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Iron Deficiency and its Prevention in the Australian Context
A Systematic Review of the Literature

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Table of Contents

Abstract

Iron deficiency is the most common nutrient deficiency for both developing and developed nations. It can affect physical work capacity, immunity and thermoregulation, and has been shown to impact behavioural development and cognitive functioning in infants and children. The full cognitive impacts in adults are not well elucidated but seem to relate to attention, concentration, memory and learning. Despite these implications, there are currently no good prevalence data for at-risk population sub-groups in Australia. The best recent adult data comes from the Queensland cohort of the Ausdiab Study and suggests that as many as 1 in 5 women aged 25-50 years has either mild (serum ferritin 12-20μg/L) or moderate (serum ferritin <12μg/L) iron deficiency (Ahmed). While there are no recent prevalence data for Australian infants and children (up to 3 years), several good studies from the late nineties show rates of iron deficiency in the range of 14-25% depending on the parameters and defining ranges used (Karr, oti-Boa, Ranmuth). While observational studies show that high intakes of dairy foods are associated with poorer iron status in this age group, it appears to be because of displacement of high iron containing foods rather than any direct effect of cow's milk. Moderate success in maintaining iron status of infants and young children has been achieved in a limited number of intervention trials using either iron fortified infant formula or good sources of haem iron (Makrides, Engelman etc). There is also high level evidence from three intervention trials in adults which suggest that increasing the haem iron content of adult diets can maintain and/or improve iron status in those at risk of iron deficiency (lyle, heath, patterosn). The optimum intake of haem iron for maintaining or improving iron status is still to be elucidated.

PART 1:

BACKGROUND

1.1 Introduction

Iron deficiency (ID) is the most prevalent nutritional deficiency worldwide. No population group is untouched, but rates are highest for women of childbearing age and infants in the first two years of life (Webb and Oski 1973; Scrimshaw 1984). It is estimated that two thirds of women of childbearing age in most developing countries suffer from iron deficiency; one third of them have the more severe form of the disorder, iron deficiency anaemia (IDA) (Scrimshaw 1991). ID however, is not merely a phenomenon of developing nations. Ten to twenty percent of women of childbearing age in the U.S., Japan and Europe have IDA and more suffer from milder forms of ID (Scrimshaw 1991). The World Health Organisation estimate that 40% of pre-school children in developing nations have IDA and that the rates in Western nations may be up around 10%.

The detrimental effects of anaemia have long been recognised, but morbidity associated with ID has also been demonstrated. ID can affect work performance, behaviour, immunity and thermoregulation, long before the development of frank anaemia (Andelman and Sered 1966; Basta, Soekirman et al. 1979; Lozoff, Brittenham et al. 1982; Oski, Honig et al. 1983; Pollitt, Hathirat et al. 1989). Despite this, actual symptoms are often absent or mild, and may be incorrectly explained by other lifestyle factors.

Women of childbearing age are at particular risk of ID due to the increased iron requirements caused by menstruation and pregnancy. Many women also make lifestyle choices which affect their risk of ID, such as moderate to high levels of exercise, blood donation and poor dietary iron intake. Total dietary iron intake, however, does not always correlate with biochemical iron status, because the type of dietary iron and the presence of various enhancers and inhibitors of iron absorption are maybe more important in determining body iron levels 9-14 (Soustre, Dop et al. 1986; Worthington Roberts, Breskin et al. 1988; Snyder, Dvorak et al. 1989; Reddy and Sanders 1990; Telford, Cunningham et al. 1993; Alexander, Ball et al. 1994).

Infants and toddlers are at increased risk of ID due primarily to the demands of growth associated with the synthesis of new tissue at a time when dietary iron intake is low. Iron requirements reach a peak of 0.1mg/kg bodyweight between 4 and 12 months. Iron stores deposited in the last trimester of pregnancy, 75mg/kg (Faldella, Corvaglia et al. 2003), are sufficient to cover the needs of growth in the first few months of life but the risk of ID develops if inadequate intake or excessive loss of iron exists.

The background to this review will examine the issues surrounding ID in Australian adults and children: the aetiology of ID, iron status measurement issues and detrimental effects on health. The body of the review examines current prevalence data for Australia and New Zealand and dietary strategies which may be important in the prevention and treatment of ID.

1.2 Aetiology of Iron Deficiency

In the absence of an active system of iron excretion, iron losses from the body are actually quite small. Basal losses occur through the desquamation of cells from the exterior and interior surfaces of the body, such as the skin, intestines urinary tract and airways (Hallberg and Rossander Hulten 1991). In adult men and postmenopausal women the daily iron losses amount to 0.9 – 1.0mg/d (Roeser 1990; Bothwell 1995). ID originates from both physiologic and pathologic conditions when the iron demands of the body fail to be met by iron absorption from the gastrointestinal tract. This situation may occur when iron demands are increased, iron losses are increased or when dietary iron absorption is inadequate. Greater iron demands occur during growth and development, while greater losses may result secondary to a chronic medical condition or due to blood loss from menstruation or blood donation. Poor dietary iron absorption is impacted by total iron, the proportion of haem versus non-haem iron and the presence of enhancers and inhibitors of iron absorption.

1.2.1 Definition/Classification

ID can be classified into three stages: iron depletion, iron-deficient erythropoiesis and iron deficiency anaemia (Cook 2005; Clark 2008). The stages are described below from least to most severe:

- *Iron depletion* occurs when tissues do not receive adequate iron, or are beginning to develop functional impairment. Characterised by low serum ferritin or a decrease in iron-binding capacity (NHMRC 2006).
- *Iron-deficient erythropoiesis (IDE)* refers to evidence of an impaired supply of plasma iron for haemoglobin synthesis. This occurs when iron stores are completely exhausted, the supply of iron to tissues is compromised and haemoglobin levels begin to decrease. Storage iron may be normal or increased due to the impaired release of iron from the storage iron compartment to the plasma. Characterised by decreased serum transferrin saturation, increased erythrocyte protoporphyrin concentration, or increased serum transferrin receptor (NHMRC 2006).
- *Iron deficiency anaemia (IDA)* develops when iron stores are absent resulting in inadequate iron to support normal red blood cell formation. Characterised by low haemoglobin and haematocrit or reduced mean corpuscular haemoglobin and volume (NHMRC 2006).

1.3 Absorption, Transport and Storage of Iron

Iron has many functions in the human body. It comprises part of haemoglobin in red blood cells, and assists to transport oxygen around the body. It is also a vital component of enzymes necessary for the production of energy from glucose and for the synthesis of major neurotransmitters required for normal brain function (NHMRC 2003). Iron status is maintained by regulation of iron absorption and storage. When red blood cells are broken down haemoglobin iron is released, recirculating iron within the body. Iron is returned to the bone marrow for the regeneration of blood cells. Haemoglobin, myoglobin and haem enzymes contain approximately 70% of total body iron. Iron

losses are minimal mainly from the gastrointestinal tract via dead cells. However, iron can also be lost via skin cells, urine, sweat and menstruation (Cobiac and Baghurst 1993). There is no established mechanism for excretion therefore absorption and storage homeostasis mechanisms function to balance iron status.

1.3.1 Absorption

There are two types of iron in the diet: haem (animal flesh foods) and non-haem (cereal and vegetable foods) iron. The mechanisms of absorption differ depending on the form of iron ingested (Hunt 2005). Dietary iron is predominately absorbed through the duodenal epithelium of the small intestine (Donovan, Roy et al. 2006). Once absorbed, non-haem iron is transported via carrier proteins by means of receptor mediated endocytosis. This process can transport a maximum of 5mg of iron per day in normal individuals and can rise to approximately 28mg per day in IDA (Werner, Roth et al. 1982). Haem iron is absorbed by a pathway distinct from that of non-haem iron (Foundation 1995). However, it eventually enters the same intracellular metabolic pool. Haem iron absorption responds to altered iron status in a manner similar to non-haem iron absorption although the relative absorption of haem iron is greater (11-22% compared to 1-7%) (Carpenter and Mahoney 1992). Due to its greater absorption rate, haem iron contributes disproportionately to bioavailable iron. Iron is either transported to the plasma (transfer pool) or retained within mucosal cells in the form of ferritin (storage pool) where it is eventually lost as mucosal cells are exfoliated (Roeser 1990; Foundation 1995). It is suggested that during times of iron repletion, more iron enters the mucosal storage pool and less enters the transfer pool. In a state of iron depletion the reverse is thought to occur.

Absorption is influenced by body iron status and dietary bioavailability of iron. Individuals with decreased iron stores absorb a larger percentage of dietary iron compared to individuals with sufficient iron stores (Higdon 2003). Bioavailability of dietary iron is essentially determined by the type of iron and the consumption of enhancing or inhibiting factors.

1.3.2 Transport and Storage

Once iron is internalised into the intestinal mucosal cells, it can be stored as ferritin or transferred to the blood stream (Nadadur, Srirama et al. 2008). Free iron is toxic to the cells of the body and it is therefore transported, bound to transferrin, to cells expressing iron transferrin receptors. Iron uptake occurs by the transferrin-transferrin receptor mediated endocytic pathway. The transferrin bound iron complex is internalised and iron is released into the cell. Iron bound to transferrin represents approximately 0.1% of total body iron content (Cobiac and Baghurst 1993).

Any iron that is not utilized in metabolic processes is bound to the iron binding protein ferritin for storage and can be released when iron supply is not adequate. Stored iron in the form of ferritin accounts for approximately 20 – 30% of total body iron (Nadadur, Srirama et al. 2008). Therefore,

the level of serum ferritin can be used as a measure of the body's iron stores. When serum ferritin stores are low or exhausted, haemoglobin levels will start to fall indicating the body is in negative iron balance (Cobiac and Baghurst 1993).

1.4 Measures of Iron Status

There remains to be no single, reliable measurement of iron status besides the 'gold standard' (bone marrow iron aspirates) (Clark 2009). Common biochemical indices include serum iron, serum ferritin, transferrin saturation, soluble transferrin receptor and total iron binding capacity (TIBC). However, changes in iron status are sequential and these indices may not be informative or change rapidly enough to reflect transient iron-deficient states (Brugnara 2003). A combination of several iron status indicators is suggested to provide the best assessment of iron status (Clark 2009). Table 1 describes the common haematological measures for each stage of ID in women. The measurements can be affected by age, gender, dehydration, exercise, infection, inflammation or malignancy (Beaton, Corey et al. 1989; Clark 2008).

A diagnosis of ID is challenging in individuals with acute or chronic inflammatory conditions as many biomarkers for iron metabolism (cytokines, acute-phase proteins, radicals) are affected by the acute-phase reaction (Brugnara 2003). Iron deficient patients may have serum ferritin levels that falsely suggest a state of iron repletion or excess iron (Coyne 2006). Inflammatory conditions can increase the synthesis of ferritin which reduces the amount of available iron, while also influencing the expression of proteins that block gastrointestinal iron absorption (Weiss 2005; Coyne 2006). The measure typically used to differentiate between ID and anaemia of chronic disease is the soluble transferrin receptor (Clark 2008). This measure is able to accurately assess tissue ID and thus may be used to accurately diagnose IDE (Baynes 1996). Overall, careful evaluation of total body iron status, including serum iron, transferrin saturation and ferritin, is warranted to prevent misdiagnosis.

When assessing the iron status of populations, serum ferritin and transferrin receptor are recommended as the best approach (Organisation 2004). In the presence of infection, serum ferritin is not a useful indicator because inflammation leads to a rise in ferritin concentration as a result of the acute phase response. In most cases, transferrin receptor concentration is not elevated in response to inflammation. Therefore, when combined with serum ferritin it is possible to distinguish between ID and inflammation. It is also beneficial to measure the concentration of an acute phase protein such as C-reactive protein (CRP) or α-1 acid glycoprotein (AGP) to account for high serum ferritin levels caused by inflammation (Organisation 2004). Furthermore, measurement of haemoglobin concentration is recommended, in conjunction with additional measures of iron status, to provide information about the severity of ID (Organisation 2004).

Table 1 Stages of iron deficiency and corresponding haematological measures for women				
	Normal	Iron Depletion	Iron Deficient Erythropoiesis	Iron Deficiency Anaemia
Serum Ferritin (μg/L)	20 – 150	< 20	< 15	< 10
Serrum Transferrin (μmol/L)	47 – 70	> 47	< 47	< 47
Serum Iron (μmol/L)	11 – 29	> 11	< 11	< 7
% Transferrin Saturation	16 – 60	> 16	< 16	< 16
Soluble Transferrin Receptor (mg/L)	2.8 – 8.5	< 8.5	> 8.5	> 8.5
Haemoglobin (g/L)	120 – 160	> 120	> 120	< 120
Erythrocytes	Normal	Normal	Normal	Microcytic Hypochromic
Reference: Bothwell, T. (1981). *Iron deficiency in women.* Washington DC, Nutrition Foundation.				

For infants and children, there is currently no universal agreement regarding diagnostic thresholds for ID and IDA. Rapid changes in iron status occur within the first year of birth as foetal haemoglobin is replaced by haemoglobin A (Organisation 2004). Minimal iron stores are also commonly seen in healthy children until adolescence (Grant, Wall et al. 2007). Presently, individual measurements do not have adequate sensitivity and specificity to be used as a sole diagnostic criterion. In a recent policy statement on ID in pre-school-aged children, diagnosis of ID is recommended to be made by two alternative approaches (Grant, Wall et al. 2007). If there is history of a recent or current infection, mean cell volume (MCV) is appropriate to identify children with ID. If no evidence of infection, health professionals can choose to demonstrate a response by giving a therapeutic trial of 3mg/kg of elemental iron given once daily for 1 month, or use designated cut-off values where ID is present if results show two or more abnormal values for MCV, iron saturation and ferritin concentration (Table 2) (Grant, Wall et al. 2007).

Table 2 Lower limit of normal cut-off values for haematological measures for iron deficiency in infants and pre-school aged children				
Age	Haemoglobin (g/L)	Serum ferritin (μg/L)	Iron Saturation (%)	MCV (fL)
Formula fed				
4 months	103	39	-	76
6 months	111	19	-	68
9 months	114	14	-	70
Breastfed				
4 months	105	20	-	73
6 months	105	9	-	71
9 months	100	5	-	71
1 – 2 years	110	10	10	73
3 – 4 years	112	10	12	75
Reference: Grant, C. C., C. R. Wall, et al. (2007). "Policy statement on iron deficiency in pre-school-aged children." Journal of Paediatrics and Child Health **43**: 513-521.				

1.5 Health Effects of Iron

About two thirds of total body iron is present in haemoglobin, which carries oxygen to body tissues via red blood cells. The remaining iron is found as myoglobin in muscles or as iron-containing enzymes in various tissues. It is well known that IDA (reduced haemoglobin iron) can negatively affect work performance, behaviour, immunity and thermoregulation (Andelman and Sered 1966; Basta, Soekirman et al. 1979; Lozoff, Brittenham et al. 1982; Oski, Honig et al. 1983; Pollitt, Hathirat et al. 1989). ID not severe enough to cause anaemia, but resulting in tissue ID, can also impact on these factors.

1.5.1 Work Performance

IDA affects work performance by limiting the oxygen supply to working muscles. There is no clear evidence of the effect of ID, not severe enough to cause anaemia, on work performance. Some studies support an effect of tissue ID causing reduced physical activity, productivity, and fatigue leading to reduced work performance (Hass and Brownlie 2001; Brownlie, Utermohlen et al. 2002; Brutsaert, Hernandez-Cordero et al. 2003). It is hypothesised that a reduction in the iron-containing mitochondrial oxidases of skeletal muscle limits cellular oxidative ATP production resulting in lactic acidosis, and that this is the method by which tissue ID affects work performance (Spodaryk 1993).

In relation to pre-anaemic ID, recent work has focused on the effects of ID on work performance in athletes. Results to date are not conclusive, with most studies failing to show an effect of reduced work performance in ID without anaemia (Newhouse and Clement 1988; Spodaryk 1993; Fogelholm,

Suominen et al. 1994; Rodenberg and Gustafson 2007). Therefore based on current literature, supplementation for the pre-anaemic iron-depleted athlete does not appear to be justified to solely improve performance (Rodenberg and Gustafson 2007).

1.5.2 Immunity

Several studies have shown a relationship between ID and frequency of infection due to depression of certain aspects of cell-mediated immunity. Andelman and Sered (1966) conducted one of the first clinical studies comparing bronchitis and gastroenteritis infection rates for infants fed an infant formula with and without iron. The rates of respiratory infection for the study group were approximately half that of the control group. ID with or without anaemia has also been reported to increase the frequency of candidiasis (Higgs and Wells 1973), herpes simplex infection (Chandra and Saraya 1975) and Helicobacter pylori infection (Bini 2001; Clark 2008).

However, providing supplementary iron to iron deficient persons with an infectious disease may actually be harmful. ID is believed to provide 'nutritional immunity' to infection by reducing iron-binding proteins (transferrin and lactoferrin) and blocking tissue release of iron. Therefore, iron is unavailable for bacterial replication and growth. The human response to infection is to reduce the availability of iron to micro-organisms through sequestration of iron into the reticuloendothelial system and by producing large amounts of unsaturated transferrin (Scrimshaw 1984). Iron supplementation overloads these iron sequestering systems and iron is thus available to the invading organisms.

