding mothers and nutritional intake

- Good nutrition is important for the health and wellbeing of all women and particularly for breastfeeding women, who have additional nutritional requirements.<sup>94</sup>
- Breastfeeding mothers have increased energy needs, and typically require an additional 2,000–2,100 kJ/day. However, this requirement will vary depending on the mother's level of milk production, rate of postpartum weight loss and physical activity levels.<sup>94</sup> Ensuring adequate energy levels may assist in prolonging breast milk production, allowing breastfeeding to continue.
- Diets containing less than 20% of energy from fat are not recommended for breastfeeding women, because they may affect the fat content of breast milk.<sup>113</sup>
- Vegan or vegetarian mothers or mothers who follow other forms of restrictive diets have a greater risk for nutrient deficiencies, including iron, zinc, calcium and vitamin B12, and may need referral to a dietitian to maximise the nutritional quality of their breast milk.<sup>94</sup>
- lodine supplementation should be continued for the duration of breastfeeding.
- Breastfeeding women should aim for 9 servings of breads and cereals (preferably wholegrain) each day.<sup>118</sup>
- Exclusion of allergenic foods from the maternal diet has not been shown to prevent allergies in the offspring and therefore do not need to be avoided by the breastfeeding mother.<sup>98</sup>
- Breastfeeding may promote postpartum weight loss. However, many women fail to return to their pre-pregnancy weight within six months, and this has been linked to the development of obesity.<sup>94</sup> Modest and gradual weight loss in women who remain overweight may be beneficial.

#### Introducing solids

- While infant feeding guidelines recommend exclusive breastfeeding until around six months of age, emerging evidence suggests that introducing solids after 17 weeks and before six months of age (while continuing breastfeeding) has potential benefits in terms of reducing the risk of some food allergies.<sup>95-97</sup>
- The Australasian Society of Clinical Immunology and Allergy (ASCIA) has advised relaxing recommendations to avoid certain food groups and allow the introduction of solid foods after 17 weeks, while continuing breastfeeding.<sup>98</sup> It is important that the introduction of solids does not occur before 17 weeks.
- Allergenic foods do not need to be avoided during the introduction of solid foods. Research is currently underway investigating the timing of introduction of allergenic foods, including peanuts and egg, into the diet of infants to reduce the risks of food allergy development.
- The order and timing of first foods do not appear to be important, providing that the first foods provided are nutrient dense and iron fortified.<sup>94</sup> Iron is particularly important to protect against iron-deficiency anaemia and to promote good cognitive development in the foetus. Good sources of iron include iron-enriched infant cereals, as well as pureed meat, poultry and fish.
- If infant formula is required in the first months of life before solid foods are introduced, there is evidence that hydrolysed formulas may reduce the risk of allergic disease in high risk infants (i.e. those with a family history of allergy).<sup>98</sup>

### Infant – six to twelve months

### Introduce a wide range of solid foods

- The introduction of a wide range of solid foods from the five food groups, with an emphasis on iron-rich foods, is important to promote growth and development in the infant. It may also assist the child to choose a broader range of foods in later life.<sup>94</sup>
- Continued breastfeeding is encouraged and should be supported. However, while breast milk continues to be a major source of nutrients, by this stage it no longer provides all of the required nutrients and energy for growth and development, and the infant's appetite is unlikely to be satisfied by breast milk alone.<sup>94</sup>
- Most infants can manage finger foods by eight months of age. 94
- Most infants are willing to accept new textures and flavours, so it is important to gradually introduce new food tastes and textures (from pureed to lumpy and then to normal textures) during this time.<sup>94</sup>

- Infants should not consume foods with added sugar, salt, honey (which may contain clostridium botulinum) or foods high in saturated fat.<sup>94</sup>
- Cow's milk as a drink should be avoided. Feeding infants with whole cow's milk before 12 months of age is associated with an increased incidence of iron deficiency,<sup>94</sup> which can affect the production of hemoglobin and red blood cells and increase the risk of anaemia. Consumption of cow's milk also reduces the bioavailability of non-haem iron provided by other foods, and may be associated with occult loss of blood from the gastrointestinal tract.<sup>94</sup>

