2 Transitions and theories: Models of diabetes prevalence

This chapter reviews the contributions made by both the thrifty genotype and programming hypotheses to understandings of patterns of diabetes prevalence within and/or between populations. This review is presented adjacent to theoretical transitions in health, from the predominance of infectious disease in determining patterns of morbidity and mortality, to the rise in diseases such as diabetes that are typically considered to be non-infectious, chronic and degenerative.

2.1 Transitions

Cause-specific patterns of morbidity and mortality in a given population change over time. These transitions may not be uniform across groups or even unidirectional. Nevertheless, some broad trends in morbidity and mortality transitions, and their causal factors, have been observed in diverse populations during different time periods, leading to the development of theoretical concepts to describe and explain these shifts, and even to predict them.

In Westernised populations with a long history of industrialisation, Type 2 diabetes is a disease usually affecting middle-aged to older adults. In some post-colonial populations, however, where diabetes rates are high overall, significant numbers of younger people are affected (for example, Dowse et al. 1991a; Fagot-Campagna and Narayan 2001). Common to the most affected groups is recent and rapid transition from ‘traditional’ lifestyles to a more ‘Westernised’ lifestyle.

Health transition models are invoked to explain the rise in Type 2 diabetes prevalence observed globally and in specific populations. Health transition theory incorporates ideas from both demographic transition theory and Abdel Omran’s (1971) theory of epidemiologic transition.

2.1.1 Demographic and epidemiologic transitions

Demographic transition theory arose in the United States following World War II, from observations that family size in ‘developed’ countries was small while those in ‘underdeveloped’ countries were large (Abernethy 1995). Creating ‘intellectual order out of chaos’ was the primary motivating force behind the theory (Szreter 1993, p. 697). The theory attempted to explain the historical changes to mortality, fertility and consequent population
dynamics that have occurred in now industrialised populations; societies undergoing modernisation evolve from a pre-modern regime of high fertility and high mortality to a modern regime where both are low (Kirk 1996). Mortality decline occurs first, followed by fertility decline (Weinstein 1976). Low mortality and low fertility result in a population with an older age structure.

Demographic transition theory proposed that fertility was in fact linked to mortality, so that improved child survival was expected to influence reproductive decision-making. The theory emphasises fertility decline as a direct consequence of economic growth. This assumption has been criticised for ignoring both cultural preferences for family size (Abernethy 1993) and recognition of fertility opportunities (Abernethy 1999), and has challenged evolutionary biologists in its paradox of declining reproductive fitness in a favourable environment (Mulder 1998). Despite these limitations and additional criticisms that it was politically motivated (Weinstein 1976; Szreter 1993), and its implication that change is unidirectional, linear and progressive (Kirk 1996), the concept of demographic transition has been extremely influential.

In 1971, Abdel Omran developed epidemiologic transition theory to explain the cause of the mortality decline that initiated demographic transition. Omran proposed that the shift that occurs from high mortality (around 30 per 1000 population) and high fertility (>40 per 1000 population) to low mortality (around 10 per 1000) and low fertility (<20 per 1000) is accompanied by changes in patterns of health and disease, so that ‘pandemics of infection are gradually displaced by degenerative and man-made [sic] diseases as the chief form of morbidity and primary cause of death’ (Omran 1971, p. 516).

Omran proposed three successive stages:

1. The Age of Pestilence and Famine - characterised by high and fluctuating mortality where life expectancy at birth is between 20 and 40 years;

2. The Age of Receding Pandemics - mortality declines progressively, the rate of decline accelerates, and life expectancy is from 30 to 50 years. In this stage population growth is sustained and becomes exponential; and

3. The Age of Degenerative and Man-Made Diseases - mortality continues to decline and becomes stable at a low level, life expectancy exceeds 50 years and fertility rather than mortality is crucial in determining population growth.
Diabetes and other so-called ‘lifestyle diseases’, ‘diseases of civilisation’, or ‘diseases of affluence’ are represented in the third stage. Omran recognised that changes in patterns of disease interact with demographic, economic and social determinants of what he called the modernisation complex. He proposed three models by which transition had or could occur: a ‘classical’ pattern, that which was observed in England and Wales from the middle of the 18th century until the 1920s; an ‘accelerated’ pattern, such as that which occurred in countries which experienced transition in the space of a few decades (such as post-World War II Japan); and a ‘contemporary’ or ‘delayed’ pattern occurring in less industrialised countries where transition has begun but is not yet ‘completed’ (much of the ‘developing’ world), creating a demographic gap where mortality has declined but fertility remains relatively high (Omran 1971).

Although Omran’s first Age approximates Aboriginal Australia before European contact, the period immediately after contact involved further illness, mortality and social disruption instead of improved health and life-expectancy specified in the model (See Chapter Four).

2.1.2. Health transition

Epidemiologic, like demographic, transition theory has been criticised for assuming change is unidirectional, progressive and linear, as barely cognisant of the importance of the role of public health interventions and medical science, and as underestimating the influence of ideas and behaviour in facilitating mortality decline (Caldwell 2001). The term ‘health transition’ was introduced to include these cultural, social and behavioural determinants of sickness and mortality, and their effect on the health of a given population (Caldwell and Caldwell 1996). It includes social and behavioural changes which result from demographic and economic changes (Vorster et al. 1999), but it differs from epidemiologic transition in the degree that these are recognised as actively promoting transition.

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1 Rogers and Hackenberg (1988) suggest adding a fourth ‘hybristic’ stage, where health is increasingly influenced by individual behaviours and lifestyle, such as decreased physical activity, nutritional excesses, excessive alcohol consumption and smoking. Under their model, diabetes occurs in the fourth stage.

2 One assumption of epidemiologic transition theory is that economic development automatically, if only eventually, leads to improved health. Simon Szreter (1997) argues the contrary: economic growth entails critical challenges and threats to the health and welfare of populations via disturbances to the ecological relationship between humans and their environment.

3 Caldwell (2001), for example, suggests that Omran’s three basic models are insufficient, and that there are probably as many models as there are societies.
A major characteristic of the health transition is that the population includes a greater proportion of older people, therefore diseases that relate to adults account for more of the total disease burden (Chaisiri et al. 1998). Older people are more at risk from degenerative disease for three primary reasons: it takes time for the body to degenerate (Caldwell 2001); chronic diseases are often the result of long-term exposures to risk factors (Manton and Stallard 1993); and latent genetic susceptibilities to conditions that increase with age may be unmasked (Sharma 1998).

Although the term ‘transition’ implies a change from one fixed state to another, the concept of health transition emphasises the plurality and complexity of change, and the role of human agency.

2.1.3. Nutrition (and lifestyle) transition
Nutrition transition has both accompanied and contributed greatly to health transition. It refers to a sequence of characteristic changes in dietary patterns and nutrient intakes associated with the social, cultural and economic changes that take place during modernisation, and in particular Westernisation. Nutrition transition describes the general, globally observed trend toward excessive intakes of total energy, often in the form of sugars and animal fats (Vorster et al. 1999). Food preferences tend towards fats, sugars and salt, abundant in a Westernised diet but usually scarce in pre-transition diets (Lev-Ran 1999). Reductions in physical activity to more sedentary modes of living parallel nutrition transition, producing an overall positive energy balance, and so physical inactivity is included in the paradigm of ‘lifestyle transition’.

In wealthy countries, a social drift of diseases such as diabetes and cardiovascular disease (CVD) has occurred, from the more affluent to less affluent groups (Marmot 1999). For example, fat intake in the United States has an inverse relationship to socioeconomic status (SES) (Vorster et al. 1999), hence related diseases are no longer those of ‘affluence’, although in less industrialised countries SES maintains a positive relationship with metabolic disease (for example in urban Indian Fijians (Zimmet et al. 1997)).

2.2. Type 2 diabetes and the insulin resistance syndrome
Type 2 diabetes occurs when insulin production fails to compensate for insulin resistance. Diabetes frequently occurs with several other metabolic disorders: obesity, especially central obesity, hypertension and dyslipidaemia (Zimmet et al. 1997; Goran 1999; Neel 1999b) - the
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insulin resistance syndrome. Symptoms of the syndrome are implicated in the development of CVD; people with diabetes are more than twice as likely as non-diabetics to have CVD (Marks and Raskin 2000). Although the diabetes is frequently associated with features of the insulin resistance syndrome, this is not universal, even among groups with high rates of diabetes. For example, a study by Simmons et al. (2001) concluded that insulin resistance was not more common among Polynesians than people of European descent, despite high rates of obesity and diabetes.

2.2.1. The obesity epidemic

In 1948, the first major prospective study to determine risk factors for heart disease began in Framingham, Massachusetts (American Heart Association 2002), which signalled factors in adult lifestyle as the cause of a number of similar diseases, and thus the term ‘lifestyle disease’ was born, whereby a positive energy balance resulting from overnutrition and under-activity leads to obesity. Both overall obesity and central obesity independently promote glucose intolerance (WHO 1994).

The most important dietary factors for increasing diabetes risk are increased consumption of refined carbohydrates and fats, especially saturated fat, and decreased consumption of fibre, as these decrease insulin sensitivity (WHO 1994). Energy-dense diets contribute directly to the diabetes risk factor of obesity, which may be the most important physiological risk for development of diabetes (AIHW 2002a). Reducing daily energy intake in diabetics, especially of fats and carbohydrates, has been demonstrated to improve the symptoms of diabetes (O’Dea 1984; Eriksson et al. 1999a) (see Section 2.3.2).

People who are obese have a risk of diabetes of between 5 and 10 times the risk of the non-obese (Zimmet 2001). One way in which obesity could be linked at a biochemical level to diabetes is through its hormonal effects. Obesity appears to increase levels of the hormone resistin, which in turn increases insulin resistance and glucose intolerance (Berger 2001; Zimmet 2001).

Over the last 20 years, the prevalence of excess body weight has been increasing in many countries. More than half of all adults in Australia, the UK and the US are now overweight

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4 This has also been called Syndrome X, the chronic metabolic syndrome, and ‘the deadly quartet’ (Zimmet et al. 1997).
A rise in diabetes prevalence in the United States over the last 10 years has been linked with increasing obesity (Frankish 2001). The association between diabetes and obesity is considered to be so strong that a new term, ‘diabesity’, has been coined to describe the epidemic, especially as it is being observed in Western countries (International Diabetes Institute 2001; Cameron-Smith et al. 2002). Obesity is not merely on the rise in populations in the West, where it tends to affect poorer socioeconomic groups disproportionately (Kumanyika 1993), but also among many Asian countries and in the Pacific region, particularly among wealthier groups (Hodge et al. 1995; Cockram 2000; Bell et al. 2001; Mudur 2003).