Despite this, it does appear that a state of ID leads to an increased risk of infection in the first instance. The actual mechanisms involved are unclear but there is evidence to suggest that iron causes several defects in both the cellular and humoral arms of immunity (Bowlus 2003). Immune defects are partly due to a reduction in peripheral T lymphocytes and atrophy of the thymus. However, growing evidence suggests T lymphocytes may also regulate iron metabolism (Bowlus 2003).

1.5.3 Thermoregulation

From animal studies, and one well-controlled human study, it is clear that ID negatively affects the ability to thermoregulate (Beard, Green et al. 1984; Beard, Tobin et al. 1989; Beard, Borel et al. 1990). This is due to effects on both heat production and heat loss rates (Brigham and Beard 1996). The effect on heat production is mediated through the alteration of thyroid function, reducing metabolic response to cold exposure. Whereas the effect on heat loss is due to competing demands for tissue oxygenation and decreased blood flow to minimize heat losses to the environment (Brigham and Beard 1996).

1.5.4 Cognitive Functioning

Brain iron content is of the same magnitude as major iron storage sites such as the liver, spleen and bone marrow. During the first years of life the brain iron content continually increases from about 10% of the adult content at birth, to about 50% at age ten. The distribution of iron in the brain suggests an association with the metabolism of neurotransmitters and/or related compounds, such as dopamine and norepinephrine (Hallberg 1991). It is postulated that ID mediates its effects on brain function through these neurotransmitters but this is yet to be confirmed (Dallman, Siimes et al. 1975; Tucker and Sandstead 1982; Youdim, Ben-Shachar et al. 1983; Youdim, Ben-Shachar et al. 1989).

Anaemic infants score poorly on the Bayley Scales of Infant Development (Lozoff, Brittenham et al. 1982; Lozoff, Brittenham et al. 1982; Walter, Kovalskys et al. 1983) and poorer motor function is also evident among non-anaemic iron deficient infants (McCann and Ames 2007; Shafir, Angulo-Barroso et al. 2008). This is a concern as current screening procedures generally do not detect ID without anaemia, despite it being more widespread (Shafir, Angulo-Barroso et al. 2008). Whether the effect is reversible with iron treatment is still debatable. A recent review of ID and child development established, from large randomized controlled trials, that there were benefits of iron supplementation on motor development and social-emotional behaviour (Lozoff 2007). This indicates adverse effects are likely to be preventable or reversed with iron initially in development or before progression to severe or chronic ID.

Studies in school aged children provide similar results to those in infants. Iron deficient anaemic and non-anaemic children have been shown to be less interactive and less able to learn, resulting in lower scores in education achievement tests and tests of concentration (Webb and Oski 1973; Walter, Kovalskys et al. 1983; Soemantri, Pollitt et al. 1985; Pollitt, Hathirat et al. 1989; Soemantri 1989; Lozoff, Wolf et al. 1996; Grantham-McGregor and Ani 2001; Grant, Wall et al. 2007; McCann and Ames 2007). Again, it is unclear as to whether there can be reversal of these effects with iron therapy. Several studies have shown an improvement with oral iron (Soemantri, Pollitt et al. 1985; Soemantri 1989; Moffatt, Longstaffe et al. 1994; Williams, Wolff et al. 1999), but not to levels seen in control children.

Research on behaviour in iron deficient adolescents and adults is very limited and provides conflicting results. While most studies point to altered cognitive functioning for iron deficient adults, the research is limited by extremely varied methodologies, particularly with regard to measures of cognitive ability and definitions of ID. Two factors greatly impaired in ID are concentration and memory (Groner, Holtzman et al. 1986; Ballin, Berar et al. 1992; Bruner, Joffe et al. 1996; Kretsch, Fong et al. 1998; Murray-Kolb and Beard 2007; Khedr, Hamed et al. 2008). In addition, follow-up studies from preschool age to adolescence report poorer cognitive, motor and social-emotional function, as well as persisting neurophysiologic differences (Lozoff 2007).

Thus, there appears to be adequate evidence of an effect of behavioural change in iron deficient infants and children. The relationship in adolescents and adults requires much further investigation, but existing studies point to similar trends. The reversibility of such behavioural changes with iron therapy may depend on the timing and severity of ID.

1.5.5 General Health and Well-Being

It is commonly perceived that a link exists between iron deficiency and fatigue. However, evidence for such a relationship is limited. Iron therapy is a well established treatment for fatigue in the presence of IDA but not in the absence of anaemia. An association between ID and increased fatigue has been found in women of child-bearing age (Patterson, Brown et al. 2000), as well as a relationship between ID and decreased physical and mental health and vitality using the validated MOS short-form survey (SF-36) (Patterson, Brown et al. 2001). A double blind randomised placebo controlled trial also highlights that non-anaemic women (18 – 55 years) with unexplained fatigue may benefit from iron supplementation (Verdon, Burnand et al. 2003). However, a cross-sectional comparison of scores on several tests of pyschological functioning for males and females with serum ferritin above and below 20ng/L, found no significant differences (Fordy and Benton 1994).

The use of the oral contraceptive pill by iron deficient women has been associated with symptoms such as depression, irritability and reduced concentration (Rangan, Blight et al. 1998). However, additional studies are required to further establish the role of oral contraceptives in iron deficient women. Lastly, ID has been found to negatively affect mother and child interactions in the areas of emotional availability, sensitivity and responsivity (Murray-Kolb and Beard 2009).

1.6 Other Morbidities Associated with Iron Deficiency

The effects of ID on work performance, immunity, behaviour and thermoregulation have been studied for a number of decades and are quite well established. However, the mechanisms of their effects remain unclear resulting in a number of adverse effects relating to ID which are perhaps less widely studied.

1.6.1 Pregnancy

ID is known to effect pregnancy and foetal outcomes, such as increasing the risk of preterm delivery and consequently low birth weight (Allen 2000). The extent to which maternal ID contributes to maternal mortality is currently unknown. However, evidence is strengthening to suggest maternal ID not only results in inadequate iron stores for the mother but also has the capacity to deplete foetal iron stores in the first year of life (Allen 2000). There is an extensive research literature on ID and iron supplementation in pregnancy, but this is beyond the scope of this review.

1.6.2 Skin and Mucosa

A minor manifestation of ID is its effect on skin and mucosa. More specifically, ID can cause changes in hair, nails, mucosa and tongue. It can result in or exacerbate pruritus, chronically sustained inflammation, dermatitis herpatiformis and photodermatitis (Sato 1991). The impact of such symptoms on general health and well-being could be great, and it has been suggested that such signs could be useful in predicting undiagnosed ID (Sato 1991). Mucosal effects of ID have also been demonstrated in the gastrointestinal tract (GIT), with mucosal atrophy glossitis, angular stomatitis and gastric achlorhydria. Fat and carbohydrate malabsorption and occult blood loss have also been reported to be effects of ID (Naiman, Oski et al. 1964; Prasad and Prasad 1991).

1.7 Possible Effects of Excess Iron

Iron is a transition metal that contains loosely bound electrons in its outer shell which can catalyse the production of free radicals (Kabat and Rohan 2007). Free radical damage is associated with diseases such as atherosclerosis, arthritis, muscular dystrophy, cataractogenesis, various neurological disorders and cancer (Cobiac and Baghurst 1993).

1.7.1 Cancer

In recent years, understanding of iron metabolism has expanded to find iron plays an important role in oxidant tissue damage and cancer (Toyokuni 2009). Excess body iron stores alone or in conjunction with increased dietary intakes may promote the release of storage iron. This has been found to induce oxidative DNA damage, contributing to an increased risk of cancer (Kabat and Rohan 2007). However, epidemiologic studies incorporating validated biomarkers of body iron stores and dietary intake of iron are required to support these findings. Further research to develop a complete understanding of iron-induced carcinogenesis is considered a high priority for efficient cancer prevention (Toyokuni 2009).

1.7.2 Cardiovascular Disease

There may be an association between excess body iron stores and an increased risk of cardiovascular disease in adults. However, a recent systematic review investigating the association of body iron stores with the development of cardiovascular disease has concluded there was a lack of consistent findings in the literature (Zegrean 2009). Out of 16 articles, five studies found a significant association with serum ferritin and heart disease, while only one study found transferrin receptor to serum ferritin ratio to be related to the development of an acute myocardial infarction. Therefore, this warrants the need for further research before a health promoting claim can be made.

1.7.3 Ageing

The accumulation of iron in the brain is hypothesised to play a role in the normal ageing process, as well as in many neurodegenerative diseases affecting the elderly (Stankiewicz and Brass 2009). Iron

concentrations in the brain increase with normal ageing. This is typically seen in structures that function in motor control which may explain the decline in observed functional capacity that is commonly seen with ageing. Many neurodegenerative diseases are associated with increased deposit of iron in the brain. The diseases that typically affect the elderly include Alzheimer's disease and Parkinson's disease. The role of iron as a mediator and marker of neurodegeneration in Parkinson's disease is well established (Stankiewicz and Brass 2009). However, controversy exists as to whether iron plays a causative role in its development (Reddy and Clark 2004). Overall, modifications in iron homeostasis are a significant contributing factor in neurodegenerative diseases, despite the reasons for the accumulation of iron in aging being relatively unknown.

1.7.4 Haemochromatosis

Haemochromatosis is a genetic disorder of iron metabolism. Inappropriate absorption of iron from the diet results in accumulation of iron in the tissues and organs of the body. This can lead to liver disease, pancreatic diabetes and damage to joints and heart muscle (Passmore and Eastwood 1986; Herbert 1992; Cobiac and Baghurst 1993). One in 300 people are homozygous for the haemochromatosis gene in Australia, which leads to iron overload (Leggett, Halliday et al. 1990). The proportion of heterozygotes is unknown but approximates 10% in the US (Herbert 1992). Recent research suggests iron overload is an increasing issue in Western countries due to fortification of cereals, use of iron-containing supplements and a high dietary intake of red meat (Fleming, Jacques et al. 2001; Huang 2003; Milman, Byg et al. 2003; Kabat and Rohan 2007).

PART 2:

METHODS

2.1 Methods

This review aims to address the following questions:

1. What is the prevalence of ID in vulnerable population groups in Australia and New Zealand?
2. What dietary strategies help to prevent ID in vulnerable groups, in the Australian context?
3. What are the gaps in scientific knowledge with regards to ID and diet in Australia and New Zealand?

2.1.1 Search strategy

A systematic literature search of electronic databases CINAHL, Cochrane, Embase, Medline, PubMed, Science Direct and Informit Medicine and Health, key government reports from Australia, UK, Europe and USA and the reference lists of published articles for papers published between 1999 and 2009 were conducted by an academic librarian at the University of Newcastle, NSW. The key words searched include: iron, anaemia, iron deficiency, iron deficiency not anaemia, iron deficiency/prevention, iron deficiency/therapy, iron status, iron stores, Australia and diet therapy. The search was limited to English language, humans and years 1993 to current.

2.1.2 Criteria for inclusion in review

Publications were included if they were experimental or observational studies conducted in humans, with randomised controlled trials that evaluated appropriate outcomes of nutrition or dietary interventions being given priority. Studies specifically pertaining to the prevalence of ID were limited to biochemical measures of iron status. While only studies that included whole foods and foods fortified with iron were included in the dietary strategies section in this review. Descriptive and qualitative studies were used to inform discussion.

Population groups were defined as follows:

- **Infants** aged 6 months up to 24 months
- **Young children** aged 24 months up to 5 years
- **Children** aged 5 years up to 15 years
- **Women of childbearing age** includes menstruating teenage girls and women up to 50 years
- **Adults** includes all genders aged 17 years and over
- **Vegetarians** includes adult vegetarians, ovolactovegetarians and vegans
- **Aborigines** includes individuals of any age from Aboriginal decent
- **Athletes** includes sport at a high or elite level with training most days of the week
- **Blood donors** donate blood at least twice a year and aged 18 years and over

Publications were excluded if they were: (1) unable to be sourced; (2) contained unsuitable biochemical values; (3) published by same author if similar content.

2.1.3 Review Method and Quality Assessment

All identified studies that met the inclusion criteria were assessed for methodological quality using the American Dietetic Association (ADA) Quality Criteria Checklist (American Dietetic Association 2008). The critical appraisal focused on the broad areas of relevance and validity. Relevance involved critique of study design, level of evidence, setting, sample size and outcomes measured. Validity incorporated both internal and external components. In examination of internal validity attention was given to heterogeneity, compliance, blinding, statistical analysis and any biases and limitations concerning selection, measurement and confounding factors. External validity mainly focused on generalisability and applicability of the results. The studies were scored as positive, neutral or negative. Studies rated as negative were not included in this review. The assigned level of evidence was then used to weight studies when formulating evidence statements. The levels of evidence and quality assessment classification of studies are highlighted below in Table 3.

Table 3 Levels of Evidence and Quality Assessment Classification of Studies

Level of Evidence[1]	
I	Evidence obtained from a systematic review of all relevant randomised controlled trials
II	Evidence obtained from at least one properly-designed randomised controlled trial
III-1	Evidence obtained from well designed pseudo-randomised controlled trials (alternative allocation or some other method)
III-2	Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomised, cohort studies, case-control studies, or interrupted time series with a control group
III-3	Evidence obtained from comparative studies with historical control, two or more single arm studies, or interrupted time series without a parallel control group
IV	Evidence obtained from case series, either post-test or pretest/post-test
Quality Rating[2]	
-	If most (6 or more) of the answers to the validity questions in the Quality Criteria Checklist are "NO", the report should be designated with a minus (-)
Ø	If the study is not exceptionally strong, the report should be designated with a neutral (Ø) symbol
+	If most of the answers to the validity questions in the Quality Criteria Checklist are "YES", the report should be designated with a plus symbol (+)

Reference: 1. National Health and Medical Research Council. (2000) *How to use the evidence: assessment and application of the scientific evidence*. Canberra: Commonwealth of Australia.

2. American Dietetic Association. (2008) *Evidence Analysis Manual: Steps in the ADA evidence analysis process.* Chicago: Scientific Affairs and Research.

PART 3:

PREVALENCE OF IRON DEFICIENCY

3.1 Prevalence of Iron Deficiency in Australia and New Zealand

The prevalence of ID in Australia and New Zealand remains inconclusive. Research has primarily been conducted in specific population sub-groups, and different parameters are commonly used to measure the stages of ID. Due to the lack of population based cohort studies and the discrepancy in reference measures, health professionals remain unable to accurately determine the iron status of Australians and New Zealanders.

Below we outline the prevalence of ID in Australian and New Zealand vulnerable population groups, as defined previously, and a brief explanation of why these groups are at higher risk. Table 4 and Table 5 summarize the current evidence describing the iron status of Australians and New Zealanders, respectively. See Appendix 1 for a complete description of prevalence studies.

3.1.1 Infants and Young Children

Infants and young children are at increased risk of ID primarily due to the demands of growth associated with the synthesis of new tissue at a time when dietary iron intake is low. Iron requirements reach a peak of 0.1mg/kg body weight between four and twelve months (Aggett, Agostoni et al. 2002). Iron stores deposited in the last trimester of pregnancy (75mg/kg) are sufficient to cover the needs of growth in the first few months of life (Faldella, Corvaglia et al. 2003). However, the risk of ID develops if inadequate intake or excessive loss of iron exists. Furthermore, the infant diet is dominated by milk that is both low in iron content and high in calcium which is known to inhibit iron absorption. Human milk contains a lower iron content (0.2-0.4mg iron/L) compared to infant formula (0.8mg iron/L) (Domellof, Dewey et al. 2002; Allen and Fischer 2005). However, human milk is more bioavailable than other milk alternatives due to the presence of lactoferrin, a major iron binding protein, which assists to facilitate iron absorption (Suzuki, Shin et al. 2001). Therefore, exclusive breastfeeding for the first six months of life is recommended (World Health Organisation 2001).

Six Australian studies investigating the prevalence of ID have been conducted in infants and young children ranging from 6 to 62 months. Overall, ID ranged from 0% to 20% in infants less than nine months, 1% to 27% in children 1 to 3 years, 1.7% in children 3 to 4 years and 0% in children 4 to 5 years (Karr, Alperstein et al. 1996; Landers and Boulton 1998; Oti-Boateng, Seshadri et al. 1998; Ranmuthugala, Karr et al. 1998; Karr, Mira et al. 2001; O'Keeffe, O'Callaghan et al. 2002). The studies of highest methodological quality that were most representative of the Australian population have been conducted in Sydney (Karr, Alperstein et al. 1996; Ranmuthugala, Karr et al. 1998) and Adelaide (Oti-Boateng, Seshadri et al. 1998). Karr et al. (1996) and Ranmuthugala et al. (1998) used a similar criteria for iron depletion (serum ferritin <12μg/L) and ID (iron depletion plus mean corpuscular volume <70fL (9-24 months) or <73 (24+ months). Results in children 9 to 36 months found 14.2% to 20.3% were iron depleted and 3.4% to 5.4% were iron deficient. A higher prevalence

of ID was reported by Oti-Boateng et al. (1998) with 25% of children 6 to 24 months. However, these findings are suggested to be attributed to Oti-Boateng et al (1998) using a slightly broader criteria for ID (Haemoglobin >110g/L and serum ferritin <15µg/L and/or transferrin >3g/L, transferrin saturation <12%, serum iron <8µmol/L).

In New Zealand, three studies have been published all of high methodological quality (Heath, Tuttle et al. 2002; Soh, Ferguson et al. 2004; Grant 2007). The prevalence of ID ranged from 5.6% to 22% in children aged 6 to 24 months. However as very different criteria has been used to define ID, please refer to Appendix 2 for further details.