### Toddler – one to three years

### Vary the child's diet and establish positive eating behaviours

- A variety of nutritious foods, plus daily physical activity, are important for the ongoing development and growth of the child. Eating behaviors are also formed during this phase of life and should be modelled on a regular routine, eating as part of the family unit, with the size of servings tailored to the child's appetite.<sup>94</sup>
- Solid foods should provide an increasing proportion of nutrients after the age of 12 months. Toddlers typically require small, frequent and nutrient-dense meals, which should be consistent with the Australian and New Zealand dietary guidelines.<sup>94</sup>
- Toddlers may go through a picky eating stage, but it is important to continue to offer a wide variety of foods and regular meals to promote healthy eating habits, behaviours and eating patterns.<sup>94</sup>
- Special milks for toddlers are not required for healthy children.
   Water and pasteurised full-cream milk are recommended drinks at this time.<sup>94</sup>
- Sugar-sweetened drinks and fruit juice should be avoided or limited/diluted. Coffee, tea and other caffeinated drinks are unsuitable for toddlers.<sup>94</sup>
- Consumption of nutrient-poor foods with high levels of saturated fat, sugar, and/or salt (e.g. potato chips, cakes, biscuits and confectionery) should be avoided or limited.<sup>94</sup>
- Parents should also follow healthy eating and physical activity guidelines, as children's eating and lifestyle behaviours are strongly influenced by parenting practices during this period of life.<sup>94</sup>

### **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.

The practical, evidence based recommendations contained in this report are designed to assist parents and healthcare professionals in their efforts to maximise this critical window of opportunity when the foundations of future health are created.

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

### **REFERENCES**

- 1. Jang H, Serra C. Nutrition, epigenetics and diseases. Clin Nut Res 2014; 3: 1–8.
- Singhal A. The global epidemic of noncommunicable disease: the role of early-life factors. Nestle Nutr Inst Workshop Ser 2014; 78: 123–32.
- Bammann K, Peplies J, De Henauw S, et al. Early life course risk factors for childhood obesity: The IDEFICS case-control study. PLOS One 2014; 9: 1–7.
- Roseboom T, van der Meulen JHP, Osmond C, et al. Coronary heart disease after prenatal exposure to the Dutch famine, 1944–45. Heart 2000; 84: 595–98.
- Roseboom T, de Rooij S, Painter R. The Dutch famine and its long-term consequences for adult health. Early Hum Dev 2006; 82: 485–91.
- Painter RC, de Rooij SR, Bossuyt PM, et al. Early onset of coronary artery disease after prenatal exposure to the Dutch famine. Am J Clin Nutr 2006; 84: 322–27.
- Eriksson JG. Epidemiology, genes and the environment: lessons learned from the Helsinki Birth Cohort Study. J Intern Med 2007; 261: 418–25.
- 8. Prescott S, Saffery R. The role of epigenetic dysregulation in the epidemic of allergic disease. Clin Epigenet 2011; 2: 223–32.
- Heart Foundation of Australia 2014. Available at http://www.heartfoundation.org.au/ information-for-professionals/data-and-statistics/Pages/default.aspx
- Heart Foundation New Zealand 2014. Available at http://www.heartfoundation.org. nz/know-the-facts/statistics
- Diabetes Australia. Understanding diabetes. Available at: http://www. diabetesaustralia.com.au/Understanding-Diabetes/
- Ministry of Health New Zealand: Diabetes; 2013. Available at https://www.health. govt.nz/your-health/conditions-and-treatments/diseases-and-illnesses/diabetes
- Australian Institute of Health and Welfare. Obesity; 2014. Available at http://www. aihw.gov.au/overweight-and-obesity/
- Ministry of Health New Zealand Survey. Obesity key facts and statistics; 2012/2013.
   Available at http://www.health.govt.nz/our-work/diseases-and-conditions/obesity/obesity-key-facts-and-statistics
- National Asthma Council of Australia. 2014. Available at http://www.nationalasthma. org.au/understanding-asthma/asthma-facts
- Asthma Foundation New Zealand. Asthma in New Zealand: the statistics; 2014.
   Available at http://asthmafoundation.org.nz/your-health/living-with-asthma/ asthma-in-new-zealand/
- Australasian Society of Clinical Immunology and Allergy. Food allergy; 2014. Available at http://www.allergy.org.au/patients/food-allergy/food-allergy
- Osborne NJ, Koplin JJ, Martin PE, et al. Prevalence of challenge-proven IgE-mediated food allergy using population-based sampling and predetermined challenge criteria in infants. J Allergy Clin Immunol. 2011; 127: 668–76.
- Allergy New Zealand. Food allergy; 2014. Available at http://www.allergy.org.nz/ news++events/Food+Allergy+Awareness+Week.html
- Amarasekera M, Prescott SL, Palmer DJ. Nutrition in early life, immune-programming and allergies: the role of epigenetics. Asian Pac J Allergy Immunol 2013; 31: 175–82.
- Royal Australian and New Zealand College of Obstetricians and Gynaecologists. Prepregnancy Counselling. College Statement C-Obs 3 (a). Current: November 2012.
- Robker RL. Evidence that obesity alters the quality of oocytes and embryos. Pathophysiology 2008; 15: 115–21.
- Hillemeier MM1, Weisman CS, Chuang C, et al. Transition to overweight or obesity among women of reproductive age. J Womens Health (Larchmt) 2011; 20: 703–10.
- Torloni AP. Betrán BL, Horta MU, et al. Prepregnancy BMI and the risk of gestational diabetes: a systematic review of the literature with meta-analysis. Obesity Reviews 2009; 10: 194–203.