Currently, diabetes in some form affects 150 million people worldwide, most of which is Type 2 diabetes, and this rate is expected to double over the next 20 years. Most of the increase will be with Type 2 diabetes (Zimmet 2001). Already in Australia, the prevalence of diagnosed diabetes has doubled since 1981 to 6.8% in women and 8% in men (Dunstan et al. 2002) and a further 30% increase is expected by 2010 (Zimmet et al. 2001). This expected increase may not be universal. A recent study by Eliasson et al. (2002) in Sweden, for example, found no increase in diabetes prevalence over 13 years to 1999.

This predicted rise is not only likely to occur in Australia as a whole, but Australia’s Indigenous people could be especially affected. A longitudinal study of Aboriginal people living in central Australia documented a substantial increase in both diabetes and obesity between 1987 and 1995; the prevalence of both nearly doubled, from 11.6% to 20.7% for diabetes and from 22.8% to 37% for obesity (McDermott et al. 2000).

The rise in obesity among children is also linked with Type 2 diabetes becoming a significant threat to the health of young people globally, where previously it was only older adults who were at risk (Fagot-Campagna and Narayan 2001; Dyer 2002).

Physical inactivity, especially when combined with overnutrition, promotes obesity; and diabetes risk declines with increasing physical activity (WHO 1994). Regular physical activity increases insulin sensitivity and improves glucose tolerance so that there may be a four-fold difference in prevalence of diabetes between most and least active individuals (Gutin and Owens 1999). Increasing physical activity can improve metabolic abnormalities associated with diabetes (for example, O’Dea 1984 and Eriksson et al 1999, see Section 2.3.2).

Physical inactivity has been blamed alongside over-consumption of energy-dense foods for the high prevalence of obesity and diabetes in some populations. Because of its association with
increased insulin sensitivity, physical activity is possibly more important than diet in both preventing and controlling diabetes (Annuzzi et al. 1985; Eriksson and Lindgärde 1991; Helmrich et al. 1991).

Despite links between diabetes and obesity, body mass index (BMI) does not relate to diabetes in all ethnic groups in the same way it does in people of primarily European descent; thresholds where BMI becomes a significant health risk may be lower or higher. This may be because BMI is not a precise measure of adiposity as it does not distinguish between lean mass and adipose tissue mass. Mean differences between population groups may therefore mask or exaggerate differences in relative fatness.

For example, if a BMI of 30 is applied in Japan, then only 3% of the population are obese and this proportion has not changed since Word War II (Kanazawa et al. 2002), despite a rapid adoption of more a Western, energy-dense and activity-poor lifestyle. To adequately reflect the change in BMI that has occurred, and the increase in diseases that accompany such change, the authors recommend that the threshold for obesity be reduced from 30kg/m² to 25kg/m². Similarly in China, the relationship between diabetes and BMI becomes apparent at much lower BMI than widely accepted thresholds of obesity (Cockram 2000; Bei-Fan 2002). Conversely, accepted thresholds for obesity may also overestimate associated diabetes risk in some populations. For example, BMI has been found to be poorly predictive of cardiovascular and diabetes risk in Polynesians (McAnulty and Scragg 1996), leading the authors to suggest that BMI is not an adequate measure of adiposity or that adiposity is not as strongly associated with CVD as in other populations. Similarly, Hodge et al. (1996) concluded that although obesity was associated with increased diabetes risk, it was not predictive of mortality from CVD and other related disorders.

How fat is distributed also differs by ethnicity and has implications for diabetes and other chronic disease risk. Some population groups, such as Polynesians, Indians, Japanese and Australian Aborigines, appear to have a greater propensity than others to store fat abdominally (for example, Rush et al. 2002; Yudkin 1996; Yajnik 2002; McNeely et al. 2001; O’Dea 1987) and are therefore at increased risk of disease than others with comparable BMI.

The relationship between obesity and Type 2 diabetes is causally complex. Type 2 diabetes is caused by a disruption to glucose homeostasis resulting from a deficiency in insulin secretion and/or insulin action, when increases in insulin secretion can no longer compensate for decreases in insulin action creating a relative insulin deficiency. Insulin resistance in peripheral
tissue may arise from ongoing exposure to excess insulin, or hyperinsulinaemia may be an early sign of insulin resistance. Obesity, in particular central adiposity, promotes the development of insulin resistance, and insulin resistance has been implicated in the development of both general and central obesity (see Section 2.4.4).

While a positive energy balance, resulting from adult lifestyles of overnutrition and underactivity, promotes general obesity, additional factors that facilitate insulin resistance and cause excess dietary energy to be preferentially stored as abdominal visceral fat have been the subject of debate for some decades. In particular, predisposition to diabetes has been argued to be either genetically based or an outcome of the early developmental environment.

2.3. The thrifty genotype

2.3.1. The early hypothesis
In 1962, geneticist James Neel attempted to explain why diabetes occurred at high rates in Westernised populations when it was detrimental to reproductive fitness. From observations of high diabetes prevalence in Westernised Amerindian groups and the notable differences in rates between ethnic groups, Neel suggested that there must exist a ‘diabetic genotype’. He proposed that in the past, humans had become genetically adapted to uncertain food availability, and had thus become extremely efficient at storing available energy during ‘feast’ times to enable survival during ‘famine’. Neel hypothesised that this diabetic genotype is exceptionally efficient in either the uptake or the utilisation of energy – a case of what he called nutritional ‘thrift’ (Neel 1962).

Neel suggested two possible mechanisms by which this thrift might occur. First, that genetic variability in insulin production causes $\beta$ cells in some groups to continue to function for longer after food is ingested. Second, that $\beta$ cells of people predisposed to diabetes are more responsive to post-prandial increases in blood glucose level, causing an overproduction of insulin. Initially Neel favoured the latter mechanism - a ‘quick insulin trigger’ - as the means of efficiency (Neel 1962).

5 Although thrifty genes were was first proposed before any clear distinction had been made between Type 1 and Type 2 diabetes, Neel subsequently clarified that it should refer to Type 2 diabetes (Neel 1982).
As too quick an insulin trigger would have been detrimental, Neel (1982) suggested that it took the form of a balanced polymorphism, similar to the sickle-cell allele. A capacity for insulin overproduction, he reasoned, would have been adaptive in a nutritionally uncertain environment, a characteristic of ‘earlier’ evolutionary ecology; individuals whose pancreas minimised post-prandial glycosuria had a selective advantage as they might have more adipose tissue to rely on in times of famine (Neel 1962). This same capacity, he hypothesised, becomes maladaptive once populations gain ready access to a constant supply of food. Overnutrition is further exacerbated by reduction in physical activity, which also occurs with Westernisation. The resulting positive energy balance can ‘trigger evidence of [diabetes] susceptibility’ in some groups (Weiss 1990, p. 106).

The thrifty genotype hypothesis thus attempts to explain the extremely high rates of diabetes in populations which have undergone recent and rapid transition to more Western modes of living. When the hypothesis was first proposed, it was thought that only small numbers of populations were highly susceptible to diabetes with Westernisation, but more recently it has become evident that obesity and insulin resistance are ‘consistent sequelae of lifestyle transition’ (O'Dea 1997, p. 282). Neel (1982) suggested that the detrimental effects of the thrifty genotype should manifest themselves early in life; at the time earlier onset of diabetes was observed in populations which had undergone rapid Westernisation to a more ‘nutritionally assured existence’ (Neel 1982, p. 286).

By the 1980s, Neel recognised that a quick insulin trigger was unlikely to be involved, and he attempted to rejuvenate the thrifty genotype hypothesis and encourage the search for an alternative mechanism (Neel 1982). That the disease was almost absent in relatively un-Westernised but closely related Amerindian groups subsequently led Neel to suggest that diabetes was predominantly a lifestyle disorder among Amerindians rather than due to a particular ethnic predisposition (Neel 1999b), but in his own words these genes are only ‘rendered detrimental’ though acculturation into a Western lifestyle,\(^6\) so one would expect Type 2 diabetes rates to be low in the absence of this lifestyle.

\(^6\) Or by ‘progress’ (Neel 1962, 1999a)
2.3.2. Revised hypotheses

Since it was first proposed, the thrifty genotype hypothesis has evolved considerably, towards an emphasis on the quality of food, rather than quantity, and the specific incorporation of physical activity into the model.

Pre-agricultural lifestyles were characterised by high energy throughput – intake may have been greater but energy expenditure was also greater than in a modern Westernised lifestyle (Eaton et al. 1988), resulting in high energy throughput. ‘Wild’ foods typically contain less fat, more protein and more fibre than most purchased foods, and carbohydrates were derived mostly from vegetables and fruits rather than from cereals (Eaton et al. 1997). Wild animal foods that are high in fat tend to have less saturated fat than most domestic species, so that even when fat intake among foragers is high, serum cholesterol levels are usually low, mitigated by the ratio of polyunsaturated and saturated fats (Eaton et al. 1997). The glycaemic index (GI)\(^7\) of wild plant foods is typically lower than those for most consumed agricultural produce, which are more rapidly absorbed (Eaton et al. 1997). Other researchers suggest that it was only populations that relied on big game who developed a thrifty genotype, as efficient energy storage or use would have been a selective advantage during periods of fasting between big kills (Wendorf and Goldfine 1991). Insulin resistance would have been adaptive during ice ages, coping with a shortage of dietary glucose from carbohydrate food (Brand Miller and Colagiuri 1994).

The thrifty genotype hypothesis has been further refined through investigations within specific groups with a high prevalence of Type 2 diabetes. Kerin O’Dea and her colleagues have conducted numerous studies of nutritional intake, physical activity and metabolic outcomes within Australian Indigenous communities at various ‘stages’ of Westernisation (for example, O’Dea et al. 1980; O’Dea 1988; O’Dea et al. 1993, Rowley et al. 2000).