3.1.2 Children and Adolescents

Rapid growth in children and adolescents leads to a greater susceptibility for ID (Tapiero, Gate et al. 2001). Children require an average of 1mg/d of absorbed iron to accommodate the needs of their growing bodies. However, to achieve this figure most children need to consume 8 – 10mg of iron per day. ID in children has long-lasting negative effects on growth rate, mental and psychomotor development. In adolescents, increases in erythrocyte volume and muscle mass, and in females commencement of the menstrual cycle all compete for iron stores resulting in a higher risk of a negative iron balance (Marx 1997).

Only two cross-sectional studies have reported the prevalence of ID in children and adolescents aged 4 to 15 years in Australia. In Townsville, a convenience sample of children (4 - 12 years) from three primary schools with high indigenous enrolment found the prevalence of iron depletion (serum ferritin <15µg/L) and ID (serum ferritin <15µg/L and mean corpuscular volume <74fL) was 6.3% and 1.6%, respectively (Heath and Panaretto 2005). These figures increased to 10.7% and 3.6% in indigenous participants only (Heath and Panaretto 2005). The National Schools Survey 1990 reported a prevalence of ID (serum ferritin <10µg/L) that ranged from 0% to 9.2% in children aged 9, 12 and 15 years. The highest prevalence of 9.2% was seen in 15 year old girls. In all other ages and genders the prevalence of ID was less than 1.7% (English and Bennett 1990).

In New Zealand only one study has been conducted in high school students (14 - 18 years) that found 18.3% of females and 1.5% of males were iron deficient (Schaaf, Scragg et al. 1999). The criteria for ID included two or more of serum ferritin <12µg/L, transferrin saturation <14% and/or red cell distribution width >14.5% (Schaaf, Scragg et al. 1999).

3.1.3 Women of Childbearing Age

Blood has the highest concentration of iron of any body tissue and any increase in physiological or pathological blood loss can have a dramatic effect on iron balance (Roeser 1990). Menstruation thus puts women of childbearing age at increased risk of ID. Studies have found that median menstrual

loss of iron, averaged over the month, increased daily iron requirements by approximately 0.45mg to 1.35mg per day (Hallberg, Hogdahl et al. 1966; Bothwell 1981; Passmore and Eastwood 1986; Roeser 1990). Although, there is a marked variation in menstrual blood loss between different women, the monthly loss for individual women remains very constant (Hallberg, Hogdahl et al. 1966). Contraceptive choice is the main external factor which will vary an individual women's menstrual blood loss. The oral contraceptive pill reduces menstral loss by half (Nilsson and Solvell 1967) and standard intrauterine devices double blood losses (Guillebaud and Bonnar 1976).

Pregnancy is another major factor contributing to the increased risk of ID for women of childbearing age. Extra iron is required for the growing foetus and placenta, but also for the expanding red cell mass of the mother. If the mother has reasonable iron stores at the start of pregnancy, a minimum of approximately 800mg of iron must be supplied from external sources if progressive depletion of iron status is to be avoided during pregnancy. If stores are inadequate, up to 1350mg of additional iron may be required. This equates to approximately 2.9 to 4.8mg of iron per day depending on maternal iron stores (Roeser 1990).

Five studies examining the prevalence of ID in women of childbearing age in Australia have been conducted. The four studies containing non-pregnant women reported a prevalence of ID that ranged from 2.0% to 12.5% (McEwin, Hinton et al. 1974; National Heart Foundation 1991; Rangan, Blight et al. 1998; Ahmed, Coyne et al. 2008). The study by Ahmed et al. (2008) is currently Australia's most recent study of prevalence in this population which was found to have high methodological quality. Data was obtained from the Australian Diabetes, Obesity and Lifestyle Study (AusDiab) using random cluster sampling of six urban sites in Queensland. In females less than 50 years of age, the prevalence of marginal ID (serum ferritin 12µg/L - <20µg/L) and ID (serum ferritin <12µg/L) was 9.7% and 10.6%, respectively. A study of pregnant and postpartum women from the Women's and Children's Hospital in Adelaide found 67.5% of pregnant women to be iron deficienct (serum ferritin <12µg/L), while the rate dropped to 26.1% of postpartum women (serum ferritin <15µg/L) that were iron deficient (Zhou, Schilling et al. 2005).

In New Zealand, to our knowledge only one cross-sectional study has been conducted in women. Ferguson et al. (2001) reported between 0.7% and 5.0% of women sampled (15 – 49 years) had ID (serum ferritin <12µg/L). These figures increased to between 8.7% and 12.6% when using a serum ferritin cut off value of less than 16µg/L. The highest prevalence was seen in participants of Maori ethnicity.

3.1.4 Vegetarians

Vegetarian diets place individuals, particularly women at higher risk of ID due to the lower rates of absorption for non-haem iron (2-20%) compared to haem iron (15-35%) (Craig 1994). Restrictive

vegetarian diets such as vegan diets are also associated with an even greater risk. However, vegetarian diets can be compatible with an adequate iron status if they are appropriately planned and well-balanced to include enhancers of iron absorption such as vitamin C in conjunction with a variety of whole grains, legumes, nuts and seeds that are rich in iron (Craig 1994).

In Australia three studies examining the prevalence of ID in vegetarians have been conducted (Helman 1987; Ball and Bartlett 1999; Wilson and Ball 1999). Of the two most recent studies, Ball and Bartlett (1999) focused on female vegetarians and Wilson and Ball (1999) studied male vegetarians. The prevalence of ID (serum ferritin <12µg/L) in female vegetarians aged 18 to 45 years was 18%, while in males 20 to 50 years it was 3%.

In New Zealand only one study has reported the prevalence of ID in vegetarians (Alexander, Ball et al. 1994). Alexander et al. (1994) found 47% of females and 29% of males were iron deficient (serum ferritin <12µg/L) in a sample aged 26 to 30 years.

3.1.5 Aborigines

The poor health of Aboriginal populations is well known (National Health and Medical Research Council 2000). ID is likely to have multiple causes including dietary inadequacies or imbalances, repeated or chronic respiratory and gastrointestinal infections and high rate of parasitic infections (Cobiac and Baghurst 1993). In particular, Hookworm infections are present in some coastal and inland communities in the north of Australia (Hopkins, Gravey et al. 1997). Hookworm infections can cause ID from gastrointestinal blood loss, caused by worms attaching to the small intestinal mucosa. The severity of the infection and consequently risk of ID is influenced by the total worm burden, level of dietary iron intake and the level of physiological iron loss (Hopkins, Gravey et al. 1997). The risk of ID is also suggested to be determined by the physical location of the Aboriginal group, and negatively associated with the intake of dietary meat and bush food (Maggiore 1990).

To the authors knowledge only three studies have investigated iron status in Aboriginal populations. However, only one study has examined ID, as opposed to anaemia (Harris, Cameron et al. 1988). In Bourke children, Harris et al. (1988) reported a 33.3% prevalence of ID (serum ferritin <10µg/L) in aboriginal children 6 months to 2 years. Corresponding rates for children 2 to 4 years and in children 4 to 6 years were 5.1% and 15.2%, respectively. However, the study was of reduced methodological quality as data was obtained using a convenience sample of children having blood tests at Bourke Hospital and from preschool centres. No inclusion or exclusion criteria were specified and measurements of outcomes and risk factors were not blinded. Results should therefore be interpreted in line with these limitations. Overall, the results highlight that Aboriginal children in particular are at potentially high risk of ID. Further research is required in order to accurately determine the level of risk and to develop strategies to prevent further deficiency in this group.

3.1.6 Athletes

Strenuous exercise can cause low iron levels by increasing iron sweat losses, gastrointestinal bleeding, haematuria, and in females, menstruation (Chatard, Mujika et al. 1999). In addition, athletes may follow dietary regimes such as low calorie, vegetarian and very high carbohydrate diets that provide inadequate amounts of absorbable dietary iron (Ryan 2004). Iron levels are found to be higher at the beginning of sweat production compared to the later phases (Chatard, Mujika et al. 1999). Gastrointestinal bleeding is suggested to be associated with exercise intensity, duration and degree of dehydration (Rehrer, Janssen et al. 1989; Nachigall, Nielsen et al. 1996). Factors causing gastrointestinal bleeding include temporary ischemia of the gastrointestinal tract related to exercise intensity and duration, exercise stress-associated gastric acid secretions, organ shock and intakes of acetylsalicylic acid commonly found in anti-inflammatory drugs and aspirin (Chatard, Mujika et al. 1999). Exercise can also produce haematuria (red blood cells in the urine), however reversion to normal urine concentration is seen within 24 to 72 hours (Chatard, Mujika et al. 1999).

Data describing the prevalence of ID in athletes is very limited. Only two studies conducted in Australia were found, with no studies from New Zealand. A convenience sample of athletes at the Australian Institute of Sport (AIS) found 3.3% of males and 19% of females met the AIS criteria for iron supplementation (serum ferritin <30µg/L) (Fallon 2008). In females this percentage was reduced to 4.4% when serum ferritin was restricted to less than 20µg/L. Results by Telford and Cunningham (1991) reported the prevalence of IDA to be less than 1 to 2% in athletes 16 to 29 years, based on haemoglobin <13g/dL and <12g/dL for males and females, respectively. However, there is no report of serum ferritin levels or any other indicator of non-anaemic ID.

3.1.7 Blood Donors

Blood donation is a well recognised risk factor for ID. A donation of 500ml, three times a year equates to an average iron loss of approximately 2.0mg per day (Beaton 1974). When menstrual losses (1mg per day) are added to this figure, the risk of ID for premenopausal women who donate blood regularly is very high. It is suggested that blood donation in this group be limited to three times per year with regular monitoring of serum ferritin and haemoglobin measures, and adoption of an individualised iron supplementation regime (Milman and Kirchhoff 1991).

Publications reporting the iron status in this population are limited. To the authors knowledge there are currently no Australian studies reporting iron status in blood donors. In New Zealand, a recent observation study has been conducted by Badami et al. (2008) reporting results of iron status and risk-profiling for deficiency. ID (serum ferritin <12µg/L) was found in 14.1% of participants overall, 19.9% in females, 19.0% in males and females aged less than 20 years and 25.1% in males and females who had donated 3 to 4 whole units of blood in the past 12 months (Badami and Taylor 2008). Risks were shown to be additive and total risks were inversely correlated with serum ferritin

levels (Badami and Taylor 2008). Future investigations considering the impacts of dietary factors, menstruation, ethnicity and body mass index using this data are currently being conducted using this cohort.

3.2 Other population sub-groups at-risk of iron deficiency

In conjunction with the population groups defined by this review, additional population sub-groups in Australia and New Zealand are at particular risk of ID. These include lactating women, the elderly, the institutionalised, the socially disadvantaged and children of Aboriginal, Maori and Pacific ethnicity. Increased risk of ID can result from increased iron needs (growth, depleted iron stores), increased iron losses (menstruation, intense physical activity, regular blood donation, other sources of blood loss), low dietary iron intake (reduced energy intake, decreased enhancers, increased inhibitors) and/or limited absorption (poor absorption or bioavailability of dietary iron).

Table 4 Summary table: iron intakes and status of Australians

	Group	Reference	Sample Size	Criteria for Iron Deficiency	% of group at risk of Iron Deficiency
Infants & Young	12 – 24 months	O'Keeffe et al. 2002	141	ZPP/Haem ratio>60µmol/mol & SF<20µg/L	12 months: 21% 24 months: 16%
Children	12 – 38 months	Karr et al. 2001	382	SF<10µg/L & MCV<70fL (12-23mths) OR MCV <73fL (24-38mths) & MCHC<22pg	9%
	6 – 24 months	Oti-Boateng et al. 1998	234	Hb>110g/L & SF<15µg/L &/or TFN>3g/L,TSAT<12%,SI<8µmol/L	6-12 months: 20% 12-18 months: 27% 18-24 months: 27%
	12 – 36 months	Ranmuthugala, et al, 1998	485	SF<12µg/L & MCV<70fL (12-23mths) OR MCV<73fL (24-36mths)	Random: 3.4% Opportunistic: 1%
	9 – 24 months	Lander & Boulton 1998	45	SF<12µg/L & MCV<70fL	9 months: 0% 12 months: 6% 18 months: 0% 24 months: 0%
	9 – 62 months	Karr et al. 1996	678	SF<12µg/L & MCV<70fL (9-24mths) OR MCV<73fL (24-62mths) OR ZPP>80µg/dL	9-23 months: 2.8% 24-35 months: 3.7% 36-47 months: 1.7% 48-62 months: 0%
Children & Adolescents	4 – 12 years	Heath & Panaretto 2005	157	SF<15µg/L & MCV<74fL	Total: 1.6% Indigenous: 3.6%
	9, 12, 15 years	English & Bennett 1990	1204	*9 years:* SF<10µg/L & TSAT<15% *12 years:* SF<10µg/L & TSAT<16% *15 year:* SF<12µg/L & TSAT<16%	Girls 9 years: 0% Girls 12 years: 1.6% Girls 15 years: 9.2% Boys 9 years: 0.4% Boys 12 years: 0.5% Boys 15 years: 1.7%
Women Only	Pregnancy & 6 mths postpartum	Zhou et al. 2005	345	SF<12µg/L (pregnant) SF<15µg/L (postpartum)	Pregnant: 67.5% Postpartum: 26.1%
	15 – 30 years	Rangan et al. 1998	255	SF≤12µg/L	12.5%
	16 – 61 years	McEwin et al. 1974	1024	MCHC<31% OR SI<50µg/dL OR TIBC: >350µg/100ml & MCV: <85[3]	4.4%
Adults	25+ years	Ahmed et al. 2008	1634	SF<12µg/L	Females <50years: 10.6% Females >50years: 2.8% Males: 0.3%
	20 – 69 years	National Heart Foundation 1989	5971	SI<8µmol/L OR SF<20µg/L (females) OR SF<10µg/L (males) OR TSAT: <10%	Males: 0.5% Females: 6.8%
Vegetarians	18 – 45 years	Ball & Bartlett 1999	74	SF<12µg/L	Vegetarians: 18% Omnivores: 12.5%
	18+ years	Helman & Darnton-Hill 1987	173	SF<20 µg/L (males) SF<15 µg/L (females)	Male vegetarians: 5% Male omnivores: 8% Female vegetarians: 27% Female omnivores: 12%
Aborigines	0.5 – 6 years	Harris et al. 1988	212	SF<10µg/L	0.5-1.9 years: 33.3% 2-3.9 years: 5.1% 4-6 years: 15.2%
	5+ years	Watson & Toxer 1986	426	Not reported	8.2%
Migrants	18 months	Nguyen et al 2004	174	SF<10µg/L & MCV<70fL	2.3%
	0 – 17 years	McGillvray et al. 2007	232	SF<6µg/L (<6yrs) OR SF<10µg/L (6-9yrs) OR SF<23µg/L (males ≥10yrs) OR SF<6µg/L (females ≥10yrs)	19%
Athletes	16 – 29 years	Telford & Cunningham 1991	706	Hb<13g/dL (males) Hb<12g/dL (females)	<1-2%

fL, femtoliters equating to one quadrillionth of a litre (10^{-16} Litre). Hb, haemoglobin. MCHC, mean corpuscular haemoglobin concentrations. MCV, mean corpuscular volumes. mol, number of atoms in 12 thousandths of a kilogram (0.012kg). pg, pictogram equating to 1000pg in 1µg (10^{-12} grams). SF, serum ferritin. SI, serum iron. TFN, transferrin. TSAT, transferrin saturation. µg, microgram equating to one millionth of a gram. µmol, micromole equating to one millionth of a mole. ZPP, zinc protoporphyrin.

Table 5 Summary table: iron intakes and status of New Zealanders

	Group	Reference	Sample Size	Criteria for Iron Deficiency	% of group at risk of Iron Deficiency
Infants & Young Children	6 – 23 months	Grant et al. 2007	324	≥ 2 abnormal values for: SF<10µg/L ISAT<10% MCV<73fL	Total: 14% Maori: 20% Pacific: 17% Other: 27% NZ European: 7%
	6 – 24 months	Soh et al. 2004	231	SF<10µg/L OR SF<12µg/L & two out of three of: MCV<73fL ZPP≥70µmol/mol haem SF<10µg/L or <12µg/L	6-11.9 months: 2.8-4.2% 12-24 months: 5.0-6.3% Total: 4.3-5.6%
	9 – 24 months	Heath et al. 2002	74	MCV<77fL & ZPP >80µg/dL	9 months: 19% 12 months: 22% 18 months: not reported 24 months: 13%
Children & Adolescents	14 – 18 years	Schaaf et al. 1999	1644	≥ 2 abnormal values for: SF<12µg/L TSAT<14% RCDW>14.5%	Females: 18.3% Males: 1.5% Maori females: 25.6% Pacific females: 20.9% Asian females: 15.4% European females: 8.3%
Women Only	15 – 49 years	Ferguson et al. 2001	1751	SF<12µg/L OR SF<16µg/L & ZPP>60µmol/mol haem	15-19 years: 0.7-12.6% 20-35 years: 3.8-8.8% 36-49 years: 5.0-8.7% Maori: 4.8-9.7% Pacific: 0.0-1.0% NZ European: 4.0-9.4%
Vegetarians	26 – 30 years	Alexander et al. 1994	100	SF<12µg/L	Male vegetarians: 29% Male omnivores: 7% Female vegetarians: 47% Female omnivores: 42%
Blood Donors	16+ years	Badami & Taylor 2008	5006	SF<12µg/L	Males: 7.8% Females: 19.9% < 20 years: 19% 21-50 years: 15.6% 50+ years: 10.4% Total: 14.1%

fL, femtoliters equating to one quadrillionth of a litre (10^{-16} Litre). Haem, haemoglobin. ISAT, iron saturation. MCV, mean corpuscular volumes. RCDW, red cell distribution width. mol, number of atoms in 12 thousandths of a kilogram (0.012kg). SF, serum ferritin. TSAT, transferrin saturation. µg, microgram equating to one millionth of a gram. µmol, micromole equating to one millionth of a mole. ZPP, zinc protoporphyrin.

