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CHILDHOOD STRESS: A LIFETIME LEGACY

ABSTRACT: The idea that events occurring in the early years of a person's life can influence their subsequent experience of morbidity and mortality occurs with increasing frequency in the literature concerning both living and past populations. In this paper we review the evidence for this association from studies of living and past populations. In living populations, follow up studies which examine the incidence of morbidity and mortality in groups of adults whose early life parameters are known provide the most reliable means of investigating this association, but such studies are restricted to those populations with comprehensive documentation of the events surrounding birth. The skeletal remains of past populations require a fundamentally different approach to the investigation of the long-term consequences of events in early life. Each skeletal series represents a set of retrospective records of childhood exposure to stress events together with indisputable evidence of the final outcome. However, in most cases the stress indicators are non-specific, the cause of death cannot be reliably determined, biological parameters such as age at death must be estimated, and non-biological parameters such as variation in socio-economic status are likely to remain obscure. Despite these problems we aim to show that the study of past populations can make a valuable contribution to understanding the association between exposure to stress during prenatal life and early childhood and adult health and longevity.

KEY WORDS: Stress – Disease – Nutrition – Early environment – Age at death

INTRODUCTION

Over the last few years the relationships between developmental stress and subsequent mortality and morbidity have become a growing focus of research in studies of living and past populations (Henry, Ulijaszek 1996). For this paper, we define stress as "a physiological disruption resulting from impoverished environmental circumstances" (Larson 1997). Goodman and colleagues (1984, 1988) have developed a model for the impact of stress on an individual or population that emphasises the interaction of three main factors. Environmental constraints include both resources and stress causing agents; cultural systems act as a buffer, but can be a cause of additional stress factors (e.g. a reduction in dietary quality); and host resistance provides a further buffer for an individual. Stress can therefore be considered in terms of the friction between an individual and his/her social, physical, nutritional and disease environment (Simpson *et al.* 1990).

The concept of biological programming is a useful framework in which to understand the long-term consequences of early life events. Lucas (1991) gives a working definition of programming as occurring "when an early stimulus or insult, operating at a critical or sensitive period, results in a permanent or long term change in the structure or function of the organism". This concept underlies the hypothesis whereby individuals who are exposed to prenatal or early childhood stress may be biologically weakened in such a way as to reduce their ability to cope with stress episodes in later life, and are at greater risk of morbidity and early mortality.

In this paper, we will review the evidence that stress suffered prenatally and during early childhood can result in poor adult health and a shortened lifespan. In the first section, we review recent studies of living populations that establish this relationship. In the second section, we investigate the effect of early stress on subsequent mortality in past populations. Skeletal and dental remains from past

populations provide an opportunity to use biological markers as retrospective indicators or "memories" of stress in early life, allowing us to analyse the association between differential exposure to childhood stress and subsequent mortality. In a third section we examine possible causes underlying the observed relationship between stress during early life and subsequent disease and mortality. Following this is a discussion of future research directions. Our major purpose is to establish a framework for the analysis of past populations, and to indicate new research directions and techniques that are pertinent to these issues.

The different stages of childhood are defined following Scheuer, Black (in print). Neonate covers the period between birth to one month of age, infant covers the period between birth to the end of the first year of life, early childhood covers the period between the end of the first year of life and the end of the fifth year, and late childhood covers the period between the sixth year of life and puberty. The term juvenile is used to describe the entire period between early embryonic life and adulthood. The authors of the various studies discussed in this review differ in the age at which they define the transition between juvenile and adult, and we have followed their respective definitions.

STUDIES OF LIVING POPULATIONS

In this section we will highlight evidence from living populations that demonstrates a link between the early environment and subsequent health and development. The first part of this section will cover foetal growth and development. Following this, infant and childhood diseases are examined in terms of their effect on predisposing individuals to subsequent disease experience. The final section will look at the long-term consequences of early nutrition. The main findings of the first two sections are summarised in *Tables 1* and *2*.

The intrauterine environment

Several studies have shown that foetal and early postnatal growth are linked to adult disease. Barker, Osmond (1986) found a geographical link between neonatal and postneonatal mortality in 1921–1925 and death rates from ischaemic heart disease in 1968–1978. Mortality rates for both periods were highest in the least affluent areas examined in the study. These results suggest that individuals exposed to more impoverished environments in foetal life, as indicated by high rates of neonatal and postneonatal mortality, were at a higher risk of developing heart disease in later life. Another study related death rates from stroke and heart disease to maternal mortality rates between 1911 and 1914, again finding a geographical association (Barker, Osmond 1987). In order to verify their earlier findings, Barker and colleagues have carried out follow-up studies using health visitors' and hospital records. In a study of 5,225 men born between 1911 and 1930 in Hertfordshire, Barker *et al.* (1989) found that weight at birth and at one year were inversely related to mortality rates from ischaemic heart disease. A further study of 13,249 men from Hertfordshire and Sheffield demonstrated that standardised mortality rates from coronary heart disease fell by an average of 10% between five successive groups of increasing birthweight (Martyn *et al.* 1996). The inverse relationship between low birth weight and heart disease is one that is seen across the entire distribution of birth weights and is not a phenomenon that is restricted only to very small babies.