Rather than the model of feast or famine, O’Dea has changed the focus of thrifty genes to subsistence or feast. Subsistence foods were those that were gathered and generally available, while feast foods were those which were hunted, and available occasionally. Conditions of continual surplus would have rarely, if ever, occurred (O’Dea 1997), so that a subsistence diet was normal. Diabetes results from the transition from a more traditional lifestyle to a more Westernised one, which is characterised by reduced levels of physical activity and an energy-

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\(^7\) Glycaemic index has fallen in and out of favour as a useful tool for selecting foods suitable for diabetics, for example Jenkins and Jenkins (1994).
dense diet high in refined carbohydrate and fat (O'Dea 1991), sources of readily accessible energy. In addition to this emphasis on subsistence, level of physical activity is also deemed very important.

Lifestyles that are more ‘traditional’ are demonstrated to benefit metabolic profiles. For example, the ‘contemporary traditional’ lifestyle in one group studied by O'Dea and Spargo (1982) was characterised by high levels of physical activity and diet derived from a variety of animals and plants. The region was characterised by seasonal variation in the foods available, so that at certain times there was very little vegetable food available. The researchers attempted to mimic the traditional diet, which was very high in protein and very low in carbohydrates, by having the study group eat seafood almost exclusively for two weeks, a marked change from the usual urban diet of white flour, sugar, white rice, powdered milk, fatty meat, soft drinks and alcohol (O'Dea and Spargo 1982). Glucose tolerance improved significantly over the two-week period as hyperinsulinaemia was ameliorated, providing evidence that a high protein, low carbohydrate diet improves glucose utilisation and insulin sensitivity (O'Dea & Spargo 1982).

In a subsequent study in the same region, O'Dea measured metabolic changes that occurred in diabetic women and men over a seven week period spent living as hunter-gatherers, consuming a low-fat diet based on lean meat, and with increased physical activity from subsistence activities. Major metabolic abnormalities of diabetes were improved and even normalised, for example mean fasting blood glucose fell from 11.6 mmol to 6.6 mmol, mean weight lost was 8kg, and insulin secretion was reduced while insulin efficiency improved (O'Dea 1984).

These and a number of similar studies led O'Dea to conclude that mild impairment in glucose tolerance and high insulin response may have been adaptive under a traditional lifestyle by facilitating fat deposition where intake of carbohydrate was low but protein intake was high (O'Dea et al. 1980; O'Dea and Spargo 1982; O'Dea et al. 1982; O'Dea et al. 1988). Some of the detrimental effects of a Westernised lifestyle are therefore potentially reversible with lifestyle change, prior to diabetes onset (O'Dea 1991; Rowley et al. 2000a).

O’Dea further suggests that some groups of Aboriginal people may be more likely than others to develop diabetes and associated metabolic disorders, depending on their ecological history. In a comparison of desert and coastal dwellers, O’Dea et al. (1988) found that those in the desert group had greater insulin response to glucose, perhaps as a more efficient metabolism would be more critical to their survival. The researchers concluded, however, that it was not possible to distinguish between genetic and lifestyle factors which may have accounted for the differences
between the two groups (O’Dea et al. 1988). Additional evidence that mild impairment of glucose tolerance and hyperinsulinaemia may be inherited arose from the observation of an absence of metabolic differences between groups of more and less urban Aboriginal men, who had similar levels of insulin response to glucose as each other, but both groups had a response that was 50% higher than a comparative urban group of European descent (O’Dea et al. 1982).

O’Dea emphasises nutritional quality of food and considers physical activity levels as well. If intake of easily available energy such as carbohydrate or fat is extremely low, then being able to use the small amounts of available energy as efficiently as possible is important to survival.

A comparative study of groups of Aboriginal and European ancestry in Victoria found no significant difference in prevalence of impaired glucose tolerance (Guest et al. 1992). Age-adjusted prevalence ratios, however, were 8.1% among the Aboriginal group and 1.9% among non-Aboriginal group (Guest et al. 1992). The authors noted that greater diabetes prevalence persists despite the high proportion of genetic admixture from Europeans, leading them to conclude that ‘…socio-economic and other environmental factors may be more important than genetic differences’ in explaining the high prevalence of diabetes among these Aboriginal groups (Guest et al. 1992, p. 234). Although genes may be involved when there is an association between diabetes risk and genetic admixture, such as among some Amerindian groups (Weiss 1990), the connection may not be independent of social factors associated with causal lifestyle factors; those who inherit more genes from those belonging to the dominant culture may also be subject to greater social and economic privilege accorded by that culture. Similarly, although Zimmet et al. (1991) use the four-fold difference in prevalence between urban Indian and Melanesian males on Fiji to support a genetic basis for predisposition, as it illustrates a substantial difference between ethnic groups, such a difference may be explained by the differing SES and lifestyles of these two groups.

Swinburn (1996) criticises the concept of the thrifty genotype for its lack of specificity, unclear as to whether it predisposes to ‘insulin resistance, reduced insulin secretion, increased insulin secretion, obesity, low metabolic rate, large appetite or lower physical activity’ (Swinburn 1996, p. 695). The thrifty genotype hypothesis has, however, evolved to become more specific. Most recently, the emphasis has been on heightened insulin resistance rather than insulin overproduction.

Insulin resistance may have been important to survival for gatherers and hunters as it impairs stimulation of glycogen formation in skeletal muscle, but with modern living and
Models of diabetes prevalence

Westernisation it predisposes to obesity, Type 2 diabetes and CVD (O'Dea 1991). Rather than efficient storage of energy, Reaven (1998) emphasises the benefit of a genotype that confers an ability to conserve muscle protein during famine so that activity remains possible.

Not all researchers have been as ready to abandon the overproduction of insulin as the primary mechanism, as Neel did 20 years ago; Bindon and Baker (1997), for example, maintain a focus on hyperinsulinaemia as a primary cause. Others suggest insulin resistance alone may not be sufficient to manifest as glucose intolerance and lead to diabetes, but that an additional insulin deficit is required (de Courten et al. 1998). Insulin resistance acts as a trigger to increase insulin demands, thereby unmasking any defect in islet cells. Normal $\beta$ cells can compensate by increasing the amount of insulin secreted, but ‘pre-diabetic’ $\beta$ cells can not, and so hyperglycaemia results (de Courten et al. 1998). Hyperinsulinaemia, however, signals what may be an attempt to compensate for insulin resistance.

**Parallel evolution or bottleneck?**

Peoples as diverse as Pima Indians, Nauruans and Australian Aborigines all exhibit remarkably similar epidemiological patterns in Type 2 diabetes (Chapter One). Either thrifty genes arose in these populations in processes of parallel evolution (Cone 2000), or were universal but then lost in populations with a long history of agriculture and industrialisation (Allen and Cheer 1996).

Some form of ‘thrifty genotype’ may exist or have existed in all populations, having evolved early in human evolution, but be exposed as diabetes only in some (Swinburn 1996). The supplementary conditions for diabetes are those of Westernisation which create a positive energy balance. For example, selection pressures may have relaxed in European populations with the advent of agriculture and the greater availability of carbohydrates (Colagiuri et al. 1997). Such populations subsequently lost their thrifty genes through selection as the advantage conferred by insulin resistance, which had been useful for diets relatively high in protein, was attenuated.

Early agriculture may not, however, have produced a nutritional environment sufficiently stable to relax selection pressure on thrifty genes. Both Allen and Cheer (1996) and Swinburn (1996) argue that the advent of agriculture and early cities created severe and uncertain environments. Uncertainties in food supply could have been mitigated by the development of trade relationships across wide geographic areas, so advantage conferred by thrifty genes could have been reduced (Allen and Cheer 1996).
A genetic bottleneck, or series of bottlenecks, may be responsible for thrifty genes manifesting at high rates in some populations but not others. Selective survival of nutritionally thrifty individuals may have occurred, for example, through long ocean voyages and periodic storms affecting food availability, as with Pacific Islanders (Zimmet et al. 1991; Bindon and Baker 1997); genes predisposing towards insulin resistance were subsequently maintained in some populations where feast or famine conditions were present (Zimmet et al. 1991). For Nauru, it has been hypothesised that severe malnutrition under Japanese occupation during WWII could have been a major selection pressure for a thrifty genotype (Dowse et al. 1991a) as more insulin resistant individuals may have been more likely to survive under such severe conditions.

Milk and honey

Allen and Cheer (1996) hypothesise that a thrifty genotype might have evolved where access to simple sugars was limited. With the advent of agriculture these became more accessible, in particular with access to milk. The authors note that lactose intolerance is rare in European populations, and so suggest adaptation to milk consumption, rather than carbohydrates in general, occurred in some populations. Under such circumstances, nutritional thrift was no longer required and those with a ‘non-thrifty genotype’ were at a selective advantage. They further suggest that a thrifty genotype could be an example of neoteny; exposed to a Western diet, those with the thrifty genotype develop diabetes in early to mid adulthood, but those with the non-thrifty genotype tend to develop it in later adulthood (Allen and Cheer 1996).

Transitions and evolution

In populations with high rates of diabetes, rapid transition to a Western lifestyle – the result of colonisation or economic expansion – generated insufficient time for any genetic adaptation away from thrifty genes to occur; certain populations may remain genetically adapted to an uncertain, or at least qualitatively different, food supply from that currently consumed. Among populations that have been Westernised for some time, lifestyle transition occurred more slowly. As diabetes tends to have its onset in later adulthood, selection pressure against diabetes may be weak. In populations with high rates of diabetes, however, the disease frequently develops in early adulthood. Even if it remains asymptomatic for many years, it may have sufficient negative effect on reproductive fitness.8

8 For example, diabetes can cause complications in pregnancy (see Section 2.4.3), and its effects on the circulatory system can cause erectile dysfunction in men (De Berardis et al. 2002).
Inheritance of the thrifty genotype is potentially complex, as capacity for efficient uptake or storage of energy is unlikely to be attributable to a single gene (O'Dea 1997). There may also be a number of potential thrifty genotypes, influencing a variety of metabolic outcomes, such as adiposity, energy metabolism and risk of associated disease (de Courten et al. 1998). Direct evidence in favour of thrifty genes has so far been slight (Spurgeon 1999). Support for the existence of a thrifty genotype (or types), however, remains strong, for example, owing to arguments that the genetic component of diabetes has been well established through evidence of familial aggregation of diabetes in high prevalence populations (Zimmet 1992). Such patterns might instead be explained by shared familial environments. For example, food preferences are ‘trained’ during childhood and adolescence, leading to preferential selection of some foods over others (Lev-Ran 1999). Maternal history of diabetes is associated with both higher birthweight and subsequent development of diabetes, but paternal influences are absent (Rich-Edwards et al. 1999) or very slight (Barker 2000), suggesting the predominance of gestational environmental influences such as overexposure to circulating glucose (Pettitt et al. 1988; Silverman et al. 1998) (Section 2.4.3) over genes. A mendelian pattern of inheritance of the thrifty genotype is therefore unlikely, suggesting inheritance may be either sex-linked or via mutations in mitochondrial DNA (Poulton et al. 1998).