PART 4:

STRATEGIES TO PREVENT IRON DEFICIENCY

4.1 Strategies to Prevent Iron Deficiency in Australia and New Zealand

Total iron intake does not appear to correlate with iron status (Soustre, Dop et al. 1986; Worthington Roberts, Breskin et al. 1988; Snyder, Dvorak et al. 1989; Reddy and Sanders 1990; Telford, Cunningham et al. 1993; Alexander, Ball et al. 1994). The bioavailability of dietary iron is complex and affected by the form of iron, the presence of enhancers and inhibitors and the iron stores of the individual. Increasing total dietary iron intake has been the primary method used to try and prevent ID. However, the role of enhancers and inhibiting factors may have a significant impact on iron status. Patterson et al. (2001) found that the most significant dietary predictors of iron status for Australian women were phytate and alcohol intake.

The recommended dietary intakes of iron and nutrient intake data from the most recent national nutrition surveys in Australia and New Zealand will be presented for each age group, followed by a review of the literature describing the dietary strategies that may assist in preventing ID in the Australian context.

4.1.1 Recommended Dietary Intakes

The National Health and Medical Research Council of Australia has produced a set of nutrient reference values (NRV) for Australia and New Zealand which describe the amount of specific nutrients required on a daily basis, for nourishment or avoidance of nutritional deficiency (Table 6) (NHMRC 2006). The NRV for iron has been created using the estimated average requirement (EAR) from which recommended daily intakes (RDI) could be derived. An EAR is defined as 'a daily nutrient level estimated to meet the requirements of half the healthy individuals in a particular life stage and gender group' (NHMRC 2006). It is used to estimate the prevalence of inadequate intakes within a group. To assess an individual's dietary intake RDI are commonly cited. The RDI is the average daily dietary intake level required to meet the nutrient requirements of 97 – 98 per cent of healthy individuals (NHMRC 2006).

The EAR for iron is based on the need to maintain iron homeostasis, with a serum ferritin concentration of 15µg/L (NHMRC 2006). Average requirements have been calculated using factorial modelling as opposed to the classical balance study method. Factorial modelling considers basal losses (faeces, urine, sweat and exfoliation of skin), and where relevant, menstrual losses and growth periods (childhood, adolescence, pregnancy).

Important notes:

- The RDI for infants 0 – 6 months relates to breast-fed babies. Formula-fed infants will have significantly higher needs as iron from formula is less bioavailabile (Lonnerdal, Keen et al. 1981; Fomon, Ziegler et al. 1993).
- Approximately 18% and 10% of iron is absorbed from a mixed western diet and vegetarian diet, respectively. Vegetarians will require an 80% increase in iron intakes.

- Assumption that females younger than 14 years do not menstruate and all females 14 – 50 years do menstruate.
- In pregnancy, the EAR and RDI were established using third trimester estimates to build iron stores during the first trimester.
- In lactation, assumption that menstruation does not resume until after 6 months of exclusive breastfeeding.

Caution must be used when interpreting food intake data into nutrient data. Nutrient databases may not contain adequate information on all food items. Consideration for product, seasonal and processing variations may not be available. In addition, the denaturation of iron with cooking and bioavailability in the presence of enhancing or inhibiting factors are unable to be estimated.

Table 6 Nutrient Reference Values for iron (mg/day)

				AI	UL
Infants		0 – 6 months		0.2	20
			EAR	**RDI**	**UL**
Infants		7 – 12 months	7	11	20
Children	*All*	1 – 3 years	4	9	20
		4 – 8 years	4	10	40
	Boys	9 – 13 years	6	8	40
		14 – 18 years	8	11	45
	Girls	9 – 13 years	6	8	40
		14 – 18 years	8	15	45
Adults	*Men*	19 – 30 years	6	8	45
		31 – 50 years	6	8	45
		51 – 70 years	6	8	45
		70+ years	6	8	45
	Women	19 – 30 years	8	18	45
		31 – 50 years	8	18	45
		51 – 70 years	5	8	45
		70+ years	5	8	45
	Pregnancy	14 – 18 years	23	27	45
		19 – 30 years	22	27	45
		31 – 50 years	22	27	45
	Lactation	14 – 18 years	7	10	45
		19 – 30 years	6.5	9	45
		31 – 50 years	6.5	9	45

AI, Adequate Intake. EAR, Estimated Average Requirement. RDI, Recommended Daily Intake. UL, Upper Limit

4.1.2 Dietary Iron Intake

The most recent Australian nutrient intake data comes from the 1995 National Nutrition Survey (NNS) and the 2007 Australian National Children's Nutrition and Physical Activity Survey (ANCNPAS). Table 7 provides a summary of the mean daily iron intakes and percentiles for Australian children and adults from the 1995 NNS, while Table 8 provides a summary of the mean daily iron intakes for Australian children from the 2007 ANCNPAS.

Table 7 Mean daily iron intake (mg) in the Australian population

Gender	Age	Mean	10th Percentile	50th Percentile	90th Percentile
All	2 – 3	7.8	5.1	7.5	11.0
	4 – 7	9.6	6.4	9.1	13.7
	8 – 11	11.7	7.6	10.9	16.6
Males	12 – 15	16.1	9.2	15.1	23.2
	16 – 18	17.9	10.1	16.2	28.5
Females	12 – 15	11.0	6.8	10.5	15.0
	16 – 18	11.1	6.6	10.1	16.4
Males	19 – 24	17.9	10.7	17.2	25.9
	25 – 44	16.7	12.0	15.9	22.5
	45 – 64	16.2	11.5	15.6	21.7
	65 and over	14.4	8.3	13.8	21.0
Females	19 – 24	11.9	7.1	11.0	18.2
	25 – 44	12.0	8.5	11.5	16.0
	45 – 64	12.3	8.3	11.8	16.7
	65 and over	11.3	7.4	10.9	15.7

Reference: Australian Bureau of Statistics. (1998) *National Nutrition Survey 1995: Nutrient Intakes and Physical Measurements*. Commonwealth of Australia.

Table 8 Mean daily iron intake (mg) in Australian children

	2 – 3 years	4 – 8 years	9 – 13 years	14 – 16 years
Males	8.3	10.5	13.6	16.3
Females	7.8	9.2	10.8	11.1
All	8.0	9.8	12.2	13.8

Reference: Commonwealth Scientific Industrial Research Organisation (CSIRO). (2008) *2007 Australian National Children's Nutrition and Physical Activity Survey*. Commonwealth of Australia.

Table 7 and Table 8 highlight a consistency in the mean daily iron intake of children and adolescents between the results obtained from the 1995 NNS and 2007 Australian National Children's Nutrition and Physical Activity Survey. Dietary data was collected using both the 24 hour recall and food frequency questionnaire (FFQ) methodology in the 1995 NNS, while only the 24 hour recall technique was used in the 2007 Australian National Children's Nutrition and Physical Activity Survey. Results from these two surveys indicate that children 2 to 16 years are meeting the EAR for iron, and in fact the 10th percentile of intake is above the EAR.

New Zealand implemented their last NNS in 1997. Table 9 provides a summary of the mean daily nutrient intakes and percentiles of iron in the New Zealand population.

Table 9 Mean daily iron intake (mg) in the New Zealand population

Gender	Age	Mean	10th Percentile	50th Percentile	90th Percentile
Males	15 – 18	15.2	9.6	14.7	21.5
	19 – 24	15.4	11.1	15.3	19.8
	25 – 44	16.1	11.0	15.5	21.9
	45 – 64	14.6	10.1	14.1	19.6
	65 and over	12.5	9.1	12.2	16.4
Females	15 – 18	10.4	6.7	10.1	14.5
	19 – 24	10.8	6.9	10.4	15.3
	25 – 44	10.5	6.8	10.1	14.6
	45 – 64	10.3	7.0	10.1	13.9
	65 and over	9.6	6.7	9.2	12.8

Reference: University of Otago. (1999) *NZ Food: NZ People Key Results from the 1997 National Nutrition Survey*. Wellington: Ministry of Health.

Results from the 1997 NNS indicate that mean intake for individuals 15 to 65+ years are above the EAR (8mg/d for 14-18 years; 6mg/day for men all ages; 8mg/day for women 19-50 years; 5mg/day for women 51+ years) for iron. Males in the 10th percentile are in fact meeting the RDI (8mg/day) for iron. However, females of childbearing age with very high iron needs are unlikely to meet requirements as not even women in the 90th percentile are reaching the RDI level (18mg/day). Similar findings were reported in Australian data from the 1995 NNS. The mean intakes for all age groups sampled were above the EAR for iron, with males in the 10th percentile also meeting the RDI for iron. Women aged 19 to 24 years in the 90th percentile were the only group of women found to meet the RDI for iron with a reported 18.2mg of iron per day.

Additional Australian Surveys have been conducted in the 1980s. In 1983 the National Dietary Survey of Adults was administered to people 25 to 64 years of age in the capital cities of Australian states (English, Cashel et al. 1987). The 24 hour recall methodology was used to obtain dietary information and this survey formed part of the second National Heart Foundation Risk Factor Prevalence Survey. The range of iron intake in 1983 was greater than the results from the 1995 NNS. In males 25 to 44 years of age, mean iron intake was similar between the two surveys (16.6mg/day in 1983 versus 16.7mg/day in 1995). However, participants from the 1983 Survey reported a larger range of iron intakes with the 10^{th} percentile and 90^{th} percentile values being 3mg lower and higher than 1995 figures, respectively. Males aged 45 to 64 years reported a lower mean iron intake in 1983 (15.0mg/day) compared to 1995 (16.2mg/day). This was also relatively consistent across the percentiles of intake. Female intake was slightly lower in 1983 for all age groups. The mean iron intake was 11.7mg/day for women 25 to 44 years and 11.2mg/day for women 45 to 64 years. Similarly, the lower iron intake was commonly seen across most percentiles of intake.

In 1985 the National Dietary Survey of School Children (aged 10 – 15 years) was conducted in urban and rural schools in Australia and dietary methodology was once again collected using 24 hour recall (English, Cashel et al. 1987). In children 12 to 15 years, the mean dietary iron intake of female children has remained relatively similar since 1985 (10.9mg/day in 1985 versus 11.0mg/day in 1995). However, the mean intake of male children has increased from a mean of 14.7mg/day in 1985 to 16.1mg/day in 1995.

4.1.3 Common Sources of Iron

The 1995 NNS data also describes the common food sources of iron (Australian Bureau of Statistics 1998). The majority of dietary iron in the Australian diet comes from breads/cereals (34.6%) and meat products (17%). This is followed by an additional 12% coming from cereal-based products, such as cakes, muffins and mixed dishes where cereal is the major ingredient, and 11% from vegetable products. Cereal and cereal products provide 39.5% of children's iron intake compared to 29.7% in adult diets. Whereas meat provides 14.5% and 19.5% of iron in children's and adult's diets, respectively. Overall, the major sources of iron are: regular breads and rolls, and mixed source breakfast cereals for all ages; and single source breakfast cereals for children and males aged 12 – 18 years. Moderate sources of iron for all ages included mixed dishes where cereal is the major ingredient, potatoes, muscle meat and also mixed dishes where beef or veal is the major ingredient. Table 10 highlights the proportion of dietary iron from selected food groups for the Australian population.

Table 10 The proportion of iron intake from selected food groups in Australia (%)					
Food Groups	**Children 2-11 years**	**Females 12-18 years**	**Males 12-18 years**	**Females 19+ years**	**Males 19+ years**
Cereal and cereal products	39.5	32.1	39.8	29.3	30.1
Bread and rolls	11.9	12.1	9.8	10.9	11.1
Breakfast cereals	12.2	8.4	13.4	14.3	15.3
Meat, poultry and game	14.5	19.1	16.9	16.9	22.1
Muscle meat	4.0	6.7	6.7	6.3	9.2
Poultry and feathered game	1.0	1.6	1.4	1.4	1.5
Beef/veal based mixed dishes	4.1	5.8	4.7	4.7	5.6
Poultry/game based mixed dishes	1.4	1.5	1.2	1.4	1.5
Vegetable products and dishes	9.0	11.9	10.8	12.9	11.7
Potatoes	4.9	5.6	6.2	4.3	4.7
Reference: Australian Bureau of Statistics. (1998) *National Nutrition Survey 1995: Nutrient Intakes and Physical Measurements*. Commonwealth of Australia.					

Results from the New Zealand 1997 National Nutrition Survey reveal popular food sources of dietary iron to be bread, beef and veal, followed by breakfast cereals, vegetables, potatoes and kumara. Together these food items contribute approximately 50% of dietary iron intake. In both genders, meat and fish contribute approximately one third of dietary iron intake. Therefore, approximately two thirds of iron is from non-haem sources with reduced bioavailability. In females, the single largest contributor of dietary iron is bread (12 – 16%), followed by beef and veal (11%). The reverse occurs in males where beef/veal and bread contribute 14% and 12%, respectively. However in males 15 – 24 years, breakfast cereals and bread-based dishes made the most substantial contribution to iron intake (12%). Lastly, non-alcoholic beverages supply 7% of dietary iron for females and 8% for males. The proportion of iron from selected food groups is highlighted in Table 11.

Table 11 The proportion of iron intake from selected food groups in New Zealand (%)		
Food Groups	**Males 15+ years**	**Females 15+ years**
Cereals and cereal products		
Bread and rolls	12.0	13.0
Breakfast cereals	9.0	8.0
Meat		
Beef and veal	14.0	11.0
Poultry	2.0	3.0
Lamb and mutton	2.0	2.0
Pork	3.0	3.0

Vegetables		
Vegetables	7.0	9.0
Potatoes and kumara	8.0	6.0
Reference: University of Otago. (1999) *NZ Food: NZ People Key Results from the 1997 National Nutrition Survey*. Wellington: Ministry of Health.		

The common food sources of iron differ between the Australian and New Zealand populations. In Australia, individuals 12 years and over report a lower intake of bread and rolls and higher intake of breakfast cereals compared to individuals 15 years and over in New Zealand. Australians also consume more vegetables but fewer potatoes than New Zealanders. Meat products are unable to be compared because of different definitions.

4.2 Dietary Strategies to Prevent Iron Deficiency

The second aim of this review (Question 2, page 18) was to research dietary strategies which may help prevent ID in vulnerable population groups in the Australian context. The number of Australian studies published concerning dietary strategies to prevent ID is limited. Therefore, the search topic has been expanded to include dietary strategies to prevent, as well as treat ID, and international literature has been searched. To ensure literature is appropriate to the Australian context, countries have been limited to those from Europe, North America, United Kingdom, New Zealand and Australia. Dietary strategies have been defined as those that include only whole foods and not manufactured supplements. They may include foods usually fortified with iron in Australia such as breakfast cereals and toddler milks, and foods specifically fortified for study purposes.

4.2.1 Intake vs Status

Dietary constituents can influence iron absorption by inhibiting or enhancing the bioavailability of the iron, if consumed in the same meal. Due to the different absorption methods of haem and non-haem iron, haem iron absorption is much less influenced by other dietary factors. Meat and calcium are the only two dietary factors known to influence haem iron absorption. Meat enhances the absorption of haem iron by preventing the formation of insoluble haem complexes (Hallberg, Bjorn-Rasmussen et al. 1979), while calcium inhibits absorption via mechanisms utilised in the transport of iron through the mucosal cells (Hallberg, Rossander Hulten et al. 1992).

In contrast, non-haem iron absorption is influenced by a number of dietary factors. Those known to bear the greatest influence are inhibitors such as phytates (from cereals, legumes), tannins/polyphenols (from tea, coffee, vegetables) and calcium, and enhancers such as meat, ascorbic acid and alcohol. High dietary fibre intakes, tea drinking with meals and the inclusion of dairy foods in the main iron containing meals is likely to lead to reduced iron status (Hallberg 1983; Hallberg, Brune et al. 1991; Hallberg, Rossander Hulten et al. 1992). The scope for manipulating intakes of tea

and dairy foods to not coincide with the main iron-containing meals is a great practical way to enhance overall iron absorption. The most significant factor which acts to enhance iron absorption is ascorbic acid (or Vitamin C).

Ascorbic acid improves the solubility of non-haem iron in a dose-dependent manner by mechanisms such as promoting acid conditions in the stomach, reducing solubilised ferric iron (Fe^{3+}) to ferrous iron (Fe^{2+}) making it unavailable to form insoluble ferric hydroxides and combining with iron to form a soluble complex (Lynch and Cook 1980; Hungerford and Linder 1982; Roeser 1990; Carpenter and Mahoney 1992). Hallberg et al. (1983) found that the addition of a glass of orange juice (70mg ascorbic acid) to a hamburger meal improved iron absorption 2.2 times, while a salad containing 45mg of ascorbic acid increased absorption 1.8 times from the same meal. One other important enhancer of iron absorption is alcohol. Alcohol ingestion stimulates gastric acid secretion, like ascorbic acid, and thus improves the solubility of iron (Cooke and Birchall 1969; Cooke 1972). However while most alcoholic drinks appear to assist iron absorption, this does not apply to some red wines due to the tannin content (Hallberg and Rossander 1982).