- 25. Bakos HW, Henshaw RC, Mitchell M, Lane M Paternal body mass index is associated with decreased blastocyst development and reduced live birth rates.
- Keltz J, Zapantis A, Jindal SK, et al. Overweight men: clinical pregnancy after ART is decreased in IVF but not in ICSI cycles. J Assist Reprod Genet 2010; 27: 539–44.
- 27. Nguyen RH, Wilcox AJ, Skjaerven R, Baird DD. Men's body mass index and infertility. Hum Reprod 2007; 22: 2488–93.
- 28. Ramlau-Hansen CH, Thulstrup AM, Nohr EA, et al. Subfecundity in overweight and obese couples. Hum Reprod 2007; 22: 1634–37.
- Veenendaal MVE, Painter RC, de Rooij SR, et al. Transgenerational effects of prenatal exposure to the 1944–45 Dutch famine. BJOG 2013; 120: 548–54.
- Ng SF, Lin RC, Laybutt DR, et al. Chronic high-fat diet in fathers programs beta-cell dysfunction in female rat offspring. Nature 2010; 467: 963–66.
- Lambrot R1, Xu C, Saint-Phar S, et al. Low paternal dietary folate alters the mouse sperm epigenome and is associated with negative pregnancy outcomes. Nat Commun 2013; 4: 2889. doi: 10.1038/ncomms3889.
- de Rooij SR, Painter RC, Roseboom TJ, et al. Glucose tolerance at age 58 and the decline of glucose tolerance in comparison with age 50 in people prenatally exposed to the Dutch famine. Diabetologia 2006; 49: 637–43.
- 33. Ravelli ACJ, van der Meulen JHP, Osmond C, et al. Obesity at the age of 50 y in men and women exposed to famine prenatally. Am J Clin Nutr 1999; 70: 811–16.
- Painter RC, Osmond C, Gluckman P, et al. Transgenerational effects of prenatal exposure to the Dutch famine on neonatal adiposity and health in later life. BJOG. 2008; 115: 1243–49.
- Gluckman PD, Lillycrop KA, Vickers MH, et al. Metabolic plasticity during mammalian development is directionally dependent on early nutritional status. Proc Natl Acad Sci USA 2007; 104: 12796–800.
- Gluckman PD, Hanson MA, Cooper C, Thornburg KL. Effect of in utero and early-life conditions on adult health and disease. N Engl J Med 2008; 359: 61e73.
- Heindel JJ, vom Saal FS. Role of nutrition and environmental endocrine disrupting chemicals during the perinatal period on the aetiology of obesity. Mol Cell Endocrinol 2009: 304: 90–96.
- Eriksson J, Forse T, Osmond C, et al. Obesity from cradle to grave. Int J Obesity 2003;
   27: 722–27.
- Kim SY, Sharma AJ, Sappenfield W, et al. Association of maternal body mass index, excessive weight gain, and gestational diabetes mellitus with large-for-gestationalage births. Obstet Gynecol 2014; 0:1–8.
- Crozier SR, Inskip, HM, Godfrey KM, et al. Weight gain in pregnancy and childhood body composition: findings from the Southampton Women's Survey. Am J Clin Nutr 2010; 91: 1745–51.
- 41. Davenport MH, Ruchat S–M, Giroux I, et al. Timing of Excessive Pregnancy-Related Weight Gain and Offspring Adiposity at Birth. Obstet Gynecol 2013; 122: 255–61.
- Lawlor DA, Lichtenstein P, Langstrom N. Association of maternal diabetes mellitus in pregnancy with offspring adiposity into early adulthood: sibling study in a prospective cohort of 280 866 men from 248 293 families. Circulation 2011; 123: 258–65
- Yessoufou A, Moutairou K. Maternal Diabetes in Pregnancy: Early and Long-Term Outcomes on the Offspring and the Concept of "Metabolic Memory". Experimental Diabetes Research 2011: 218598, doi:10.1155/2011/218598.
- Hohwü L, Li J, Olsen J, Sørensen TI, Obel C. Severe maternal stress exposure due to bereavement before, during and after pregnancy and risk of overweight and obesity in young adult men: a Danish national cohort study. PLoS One 2014; 9: e97490. doi: 10.1371/journal.pone.0097490.