Birth weight has also been related to rates of coronary heart disease in Mysore, southern India, giving further support to the evidence suggesting that foetal malnutrition increases the risk of developing heart disease in adulthood (Stein *et al.* 1996). Low birth weight, short body length and small head circumference were associated with increased rates of the disease in a follow-up study of 517 men and women. In addition, low maternal weight during pregnancy resulted in increased prevalence of the disease in children born to these women.

More recently, work by Leon *et al.* (1998) has shown that it is birth weight for gestational age rather than birth weight alone that predicts mortality from ischaemic heart disease. Birth weight for gestational age gives a measure of foetal growth rate and the authors suggest that variation in foetal growth rate rather than size at birth is the crucial factor for predicting death from heart disease in adult life. This finding is based on a cohort study of 15,000 men and women born in Uppsala, Sweden between 1915 and 1929 for whom there are detailed obstetric records. Follow up studies have been carried out during the entire life of these individuals (up to 1995) and this information has also been linked to census data. Ischaemic heart disease was inversely associated with birth weight for gestational age in both men and women, although it was only significant in men. Socio-economic factors were found to have an effect on the strength of the association between foetal growth rate and ischaemic heart disease. However, the effect of socio-economic factors was not large enough to confound this association. Interestingly, the study by Leon *et al.* also found that other measures of foetal growth retardation, such as ponderal index and head circumference, did not predict mortality from cardiovascular disease after controlling for gestational age.

Research has also focused on rates of ischaemic heart disease in twins since twins have lower birth weights than singletons and might therefore, be expected to have higher death rates from this disease. A study by Vågerö, Leon (1994) has shown that in fact twins do not have higher mortality rates from the disease than singletons. This may be the result of a different type of growth retardation in twins – occurring in the third trimester of pregnancy – than in singletons. However, the study did find that the shorter twin of a pair is more likely to die of cardiovascular disease. The authors suggest that in addition to prenatal factors, postnatal factors such as nutrition and differential treatment by the family or society may also produce an effect on ischaemic heart disease mortality.

Hypertension in later life has been related to placental and birth weight. Barker *et al.* (1990) examined blood pressure in 9,921 children aged 10 years and 3,259 adults and found that blood pressure was highest in those individuals who had been small neonates with large placentas. Small neonatal size and a large placenta in relation to neonatal size can be caused an inadequate supply of nutrients and oxygen in foetal life. Intrauterine infection is also associated with a large placental size and low birth weight (R. K. Chandra, commenting in Barker 1991: 12). Contrary evidence relating to placenta size has been put forward by Leon (1999) in a longditudinal study of 599 men born in Uppsala, Sweden. The research showed that placental weight was positively correlated with birth weight, and that blood pressure declined with increasing placental weight for every birth weight category examined. Another longitudinal study of 1,895 children (ranging from 0–10 years of age) and three follow-up studies of adults (3,240 men and women aged 36 years, 459 men and women ranging between 46 and 54 years of age, and 1,231 men and women aged 59–71 years), also found that hypertension is initiated *in utero* (Law *et al.* 1993). The study also

TABLE 1. Summary of main studies conducted on living populations that indicate an association between prenatal, perinatal and early postnatal stress, and adult disease.

Author(s)	Stress indicator	Associated outcome measure	Suggested long-term outcome
Barker *et al.* 1989	low birth weight	cardiovascular disease in adulthood	
Stein *et al.* 1996	low birth weight, short body length & small head circumference at birth	cardiovascular disease in adulthood	
Barker *et al.* 1990	low birth weight & placental weight	hypertension in adulthood	cardiovascular disease
Leon *et al.* 1996; Koupilová *et al.* 1999; Leon 1999	low birth weight and length & adult body size	hypertension in adulthood	cardiovascular disease
Barker *et al.* 1993	small abdominal circumference at birth	raised serum cholesterol levels in adulthood	cardiovascular disease
Law *et al.* 1992	low birth weight	abdominal storage of fat in adulthood	cardiovascular disease, and impaired glucose tolerance & NIDDM
Hales *et al.* 1991	low birth weight & weight at one year	impaired glucose tolerance & NIDDM, and hypertension in adulthood	
Phipps *et al.* 1993	low birth weight, small head circumference & low ponderal indices (thinness) at birth, and a large placental weight relative to birth weight	impaired glucose tolerance & NIDDM in adulthood	
McKeigue *et al.* 1998	low ponderal index & adult obesity	impaired glucose tolerance & NIDDM	
Yajnik *et al.* 1995	low birth weight	high glucose & plasma insulin concentrations at age 4	impaired glucose tolerance & NIDDM
Fall *et al.* 1998	short body length & high ponderal indices	high glucose & insulin concentrations, and impaired glucose tolerance in adulthood	NIDDM
Ekbom *et al.* 1996, 1997; Ekbom 1998	high birth weight, jaundice, severe prematurity & dizygotic twins	morbidity and mortality from breast, prostate & non-seminona cancer	

TABLE 2. Summary of main studies conducted on living populations that indicate an association between childhood infection and adult disease.