4.2.2 Dietary Strategies in Infants, Children and Adolescents

The literature shows there is currently no direct evidence for the role of dietary strategies in the prevention of ID in infants, children and adolescents. The factors recognised as being associated with the development of ID include the volume and duration of cow's milk feeding. However, the level of evidence is at best satisfactory with Level III-2 evidence suggesting that the consumption of more than 550 to 600ml/day of cow's milk in 8 to 9 month old infants (Thorsdottir, Gunnarsson et al. 2003; Hopkins, Emmett et al. 2007) and more than 650ml/day of cow's milk in children over 12 months (Male, Persson et al. 2001) is associated with ID.

Furthermore, the risk of infants developing ID has been found to be significantly associated with the length of cows' milk consumption (Male, Persson et al. 2001; Hopkins, Emmett et al. 2007). Cows' milk is a poor source of iron and also reduces the bioavailability of iron provided by other foods (Male, Persson et al. 2001). Calcium is a known inhibitor of iron absorption and it has been further suggested that the calcium in milk inhibits the absorption of iron (Soh, Ferguson et al. 2002). Male et al. (2001) found cows' milk was the most consistent risk factor negatively influencing iron status. Logistic regression models showed cows' milk duration of feeding (months) to be significantly associated with the risk of ID and IDA, with an odds ratio of 1.18 (1.05 to 1.35; $P<0.01$) and 1.39 (1.14 to 1.69; $P<0.001$), respectively (Male, Persson et al. 2001). Therefore for each month of cows' milk feeding, the risk of developing ID and IDA increased by 18% and 39%, respectively (Male, Persson et al. 2001). A multivariate analysis conducted by Mira et al. (1996) determined that the effects of the introduction of cows' milk before 12 months of age and intake of haem iron were independent (Mira, Alperstein et al. 1996). The odds ratio for low intake of haem iron in this model

was 3.0 (1.3 to 6.8; *P*=0.009) and for cows' milk introduced before 12 months of age was 2.44 (1.09 to 5.44; *P*=0.03). In addition, analyses conducted by Hopkins et al. (2007) also suggested that for every standard deviation increase (about 250mg) in the calcium content of an infants' diet, a 20% drop in mean serum ferritin concentration was observed. In children 18 months of age taking part in the Avon Longitudinal Study of Pregnancy and Childhood (n=796), Cowin et al. (2001) also found that serum ferritin was negatively associated with the amount of cows' milk consumed (r= -0.2462, P<0.001) and calcium intake (equivalent to a 4 ± 5% drop in SF for a 100 mg increase in energy-adjusted calcium) (Cowin, Emond et al. 2001). However, care should be taken in applying this recommendation because milk products are a good source of calcium and the findings appear dependent on the total energy intake from cow's milk products. Overall, these studies have found the avoidance of cows' milk feeding during the first year of life is a key measure in the prevention of iron deficiency (Male, Persson et al. 2001; Hopkins, Emmett et al. 2007). Although, this theory was not supported by a Level III-1 trial that showed no impact of calcium on absorption of iron in children aged 3 to 5 years (Ames, Gorham et al. 1999).

It appears that ID in children with high intakes of milk may be more commonly due to the displacement of iron containing foods. Egg yolks have been suggested as a useful iron source during the weaning period (Makrides, Hawkes et al. 2002). Makrides et al. (2002) conducted a randomised controlled trial in South Australia to investigate the effect of consuming four egg yolks per week on infant decosahexaenoic acid (DHA) status, haemoglobin, ferritin and plasma cholesterol concentrations. Six month old infants that were both formula fed and breast fed (n=137) were randomised to an intervention group that received either four egg yolks per week, four egg yolks enriched with omega-3 fatty acids or no dietary intervention. The results at 6 and 12 months found no significant differences in haemoglobin, serum ferritin and transferrin between intervention groups or feeding type (formula fed and breast fed). However at 12 months, serum iron and transferrin saturation was higher in both intervention groups compared to the control group (see Appendix 3).

In addition, ID may possibly be prevented by increasing the meat intake in late infancy (Engelmann, Sandstrom et al. 1998) or by consuming iron fortified formula (Morley, Abbott et al. 1999). In Denmark, infants 8 months of age were randomised to a 'low meat group' containing a mean meat content of 10g/d or a 'high meat group' with a mean meat content of 27g/day (Engelmann, Sandstrom et al. 1998). Results found significant changes in haemoglobin concentration (*P*=0.008), but there was no effect on iron stores or on cellular iron deficiency evaluated by serum ferritin and transferrin receptor levels, respectively (Appendix 3). In the United Kingdom, Morley et al. (1999) tested the hypothesis that feeding iron supplemented formula would improve developmental performance in 9 month old infants. Infants were randomised to either a control group receiving cows' milk (~0.05mg iron/L), an unfortified formula group (~0.9mg iron/L) or a fortified formula group (~1.2mg iron/L). Results found infants fed the iron fortified formula had significantly higher plasma ferritin

concentrations (control 14.3±0.28µg/L; unfortified 13.1±0.24µg/L; fortified 21.7±0.22µg/L, *P*<.0001). However, no significant intergroup differences in development or growth were found. These results are contradicted by Makrides et al. (1998) that found increasing iron intake from weaning foods such as iron fortified cereal (~4.1mg iron/day) and meat (~0.9mg iron/day) had little effect on iron status at 6 to 12 months (Makrides, Leeson et al. 1998). It was further suggested that iron stores at birth may be an important determinant of iron levels at 12 months, however larger trials are needed (Makrides, Leeson et al. 1998).

In adolescence, only one Level II study was retrieved that suggested incorporation of foods with absorbable iron (haem iron) is an effective strategy to maintain iron status (Snetselaar, Stumbo et al. 2004). Seventh and eighth grade school students in the United States participated in a study that aimed to compare the serum ferritin, zinc and cholesterol levels of adolescents following cholesterol-lowering eating patterns (Snetselaar, Stumbo et al. 2004). All students (n=86) were required to limit saturated fat intake to 20g/day and consume their designated study meat (lean beef (LB) or lean poultry/fish (LPF)) at a minimum of five meals per week and the comparison meat less than twice per week. Results found significant differences (*P*<0.01) in the change of serum ferritin level at baseline and 3 months between the LB and LPF intervention groups (median [interquartile range] 0.7 [-6, 8] and -6.8 [-12, 2] g/dL, respectively). It was suggested that the reduced serum ferritin level reported in the LPF group was possibly due to the reduced haem iron in poultry and fish compared to beef. Therefore, Snetselaar et al. (2004) concluded that diets should include foods with absorbable iron to maintain iron status.

The limited strength of the above evidence is further weakened by inconsistency in the biochemical definition of ID. There was a wide variety of values used to define ID in the studies examined and it is possible that different conclusions would be reached if the measures were standard. Overall, the body of evidence provides some support suggesting dietary strategies including egg yolk, meat or iron fortified formula may prevent iron deficiency (Engelmann, Sandstrom et al. 1998; Morley, Abbott et al. 1999; Makrides, Hawkes et al. 2002). There is also some support that calcium or cows' milk consumption may have a negative association with iron status (Mira, Alperstein et al. 1996; Cowin, Emond et al. 2001; Male, Persson et al. 2001; Thorsdottir, Gunnarsson et al. 2003; Hopkins, Emmett et al. 2007).

4.2.3 Dietary Strategies in Women of Childbearing Age

There is some high level evidence from randomised controlled trials for the role of dietary strategies in the prevention of ID in women of childbearing age. The literature supports the consumption of high bioavailable iron to maintain and/or improve iron status in this population (Lyle, Weaver et al. 1992; Heath, Skeaff et al. 2001; Patterson, Brown et al. 2001). In previously sedentary American college women (17 to 22 years) participating in a 12 week moderate aerobic-exercise program, Lyle et

al. (1992) found meat supplements that contained 18mg/d total iron were more effective in protecting haemoglobin and serum ferritin status than iron supplements over the 12 week exercise program (Lyle, Weaver et al. 1992). Serum ferritin increased from 23.7±14.9µ/L to 29.2±16.0µg/L and there was a significant difference in haemoglobin from 116±12g/L to 124±13g/L (Lyle, Weaver et al. 1992).

In Australia, Patterson et al. (2001) showed that a high iron diet, containing 2.25mg of absorbable iron, increased serum ferritin levels from 8.9±3.1µg/L to 11.0±5.9µg/L in 12 weeks, with further increases to 15.2±9.5µg/L after a 6 month non-intervention phase. The dietary intervention involved: (a) encouraging participants to count the number of servings each day of high, medium and low iron containing foods; (b) strategies to maximise iron absorption such as promoting red meat, iron fortified breakfast cereals and vitamin C rich foods if eating medium and low iron plant foods; (c) ensuring foods high in calcium and drinks such as tea, coffee and milk are only enjoyed between meals to avoid inhibiting iron absorption (Patterson, Brown et al. 2001).

In New Zealand, Heath et al. (2001) demonstrated that an intensive dietary program over 16 weeks has the potential to improve iron status in women with mild ID (serum ferritin <20µg/L and haemoglobin ≥120g/L). The dietary intervention was based on the following principles: (a) increase the intake of iron containing foods (i.e. ≥ 1 serve of high haem iron foods (red meat) and > 1 serve of medium iron foods (chicken, fish, legumes) per day; (b) increase the intake of foods containing factors believed to enhance non-haem iron absorption (i.e. high non-haem iron, iron fortified foods, vitamin C, cast-iron cookware); (c) decrease the intake of foods containing factors believed to inhibit non-haem iron absorption (high phytates and polyphenols); and (d) modify eating patterns so that enhancers of non-haem iron absorption were eaten with meals and potential inhibitors eaten between meals (Heath, Skeaff et al. 2001). The intervention group showed a 26% increase in serum ferritin compared to the control group. While, the mean serum transferrin receptor to serum ferritin (sTfR:SF) ratio dropped from 564.0 at baseline to 393.5 at 16 weeks (Heath, Skeaff et al. 2001).

Lower levels of evidence from three cross-sectional studies also support a role for dietary strategies which increase iron bioavailabilty (Worthington Roberts, Breskin et al. 1988; Rangan, Blight et al. 1998; Patterson, Brown et al. 2001). In the United States, superior iron status was found to be established and maintained in non-pregnant, premenopausal women aged 25 to 35 years that consumed food sources high in bioavailable iron such as red meat (Worthington Roberts, Breskin et al. 1988). Similarly in Perth, low haem iron intake was found to be associated with low iron stores and may lead to iron deficiency in adults 17 to 30 years (n=255) (Rangan, Blight et al. 1998). In addition, even though Patterson et al. (2001) did not find an association between iron status and total iron intake or haem iron intake, iron status was positively associated with alcohol intake (P=0.001)

and negatively associated with phytate intake (P=0.05) in Australian women of childbearing age (Patterson, Brown et al. 2001).

Overall, the body of evidence provides some support for dietary interventions that include food sources containing high bioavailable iron to prevent and treat ID. Further replication and research using larger sample sizes are required to substantiate the findings.

PART 5:

CONCLUSION

5.1 Clinical and Research Implications

This review of the current scientific knowledge with regards to ID and diet in Australia has identified the following areas for future investigation:

- Prevalence data from nationally representative samples is required to accurately determine the risk of ID in Australia and New Zealand. In particular, prevalence data is needed on vulnerable population groups such as vegetarians, aborigines, athletes and blood donors.
- Further research is needed to examine the effects of ID on cognition, general health and well-being, fatigue and depression in adults.
- Continued investigation into the role of iron in cancer aetiology is a high priority for efficiency in cancer prevention. Epidemiological studies that incorporate validated biomarkers of body iron stores and dietary intake of iron are required.
- The development of methods to optimise iron stores in infants and toddlers is needed as a key prevention strategy to minimise the risk of iron deficiency in children.
- There appears to be limited information describing the role of haem and non-haem iron intakes in the development of iron deficiency in both children and adults. This knowledge will assist our understanding of dietary patterns which protect against ID.
- Iron status for Australian women has been shown to be positively associated with the use of oral contraceptive pill (P=0.01) (Patterson, Brown et al. 2001). Further investigations are needed into the role of menstrual blood loss and oral contraceptive pill use in the development of ID.
- Investigation into the amount of red meat intake that is suggested to prevent ID while also being consistent with other good health outcomes is highlighted as an important public health priority.
- Further research into the role of blood donation in the development of ID. It would be important to obtain more information on whether at risk sub-groups should be encouraged to donate, the optimal number of donations to avoid depletion and whether regular serum ferritin testing should be implemented.
- The development of food haem and phytate content data is important for use in dietary intake research.
- The development of a brief iron intake assessment tool that can reliably assess total iron and haem iron content, as well as assess enhancers and inhibitors of iron absorption is required for research purposes. Such a tool will also assist to standardisation of research findings.
- Indigenous populations have high rates of ID that may be due to differing causes when compared to Caucasian populations. Individualised research into this area is required to enable development of specifically targeted strategies to prevent and/or treat ID in these vulnerable populations.

5.2 Conclusions

This report aimed to examine the current state of prevalence data for iron deficiency in at-risk population sub-groups in Australia and review the evidence with regards to dietary interventions for preventing iron deficiency.

A systematic search of the scientific literature and Australian government publications found that good recent prevalence data on iron status of Australians is lacking. Recent adult data is available for men and women 25+ years and shows that around 20% of women 25-50 years is likely to be suffering from mild or moderate iron deficiency (Ahmed, Coyne et al. 2008). The only available prevalence data for infants and children is now more than 10 years old, but several studies suggest that rates of iron deficiency are highest between 6 and 36 months of age, and range from about 14-25% depending on parameters and definitions used. There is no reasonable prevalence data for other at-risk population sub-groups in Australia; including vegetarians, blood donors, Aboriginal populations, the elderly etc.

A limited number of intervention trials have examined dietary strategies for preventing and treating iron deficiency in children and adults. Those in children have concentrated on the weaning diet and have either increased haem iron intake through the use of meat or egg yolk, or used iron fortified infant formula. Both strategies resulted in only mild to moderate success with improvements seen for some iron status measures, but not others. Intervention trials in adults have been more consistent, with increased haem iron intake and iron bioavailability resulting in either better maintenance of iron status or actual improvement for participants who were iron deficient.

The overwhelming outcome of this review is to highlight the lack of good Australian data on rates of iron deficiency and the best dietary strategies for prevention. It would appear that haem iron intakes are an important determinant of iron status, but there is no good data to suggest optimum levels of intake for promoting good iron stores while minimising any potentially adverse effects associated with excessive red meat consumption. Research in the area is also limited due to a lack of good tools for assessing dietary iron intakes and the potential role of enhancers and inhibitors of iron absorption.

PART 6:

REFERENCES & APPENDICES

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6.2 Appendices

Summary Table: iron intakes & status of Australians

	Group	Purpose	Sample	Criteria for risk	% of group at risk
Infants & Young Children – Aged 0 – 3 years					
2002 O'Keeffe, M., et al. Brisbane	12 months & 2 years Premature infants	Determine prevalence of iron deficiency and its association with neuro-developmental problems and dietary risk factors	n=141 12mths: n=72 2yrs: n=69 Convenience sampling from Special Care Nursery of the Mater Mother's Hospital, Brisbane Quality: III-2 / Ø - cohort study - no incl/excl criteria - measurement times may miss ID at other ages - inflammation not explored	Iron Deficiency (ID): **ZPP/Haem ratio:** >60µmol/mol & **SF:** <20µg/L	**12mths:** ID: 21% **2yrs:** ID: 16%
2001 Karr, M., et al[1] Sydney	12 – 38 months Australian born, Arabic background	Determine prevalence of iron depletion, iron deficiency, and iron-deficiency Anaemia	n=382 Ferritin samples: n=382 Hb & ferritin samples: n=315 Quota sampling from five Sydney hospitals Quality: IV / + - cross-sectional study - acknowledged possible under-reporting of prevalence due to inflammation	Iron Depletion (Dep): **SF:** <10µg/L. Iron Deficiency (ID): **SF:** <10µg/L & **MCV:** <70fL (12-23mths) or <73fL (24-38mths) PLUS **MCHC:** <22pg Iron Deficiency Anaemia (IDA): ID & **Hb:** <110g/L	Dep: 23%. ID: 9%. IDA: 6%.