Neel (1999b) believed that the presence of the insulin resistance syndrome posed a problem for his hypothesis, but considered the clustering as a chance association, given the high prevalence of all components in some populations. Insulin resistance, however, can be accommodated within the thrifty genotype framework as propensity to develop resistance may be subject to genetic variability, and insulin resistance could promote additional features of the insulin resistance syndrome, including diabetes. Although the original thrifty genotype hypothesis presented an overly simplistic view of physiological alterations in those undergoing rapid lifestyle transition (Neel 1999b), the concept can be redirected towards the development of insulin resistance under certain ecological conditions (or the loss of insulin resistance in others), and expanded to include other features of the insulin resistance syndrome.

Genetic variability predisposing some individuals and groups to insulin resistance may be unmasked as diabetes under circumstances of rapid change in dominant lifestyle patterns away from traditional habits.

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9 A dominant inheritance pattern is expressed by MODY (mature onset diabetes in youth – similar to Type 2 in its presentation, but occurs typically in teenagers and young adults) but this form of diabetes is rare (Childs and Scriver 1986).
from subsistence living towards high energy diets combined with low physical activity. Such rapid transitions may also promote diabetes through discord between early life environment and subsequent adult lifestyle.

2.4. The programming hypothesis

Over the last decade, phenotypic responses to the developmental environment, rather than genetic adaptation, have been presented as an alternative to the thrifty genotype in explaining variation in diabetes prevalence.

2.4.1. Background

Anders Forsdahl was among the first to suggest that poor social conditions and nutritional deprivation in childhood, followed by an abundant diet in later life, could increase risk of heart disease (Forsdahl 1977). This theme was subsequently expanded by a research group in the UK, headed by David Barker, whose early studies focused on heart disease, finding geographical differences in death rates from ischaemic heart disease (IHd) correlated with infant mortality rates and low birthweight of their study cohort, 70 years previously (Barker and Osmond 1986; Barker et al. 1992d). Hence it was assumed that both low birthweight and high neonatal mortality were markers of an early adverse environment, and that maternal nutrition during gestation was especially important in altering metabolism (Barker 1991; Barker and Martyn 1992).

‘Programming’ is a term that was introduced by Lucas (1991) to describe how early life events may have long-term consequences. The programming hypothesis refers to changes to metabolic processes that have been wrought by features of the environment during ‘critical periods’ in development, in particular that poor nutrition in early life heightens susceptibility to the detrimental health effects of an ‘affluent’ diet (Barker and Osmond 1986). Although the Barker group studies began with a focus on heart disease, the hypothesis was later expanded to include Type 2 diabetes, so that ‘poor fetal and early postnatal nutrition imposes mechanisms of nutritional thrift on the growing individual’ (Hales and Barker 1992, p. 258), creating a ‘thrifty phenotype’.

10 Neonatal death (defined as up to 28 days after birth) is strongly dependent on factors during pregnancy, birth and immediately after. Post-neonatal or infant death (defined as death between 28 days and one year) primarily depends on environmental factors during infancy (Robinson 1992).
Analogous to the thrifty genotype, the programming hypothesis is one of adaptation to one environment being at odds with welfare in another. In this case, the focus is adaptation during development, in particular nutrition during prenatal and early postnatal life. Pathological expression in later life on subsequent exposure to excessive dietary intake may reflect early nutritional variation rather than simply current lifestyle practices, and thus programming may help explain why known adult lifestyle risk factors for CVD and other lifestyle disorders such as diabetes are poorly predictive (Barker and Martyn 1992). For example, during the 1970s it was observed that variations in blood pressure, smoking, and serum cholesterol did not account for social and geographical variations in rates of heart disease (Kuh and Smith 1993).

Critical periods of growth coincide with periods of rapid cell division in specific tissues (Barker 2000), so that prenatal growth is hypothesised to be more important in programming potential than postnatal growth, given that rates of cell division fall after birth (Barker 1996). Poor nutrition in early life is hypothesised to have profound effects on physiology, although these effects may remain latent until maturity and subsequent exposure to an ‘affluent’ diet (Barker and Martyn 1992). Lower birthweight in particular has been the focus of programming studies, in relation to CVD and Type 2 diabetes (Table 2.1). Under the programming hypothesis, both newborn body size and proportion are markers of adaptations the fetus has made during development, whether through metabolic changes, redistribution of blood flow and changes in production of growth hormones (Barker 2000).

Programmed effects of early nutritional environment first become apparent among children. Barker et al. (1992c) found for example that systolic blood pressure in ten-year old children was inversely related to birthweight, and that this effect was independent of gestational age. Law et al. (1992a) found markers in childhood to be inversely related to both birthweight and ponderal index, and positively associated with placental weight. Law et al. (1992a) also found that children born to women who had anaemia during pregnancy had higher blood pressures.

Within the programming hypothesis, adverse adult lifestyle factors are still recognised as unmasking the disease, but early environment promotes an ‘increased propensity to develop these diseases when adult lifestyle are conducive to them’ (Scrimshaw 1997:825). Programming effects of early life nutrition become detrimental only when the subsequent environment is one of relative overnutrition. If adult diet remains very low in fat, for example, any programming effects might be irrelevant. Continued energy-poor diet throughout the lifespan, as in some less industrialised countries, may have a protective effect so that rates of
metabolic disorders remain low despite high rates of low birthweight (Walker and Walker 1993).

That maternal and early infant nutrition are important to long-term health is not a new concept. In the early 20th century, the maternal and child welfare movement aimed to promote good nutritional practice to reduce infant mortality rate from infections (Mein Smith 1991), and in countries such as Australia, received government support with the view to nation building as the wartime milieu provided the rationale to establish a strong and healthy population. Scrimshaw (1997) cites other instances where the role of the fetal environment has been accepted – iodine and iron deficiency permanently affect cognitive performance, for example – and perceives the programming hypothesis as simply extending the concept that adverse early environmental factors limit the potential for a long and healthy life.

**Summary of studies**

All features of the insulin resistance syndrome (obesity, central obesity, hypertension, dyslipidaemia and insulin resistance) have been associated with low birthweight and poor child growth. The findings have not been entirely consistent across different studies and different study populations (for example, see Elford et al. 1991; Kramer and Joseph 1996; Kramer 2000) for comprehensive reviews and methodological critiques). This suggests the relationship may be a complex one that does not hold true in all contexts. A selection of major positive findings is summarised in Table 2.1 to demonstrate the breadth of disorders that may have their origins in very early life.
Table 2.1. Chronology of selected studies supporting the programming hypothesis in relation to features of the insulin resistance syndrome.

<table>
<thead>
<tr>
<th>Study</th>
<th>Exposure</th>
<th>Results and Conclusions</th>
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<tbody>
<tr>
<td>England and Wales Adult men (Barker and Osmond 1986)</td>
<td>Geographical region of high infant mortality 1921-1925</td>
<td>Regions with high infant mortality rates 1921-1925 had high mortality rates from IHD 1968-1978. Correlations found also for bronchitis, stomach cancer, and rheumatic heart disease. Authors conclude that poor nutrition in early life heightens adult susceptibility to effects of an ‘affluent’ diet.</td>
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<tr>
<td>England, Norway, Finland Adult men (Barker et al. 1992d)</td>
<td>a) Birthweight &lt; mean b) Lower weight at one year c) Shorter adult stature</td>
<td>a) Associated with higher than mean death rate from IHD, regardless of variations in infant growth; b) Associated with three-fold increase in mortality rate from IHD compared with the heaviest one-year olds (except among formula-fed infants); c) Inverse relationship with cardiovascular mortality Combination of poor pre-and postnatal growth had highest death rate from IHD Attained adult height indicates quality of childhood nutrition, and such adult markers of childhood nutrition are associated with risk of mortality.</td>
</tr>
<tr>
<td>UK Adult men (Barker et al. 1992b)</td>
<td>a) Low ponderal index at birth b) High ratio of head circumference to body length at birth</td>
<td>a) and b) both associated with higher systolic blood pressure, therefore body proportions, rather than simply size at birth, indicate timing of nutritional deprivation. Conclude that timing of prenatal nutritional deprivation appears important for adult disease.</td>
</tr>
<tr>
<td>Gambia 8 year old children (Margetts et al. 1992)</td>
<td>Low birthweight as a result of being born during the rainy season (when food stocks from previous harvest decline but adult energy expenditure remains high)</td>
<td>Highest blood pressures at 8 years old. Authors conclude prenatal environment appears sensitive to maternal nutritional influences.</td>
</tr>
<tr>
<td>UK 60-70 year old men (Law et al. 1992b)</td>
<td>a) Low birthweight b) Low weight at one year</td>
<td>Waist-hip ratio (WHR) fell with increasing birthweight, and with increasing weight at one year.</td>
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<td>Study</td>
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| UK Men in their 60s (Hales et al. 1992) | Low birthweight  
Low weight at one year | Plasma glucose levels fell with increasing birthweight and weight at one year. Those with impaired glucose tolerance (IGT) or Type 2 diabetes were on average 227g lighter at birth and 450g lighter at one year. Lighter infants also had higher BMI and WHR as adults. Conclude low birthweight and low weight at one year increase risk of diabetes in later adulthood. |
| UK 18-25 year old men (Robinson et al. 1992) | Low birthweight | Every 1000g increase in birthweight was associated with a decrease in plasma glucose concentrations of 1.5mmol/L 30 minutes post 75g glucose load. Association was independent of gestational age, and not associated with current BMI, WHR, height, alcohol intake or smoking. Conclude lower birthweight babies are at increased risk from poor glucose control as young adults. |
| Netherlands (Dutch Famine Study)  
Adult men (Susser and Stein 1994) | a) Famine in the first trimester  
b) Famine in the third trimester | a) Higher rates of still birth and higher rates of obesity in adulthood in those who survived;  
b) Shorter gestation and reduced birthweight and lower rates of obesity in adulthood;  
Conclude that timing of prenatal nutritional deprivation affects later outcomes, and any environmentally induced change in maternal birthweight e.g. result of famine is transmitted to offspring with same force as any other determinant, including genetic. |
| UK Adult men (Fall et al. 1995b) | Low weight at one year | Increase in coronary heart disease (CHD) risk (indicated by raised blood pressure, cholesterol and fibrinogen concentrations and IGT). Conclude that low weight at one year modifies metabolism so that risk of CVD is increased. |
| South India Adult men (Stein et al. 1996) | Low birthweight | Prevalence of CHD fell from 11% among adults who were low birthweight to <3% in those weighing more than 3100g. Conclude risk of CHD is highest among adults who were low birthweight babies. |