- 45. Godfrey KM, Sheppard A, Gluckman PD, et al. Epigenetic gene promoter methylation at birth is associated with child's later adiposity. Diabetes 2011; 60: 1528–34.
- Gardosi J. Intrauterine growth restriction: new standards for assessing adverse outcome. Best Pract Res Clin Obstet Gynaecol 2009; 23:741e9.
- Osmond C, Barker DJ, Winter PD, et al. Early growth and death from cardiovascular disease in women. Br Med J 1993; 307: 1519–24.
- 48. Gluckman, PD, Hanson MA. Living with the past: evolution, development, and patterns of disease. Science 2004; 305: 1733–36.
- Gluckman, PD, Hanson, MA Low, FM. The role of developmental plasticity and epigenetics in human health. Birth Defects Res. C Embryo Today 2011; 93, 12–18.
- Eriksson JG, Forsen T, Tuomilehto J, et al. Early growth, adult income, and risk of stroke. Stroke 2000: 31: 869–74.
- Osmond C, Kajantie E, Forsen TJ, et al. Infant Growth and Stroke in Adult Life. The Helsinki Birth Cohort Study. Stroke. 2007; 38: 264–70.
- Curhan GC, Chertow GM, Willett WC, et al. Birth weight and adult hypertension and obesity in women. Circulation 1996; 94: 1310–15.
- Barker DJP, Osmond C, Winter PD, Margetts B, Simmonds SJ. Weight in infancy and death from ischaemic heart disease. Lancet 1989; 2: 577–80.
- Anderson NH, Sadler LC, Stewart AW, et al. Independent risk factors for infants who are small for gestational age by customised birthweight centiles in a multi-ethnic New Zealand population. Aust NZ J Obs Gynaecol 2013; 53: 136–42.
- Brion M-J, Ness AR, Rogers I et al. Maternal macronutrient and energy intakes in pregnancy and offspring intake at 10 y: exploring parental comparisons and prenatal effects. Am J Clin Nutr 2010: 91: 748–56.
- Lussana F, Painter RC, Ocke MC, et al. Prenatal exposure to the Dutch famine is associated with a preference for fatty foods and a more atherogenic lipid profile.
- Langley-Evans SC, Bellinger L, McMullen S. Animal models of programming: early life influences on appetite and feeding behaviour. Matern Child Nutr 2005; 1: 142–48.
- 58. Prescott SL. Early origins of allergic disease: a review of processes and influences during early immune development. Curr Opin Allergy Clin Immunol 2003; 3:125–32.
- Prescott SL, Clifton VL. Asthma and pregnancy: emerging evidence of epigenetic interactions in utero. Curr Opin Allergy Clin Immunol 2009; 9:417–26.
- Sausenthaler S, Heinrish J, Koletzko S, for the GINIplus and LISDA plus study groups.
   Early diet and the risk of allergy: what can we learn from the prospective birth cohort studies GINIplus and LISAplus? Am J Clin Nutr 2011; 94: 2125–175.
- Azad MB, Konya T, Maughan H, et al. Gut microbiota of healthy Canadian & infants: profiles by mode of delivery and infant diet at 4 months. CMAJ 2013; 185: 385–94.
- Kolokotroni O, Middleton N, Gavatha M, et al. Asthma and atopy in children born by caesarean section: effect modification by family history of allergies: a population based cross-sectional study. BMC Pediatr 2012; 12: 179.
- Abrahamsson TR, Jakobsson HE, Andersson AF, et al. Low diversity of the gut microbiota in infants with atopic eczema. J Allergy Clin Immunol 2012; 129: 434–40.
- Ismail IH, Oppedisano F, Joseph SJ, et al. Reduced gut microbial diversity in early life is associated with later development of eczema but not atopy in high-risk infants. Pediatr Allergy Immunol 2012; 23: 674–81.
- 65. Pike KC, Crozier SR, Lucas JSA, et al. Patterns of fetal and infant growth are related to atopy and wheezing disorders at age 3 years. Thorax 2010; 65: 1099–106.
- 66. Utsugi M, Dobashi K, Ishizuka T, et al. c-Jun N-terminal kinase negatively regulates lipopolysaccharide-induced IL-12 production in human macrophages: role of mitogen-activated protein kinase in glutathione redox regulation of IL-12 production. J Immunol 2003; 171: 628–35.