1. Values calculated from original publication

1998 Oti-Boateng, P., et al. Adelaide	6 - 24 months Caucasian & Asian	Assess iron status and dietary intake	n=234 Caucasian (C): Total: n=191 6-12mths: n=69 12-18mths: n=70 18-24mths: n=52 Asian (A): Total: n=43 6-12mths: n=19 12-18mths: n=12 18-24mths: n=12 Quota sampling from health/medical centres by postcode Quality: III-2 / +	Iron Deficiency (ID): **Hb:** >110g/L & **SF:** <15µg/L &/or **TFN:** >3g/L, **TSAT:** <12%, **SI:** <8µmol/L. Iron Deficiency Anaemia (IDA): ID & **Hb:** <110g/L	**Total:** ID: (C) 25%; (A) 14%, IDA: (C) 6%; (A) 14%. **6-12mths:** ID: (C) 20%; (A) 5%, IDA: (C) 3%; (A) 11%. **12-18mths:** ID: (C) 27%; (A) 0%, IDA: (C) 7%; (A) 25%. **18-24mths:** ID: (C) 27%; (A) 42%, IDA: (C) 10%; (A) 8%
1998 Ranmuthugala, G., et al. Central Sydney	12 – 36 months	Compare results from two sampling strategies to determine prevalence of elevated blood lead concentrations and iron status	n=485 Random sample: n=182 Opportunistic sample: n=303 Stratified random sampling & convenience sampling from six early childhood centres Quality: III-2 / +	Iron Depletion (Dep): **SF:** <12µg/L Iron Deficiency (ID): **SF:** <12µg/L & **MCV:** <70fL (12-23mths) or <73fL (24-36mths). Iron Deficiency Anaemia (IDA): ID & **Hb:** <11g/dL	**Random Sample:** Depleted: 20.3%; ID: 3.4%; IDA: 1.7% **Opportunistic Sample:** Depleted: 19.1%; ID: 1%; IDA: 0.7%
1998 Lander, M. & Boulton, T. Toowoomba	9 – 24 months Wyeth Toowoomba Children's Nutrition Survey	Describe iron intakes and iron status	n=45 9mths: n=24 12mths: n=36 18mths: n=22 24mths: n=17 Simple random sample Quality: III-2 / + - longitudinal study	Iron Depletion (Dep): **SF:** <12µg/L Iron Deficiency (ID): **SF:** <12µg/L & **MCV:** <70fL Anaemia: **Hb:** <105g/fL	**9mths:** Dep: 8%; ID: 0%; Anaemia: 0% **12mths:** Dep: 20%; ID: 6%; Anaemia: 0% **18mths:** Dep: 36%; ID: 0%; Anaemia: 0% **24mths:** Dep: 18%; ID: 0%; Anaemia: 0%

1. Values calculated from original publication

1996 Karr, M., et al. Sydney	9 – 62 months	Determine the iron status of preschool children	n=678 9-23mths: n=182 24-35mths: n=176 36-47mths: n=148 48-62mths: n=172 Stratified random sampling by socioeconomic status Quality: IV / + - cross-sectional	Iron Depletion (Dep): **SF:** <12µg/L Iron Deficiency (ID): **SF:** <12µg/L & **MCV:** <70fL (9-24mths) or <73fL (24-62mths) OR **ZPP:** >80µg/dL Iron Deficiency Anaemia (IDA): ID & **Hb:** <110g/L	**Total:** Dep: 10.5%; ID: 2.8%; IDA: 1.1% **9-23mths:** Dep: 18.7%; ID: 5.4%; IDA: 1.4% **24-35mths:** Dep: 14.2%; ID: 3.7%; IDA: 3% **36-47mths:** Dep: 6.8%; ID: 1.7%; IDA: 0% **48-62mths:** Dep: 1.2%; ID: 0%; IDA: 0% *Data of 9 – 23 months only: (n=182)*[1] Dep: 69.8%; ID: 20.3%; IDA: 5.5%
1972 Lovric, V., et al. Sydney	6 – 36 months	Examine nutritional patterns in various social strata and national subgroups, and assess iron intake	n=1000 6-12mths: n=530 12-24mths: n=370 26-36mths: n=100 Stratified random sampling according to suburb Quality: IV / Ø - IDA criteria not specified	Iron Deficiency Anaemia (IDA): **Hb:** <10g/dL or <11g/dL and diagnosed with IDA	*Hb: <10g/100ml* IDA: 3% *Hb: <11g/100m* IDA: 15%
Children					
2005 Heath, D. & Panaretto, K. Townsville	4 – 12 years	Assess the nutritional health status of children	n=157 (M): n=85; (F): n=72 Indigenous: n=72 Non-indigenous: n=85 Convenience sampling from three primary schools with high indigenous enrolment Quality: IV / +	Iron Depletion (Dep): **SF:** <15µg/L Iron Deficiency (ID): **SF:** <15µg/L & **MCV:** <74fL Iron Deficiency Anaemia (IDA): **SF:** <15µg/L **& MCV:** <74fL & **Hb:** <115g/L	**Total:** Dep: 6.3%; ID: 1.6%; IDA: 1.6% **Indigenous:** Dep: 10.7%; ID: 3.6%; IDA: 1.6% **Non-indigenous:** Dep: 2.8%; ID: Not reported; IDA: Not reported

1. Values calculated from original publication

1990 English, R. & Bennett, S. Australia	9, 12 and 15 years National Schools Survey	Determine iron status of Australian children	n=1204 Girls: 9 yrs: n=243 12 yrs: n=191 15 yrs: n=142 Boys: 9 yrs: n=251 12yrs: n=203 15yrs: n=174 Multistage random sampling of school and students Quality: IV / +	<u>Iron Deficiency (ID):</u> 9yrs: **SF:** <10µg/L & **TSAT:** <15% 12yrs: **SF:** <10µg/L & **TSAT:** <16% 15yrs: **SF:** <12µg/L & **TSAT:** <16%	*Girls* **9yrs:** ID: 0% **12yrs:** ID: 1.6% **15yrs:** ID: 9.2% *Boys* **9yrs:** ID: 0.4% **12yrs:** ID: 0.5% **15yrs:** ID: 1.7%
Women Only					
2005 Zhou, S., et al. Adelaide	Pregnancy & 6 months postpartum	Develop and validated an iron checklist for assessing dietary iron intake	n=345 Pregnant: n=168 Postpartum: n=177 Simple random sampling from antenatal clinic at the Women's & Children's Hospital Quality: III-2 / +	<u>Iron Deficiency (ID):</u> **SF:** <12µg/L (pregnant); <15µg/L (postpartum) <u>Iron Deficiency Anaemia (IDA):</u> ID & **Hb:** <110g/L (pregnant); <120g/L (postpartum)	**Pregnant:** ID: 67.5%; IDA: 11.6% **Postpartum:** ID: 26.1%; IDA: 1.1%
1998 Rangan, A., et al. Perth	15 – 30 years Students	Examine the relationship between iron status and non-specific symptoms.	n=255 Secondary: n=41 University: n=214 Volunteer sampling Quality: IV / +	<u>Iron Deficiency (ID):</u> **SF:** ≤12µg/L <u>Iron Deficiency Anaemia (IDA):</u> ID & **Hb:** <12g/dL <u>Anaemia:</u> **Hb:** <12g/dL	ID: 12.5%. IDA: 4.3%. Anaemia: 9.8% (Anaemia values includes IDA value)

1. Values calculated from original publication

1974 McEwin, R., et al. Victoria, South Australia & New South Wales	16 – 61 years Hospital staff	Provide more evidence of the extent of iron deficiency anaemia	n=1024 <20yrs: n=291 20-29yrs: n=475 30-39yrs: n=138 40-49yrs: n=88 50-59yrs: n=24 >60yrs: n=2 Convenience sampling of new staff Quality: IV / Ø - some participants unaccounted for - ID criteria could have been more rigid	Iron Deficiency (ID): **MCHC:** <31%, **SI:** <50µg/dL **TIBC:** >350µg/100ml and **MCV:** <85[3] Anaemia: **Hb:** <12g/dL	**Total:** ID: 4.4%; Anaemia: 4.5% **<20yrs:** Anaemia: 2.1% **20-29yrs:** Anaemia: 4.8% **30-39yrs:** Anaemia: 8% **40-49yrs:** Anaemia: 6.8% **50-60+yrs:** Anaemia: 0%
1969 Davis, R., et al. Brusselton, Western Australia	20 – 70+ years	Describes haemoglobin levels and investigates any abnormalities	n=1693 Range: 21 – 102yrs 20-29yrs: n=273 30-39yrs: n=322 40-49yrs: n=355 50-59yrs: n=322 60-69yrs: n=248 >70yrs: n=173 Volunteer sampling from electoral roll Quality: IV / +	Anaemia: **Hb:** <13g/dL (M); <11.5g/dL (F)	**Total:** 5.4% **20-29yrs:** 1.1% (M); 1.8% (F) **30-39yrs:** 2.1% (M); 5% (F) **40-49yrs:** 0.6% (M); 3.9% (F) **50-59yrs:** 2.5% (M); 1.6% (F) **60-69yrs:** 4.5% (M); 1.2% (F) **70+yrs:** 8.6% (M); 1.2% (F)
Adults					
2008 Ahmed, F., et al. Queensland	25+ years Australian Diabetes, Obesity and Lifestyle Study (AusDiab)	Describe the concentrations of serum ferritin among Australian adults by age and sex	n=1634 (M): n=688; (F): n=946 25-39yrs: n=340 40-49yrs: n=398 50-59yrs: n=349 60-69yrs: n=284 70+ yrs: n=226 Random cluster sampling of six urban sites Quality: III-2 / +	Marginal Iron Deficiency (MID): **SF:** 12µg/L - <20µg/L Iron Deficiency (ID): **SF:** <12µg/L Anaemia: **Hb:** Males <130g/L; Females <120g/L	**Females <50yrs:** MID: 9.7%; ID: 10.6%; Anaemia: 3.8% (ID: 7.1% with Ferritin: <10µg/L) **Females >50yrs:** MID: 2.2%; ID: 2.8%; Anaemia: 3.8% **Males:** MID: 1.2%; ID: 0.3%; Anaemia: 0.6%

1. Values calculated from original publication

2002 Booth, C. & Coad, R. Kapooka, New South Wales	17 – 36 years	Determine the adequacy of Army recruits' usual diet before commencement of training	n=184 (M): 159; (F): 25 Convenience sample of army recruits on first day at Kapooka Army Base Quality: IV / +	<u>Iron depletion (Dep):</u> **SF:** <15µg/L	Dep: 4.4% (2.2% F)
1989 National Heart Foundation Australia	20 – 69 years NHF Risk Factor Survey	Analysis of 1989 Risk Factor Prevalence Survey in relation to iron status	n=5971 (M): n=1704 (F): n=4267 20-29yrs: n=1132 30-39yrs: n=1492 40-49yrs: n=1443 50-59yrs: n=995 60-69yrs: n=909 Simple random sampling Quality: IV / +	<u>Iron Deficiency (ID):</u> **SI:** <8µmol/L, **SF:** <20µg/L (F) or **SF:** <10µg/L (M), **TSAT:** <10%	**Total:** 0.5% (M); 6.8% (F) **20-29yrs:** 0.3% (M); 6.9% (F) **30-39yrs:** 0.7% (M); 7.1% (F) **40-49yrs:** 0% (M); 12.2% (F) **50-59yrs:** 1.4% (M); 2.7% (F) **60-69yrs:** 0% (M); 2% (F)
Vegetarians 1999 Ball, M. & Bartlett, M. Victoria	18 – 45 years Females	Investigate the nutritional intake and iron status of vegetarian women	n=74 Vegetarians: n=50 Omnivores: n=24 Convenience sampling via paper advertisements and recruited participants Quality: IV / +	<u>Iron Deficiency (ID):</u> **SF:** <12µg/L	**Vegetarians:** ID: 18% **Omnivores:** ID: 12.5%

1. Values calculated from original publication

1999 Wilson, A. & Ball, M. Melbourne	20 – 50 years Males	Investigate the iron intake and status of male vegetarians	n=74 Ovolactovegetarians: n=39 Vegans: n=10 Omnivores: n=25 Convenience sampling via paper advertisements and recruited participants Quality: IV / +	<u>Beginning of iron depletion (BDep):</u> **SF:** <25µg/L <u>Iron Depletion (Dep):</u> **SF:** <12µg/L	**Ovolactovegetarians:** BDep: 20.5%; Dep: 3% **Vegans:** BDep: 30%; Dep: 25% **Omnivores:** BDep: 0%; Dep: 0%
1987 Helman, A. & Darnton-Hill, I. Sydney	18+ years	Assess biochemical status of a number of vitamins and iron in a group of new vegetarians	n=173 Mean age: 29.3yrs (V); 31yrs (O) Vegetarians (V): n=60 (M); n=60 (F) Omnivores (O): n=13 (M); n=40 (F) Convenience sample from a meditation centre and two laboratories Quality: III-2 / + - minimal iron info	<u>Iron deficiency (ID):</u> **SF:** <20 µg/L (M); <15 µg/L (F)	**Vegetarians:** ID: 5% (M); 27% (F) **Omnivores:** ID: 8% (M); 12% (F)
Aborigines					
2007 Mackerras, D. & Singh, G. Northern Territory	9 – 13 years Aboriginal Birth Cohort Study	Compared the prevalences resulting from different iron status definitions and explored the reasons for the variations	n=517 Cross-sectional survey within The Aboriginal Birth Cohort Study. Multistage random sampling. Quality: IV / +	<u>Anaemia:</u> 9-12 years - **Hb:** <11.5g/dl 12-13 years - **Hb:** <12g/dl	**Total children:** 13.2% **9-11yrs:** 9.4% **Boys 12-13yrs:** 13.6% **Girls 12-13 yrs:** 28.9%

1. Values calculated from original publication

1988 Harris, M., Cameron, B. & Florin, S. New South Wales	0.5 – 6 years	Examines prevalence of iron deficiency in Bourke children	n=212 Aboriginal (A): n=121 Non-aboriginal (O): n=91 Convenience sample of children having blood tests at Bourke Hospital and preschool centres Quality: IV / Ø - No incl/excl criteria - Not representative sample - measurements of outcomes and risk factors not blinded	<u>Iron deficiency (ID):</u> SF <10µg/L	**0.5 – 1.9 years:** ID: (A) 33.3%; (O) 13.6% **2 – 3.9 years:** ID: (A) 5.1%; (O) 8% **4 – 6 years:** ID: (A) 15.2%; (O) 2.3% **Total:** ID: (A) 17.4%; (O) 6.6%
1986 Watson, D. & Toxer, R. Northern Territory	5+ years	Establish the prevalence and causes of anaemia	n=426 *24% ≤ 12yrs* (M): n=183; (F): n=243 Convenience sample from health care centre Quality: IV / Ø - ID criteria not reported - no incl/excl criteria - many assumptions	<u>Iron deficiency (ID):</u> Not reported <u>Anaemia:</u> **Hb:** <110g/L	ID: 8.2% Anaemia: 11% (ID: 77%)
Migrants					
2004 Nguyen, N., et al. Sydney	18 months Vietnamese Infant Growth Study	Estimate the prevalence of iron deficiency in Vietnamese children living in Australia and identify associated risk factors	n=174 Simple random sampling via antenatal clinics from three main public hospitals in South-western Sydney Quality: III-2 / +	<u>Iron Depletion (Dep):</u> **SF:** <10µg/L. <u>Iron Deficiency (ID):</u> **SF:** <10µg/L & **MCV:** <70fL <u>Iron Deficiency Anaemia (IDA):</u> ID & **Hb:** <110g/L	Dep: 19.4%; ID: 2.3%; IDA: 3.9%

1. Values calculated from original publication

2007 McGillvray, G., et al. Melbourne	0 – 17 years East African	Assess the pattern of and risk factors for Vitamin D Deficiency in immigrant East African children	n=232 (8.9±4.4yrs) (M): n=125; (F): n=107 Convenience sample of children attending an immigrant health clinic at the Royal Children's Hospital Quality: III-2 / +	<u>Iron Deficiency (ID):</u> **SF:** <6µg/L (<6yrs), <10µg/L (6-9yrs), <23µg/L (males ≥10yrs), <6µg/L (females ≥10yrs) <u>Iron Deficiency Anaemia (IDA):</u> **Hb:** <105g/l (<2yrs), <110g/l (2-5yrs), <115g/l (6-11yrs), <120g/l (≥12yrs) & hypoferritinaemia	ID: 19%; IDA: 10%
Athletes					
2008 Fallon, K. Australian Institute of Sport (AIS)	9 – 34 years	Determine the clinical and performance related utility of haematological and iron-related screening in elite athletes	n=576 (M): 303; (F): 273 Convenience sampling of AIS athletes Quality: III-2 / +	<u>AIS criteria for iron supplementation:</u> **SF**: <30µg/L	**Males:** 3.3% (range: 11.4 – 29.5µg/L) **Females:** 19% (4.4% with SF <20µg/L) **Total:** 10.8%
1991 Telford, R & Cunningham, R	16 – 29 years	Investigate the relationship of five routine haematological measures for a particular sport for which the athlete was trained	n=706 (M): n=368; (F): n=238 - difference of 100 Quality: IV / Ø	<u>Iron deficiency (ID):</u>[2] **Hb:** (M) <13g/dL; (F) <12g/dL	ID: <1-2% [2]

1. Values calculated from original publication

Conclusion – Infants and Children (0 – 5 years) – Caucasian ethnicity only

Iron depletion:	9 months	8%
	1 – 3 years	14.2% - 36%
	3 – 4 years	6.8%
	4 – 5 years	1.2%
Iron deficiency:	9 months	0%
	1 – 3 years	1% - 27%
	3 – 4 years	1.7%
	4 – 5 years	0%
IDA:	9 months	1.4%
	1 – 3 years	1.4% - 6%
	3 – 4 years	0%
	4 – 5 years	0%