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<tr>
<td>Jamaica</td>
<td>a) Lower birthweight&lt;br&gt;b) Short birth length, child height deficit and childhood obesity</td>
<td>a) Birthweight had inverse relationship with systolic blood pressure among 6-16 year olds (while blood pressure was directly related to current weight);&lt;br&gt;b) Associated with poorer glycaemic control and higher serum cholesterol.&lt;br&gt;Conclude low birthweight and poor growth increased CHD risk factors.</td>
</tr>
<tr>
<td>US</td>
<td>Low birthweight</td>
<td>Those who weighed less than 5.5 lbs (2500g) at birth had an age-adjusted odds ratio for diabetes of 1.75, even when adult BMI and parental history was adjusted for.&lt;br&gt;Conclude low birthweight babies are at increased risk of diabetes as adults.</td>
</tr>
<tr>
<td>France</td>
<td>Born small for gestational age (SGA)</td>
<td>SGA babies had shorter stature at age 20 years than those with normal birthweight, and had higher insulin concentrations (fasting and post-prandial).&lt;br&gt;Conclude that higher insulin might be an early marker of changes to insulin sensitivity and that the prenatal environment has long lasting effects.</td>
</tr>
<tr>
<td>UK</td>
<td>a) Birthweight&lt;br&gt;b) Head circumference&lt;br&gt;c) Placental weight</td>
<td>a) Systolic blood pressure in children was inversely related to their birthweight;&lt;br&gt;b) Head circumference and placental weight inversely associated with blood pressure in girls;&lt;br&gt;c) Placental weight was positively associated with blood pressure in boys.</td>
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<tr>
<td><strong>US</strong>&lt;br&gt;Adult women (Nurses’ Longitudinal Health Study) (Rich-Edwards et al. 1997)</td>
<td>Birthweight</td>
<td>Birthweight and risk of CVD (non-fatal event) were inversely associated. Risk of CHD and stroke decreased as birthweight increased. Those at the extremes of the birthweight spectrum were largely responsible for the association. Association found largely independent of established lifestyle risk factors.</td>
</tr>
<tr>
<td><strong>UK</strong>&lt;br&gt;14-16 year old girls (Barker et al. 1997)</td>
<td>Birthweight</td>
<td>Subscapular to triceps skinfold ratio increased by 9% for every kilogram decrease in birthweight. Conclude increased central obesity among those who were smallest at birth.</td>
</tr>
<tr>
<td><strong>UK</strong>&lt;br&gt;70 year old men (McKeigue et al. 1998)</td>
<td>Low ponderal index at birth</td>
<td>Ponderal index had U-shaped association with both glucose tolerance and insulin resistance in later life. Both thin babies and fat babies are therefore at increased risk of glucose intolerance and insulin resistance as adults.</td>
</tr>
<tr>
<td><strong>Finland</strong>&lt;br&gt;Adult women and men (Forsén et al. 1999)</td>
<td>Birthweight</td>
<td>Risk of CHD was associated with low birthweight, and with short birth length especially among women, and thinness at birth among men. Effects were greatest among those who underwent catch-up growth.</td>
</tr>
<tr>
<td>Study</td>
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<tr>
<td>US</td>
<td>Low birthweight</td>
<td>Strong inverse association between birthweight and risk of Type 2 diabetes (after controlling for several potential confounds such as prematurity, multiple birth, and breast-feeding). The highest risk of diabetes was among women who had been low birthweight babies but grew to be obese women. Associations were strongest among those whose mothers had no diabetes history.</td>
</tr>
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</tr>
<tr>
<td>Adelaide 20 year olds, women and men (Flanagan et al. 2000)</td>
<td>Low birthweight and short birth length</td>
<td>Men who were lighter or shorter as babies were less sensitive to insulin and had higher insulin secretion regardless of their BMI or fat distribution. No such associations were found in women. Birthweight did not correlate with BMI or fat distribution in men or women.</td>
</tr>
<tr>
<td>Africa 7 year olds, girls and boys (Crowther et al. 2000)</td>
<td>Birthweight Weight at 7 years</td>
<td>Those with low birthweight and low weight at 7 years had reduced β cell activity, while those with low birthweight and high weight at 7 years had high β cell activity.</td>
</tr>
<tr>
<td>Sweden Women and men (Hyppönen et al. 2001)</td>
<td>Birthweight</td>
<td>Birthweight was inversely associated with risk of haemorrhagic stroke in adults.</td>
</tr>
<tr>
<td>Finland Men (Barker et al. 2001)</td>
<td>Low ponderal index at birth</td>
<td>Those who grow slowly prenataally are more vulnerable to health effects of low SES (including associated lifestyle factors). Effects of low social class were greatest among those who had accelerated postnatal growth.</td>
</tr>
</tbody>
</table>
There is therefore some considerable support for the programming hypothesis in a range of populations, in particular as it relates to low birthweight and intrauterine growth retardation (IUGR), for every feature of the insulin resistance syndrome. Numerous theoretical and methodological concerns have been raised, however, particularly in relation to earlier studies.

2.4.2. Refinements

The programming hypothesis has been criticised on several grounds: for relying too heavily on birthweight as a marker of prenatal nutrition, as inconsistent, and, like the thrifty genotype, for being too general. For example, Elford et al. (1992) criticised the programming hypothesis for lacking specificity in the timing of early life disadvantage as this has varied between studies, making the ‘critical period’ in development difficult to define. In particular, the early studies, which relied on geographical similarities in distribution between infant mortality and adult mortality, suffered from the major potential confounding factors that both arose independently from relative socioeconomic deprivation. Since the early studies which focused primarily on birthweight, several refinements to the hypothesis have been made, regarding maternal influences, the timing of prenatal nutritional deprivation, the specific nutrients affecting fetal growth, and the influence of catch-up growth in children.

Proxy measures

Between-population variation in birthweight is mostly attributable to differences in maternal environmental factors (Ulijaszek 1998a). The indirectness of birthweight as a measure of maternal nutrition has, however, been a frequent basis for criticism of the methodology to test the programming hypothesis. Not only is birthweight used as a proxy for IUGR, which is itself a proxy for prenatal nutrition. Fetal insulin, and insulin-like growth factors (IGFs) in particular, however, may have a central role in regulating growth. These respond rapidly to changes in fetal nutrition so that reduced maternal intake leads to decreased fetal insulin, IGFs and glucose concentrations, leading to reduced transfer of amino acids and glucose from the mother, and results in reduced fetal growth (Barker 2000). In late gestation and postnatally, fetal growth hormone IGFs take over from insulin in driving linear growth so that reduced concentrations produce smaller newborns (Barker 2000).

Past infant mortality rates have also been treated as indicative of adverse effects for the fetus and the infants who survived that time (within the same geographical location and cohort), and maternal mortality rates have been treated as indicative of past poor maternal health and
nutrition. Including the use of qualitative data in such circumstances, such as in the present study, may be especially useful in determining past nutritional environments.

**Timing of prenatal nutritional deprivation**

Although birthweight may say very little about relative length and accumulation of soft tissue mass (Miller and Hassaein 1971), it remains the ‘single most important determinant of the child’s survival and subsequent healthy growth and development’ (Himes 1998, p. 371), hence the emphasis that has been placed on its measurement for many decades.

The programming hypothesis focuses on inadequate prenatal nutrition as the primary cause of IUGR, and the earlier studies in particular assess IUGR by birthweight. A further ground for criticism is that birthweight does not distinguish between long thin babies and short fat babies of the same weight. More recent studies on birthweight have used ponderal index and ratio of head circumference at birth to birth length to distinguish better those who are disproportionate from those who are not, which may indicate particular timing of prenatal nutritional deprivation. Ponderal index is a measure of relative thinness; babies with high ponderal index also have smaller arm circumference, which may indicate both less subcutaneous fat and reduced skeletal muscle (Barker 2000). Babies that are thin relative to their length at birth or have a large head circumference relative to their length were probably nutritionally deprived in later pregnancy, as glucose and other nutrients are directed away from growth of peripheral tissue towards vital organs, affecting greater length and head size in proportion to fatness (Barker 1996). A large head circumference in relation to length also suggests that limited nutrients were preferentially directed towards brain and away from the trunk, at the expense of total growth (Barker 1996). Alternatively, if slow growth due to undernutrition is established early in gestation, Barker (1996) argues that slow but sustainable growth occurs reducing the subsequent demand for nutrients and such babies are born small but in proportion.

**Specific nutrients and mothers’ pre-pregnancy weight**

Maternal undernutrition, measured by low pre-pregnancy weight and low weight gain during pregnancy, contributes to low birthweight and poorer obstetric outcomes (Dugdale *et al.* 1990b; Gracey 1991; Sayers and Powers 1997a). There remains, however, a lack of consensus in the degree to which low birthweight should be attributed to poor maternal nutrition (Cameron 1996).
Inadequate maternal nutrition is presumed to restrict fetal growth, producing an infant that is small for gestational age (SGA). Although birthweight is commonly used as a proxy measure of fetal nutrition, birthweight and associated measures of fetal growth may be doubtful measures of maternal nutritional intake (Paneth and Susser 1995), as a developing fetus is somewhat protected from maternal malnutrition. Susser (1991) found that calorie intake in malnourished women is related directly to birthweight, without the mother necessarily gaining weight proportionally. Birthweight is therefore associated with maternal nutrition, but not necessarily linearly with maternal weight gain. Others, however, have found linear associations. For example, Caulfield et al. (1998) established a linear relationship between total weight gain in pregnancy and risk of delivering a macrosomic infant, and Catalano et al. (1998) found a similar relationship between maternal weight gain and birthweight, although this was strongest for women who had lower pre-pregnancy weights. Sayers and Powers (1997a) found that maternal BMI was associated with birthweight, with 36g increase for every unit of maternal BMI. Karim (1998) found a linear association between pregnancy weight gain and birthweight, and concludes that this association holds if the women were adequately nourished before pregnancy.