- Devereux G, Turner SW, Craig LC, et al. Low maternal vitamin E intake during pregnancy is associated with asthma in 5-year-old children. Am J Respir Crit Care Med 2006; 174: 499–507.
- Martindale S, McNeill G, Devereux G, et al. Antioxidant intake in pregnancy in relation to wheeze and eczema in the first two years of life. Am J Respir Crit Care Med 2005; 171: 121–28.
- Dunstan JA, Mori TA, Barden A, et al. Fish oil supplementation in pregnancy modifies neonatal allergen-specific immune responses and clinical outcomes in infants at high risk of atopy: a randomized, controlled trial. The Journal of allergy and clinical immunology. J Allergy Clin Immunol 2003; 112: 1178–84.
- Palmer DJ, Sullivan T, Gold MS, et al. Effect of n-3 long chain polyunsaturated fatty acids (LCPUFA) supplementation in pregnancy on infant allergies in the first year of life: a randomised controlled trial. BMJ 2012; 344: e184.
- Prescott SL, Barden AE, Mori TA, Dunstan JA. Maternal fish oil supplementation in pregnancy modifies neonatal leukotriene production by cord-blood-derived neutrophils. Clin Sci 2007; 113: 409–16.
- 72. Innis SM. Metabolic programming of long-term outcomes due to fatty acid nutrition in early life. Mat Child Nutr 2011; 7 (Suppl 2): 112–23.
- Forsyth JS, Willatts P, Agostoni C, et al. Long chain polyunsaturated fatty acid supplementation in infant formula and blood pressure in later childhood: follow up of a randomised controlled trial. BMJ 2003: 326: 953.
- Skilton MR, Ayer JG, Harmer JA, et al. Impaired fetal growth and arterial wall thickening: a randomized trial of omega-3 supplementation. Pediatr 2012; 29: e698–703.
- Kimlin M. Geographic location and vitamin D synthesis. Molec Aspects Med 2008; 29: 453–61.
- Weiland SK, Husing A, Strachan DP, et al. Climate and the prevalence of symptoms of asthma and atopic eczema in children. Occ Environ Med 2004; 61: 609–15.
- Camargo CAJ, Clark S, Kaplan MS, et al. Regional differences in EpiPen prescriptions in the United States: the potential role of vitamin D. J Allergy Clin Immunol 2007; 120: 131–36.
- 78. Krstic G. Asthma prevalence associated with geographical latitude and regional insolation in the United States of America and Australia. PLoS One 2011; 6: e18492.
- 79. Jones AP, Palmer D, Zhang G, Prescott SL. Cord blood 25-hydroxyvitamin D3 and allergic disease during infancy. Pediatr 2012; 130: e1128–35.
- 80. Cordain L, Eaton SB, Sebastian A, et al. Origins and evolution of the Western diet: health implications for the 21st century. Am J Clin Nutr 2005; 81: 341–54.
- 81. Kuhnlein HV, Receveur O. Dietary change and traditional food systems of indigenous peoples. Ann Rev Nutr 1996; 16: 417°42.
- Renz H, Brandtzaeg P, Hornef M. The impact of perinatal immune development on mucosal homeostasis and chronic inflammation. Nature Rev Immunol. 2012; 12: 9–23.
- Rautava S, Luoto R, Salminen S, et al. Microbial contact during pregnancy, intestinal colonization and human disease. Nature Rev Gastroenterol Hepatol 2012; 9: 565–76.
- Nauta AJ, Ben Amor K, Knol J, et al. Relevance of pre- and postnatal nutrition to development and interplay between the microbiota and metabolic and immune systems. Am J Clin Nutr 2013; 98: 5865–935.
- Nylund L, Satokari R, Nikkila J, et al. Microarray analysis reveals marked intestinal microbiota aberrancy in infants having eczema compared to healthy children in atrisk for atopic disease. BMC Microbiol 2013; 13: 12.
- Renz H. Development and regulation of immune responses in pre- and postnatal life. Clin Biochem 2011; 44: 495.