Conclusion – Children & Adolescents – Caucasian ethnicity only

Iron depletion:	4 – 12 years	2.8%
Iron deficiency:	9 years	(F) 0%, (M) 0.4%
	12 years	(F) 1.6%, (M) 0.5%
	15 years	(F) 9.2%, (M) 1.7%

Conclusion – Vegetarians

Iron depletion:	20 – 50 years	(Ovo) 3%, (Vegan) 25%
Iron deficiency:	18 – 45 years females	18%
	18 + years	(M) 5%, (F) 27%

Conclusion – Migrants

(a) Vietnamese		
Iron depletion:	18 months	19.4%
Iron deficiency:	18 months	2.3%
IDA:	18 months	3.9%
(b) East African		
Iron deficiency:	0 – 7 years	19%
IDA:	0 – 7 years	10%

Conclusion – Women – Caucasian ethnicity only

Iron depletion:	17 – 36 years	2.2%
Iron deficiency:	Pregnant	67.5%
	6 months postpartum	26.1%
	15 – 30 years	12.5%
	16 - 61 years	4.4%
	25 – 50 years	10.6%
	> 50 years	2.8%
IDA:	Pregnant	11.6%
	6 months postpartum	1.1%
	15 – 30 years	4.3%

Conclusion – Males – Caucasian ethnicity only

Iron deficiency:	15 – 30 years	0.3 – 5%
	20 – 69 years	0.5%
	25 + years	0.3%

Conclusion – Aborigines

Iron deficiency:	6 – 24 months	33.3%
	2 – 4 years	5.1%
	4 – 6 years	15.2%
	5 + years	8.2%

Conclusion – Athletes

SF <30µg/L:	9 – 34 years	(M) 3.3%, (F) 19%

1. Values calculated from original publication

Summary Table: iron intakes & status of New Zealanders

	Group	Purpose	Sample	Criteria for risk	% of group at risk
Infants & Young Children					
2007 Grant, C. Auckland	6 – 23 months	Estimate the prevalence of iron deficiency and the associated factors	n=324 Pacific: 24% Maori: 18% European/other: 58% Ethnically stratified sample identified from random residential address start points Quality: III-2 / +	Iron Deficiency (ID): ≥ 2 abnormal values for: **SF:** <10µg/L, **ISAT:** <10%, **MCV:** <73fL Iron Deficiency Anaemia (IDA): ID & **Hb:** <110g/L	ID: 14% (Maori 20%, Pacific 17%, Other 27%, NZ European 7%). IDA: 6%
2002 Heath, A., et al. Dunedin	9, 12, 18 & 24 months	(i) Investigate energy, iron, zinc, calcium and vitamin C intakes prospectively (ii) Determine the prevalence of iron deficiency anaemia	n=74 Self-selected Sample from Births, Deaths and Marriages, and from birth notices in the local newspaper Quality: III-2 / +	Iron-Deficient Erythropoiesis (IDE): **MCV:** <77fL & **ZPP:** > 80µg/dL Iron Deficiency Anaemia (IDA): **Hb:** <110g/L & **MCV:** <77fL	**9 months:** IDE: 19%; IDA: 7% **12 months:** IDE: 22%; IDA: 7% **18 months:** IDE: Not reported; IDA: 7% **24 months:** IDE: 13%; IDA: 0%
2004 Soh, P., et al. South Island	6 – 24 months	Determine the prevalence of biochemical iron deficiency and identify factors associated with ferritin levels	n=231 6-11.9mths: n=72 12-24mths: n=159 Multistage random sampling of children in Christchurch, Dunedin and Invercargill Quality: IV / +	Iron Depletion (Dep): **SF:** <10µg/L or <12µg/L Iron Deficiency (ID): **SF:** <10µg/L or <12µg/L & two out of three of **MCV:** <73fL **ZPP** ≥70µmol/mol haem, **SF:** <10µg/L or <12µg/L Iron Deficiency Anaemia (IDA): ID & **Hb:** <110g/L	*SF: <10µg/L* **6-11.9mths:** Dep: 4.2%, ID: 2.8%, IDA: 5.6% **12-24mths:** Dep: 14.4%, ID: 5%, IDA: 2.5% **Total:** Dep: 12.6%, ID: 4.3%, IDA: 3.5% *SF: <12µg/L* **6-11.9mths:** Dep: 8.3%, ID: 4.2%, IDA: 6.9% **12-24mths:** Dep: 23.3%, ID: 6.3%, IDA: 3.1% **Total:** Dep: 18.6%, ID: 5.6%, IDA: 4.3%

1. Values calculated from original publication

Children					
1999 Schaaf, D., et al. Auckland	14 – 18 years High school students	Determine the frequency and possible causes of iron deficiency and anaemia	n=1644 Pacific: n=765 Asian: n=350 European: n=295 Maori: n=234 Convenience sample from eight schools with ≥15% Pacific ethnicity Unable to determine quality	Iron Deficiency (ID): Two or more of **SF:** <12µg/L, **TSAT:** <14%, **RCDW:** >14.5% Anaemia: **Hb:** <120g/L females; <130g/L males	**Total:** ID: 18.3% (F); 1.5% (M), Anaemia: 11.5% (F); 1.4% (M) **Maori (F):** ID: 25.6%, Anaemia:11.2% **Pacific (F):** ID: 20.9%, Anaemia: 12.1% **Asian (F):** ID: 15.4%, Anaemia: 15.9% **European (F):** ID: 8.3%, Anaemia: 4.2%
Women Only					
2001 Ferguson, E., et al. New Zealand	15 – 49 years Females only	Assess dietary iron intakes and biochemical iron status	n=1751 15-19yrs: n=163 20-35yrs: n=894 36-49yrs: n=694 Maori: n=373 Pacific: n=166 NZ European/other: n=1212 Random sampling in the NNS 97 - nationally representative Quality: IV / +	Iron Deficiency (ID): **SF:** <12µg/L or <16µg/L & **ZPP:** >60 µmol/mol haem or only **SF:** <12µg/L or <16µg/L Iron Deficiency Anaemia (IDA): ID & **Hb:** <120g/L	*SF: <12µg/L* **15-19yrs:** ID: 0.7%, IDA: 5.5% **20-35yrs:** ID: 3.8%, IDA: 2% **36-49yrs:** ID: 5%, IDA: 4.1% **Maori:** ID: 4.8%, IDA: 7.3% **Pacific:** ID: 0%, IDA: 5% **NZ European & other:** ID: 4%, IDA: 2.5% *SF: <16µg/L* **15-19yrs:** ID: 12.6%, IDA: 5.5% **20-35yrs:** ID: 8.8%, IDA: 3% **36-49yrs:** ID: 8.7%, IDA: 4.1% **Maori:** ID: 9.7%, IDA: 7.3% **Pacific:** ID: 1%, IDA: 5% **NZ European & other:** ID: 9.4%, IDA: 3.1%
Vegetarians					
1994 Alexander, D. et al. New Zealand	26 – 30 years	Investigate nutrient intake and haematological status	n=100 Vegetarian: (M) n=14; (F) n=36 Omnivores: (M) n=14; (F) n=36 Volunteer sampling Quality: IV / +	Iron Deficiency (ID): **SF:** <12µg/L	**Vegetarian:** ID: (M) 29%; (F) 47% **Omnivores:** ID: (M) 7%; (F) 42%

1. Values calculated from original publication

Blood Donors					
2008 Badami, K. & Taylor, K. Christchurch & Waikato	16+ years	Assess iron status of New Zealand blood donors	n=5006 Waikato: n=3001 Christchurch: n=2005 (M): n=2395 (F): n=2611 <20yrs: n=415 21-50yrs: n=2867 50+ yrs: n=1724 Convenience sample at two blood services Quality: IV / +	Borderline Iron Deficiency (BID): **SF:** 12-20µg/L Iron deficiency (ID): **SF:** <12µg/L	**Waikato:** BID: 17.5%; ID: 13% **Christchurch:** BID: 24.6%; ID: 15.8% **Males:** BID: 20.2%; ID: 7.8% **Females:** BID: 20.5%; ID: 19.9% **<20yrs:** BID: 26.2%; ID: 19% **21-50yrs:** BID: 20.4%; ID: 15.6% **50+ yrs:** BID: 18.9%; ID: 10.4% **Overall:** BID: 20.4%; ID: 14.1%

Conclusion – Infants and Children (0 – 5 years) – All ethnicities

Iron depletion:	12 months	4.2%
	24 months	14.4%
IDE:	9 months	19%
	12 months	22%
	24 months	13%
Iron deficiency:	9 - 23 months	14%
	12 months	2.8%
	24 months	5%
IDA:	9 – 23 months	6%
	9 months	7%
	12 months	5.6% - 7%
	18 months	7%
	24 months	0%

Conclusion – Children & Adolescents – All ethnicities

Iron deficiency:	14 – 18 years	(F) 18.3%, (M) 1.5%

Conclusion – Blood Donors

Iron deficiency:	< 20 years	19%
	21 – 50 years	15.6%
	50 + years	10.4%
	Males	7.8%
	Females	19.9%

Conclusion – Women – All ethnicities

Iron deficiency:	15 – 19 years	0.7%
	20 – 35 years	3.8%
	36 – 49 years	5%
IDA:	15 – 19 years	5.5%
	20 – 35 years	2%
	36 – 49 years	4.1%

Conclusion – Vegetarians

Iron deficiency:	26 – 30 years	(F) 47%, (M) 29%

1. Values calculated from original publication

Key:

MCHC = Mean corpuscular haemoglobin concentrations
SF = Serum Ferritin
SI = Serum Iron
TFN = Transferrin
TSAT = Transferrin saturation
ISAT = Iron saturation
MCV = Mean corpuscular volumes
ZPP = Zinc protoporphyrin
Hb = Haemoglobin
RCDW = Red cell distribution width
TIBC = Total iron binding capacity
F = Females
M = Males
mole = Number of atoms in 12 thousandths of a kilogram (0.012kg)
µmol = Micromole, one millionth of a mole
µg = Microgram, one millionth of a gram
fL = Femtoliters, one quadrillionth of a litre (10^{-16} Litre)
pg = Picogram, 1000pg in 1µg (10^{-12} grams)

1. Values calculated from original publication

Iron: Dietary Strategies – Interventions only

	Group	Purpose	Study Sample	Study Design	Findings	Conclusion
Infants & Young Children – Aged 0 – 3 years						
2002 Makrides, M., et al. South Australia (P)	6 months	Investigate effect of consumption of 4 egg yolks/wk on infant DHA status, haemoglobin, ferritin and plasma cholesterol concentrations	n=137 Breastfed (BF): n=70 (CG: n=23; IG1:n=23; IG2: n=24) Formula fed (F): n=67 (CG: n=23; IG1:n=24; IG2: n=20) Inclusion criteria: - healthy infants - 6mths age - >37 wk gestation - birth weight >2500g - No protein allergies / intolerances Simple random sampling Quality: II / +	Randomised Controlled Trial Intervention: (6 months) - CG: no dietary intervention - IG1: 4 x egg yolks/wk - IG2: 4 x n-3 fatty acid enriched egg yolks/wk NB: Egg yolk intervention (Y) includes IG1 & IG2 Assessment: - 6, 9 and 12 months	*6 & 12 mths:* - Hb, SF and TFN values didn't differ significantly between IG1, IG2 and CG (both breastfed and formula fed) - No significant difference in iron status (both breastfed and formula fed) *12 mths:* SI and TSAT higher in Egg yolk intervention vs CG: - Breastfed: SI:10.5±4.5µmol/L (Y); 8.3±3.4µmol/L (CG). TSAT: 14.3±6.8% (Y);10.8±4.6% (CG) - Formula fed: SI:10.5±4.7µmol/L (Y); 8.2±2.9µmol/L (CG). TSAT: 14.6±6.6% (Y); 11.6±4.5% (CG)	Egg yolks may be useful source of iron during weaning period
1999 Morley, R. et al. United Kingdom (T)	9 months	Test hypothesis that feeding iron supplemented formula would improve developmental performance	n=493 CG: n=166 IG1: n=165 IG2: n=162 Inclusion criteria: - healthy, singleton infants - birth weight ≥2500g - fed unfortified milk - no disease that impairs growth or development - no history iron supplementation Convenience sample with random sampling Quality: II / +	Randomised Controlled Trial Intervention: (9 months) - CG: cows' milk [1](~0.05 mg iron/L) - IG1: unfortified formula milk (~0.9 mg iron/L) - IG2: formula milk (~1.2 mg iron/L as ferrous sulphate) Assessment: - 18 months	Iron fortified formula had significantly higher plasma ferritin concentrations (P<.0001): CG: 14.3±0.28µg/L IG1: 13.1±0.24µg/L IG2: 21.7±0.22µg/L No significant intergroup differences in development or growth	No developmental or growth advantages in children given iron supplemented formula Cannot exclude possible benefit for anaemic children or the possibility that a benefit may emerge at a later age

1. Values calculated from original publication

1998 Makrides, M., et al. South Australia (P)	6 months	Determine if increasing dietary iron from weaning foods would improve iron status of breastfed infants	n=62 CG: n=26 IG: n=36 Inclusion criteria: - Socially advantaged families - >37 wk gestation - birth weight >2500g - exclusively breastfed to 6mths with intent to 12mths - No chronic disease or iron supplements Random sampling Quality: II / +	Randomised Controlled Trial Intervention: - 4 x jars iron fortified cereal/wk (~4.1mg iron/day) - 4 x serves meat/wk (~0.9mg iron/day) Dietary intake assessed at 6, 9, 12 months Iron status assessed at 6, 12 months If IDA developed, infants withdrwn for treatment	Iron intake at 12mths: - IG: 8.2±2.9 mg/d - CG: 5.2±3.4 mg/d Haemoglobin at 12mths: - IG: 120±7 mg/L - CG: 115±9 mg/L No differences in SF, TFN, SI & TSAT ID (SF <10mg/L): 11.3% - IG: n=5; CG: n=2 IDA at 12mths: 0%	Increasing iron intake from weaning foods had little effect on iron status at 6 – 12mths Larger trials needed Possible iron stores at birth may be important determinant of iron levels at 12 months Findings may not apply to malnourished and low birth weight populations
1998 Engelmann, M. et al. Denmark (P)	8 months	Examine effect of increased meat intake iron indices in late infancy	n=41 LMG: n=20 HMG: n=21 Inclusion criteria: - term birth - birth weight ≥2500g - no neonatal disease or malformation - no severe illness - partially breast-fed Simple random sampling Quality: III-1 / +	Blind, parallel intervention study Intervention: (2 months) - LMG: low-meat group with mean meat content 10g/d (average in observational study of infants from the same area) - HMG: high-meat group diet with mean meat content 27g/d Assessment: - baseline and 2 months Iron depletion (Dep): SF <10µg/L Iron deficiency anaemia (IDA): Hb <105g/L and SF <10µg/L	Significant changes in Hb conc. (P=.008): LMG: -4.9 g/l (range, -12.9-5.6 g/l) and HMG -0.6 g/l (range, -12.1-7.3 g/l) No significant difference in SF or TFR between LMG and HMG Mean iron intake from meat significantly higher (p = 0.0001) in HMG (0.4 mg/day) than LMG (0.1 mg/day) No significant difference in total iron intake between the HMG (3.1 mg/day) & LMG (3.4 mg/day)	Increase in meat intake can prevent a decrease in Hb in late infancy However, there was no effect on iron stores or on cellular iron deficiency, evaluated by SF and TfR levels, respectively
Children						
2004 Snetselaar, L. et al. United States (P)	Adolescents 7th and 8th grade at school	Compare ferritin, zinc and cholesterol levels of adolescents following cholesterol-lowering eating patterns	n=86 LB: n=42 LPF: n=44 Inclusion criteria: - LDL cholesterol levels in top half of distribution Random sampling Quality: II / +	Randomised Controlled Trial Intervention: (3 months) -All: Limit saturated fat 20g/d. Consume study meat minimum 5 meals/wk & comparison meat ≤2 meals/wk IG1 = LB: Lean beef IG2 = LPF: Lean poultry/fish Assessment: - baseline and 3 months	Significant difference (p<0.01) in SF between both groups: - LB: unchanged [baseline 31.2µg/L (26, 43); 3 mths 38.7µg/L (22, 45)] - LPF: decreased by median 6.8µg/L (IQR: -12,2) [baseline 32.5µg/L (25, 43); 3 mths 26.7µg/L (17, 39)] Similar iron intake in both groups	Reduced SF possibly due to reduced haem iron in poultry & fish Incorporate foods with absorbable iron to maintain iron status