Pre-pregnancy maternal weight may contribute to birthweight at least as much as weight gain during pregnancy; women who have both low pre-pregnancy weight and low weight gain during pregnancy are most at risk of delivering a low birthweight baby as these factors combine (Krasovec and Anderson 1987). Some authors argue that only babies of those women exposed to severe nutritional deprivation in pregnancy or who were severely malnourished before pregnancy are affected by poor nutrition during gestation, as the maternal environment provides a buffer of sorts as the growing fetus uses the mother’s energy stores (Cameron 1996). If pre-pregnancy nutrition was good, there is therefore likely to be little if any correlation observed between maternal intakes of fat, protein, carbohydrate, calories, calcium and birthweight (Cameron 1996).

Nutrient balance as well as total energy intake may be important in determining the effects of inadequate intake. For example, Mathews et al. (1999) found that birthweights were unrelated to the intake of any macronutrient, but that vitamin C intake in the first trimester was positively associated with birthweight. This study took place in a population of relatively well nourished women in southern England, hence overall energy intake was unlikely to be deficient. Iron

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11 IUGR (also fetal growth retardation) is the process, SGA is the outcome (also small for dates: SFD). The terms are treated as fairly synonymous (Martin 2000).
deficiency in pregnancy contributes to low birthweight, as do deficiencies in zinc and vitamin B12 (Neumann et al. 2002). High protein intake can negatively affect birthweight if it is not balanced with total energy intake (Susser 1991). Godfrey et al. (1996) found that a combination of high carbohydrate intake in early pregnancy and low protein in late pregnancy suppressed fetal growth. Yajnik (2002) found among urban dwelling women in India that neither total energy or amount of protein consumed by the mother affected the birthweight of her child, but the amount of fat consumed was positively associated with birthweight, as was frequency of intake of green leafy vegetables, fruit and milk.

Mathews et al. (1999) suggest that maternal nutrition is an important determinant of fetal growth only in less industrialised countries, and less so where severe malnutrition is uncommon, but that micronutrients probably play a larger role where severe malnutrition is uncommon. Miller and Hassaein (1971) conclude that defining IUGR may be problematic or thresholds could be population-specific.

These findings suggest that maternal nutrition during pregnancy has the potential to affect fetal growth, with relationships strongest in those who were undernourished before pregnancy who have few nutritional stores of their own. Fetal growth also appears to be affected by specific nutrients and not just overall energy intake, especially where overall energy intake is adequate. Details of individual maternal nutritional status are not available for the present study, although qualitative evidence suggests that intake of some nutrients may have been inadequate in the community for many years, even if overall energy intake was sufficient (see Section 4.3.4).

**Placental weight**

A large placenta, in relation to the size of the baby, indicates undernutrition in early pregnancy (Barker 1996) as the placenta responds to inadequate maternal nutrients with increased vascularisation. Placental size is affected by deficiencies in particular nutrients, and depend on maternal nutritional status before pregnancy. Increased placental size may result, for instance, from low iron stores in early pregnancy (Howe and Wheeler 1995). Placental size is also greater in taller women, women who smoke, and those who are multiparous, and is affected by gestational age (Beaulac-Baillargeon and Desrosiers 1987; Dombrowski et al. 1994; Howe and Wheeler 1995). Height, smoking and parity are also independently associated with the insulin resistance syndrome, complicating any associations between metabolic disorders and placental weight, suggesting that placental weight is not a useful indicator of maternal nutrition under the programming hypothesis unless these additional variables are also known. Placental weight is not available for the present study.
Maternal infection

Infection during pregnancy can deplete a woman’s own nutritional status, or it can reduce blood flow to the placenta (Tomkins et al. 1994) so nutrients are less available to the fetus. Infection can reduce maternal nutrient intake by reducing appetite or specific food avoidance, or nutrient absorption may be impaired; intestinal parasite infection decreases the absorption of energy, protein, iron and vitamin A, while nutrient needs also often increase due to infection and the metabolic changes that accompany it (Tomkins et al. 1994). Not all maternal infection produces lower weight babies. For example, Caulfield et al. (1998) found in a study of Native Canadian women that those with pyelonephritis were three times more likely to deliver a macrosomic baby, although this could be due to a link between renal infection and poor glycaemic control among diabetic women. Details on maternal infection for individuals is not available for the present study, but frequency of infection at a community level was, and remains, high (see Sections 3.2.2 and 3.2.4).

Catch-up growth

Although the emphasis of the early studies of the programming hypothesis has been on fetal origins of disease, some of the observed effects are more recently thought to be postnatally acquired or enhanced. Consistent with the theme of environmental discord, strongest support for programming comes from studies of adults who are relatively large but had been relatively small as infants so that discrepancy in body size appears most strongly to promote the development of metabolic disorders. For example, studies by Forsén et al. (1999) and Eriksson et al. (1999b) found that the risk of developing CHD among Finnish women was greatest in those who had been short at birth but who were tall as children, while among men most at risk were those who had been thin at birth but relatively heavier as children. Leon et al. (1996) concluded that Swedish men who were light at birth but above median height as adults had an especially high increase in blood pressure compared with those who were not especially tall. Those who are born small and later become obese, or at least larger later relative to early size, are also at greatest risk from metabolic disorders (Fall et al. 1995a; Yajnik 2002).

A relationship between childhood catch-up growth and adult obesity is supported by Law (2001), who notes that the increase in the prevalence of obesity among children in Western countries is mirrored by increases among adults. If these are causally related, one would expect rises in prevalence of adult obesity to follow from rises in childhood obesity. That child growth, not just fetal growth as measured by birthweight, might be associated with mortality from various adult diseases has important implications for infant health promotion practices, as catch-
up growth has been promoted for decades to parents of children who were failing to gain the amount of weight expected (see Sections 7.3 and 10.1.3).

Inadequate prenatal nutrition diminishes concentrations of both IGF-I and insulin in peripheral tissues so that a postnatal surge in these hormones, promoting catch-up growth, may provoke insulin resistance to protect against hypoglycaemia (Cianfarani et al. 1999). Full postnatal growth recovery from IUGR may increase risk of insulin resistance occurrence in adulthood (Cianfarani et al. 1999).

Although catch-up growth may amplify changes that have already occurred in utero (Barker 2000), Lucas et al. (1999) note that birthweight and current weight may work in opposite directions in their effect on subsequent disease risk, and it is therefore early size in relation to later size – the measure of change in size - that is the relevant factor, not early size itself. Lucas et al. (1999) further urge awareness of the problem of measuring catch-up growth: small babies tend to show more upward centile crossing than large babies, so there is a heightened correlation between birthweight and centile crossing.

Different mechanisms may also be at work among different individuals. Stern et al. (2000) found that there were positive associations between birthweight and features of the insulin resistance syndrome among those who had had no significant change in direction of postnatal growth, while inverse associations were seen in the upward centile crossers.

2.4.3. Confounding factors
A number of additional factors potentially complicate the relationship between birthweight and adult diabetes risk.

Maternal diabetes
In populations with a high prevalence of diabetes, such as the Pima Indians, the association between birthweight and later development of diabetes is U-shaped, as both low birthweight (<2500g) and high birthweight (>4500g) increase subsequent diabetes risk (Pettitt and Knowler 1998). Bennett (1999) found that if the offspring of diabetic women were excluded from analysis, the relationship between birthweight and the risk of developing diabetes became inverse and linear.

Gestation in a diabetic intrauterine environment leads to heavier babies who are more likely to become obese and to develop diabetes in later life (Caulfield et al. 1998; Pettitt and Knowler...
Silverman et al. (1998) found, for instance, that 36% of offspring of diabetic mothers had impaired glucose tolerance (IGT) or Type 2 diabetes by 17 years of age. Increased birthweight and later obesity from gestation in a diabetic environment result from exposure to abnormal levels of glucose and lipids, which also influence the development of insulin resistance in the fetus (Battaglia and Thureen 1998; de Courten et al. 1998). High concentrations of circulating glucose during fetal development may also impair the development of β cells and lead to insulin deficiency (Barker 1999). High concentrations of circulating insulin also enhance fetal growth (Hill et al. 1998), and neonatal hyperinsulinaemia is hypothesised to change patterns of regulatory function of the hypothalamus, altering responses of the hypothalamo-pancreatic system, increasing life-long susceptibility to Type 2 diabetes through influencing patterns of hunger and eating (de Courten et al. 1998). Successive generations may thus be open to increased risk of diabetes, by increasing propensity for obesity through over-eating.

Obese women without diabetes are also likely to have increased insulin resistance and are therefore less able to maintain glucose homeostasis during pregnancy, exposing the fetus to higher amounts of circulating glucose; even mild obesity in pregnancy may be sufficient to cause disruption to homeostasis (Fall et al. 1998). Thus although large babies are at increased risk of diabetes, the causal mechanisms are different from those for small babies.

**Intergenerational effects: maternal anthropometry and nutritional history**

Other maternal factors influence birthweight, including mother’s height and her own birthweight (Dugdale et al. 1990a; Barker et al. 1992d; Susser and Stein 1994). Yajnik (2002) found that mother’s height and head circumference, both indicators of early nutritional status, were significant predictors of infant birthweight. Effects of maternal nutrition may therefore persist between generations (Dugdale et al. 1990a; Blair 1996; Streatfield 1996), effects that appear to be stronger between mothers and daughter than between mothers and sons (Streatfield 1996), with little to no influence from fathers (but see Hyppönen et al. 2003 below).

A woman’s own growth during childhood has also been found to be also associated with postnatal growth of her children (Alsop-Shields and Dugdale 1995). Both prenatal and postnatal nutritional environment of females may therefore affect the growth and development of subsequent generations. An acquired trait may be passed on phenotypically to the next generation through the mother’s prenatal nutritional state, demonstrating how intrauterine under- and overnutrition can mimic genetic effects (Swinburn 1996).
Maternal age and parity

An inverse U-shaped relationship is usually apparent between birthweight and both maternal age and parity (Bogin 1996). Low maternal age increases the likelihood of delivering a low birthweight baby. Mothers who are under 20 years of age are more than twice as likely as older mothers to have an IUGR infant (Sayers and Powers 1997a); pregnant women who are still completing adolescence require nutrients specifically for their own growth as well as that of the fetus. Very high maternal parity (and therefore older mothers) is also associated with reduced birthweight (Humphrey and Holzheimer 2000), an association that in some populations at least might be due to increasing maternal age rather than parity (Rauh et al. 2001). Birthweight also decreases with shorter interbirth intervals (Bogin 1996).