- 87. Sudo N, Sawamura S, Tanaka K, et al. The requirement of intestinal bacterial flora for the development of an IgE production system fully susceptible to oral tolerance induction. J Immunol 1997; 159: 1739–45.
- 88. Turnbaugh PJ, Ley RE, Mahowald MA, et al. An obesity-associated gut microbiome with increased capacity for energy harvest. Nature 2006; 444: 1027–31.
- van Hoffen E, Ruiter B, Faber J, et al. A specific mixture of short-chain galactooligosaccharides and long-chain fructo-oligosaccharides induces a beneficial immunoglobulin profile in infants at high risk for allergy. Allergy 2009; 64: 484–87.
- Cani PD, Possemiers S, Van de Wiele T, et al. Changes in gut microbiota control inflammation in obese mice through a mechanism involving GLP-2-driven improvement of gut permeability. Gut 2009; 58: 1091–103.
- 91. Dogaru CM, Nyffenegger D, Pescatore, AM, et al. Breastfeeding and Childhood Asthma: Systematic Review and Meta-Analysis. American Journal of Epidemiology Advance Access published April 11, 2014. DOI: 10.1093/aje/kwu072
- Arenz S, Ruckerl R, Koletzko B, et al. Breast-feeding and childhood obesity a systematic review. Int J Obesity 2004; 28: 1247–56.
- Kramer MS, Aboud F, Mironova E, et al. Breastfeeding and child cognitive development: new evidence from a large randomized trial. Arch Gen Psychiatry 2008; 65: 578–84.
- National Health and Medical Research Council (2012) Infant Feeding Guidelines.
   Canberra: National Health and Medical Research Council.
- Du Toit G, Katz Y, Sasieni P, et al. Early consumption of peanuts in infancy is associated with a low prevalence of peanut allergy. J Allergy Clin Immunol 2008; 122: 984–91
- Prescott SL, Smith P, Tang M, et al. The importance of early complementary feeding in the development of oral tolerance: concerns and controversies. Pediatr Allergy Immunol 2008: 19: 375–80.
- Koplin JJ, Osborne NJ, Wake M, et al. Can early introduction of egg prevent egg allergy in infants? A population-based study. J Allergy Clin Immunol 2010; 126: 807–13.
- Australasian Society of Clinical Immunology and Allergy. Infant feeding advice, 2010.
   Available at www.allergy.org.au/content/view/350/287
- Pearce J, Taylor MA, Langley-Evans SC. Timing of the introduction of complementary feeding and risk of childhood obesity: a systematic review. Int J Obes 2013; 37: 1295–306
- Weber M, Grote V, Closa-Monasterolo R, et al. Lower protein content in infant formula reduces BMI and obesity risk at school age: follow-up of a randomized trial.
   Am J Clin Nutr. 2014 Mar 19.
- 101. Hörnell A, Lagström H, Lande B, Thorsdottir I. Protein intake from 0 to 18 years of age and its relation to health: a systematic literature review for the 5th Nordic Nutrition Recommendations. Food Nutr Res 2013; 57.doi: 10.3402/fnr.v57i0.21083.
- Baird J, Fisher D, Lucas P, Kleijnen J, Roberts H, Law C. Being big or growing fast: systematic review of size and growth in infancy and later obesity. BMJ 2005; 331: 929.
- Monteiro PO, Victora CG. Rapid growth in infancy and childhood and obesity in later life – a systematic review. Obes Rev 2005; 6: 143–54.
- 104. Druet C, Stettler N, Sharp S, et al. Prediction of childhood obesity by infancy weight gain: an individual-level meta-analysis. Paediatr Perinat Epidemiol 2012; 26: 19–26.
- 105. Forsen T, Eriksson JG, Tuomilehto J, et al. Growth in utero and during childhood among women who develop coronary heart disease: longitudinal study. BMJ 1999; 319: 1403–07.\