1. Values calculated from original publication

1999 Ames, S. et al. United States	3 – 5 years	Evaluate relation between calcium intake and calcium absorption and iron incorporation into red blood cells	n=11 (M): n=6; (F): n=5 Inclusion criteria: - no chronic disease - no medications or vitamin supplements Quality: III-1 / +	Pseudo-randomised trial Intervention: (5 weeks) - High Ca^{2+} diet - Low Ca^{2+} diet After 5 weeks: - 10µg Ca^{2+} IV infusion - Meal with Ca^{2+} isotopes & Fe After 15 days, participants switched to other diet Assessment: - baseline, 5 and 10 weeks	Iron intakes didn't differ significantly: - High: (9.7 ± 5.0 mg Fe/d) and Low: (9.0 ± 3.6 mg Fe/d) RBC incorporation of iron didn't differ significantly between two diets	Small children may benefit from calcium intakes similar to those recommended for older children without adverse effects on dietary iron utilization
Women Only						
2009 Navas-Carretero, S., et al. Spain (P)	21 – 25 years Females	Compare iron bioavailability of three meat pate products	n=17 Inclusion criteria: - healthy women - non-smoker - non-pregnant - Hb >110g/L - SF <30µg/L - History IDA or family history of anaemia - No iron supps, blood donor, medication influence iron metabolism in past 12mths Volunteer sampling from university Quality: II / +	Three-way randomized, crossover, double-blind postprandial intervention Intervention: (6 hours) 2 x slices white bread (25g) with either: - P1: Pate fortified with ferrous sulphate (iron = 20.19±1.08) – NB: 6.5g of P1 discarded before eating to ensure equivalent iron content in each meal - P2: Pate fortified with ferric pyrophosphate encapsulated in liposomes (Lipofer) (iron = 18.42±1.47) - P3: Pate fortified with with Lipofer and an added pigment (Aprored) (iron = 18.95±0.93) Assessment: - hourly	Biomarker results only given for SI: Evolution of SI concentration similar with the three meals - maximum concentrations obtained between 2 – 4 hours - Approx 20 - 23 µmol/L Type of fortificant not significant Baseline: (mean ± s.d.) - SF: 18.03±12.26 µg/L - SI: 14.5±7.39 µmol/L - TFN: 307.87±46.10 mg/dL - TSAT: 25.16±13.47%	Consumption of meat pate fortified with ferric pyrophosphate encapsulated in liposomes can be part of dietary strategy for preventing ID Further research into addition of larger quantities of meat pigment rich in haem iron required

1. Values calculated from original publication

2001 Patterson, A. J., et al. New South Wales (T)	18 – 50 years Female only	Compared effects of iron supplementation and a high-iron diet on serum ferritin and hemoglobin in iron-deficient women	n=66 CG: n=22 IG1: n=22 IG2: n=22 Inclusion criteria: - no major illness - childbearing age - menstruation - non-pregnant - no hysterectomy - haemoglobin ≥90g/L Quality: III-1 / +	Pseudo-randomised trial Intervention: (12 weeks) - CG: no intervention - IG1: supplement of 105mg iron per day as 350mg ferrous sulphate - IG2: dietary counselling to increase haem intake & non-haem absorption by combining with vitamin C and meat; decrease inhibitors by tea/dairy in between meals (recommended intake of 2.25mg absorbable iron) <u>Iron Repletion:</u> Hb ≥120g/L & SF >20µg/L <u>Iron Deficiency:</u> SF <15µg/L or SF 15-20µg/L & two of SI <10µmol/L, TIBC >68µmol/L, TSAT <15% Assessment: - baseline, 12 weeks, 6 months	IG1: Mean SF increased from 9.0±3.9µg/L at baseline to 24.2±9.8µg/L after intervention and remained stable during follow-up. IG2: Mean SF increased from 8.9±3.1µg/L to 11.0±5.9µg/L but continued to increase during follow-up to 15.2±9.5µg/L Mean haemoglobin improved in both intervention groups but only significant in IG1	High-iron diet produced smaller increases in SF compared to iron supplementation. But resulted in continued improvements in iron status during 6mth follow-up
1992 Lyle, R. et al. United States (P)	17 – 22 years Females only	Report effect of oral consumption vs increased muscle food consumption on iron status in previously sedentary women participating in 12 week moderate aerobic-exercise program	n=60 IG1: n=10 IG2: n=10 IG3: n=14 IG4: n=12 CG: n=13 Inclusion criteria: - Caucasian women - live on Purdue University Campus - no participation in exercise program in previous 6 months Convenience sample randomised to intervention group Quality: II / +	Randomised controlled trial: Intervention: (12 weeks) - IG1: 50mg iron capsule, low food-iron diet, exercise - IG2: 10mg iron capsule, low food-iron diet, exercise (total iron intake 18mg/d) - IG3: placebo, free-diet, exercise - IG4: high iron diet with low fat muscle-food (total iron 18mg/d), exercise - CG: free-diet, no exercise Assessment: - baseline, 4, 8 and 12 weeks	Iron status in IG1 and IG4 improved after week 4 as indicated by increase in SF, SI, Hb **IG4: SF** - baseline: 23.7±14.9µg/L - 4 wk: 20.9±19.9µg/L - 8 wk: 24.4±13.9µg/L - 12 wk: 29.2±16.0µg/L **SI:** - baseline: 16.3±1.6µmol/L - 4 wk: 13.3±4.4µmol/L - 8 wk: 15.2±5.7µmol/L - 12 wk: 16.4±6µmol/L **Hb:** - baseline: 116±12g/L - 4 wk: 110±12g/L - 8 wk: 117±11g/L - 12 wk: 124±13g/L (significantly different at 12wks compared to baseline)	Short-term, moderate aerobic exercise resulted in compromised iron status offset by varying degrees by ingesting iron or meat supplements Meat supplements more effective in protecting Hb and SF status than iron supplements

1. Values calculated from original publication

Adults						
2007 Hodgson, J. M., et al. Western Australia (P)	20+ years	Determine if increase in unprocessed lean red meat intake adversely influences markers of oxidative stress and inflammation	n=60 CG: n=31 IG: n=29 Inclusion criteria: - Non-smoker - elevated blood pressure - ≤3 antihypertensive agents - No change in drug therapy within 3mths - No confounding medical conditions - Alcohol <200g/wk (F); <300g/wk (M) Simple random sampling Quality: III-1 / +	Parallel-designed study Intervention: (8 weeks) - CG: maintain current diet - IG: partially replace energy from carbohydrate with protein from lean red meat for 8 weeks (~215g/d raw wt). Objective: ↑ 35-40g/d compared to CG Assessment: - baseline, 8 weeks	IG: increased iron intakes [3.2 (1.1, 5.4) mg/d] IG: Partial replacement of dietary carbohydrate with lean red meat did not increase any markers of iron status IG: SI and TSAT significantly lowered from baseline compared to CG SF not affected by the diets	Results show partial replacement of dietary carbohydrate with protein from lean red meat does not elevate oxidative stress or inflammation But doesn't rule out link between iron status and oxidative stress and inflammation Study not showing benefit of increased dietary iron intake on iron status, yet study wasn't designed to do so
2003 Wells, A. et al. United States (P)	59 – 78 years Males only	Test that older men who consumed a vegetarian (lacto-ovo) diet would develop a lower iron status compared with older men who consumed a beef containing diet, during a period of resistive training	n=21 Beef group: n=10 Vegetarian (CG):n=11 Inclusion criteria: - BMI <35kg/m^2 - No participation in resistance training over past year - No adverse conditions Simple random sampling Quality: III-1 / Ø - small sample size - inability to separate effects of diet and RT on iron and haematological indicators	Experimental, repeated measures study Intervention: (14 weeks) - All: consumption of vegetarian diet for 2 weeks (baseline) - 0.6g protein/kg/d texturized vegetable protein meat-analog products - IG: Beef group: 0.6g protein/kg/d beef products - CG: continued vegetarian diet above Assessment: - baseline at 2 weeks, 7 weeks (after 5 weeks resistance training), 14 weeks (after 12 weeks resistance training)	Similar total iron intake between the two groups Beef group had 3-4 times greater intake bioavailable iron No significant differences in SI, TIBC, TSAT and TFR between beef and vegetarian groups SF decreased over time in both beef and vegetarian groups during resistive training	Resistance training suggested to reduce iron stores Older men who consume a beef containing, higher-bioavailable-iron diet, compared with a vegetarian, lower-bioavailable-iron diet, have an increased hematological profile during a 12-week period of resistance training

1. Values calculated from original publication

2001 Heath, AL., et al New Zealand (T)	18 – 40 years	Investigate efficacy of: (1) dietary regime with increased consumption of iron-rich foods and enhancers, and decreased consumption of inhibitors; (2) low dose iron supplement	n=57 CG: n=19 IG1: n=16 IG2: n=22 Inclusion criteria: - not pregnant or lactating - regular menstruation - no health problems likely to influence iron status - No anorexia, bulimia or veganism Quality: II / +	Randomized placebo-controlled Study Intervention: (16 weeks) - CG: placebo - IG1: supplement of 50mg iron/ day as amino acid chelate - IG2: diet counselling <u>Mild iron deficiency (MID):</u> SF <20µg/L and Hb ≥120g/L Assessment: - baseline, 4, 8, 12 and 16 weeks	IG2 significantly increased intake of flesh foods, haem iron, vitamin C and foods cooked in cast-iron cookware IG2 significantly decreased intake of phytate and calcium SF increase compared to CG: IG1: 59%; IG2: 26% Mean SF for IG2: - baseline: 10.3µg/L - 4 weeks: 10.7µg/L - 8 weeks: 11.7µg/L - 12 weeks: 11.9µg/L - 16 weeks: 14.0µg/L Mean sTfR:SF ratio for IG2: - baseline: 564.0 - 4 weeks: 524.1 - 8 weeks: 451.5 - 12 weeks: 472.2 - 16 weeks: 393.5	Demonstrates that an intensive dietary program has the potential to improve the iron status of women with iron deficiency

1. Values calculated from original publication

Iron: Dietary Strategies – Other Studies

	Group	Purpose	Study Sample	Study Design	Findings	Conclusion
Infants & Young Children – Aged 0 – 3 years						
2007 Hopkins, D. et al. United Kingdom ALSPAC 1993-1994	8 months	Investigate relationship between iron status and type of milk and weaning solids consumed	n=928 8 mths: n=928 12 mths: n=782 Inclusion criteria: - delivery between Apr '91 – Dec '92 Simple random sampling Quality: III-2 / + - although no inclusion criteria	Observational Cohort Study Study groups: - Breast milk group (BM): breast milk with/without cows milk Formula milk group (FM): formula with/without breast milk and/or cows' milk - Cows' milk group (CM): cows milk only <u>Low SF:</u> <16µg/L <u>Anaemia:</u> Hb <110g/dL Assessment: - Blood samples at 8 and 12 months - 3 day record at 8 months	12 months: Low ferritin associated with calcium intake (OR = 4.16, p = 0.003) Every standard deviation increase (about 250 mg) in calcium content of the diet there was a drop in mean ferritin concentration of about 20%. Largest contributor to iron intake: commercial baby food (90.7%), fortified breakfast cereals (71.6%)	Feeding high volumes of milk reduced energy and iron intake from solid foods Protein and non-haem iron intake generally had a positive influence on markers of iron status, while calcium had a negative effect
2003 Thorsdottir, I. et al Iceland	6 months	Investigate effects of growth and food intake on iron status in a population with high birth weight and high frequency of breast-feeding	n=171 CG: n=57 SG: n=114 Inclusion criteria: - singleton birth - 37-41wks gestation - birth weight 10-90th percentile - no birth defects or diseases - Icelandic parents - regular antenatal care Random sample Quality: III-2 / +	Longitudinal Observation Study <u>Iron Deficiency (ID):</u> SF <12µg/L & MCV <74fL <u>Iron Deficiency Anaemia (IDA):</u> Hb <105g/L, and ID Assessment: - Weighed 2 day record at 6, 12 and 18 months - CG only at 9 months	9 – 12 months: Iron status indices negatively associated with cow's milk consumption, significant above 460 g/day, but positively associated with iron-fortified breakfast cereals, fish and meat consumption	Diet of 9 – 12-month-olds should avoid cow's milk above 500 g/day and include fish, meat and iron-fortified breakfast cereals to improve iron status

1. Values calculated from original publication

2001 Male, C. Europe Euro Growth Study	Newborns	Assess prevalence of iron deficiency and to study influence of socio-economic status, dietary factors, growth and morbidity on iron status	N=488 (M) 261; (F) 222 Inclusion criteria: - healthy term infants - primary healthcare centres in 11 European areas - Euro Growth Study Criteria Quality: III-2 / +	Longitudinal Cohort Study Assessment: - semi-quantitative recall within 4 days of age 30, 60, 91, 122, 153, 183 days and within 14 days of age 274 and 365 days - Blood samples at 365 days	12 months: - Early introduction of cows' milk strongest negative determinant of iron status (every month of cows' milk = average decrease of 2 g/L in Hb at 12 months) - Iron-fortified formula main factor positively influencing iron status - No significant role for other dietary factors, including breastfeeding	Avoidance of cows' milk when feeding during the first year of life is the key measure in the prevention of iron deficiency
2001 Cowin, I. et al. United Kingdom ALSPAC	18 months	Investigate associations between composition of the diet, ferritin and haemoglobin levels	n=796 Hb: n=796 SF: n=718 Inclusion criteria: - delivery between Apr '91 – Dec '92 Simple random sampling Quality: IV / + - 3d unweighed food record to assess diet	Cross-sectional Study Assessment: - 3 day unweighed food record and heel-prick capillary blood sample at 18 months	SF negatively associated with amount of cows' milk consumed (r= -0.2462, P<0.001) and calcium intake (equivalent to a 4 ± 5% drop in SF for a 100 mg increase in energy-adjusted calcium) Hb positively associated with energy-adjusted vitamin C intake - higher in children who ate any fruit (P.0.024) or any vegetables (P.0.030)	Higher levels of milk and dairy products associated with lower SF Fruit and vegetable consumption should be encouraged Inclusion of a little meat or fish in the diet of small children is advisable

1. Values calculated from original publication

1996 Mira, M. et al. New South Wales	12 – 36 months	Compare intakes of haem and non-haem iron in iron depleted and iron replete children	n=124 Iron depleted: n=56 Iron replete: n=68 Inclusion criteria: - aged 12 – 36mths Convenience sampling Quality: III-2 / +	Case-control study Intervention: - CG: iron replete - 3 day weighed record - IG: iron depleted – 3 day weighed record <u>Iron Depletion (Dep):</u> SF ≤10µg/L	Average daily intake of haem iron significantly lower in iron depleted group (P=0.018) Low intake of haem iron significantly associated with iron depletion with odds ratio of 3.0 (P=.005) Proportion of iron depleted children given cows milk before 12mths almost double that of iron replete	A lower haem iron intake and introduction of cows milk before 12mths are major risk factors for iron depletion
Females only						
2001 Patterson, A., Brown, W. & Roberts, D. New South Wales	18 – 50 years	(1) Examine dietary and lifestyle variables important in determination of iron status (2) Calculate bio-available dietary iron using algorithms	n=76 Iron-deficient: n=52 Iron-replete: n=24 Inclusion criteria: - no major illness - no known organic cause of iron deficiency - no iron supps in past 3 months - menstruating - non-pregnant - no hysterectomy Quality: IV / +	Cross-sectional study - 7d weighed food record - bio-available iron calculated using algorithm,s of Monsen et al 1978, Monsen and Balintfy 1982 and Tseng et al 1997 <u>Iron replete:</u> Hb ≥120g/L and SF >20µg/L <u>Iron depletion (dep):</u> SF <20µg/L <u>Iron deficiency (ID):</u> SF <15 µg/L or SF 15-20 µg/L, with two of either SI <10µmol/L, TIBC >68 µmol/L, TSAT <15%	Oral contraceptive pill and alcohol intake positively associated with SF Phytate intake negatively associated with SF Total iron, haem iron and bio-available dietary iron intakes not associated with iron stores	Further studies required to assess whether these dietary factors can explain variations in iron status Dietary iron intake positively associated with alcohol intake and the oral contraceptive pill, and negatively associated with phytate intake
1997 Rangan, A., Binns, C. & Blight, G. Perth	17 – 30 years	(1) Determine intake of total iron, haem iron and calcium (2) Investigate differences in nutrient intake according to type of diet consumed	n=141 Omnivores (O): n=92 Semi-vegetarians (S): n=26 Vegetarians (V): n=21 Inclusion criteria: - <30 years age - Not pregnant - Lived Australia >1yr Quality: IV / +	Cross-sectional study Assessment: - Validated 270-item FFQ	Total dietary iron (mg) intake similar: (O): 12.7±3.8; (S): 11.2±2.8; (V): 13.7±5.4 Haem iron (mg) intake statistically different: (O): 1.39±0.75; (S): 0.41±0.39; (V): 0.01±0.02	Vegetarian and semi-vegetarian diet associated with low intakes of haem iron Low haem intake associated with low iron stores and may lead to iron deficiency Separate main iron-containing foods from foods rich in calcium to improve iron intake

1. Values calculated from original publication

1988 Worthington-Roberts, B. et al. United States	25 – 35 years	Evaluate dietary intake and iron status	n=51 Red meat (RM): n=16 Fish/poultry (FP): n=15 Lacto-ovovegetarian (LV): n=20 Inclusion criteria: - non-smoker - no medications/supp - no chronic disease Quality: IV / +	Cross-sectional study <u>Iron Deficiency:</u> SF <15µg/L	Total iron intake (mg) similar between groups: (RM): 12.7; (FP): 11.9; (LO): 11.8 (RM) had highest SF: mean approx. 30µg/L (visual estimate) (FP) had lowest SF: mean approx. 12µg/L (visual estimate) ID: (RM): 30%; (FP): 52%; (LV): 42% (visual estimate)	Superior iron status established and maintained in individuals that consume red meat

Key:

IG = Intervention group
CG = Control group
SG = Study group
ID = Iron deficiency
SF = Serum Ferritin
SI = Serum Iron
TFN = Transferrin
TSAT = Transferrin saturation
TFR = Transferrin receptor
LDL = Low density lipoprotein
B = Breakfast
L = Lunch
D = Dinner
RBC = Red Blood Cell

1. Values calculated from original publication