Social immobility and adult lifestyle

Both diabetes and low birthweight occur more frequently among those with lower SES in Westernised countries (Hales 1994). For example, Rich-Edwards et al. (1999), in a study of female nurses in the United States, found childhood SES was inversely associated with birthweight, and Turrell and Mathers (2001) found in Australia that prevalence of Type 2 diabetes was inversely associated with adult SES.

The programming hypothesis has been widely criticised on the grounds that those born into an underprivileged environment tend to remain in one and continue to experience adversity throughout life; factors relating to both infant and adult health may therefore be difficult to separate. Thus, in relation to the early Barker studies, areas of past high mortality have probably remained areas of high mortality, and associations may be confounded by ‘persisting geographical differentials in social and economic conditions’ (Elford et al. 1992, p. 7). The method of the early Barker studies, which analysed place of origin, introduces potential for additional confounding variables of adult SES (Paneth and Susser 1995). Subsequent studies have attempted to control for known adult risk factors, and associations that are found between birthweight and adult disease have been found to occur independently of social class and adult behaviours (for example, Fall et al. 1995a; Fall et al. 1995b; Barker 1996, 2000; Barker et al. 2001; Wamala et al. 2001) and are compounded by them (Davey Smith et al. 1997). Kramer and Joseph (1996) further suggest that studies examining relationships between chronic health and disease should therefore consider SES at birth and in early childhood.

Sampling bias

Sampling methods used in the early programming studies have also been heavily criticised as the follow-up of adults from their birth records within an area has led to high attrition rates.
Although critical of attrition rates, Kramer and Joseph (1996) concede there is no obvious reason why this might introduce bias. Susser and Levin (1999), however, believe the high rate of attrition is problematic in that it can introduce selection bias, causing greater follow-up of those who had not moved out of the area who may also be less healthy than those who moved (the healthy migrant effect). This remains a difficult issue to address. In the present study, the potential confound was ameliorated by tracing adult individuals in the community back to their child records, to compare diabetes risk among adults currently living within the community, rather than following up adults from their birth records.

**Twins**

To date, twin studies have been unsupportive of the programming hypothesis. Twins often experience IUGR, but Christensen et al. (1995) found no significant mortality differences between twins and singletons. In a New Zealand sample, Williams and Poulton (1999) found that twins had lower birthweights and lower systolic blood pressures at ages nine and 18 years than singletons, not higher blood pressure as would be expected given effects hypothesised under programming. Although twins do experience growth restrictions in the third trimester, Williams and Poulton (1999) conclude that the programming hypothesis did not apply to this form of growth retardation, as IUGR among twins reflects something other than inadequate nutrition in pregnancy, such as cramped conditions in later gestation.

**Gestational age**

A study of 70-year-old men by McKeigue et al. (1998) found that for those born small at term there was a positive relation of insulin sensitivity to birthweight, while the reverse association occurred with those born pre-term. They suggest that inconsistencies may arise in studies where gestational age is not considered. The primary cause of low birthweight in less industrialised countries is IUGR, while pre-term delivery is the main cause in industrialised countries (Kramer 1987). In the present study, no reliable data on gestational age was available, but evidence from other studies suggest that lower birthweight among Aboriginal infants is more likely to be due to IUGR than prematurity (see Section 3.2.2).

**Tobacco and alcohol**

Tobacco smoking and alcohol consumption during pregnancy are associated with reduced birthweights. Maternal smoking causes mean birthweight to decline by approximately 100g (Shu et al. 1995), although in a study by Humphrey and Holzheimer (2000) it was found that lower levels of tobacco and alcohol use had no significant relationship with birthweight. Vik et al. (1996) suggest that dietary fats comprise relatively a higher proportion of energy intake
among pregnant smokers than non-smokers and that a smoker’s diet might contain less protein, calcium, iron and vitamins. Similar associations may also occur for alcohol consumption. These nutrient shortfalls could contribute to birthweight differences, so that the effects of tobacco and alcohol might be compounded by poor nutrition related to socioeconomic factors (Shu et al. 1995) and reduced levels of physical activity (Goldberg 1998) among those who smoke and consume alcohol during pregnancy.

Generalisability

Studies on the programming hypothesis have found inconsistent results in different populations. In South India, for example, although birthweight was inversely associated with CHD (CHD prevalence fell from 11% in those born weighing ≤2.5kg to <3% in those weighing >3.1kg), short birth length was found to be more important than low weight for CHD risk, and low ponderal index at birth was unrelated to CHD prevalence in adults (Stein et al. 1996). This contrasts with findings from most of the programming hypothesis studies which have taken place in more industrialised countries. However, a population living a foraging lifestyle or one undergoing lifestyle transition (such as South India), will have very different nutritional availability and energy expenditure pressures (for example, high levels of physical activity among adults) from populations living a more Westernised lifestyle (Crowther et al. 1998). There is substantial value in this diversity of results, as it could refine understandings of particular environments that may be conducive to diabetes development; it appears that small infants in less industrialised countries are more likely to be in proportion, while those in more industrialised countries tend to be relatively thin.

2.4.4. Physiological mechanisms

The precise mechanisms behind the observed relationships between Type 2 diabetes and low birthweight continue to be investigated.

Insulin secretion

Earlier studies concluded that IUGR babies have reduced number and size of pancreatic β cells (Robinson et al. 1992), hence a reduced capacity to make insulin, with risk of eventual pancreatic exhaustion as adults (Barker 1996). Nutritional and possibly other factors influencing fetal growth (such as infection) may determine size and function of adult β cells (Barker 2000). In addition to a reduced complement of β cells, the function of islets may also be reduced by early poor nutrition. Deficiency of dietary protein, especially in early gestation, not only reduces β cell mass, but also restricts vascularisation of islets (Hales and Barker 1992;
Hales 1994) thus affecting their function. Godfrey et al. (1996) found that low birthweight babies and those with small placentas had lower cord plasma concentrations of split proinsulin and insulin, and thin babies had lower proinsulin, split proinsulin and insulin, supporting the hypothesis that reduced fetal insulin secretion may be an underlying factor in both low birthweight and later Type 2 diabetes and CHD.

Experimental studies on animals have lent support to the proposition that nutritional deprivation during development leads to insulin deficiency. An early study by Winick and Noble (1966) found that underfeeding infant rats led to lower adult plasma insulin. Snoeck et al. (1990) established that protein deficiency in pregnant rats produced offspring with a reduced number of β cells. Intergenerational effects of prenatal underfeeding also persist; a mother’s prenatal exposure to protein affects the development of her offspring, so that normal development is not achieved even when fed a normal protein diet after birth (Snoeck et al. 1990). Pregnant rats deprived of adequate protein also produce offspring with increased blood pressure as adults (Langley and Jackson 1994). In addition, a low protein diet fed to pregnant rats led to a doubling of liver PEPCK activity (a key enzyme for gluconeogenesis) and a halving of glucokinase activity (a key enzyme for glycolysis) in adult offspring (Lucas 1998).

**Insulin resistance**

Lithell et al. (1996) inferred that size at birth and development of Type 2 diabetes are more likely to be mediated through insulin resistance rather than impaired β cell function, after finding only a weak inverse correlation between ponderal index and one-hour insulin concentrations after intravenous glucose, but a stronger inverse association between ponderal index and diabetes. In addition, the findings of Whincup et al. (1997) in 10-11 year old children who had low birthweights and were thin at birth, favour insulin resistance as the mediating mechanism.

Choi et al. (2000) also found that low birthweight was associated with insulin resistance in young Korean men. Insulin resistance as the basis for diabetes predisposition through programming is further supported in studies by Fall et al. (1995a), Leon et al. (1996), Leger et al. (1997), McKeigue et al. (1998), and Flanagan et al. (2000).

Whether reduced insulin secretion or insulin resistance is more important may be population-specific. In African children, Crowther et al. (2000) concluded that those with low weights at birth and at seven years had relatively low β cell activity, while those with low birthweight and high weight at seven had high β cell activity. Similarly in South India, Fall et al. (1998) found
that higher ponderal index at birth was associated with lower 30 minute post-prandial insulin secretion in adults.

Diabetes occurs when insulin production can no longer compensate for insulin resistance, deficiencies in both insulin secretion and/or insulin action may be important in the development of Type 2 diabetes (Barker 2000). The relative importance of each could depend on overall nutrition and socioeconomic environment; the current ‘stage’ of nutrition transition may be pivotal in creating this distinction. Whether impaired insulin secretion or impaired action is the primary cause may heavily depend on the timing and duration of prenatal undernutrition.

If undernutrition occurs early in gestation, then the overall growth of the fetus is likely to be reduced, the baby’s body will be in proportion, but insulin secretion may be impaired. This pattern might be expected in a more nutritionally marginal environment, such as one characterised by poverty and flux. If inadequate nutrition occurs later in gestation once organs are further developed (or micronutrients which promote fetal growth are lacking) then insulin resistance in skeletal muscle tissue, associated with thinness at birth, may be the underlying cause (for instance, Barker 1996), via permanent reduction in glucose transporters, eventually leading to islet exhaustion (Cianfarani et al. 1999). Given that both proportionate and disproportionate small size at birth are thought to predispose to adult diabetes, and provided reduced birthweight is the result of IUGR rather than prematurity, it is less important that birthweight is the only measure of nutritional status at birth that is available for the present study (Section 7.1).

**Stress and the HPA axis**

Physical stress has for several years been associated with poor glucose control in diagnosed diabetics (Surwit and Feinglos 1988; WHO 1994), and depression and anxiety are commonly associated with diabetes (for example, Téllez-Zenteno and Cardiel 2002), but it is unclear as to which, if either, is primary. The absence of similar levels of depressive symptoms in people who report other chronic disease, such as hypertension, high cholesterol and heart disease, implies that anxiety and depression are not simply the result of diabetes diagnosis (Grandinetti et al. 2000).