- 106. National Health and Medical Research Council (2013) Clinical practice guidelines for the management of overweight and obesity in adults, adolescents and children in Australia. Melbourne: National Health and Medical Research Council.
- 107. Royal Australian and New Zealand College of Obstetricians and Gynaecologists. Management of Obesity in Pregnancy. College Statement C-Obs 49; Current: September 2013a.
- National Institute of Health and Clinical Excellence. Weight management before, during and after pregnancy. NICE public health guidance no. 27. July 2010. Available at guidance.nice.org.uk/ph27
- 109. Rasmussen KM, Yaktine AL. Committee to Reexamine IOM Pregnancy Weight Guidelines. Weight gain during pregnancy: reexamining the guidelines. Washington: The National Academies Press: 2009.
- 110. Royal Australian and New Zealand College of Obstetricians and Gynaecologists. Women and smoking. College Statement C-Obs 53. Current: November 2011.
- National Institute of Health and Clinical Excellence. Diabetes in pregnancy:
   Management of diabetes and its complications from pre-conception to the postnatal period. NICE clinical guideline 63. March 2008; Available at guidance.nice.org.uk/cg63
- Royal Australian and New Zealand College of Obstetricians and Gynaecologists.
   Vitamin and Mineral Supplementation and Pregnancy. College Statement C-Obs 25;
   Current March 2013.
- 113. Ministry of Health New Zealand. Food and Nutrition Guidelines for Healthy Pregnant and Breastfeeding Women: A background paper. Wellington: Ministry of Health. 2006. Available at http://www.health.govt.nz/publication/food-and-nutrition-quidelines-healthy-pregnant-and-breastfeeding-women-background-paper
- 114. Food Standards Australia & New Zealand. Advice on fish consumption: Mercury in fish. 2011. Available at http://www.foodstandards.gov.au/consumer/chemicals/mercury/Pages/default.aspx
- 115. Steward CP, Christian P, Schulze KJ, et al. Low maternal vitamin b-12 status is associated with offspring insulin resistance regardless of antenatal micronutrient supplementation in rural Nepal. J Nutr 2011 141: 1912–17.
- Brunvand L, Quigstad E, Urdal P, et al. 1996. Vitamin D deficiency and fetal growth.
   Early Human Development 1996; 45: 27–33. Am J Clin Nutr 2008; 88(6): 1648–52.
- 117. Zhu K, Whitehouse AJ, Hart P, Kusel M, Mountain J, Lye S, et al. Maternal Vitamin D status during pregnancy and bone mass in offspring at 20 years of age: a prospective cohort study. J Bone Miner Res 2014; 29: 1088–95.
- 118. National Health and Medical Research Council (2013b) Australian Eating Guidelines. Recommended number of serves for adults; 2013. Available at https:// www.eatforhealth.gov.au/food-essentials/how-much-do-we-need-each-day/ recommended-number-serves-adults
- Laitinen K, Poussa T, Isolauri E and the Nutrition, Allergy, Mucosal Immunology and Intestinal Microbiota Group. Probiotics and dietary counselling contribute to glucose regulation during and after pregnancy: a randomised controlled trial. Br J Nutr 2009; 101: 1679–87.
- Osborn DA, Sinn JK. Prebiotics in infants for prevention of allergy. Cochrane Database Syst Rev 2013 Mar 28;3:CD006474. doi: 10.1002/14651858.CD006474.pub3.
- 121. Department of Health Victoria. Better Health Channel. Breast Milk Expressing Available at http://www.betterhealth.vic.gov.au/bhcv2/bhcarticles.nsf/pages/Bottle\_ feeding\_with\_expressed\_breast\_milk following assisted reproductive technology. Fertil Steril 2011; 95: 1700–04.