Recent studies suggest that the underlying mechanism promoting development of the insulin resistance syndrome through insulin resistance result from a rise in cortisol concentrations, due to a failure of usual feedback mechanisms (Björntorp et al. 1999; Björntorp and Rosmond 2000), in particular the effects of cortisol secretion on promoting central obesity and insulin
Models of diabetes prevalence

resistance (for example, Björntorp et al. 1999; Levitt et al. 2000; Vicennati and Pasquali 2000). Björntorp (1997; 1999) hypothesises that central obesity and insulin resistance result from neuroendocrine abnormalities arising from hypersensitivity in the hypothalamic-pituitary-adrenal (HPA) axis. Ongoing stress enlarges adrenal glands, causes increased deposition of visceral abdominal fat and promotes insulin resistance, hypertension and dyslipidaemia (Björntorp 1999; Björntorp et al. 1999). Environmental stressors, such as psychosocial stress, alcohol and tobacco, activate the HPA axis producing an hypothalamic arousal syndrome (Björntorp et al. 1999). While levels of cortisol vary throughout the day where the HPA axis functions normally, sustained cortisol secretion with low variability – i.e. cortisol secretion becomes less responsive to stimuli – occurs when feedback mechanisms fail. Even moderate stress is sufficient to induce changes to the HPA axis (Björntorp et al. 1999).

Disturbances in the HPA axis influence diabetes risk chiefly through instigating insulin resistance (Björntorp et al. 1999), but also contribute to CVD risk by increasing blood pressure and promoting dyslipidaemia. Prolonged elevated cortisol levels direct excess fat to be deposited preferentially as abdominal visceral fat and promote insulin resistance and compensatory insulin secretion (Björntorp 1999; Vicennati and Pasquali 2000). It also promotes hepatic gluconeogenesis and glycogenolysis, and enhances the release of free fatty acids (FFA) from visceral adipose tissue, causing dyslipidaemia. Levitt et al. (2000, p. 4611) conclude that cortisol axis activation is an ‘early feature in the process linking low birthweight with adult cardiovascular and metabolic disease’.

Elevated blood pressure may result from HPA axis disturbances to homeostasis, which reset ‘normal’ blood pressure, rather than as a result of elevated insulin levels as had been previously accepted (Björntorp et al. 1999; Barker 2000; Levitt et al. 2000); perceived stress and blood pressure are positively associated (James and Bovbjerg 2001). Low SES in more industrialised countries is associated with increased cortisol secretion (Björntorp 1999), probably due to increased psychosocial stress, but not independently of other lifestyle contributions of alcohol and tobacco consumption.

Disruption to the HPA axis might be programmed in early life. An adverse intrauterine environment, such as via inadequate nutrition, could promote early activation of the HPA axis; excessive levels of maternal cortisol during gestation have been found to be associated with reduced birthweight (Challis et al. 2001), as excess cortisol may reduce the linear growth of the fetus (Allen 2001). Stress hormones therefore provide a plausible link between observations that low birthweight is associated with insulin resistance in adults.
Phillips et al. (2000), for instance, found that low birthweight was associated with raised fasting plasma cortisol concentrations in adults, and that these in turn were linked with increased blood pressure. The relationships were strongest in subjects who were also obese. They concluded that increased activity of the HPA axis, programmed in utero, may link low birthweight with raised adult blood pressure (Phillips et al. 2000).

**Additional programming relationships**

Health and social outcomes other than Type 2 diabetes and the insulin resistance syndrome have been linked to birthweight and early child health in various populations. Lung function (Barker et al. 1992a) and suicide in the UK (Barker et al. 1995) and age at menopause in an Australian study (Treloar et al. 2000) are among some which have been investigated. Prenatal exposure to the Dutch famine was found to be associated with a two-fold increase in the risk of schizophrenia in adults (Susser and Stein 1994). Low birthweight and poor child growth were associated with poorer psychological health among adults (Cheung et al. 2002), again in the UK. IUGR was associated with cognitive delays in development in Italian children (Sansavini et al. 1996) and poorer cognitive abilities in childhood and adulthood in the UK (Sørensen et al. 1997; Matte et al. 2001; Richards et al. 2001), and sensory impairments and other disability in children in Britain and Sweden (Roth et al. 1999; Power and Li 2000). Birthweight among British men has also been linked with their likelihood of marriage (Phillips et al. 2001), but a similar relationship was not found among women when tested in Sweden (Vågerö and Modin 2002).

### 2.5. Synthesis

Most recent studies on diabetes within the framework of the programming hypothesis have reached similar conclusions to those of the thrifty genotype hypothesis; that insulin resistance rather than reduced secretion may be more important in diabetes aetiology, and protein could be a key factor in nutrition.

O’Dea suggests that low birthweight may have a ‘multiplier effect’ on possible genes predisposing to diabetes (O’Dea 1997). Neel et al. (1998) see no conflict between the concept of programming and the thrifty genotype, but favour multiple pathways. They note that a phenotype requires a ‘genetic architecture’, which leaves room for the thrifty genotype within the context of phenotypic modification by the environment. Barker (1999) also concedes that causality in the relationship between early growth and later disease is potentially gene-based,
and argues that if there is a genetic component, these influences first show themselves in early life as reduced growth and are later revealed as chronic degenerative disease.

Recently, rates of progression from normal glucose tolerance to IGT in some populations with extremely high prevalence of diabetes have declined. Dowse et al. (1991a) suggest that the high rate of diabetes on Nauru has itself provided a selective pressure, and has already removed genetically susceptible people from the population. This hypothesis arises because mortality is higher and fertility lower among diabetics. However, this decline in prevalence may also indicate that nutrition transition from subsistence to excess has been ‘completed’, so that the current generation of adults were exposed as children to a nutritional regime similar to the present situation, while there was discord in their parents’ and grandparents’ generations exposed to nutritional excess as adults relative to their own early environment. CVD mortality rates have also declined slightly in South Korea over the last 20 years as mean energy intake has decreased, even though intake of fat as a percentage of energy has increased (Suh 2001). Perhaps this too is a sign that nutrition during development has started to parallel that of adulthood, thus rendering the two less discordant.

A similar pattern has emerged for heart disease. Baker et al. (1993) and Paneth and Susser (1995) note the falls in IHD and CHD that have occurred in more Westernised countries over recent years with the adoption of a more healthy lifestyle. Paneth and Susser (1995) propose that if early life is important, there would be a lengthy delay between healthy lifestyle and a decline in disease, rather than the reduction in mortality that has already been observed with occurred with the uptake of healthier lifestyles in Western countries in recent decades. From the studies reviewed in this chapter which support the programming hypothesis, it seems not that later lifestyle is unimportant, but that it operates synergistically with early environment.

**Surviving small baby**

Some researchers offer a modification to the programming hypothesis that embraces a possible genetic basis, that increased mortality among low birthweight infants permits selective survival in infancy in famine-prone populations of those genetically predisposed to insulin

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12 In Australia for example, the category of CVD has only recently been displaced by cancer as the highest ranking cause of mortality overall, due to a fall in deaths from CVD, but remains the primary cause of death among Indigenous Australians (AIHW 2002a) (see following chapter).

13 Low birthweight babies are at greater risk of morbidity and mortality from malnutrition and infection within the first five years of life (Shapiro et al. 1980), discussed in the following chapter (Section 3.3.4).
resistance and Type 2 diabetes (Waldhäusl and Fasching 1993; McCance et al. 1994). Thus individuals who were low birthweight – and survived – are more prone to develop diabetes than higher birthweight babies, if they encounter greatly changed conditions in later life. In Australia, low birthweight Aboriginal infants are more likely to survive than non-Aboriginal infants of comparable birthweights (see Section 3.2.2), which lends some support to this possibility.

**Fetal insulin hypothesis**

More recently, the surviving small baby hypothesis has evolved to become the ‘fetal insulin hypothesis’, whereby genetic polymorphisms are thought to lead to both suboptimal prenatal growth and to insulin resistance in later life (Hattersley and Tooke 1999; Lawlor et al. 2002). Hyppönen et al. (2003) for example, found a relationship between paternal diabetes and reduced birthweight in offspring, and as paternal height has some limited independent influence on birthweight and body composition (Blair 1996; Catalano et al. 1998; Yajnik 2002), it is possible that there are also some genetic factors involved. Such a relationship does not rule out shared environmental effects. Fathers with diabetes are likely to have diets that are less nutritious, for instance; although energy-dense they might be lacking in specific nutrients required for healthy prenatal growth (assuming the father and the mother are sharing a household). There are most likely additional factors associated with social class that relate both to a father’s diabetes status and the birthweight and health of his children. High birthweight resulting from diabetic pregnancies is due to poor metabolic control and under the fetal insulin hypothesis could mask genetic effects which may otherwise act to limit prenatal growth (Hyppönen et al. 2003). The fetal insulin hypothesis, which associates parental diabetes status with the birthweight of their offspring, does not preclude the programming hypothesis, as programming associates the intrauterine environment with later risk of diabetes. Parental diabetes status and that of their adult offspring may be linked, and genes may or may not play a significant role.

**Genetic basis to HPA axis variation**

Further synthesis of the thrifty genotype and programming hypotheses can be seen in the potential role of the HPA axis. Exposure to stress during development may program subsequent stress response, while variation in the ability of the HPA axis to provide appropriate feedback may be the result of environmental stress interacting with genetic factors (Björntorp et al. 1999).
2.5.1. Conclusions

Rather than being a disease of ‘affluence’ or ‘civilisation’, Type 2 diabetes as it affects numerous indigenous groups throughout the world would more aptly be described as a ‘disease of colonisation’. Whether this is in the classic sense, such as took place in the Americas and Australia, or in a more metaphorical sense, in terms of changed economic and sociocultural structures such as in Nauru, transitions towards more Westernised ways of living, characterised by high energy input and low energy expenditure, have occurred. The term ‘affluence’ confuses quality with quantity. For example, many post-colonial indigenous groups have access to sufficient food in terms of energy requirements, but the quality of food may be poor and contingent on wider socioeconomic disadvantage.

High rates of diabetes, lower birthweight and disrupted growth are commonly experienced in Australia’s Aboriginal population (see following chapter). O’Dea (1997) describes this as a ‘double jeopardy’, where Australian Indigenous people have experienced or are experiencing both poor nutrition in early life and the detrimental effects of Westernisation of diet and lifestyle in later life. Given the evidence from other populations, investigating potential relationships between nutrition in early life and subsequent development of diabetes in the Aboriginal population is therefore important.

The recent evidence, in particular that highlighting the importance of insulin resistance, suggests that the thrifty genotype and programming hypotheses need not be diametrically opposed. While the former developed to explain variation between ethnically diverse populations, the latter has focused more on variation between individuals within populations. In the present study, the framework of the programming hypothesis is expanded to consider exposure of whole populations to adverse prenatal and postnatal environments, and the influence this may have on diabetes prevalence.