Author(s)	Disease	Associated outcome measure
Barker, Osmond 1989	lower respiratory tract infection during infancy	chronic bronchitis in adulthood
Pullan, Hey 1982	infection with respiratory syncytial virus during infancy	recurrent wheezing up to age 10
Mok, Simpson 1984	lower respiratory tract infection during infancy	recurrent coughing & wheezing, and increased rates of chest infections & colds up to age 7
Martyn, Barker 1988	poliomyelitis after age 10	

suggested that although variation in blood pressure between low and normal birth weight children may be small at birth, this difference is amplified during later life. Continuing research on the Uppsala cohort (1,334 individuals) has shown that birth weight and length has an inverse association with blood pressure in men aged between 50 and 75 years of age (Leon *et al.* 1996, Leon 1999, Koupilová *et al.* 1999). This research has found that adjustment for adult body size (body mass index and height) strengthened the relationship. Men who were light at birth but tall as adults had raised blood pressure. These findings have implications for mortality from circulatory disease. Leon *et al.* (1996) suggest that metabolic disturbances, perhaps through insulin resistance, may be the route by which foetal growth affects blood pressure.

An association between low weight at birth and at one year and impaired glucose tolerance and the onset of non-insulin-dependent diabetes mellitus (NIDDM) in adult life also suggests a link between foetal growth retardation and subsequent morbidity. A follow-up study of 468 men born in east Hertfordshire and still living there as adults, showed a tendency for impaired glucose tolerance and hypertension to coincide in adults who had low weights at birth (Hales *et al.* 1991). Subsequent studies have shown that, in addition to low birth weight, other indicators of an impoverished foetal environment are also linked to the development of NIDDM in adults. In a follow-up study of 140 men and 126 women in the UK, Phipps *et al.* (1993) found that low birth weight, smaller head circumference and thinness (indicated by a low ponderal index) at birth, together with a higher ratio of placental weight to birth weight were associated with later impairment of glucose tolerance. Interestingly, Martyn *et al.* (1998) found that adult plasma insulin concentrations were more strongly correlated with abdominal circumference at birth than with birth weight, indicating that the development of liver in intrauterine life predicts subsequent disease experience. After adjusting for body mass index, McKeigue *et al.* (1998) have also found an inverse association between size at birth and glucose intolerance in a cohort of adult males aged between 63–79 years from Uppsala, Sweden. The study found that men who were thin at birth and became obese as adults had raised insulin levels at the age of 50 and diabetes by the age of 60.

There are also indications in non-western populations that NIDDM is programmed in foetal life. Yajnik *et al.* (1995) found that among 379 four-year-old children in Pune, India, those who had low birth weights had higher plasma glucose and insulin concentrations than children born with a normal birth weight. In another follow-up study carried out in Mysore, southern India, Fall *et al.* (1998) showed that there were higher rates of the disease in individuals who had been short at birth, had high ponderal indices at birth and whose mothers had been mildly obese. The authors suggest the increase in NIDDM in Indian urban populations is initiated by mild maternal obesity in pregnancy which results in insulin deficiency during adult life in their children.

The timing of foetal growth retardation may be an important factor in the development of impaired glucose tolerance during adult life. Ravelli *et al.* (1998) carried out a follow-up study of 702 individuals who were born during the Dutch famine during 1944 and 1945 using prenatal and birth records. They found that glucose concentrations were highest among individuals who were exposed to the famine during middle and late gestation. The study also showed that individuals who were thin at birth, and became obese as adults and, in contrast to the study by Fall *et al.* (1998), were born to mothers with a low body weight, had the highest glucose concentrations.

The tendency to store fat abdominally in adulthood is an indicator of foetal growth retardation. Law *et al.* (1992) carried out a follow-up study of 845 men born in Hertfordshire and 239 men born in Preston and still living in those areas, and found that, controlling for body mass index, average hip to waist ratio decreased as birth weight increased. They suggest that this is a lasting response to an impoverished foetal environment. Abdominal storage of fat increases the risk of developing cardiovascular disease and diabetes in later life.

Another long-term consequence of foetal growth retardation is an alteration to the programming of cholesterol metabolism. Barker *et al.* (1993) carried out a follow-up study of 219 men and women born in two hospitals in Sheffield during 1939 and 1940 and found that a small abdominal circumference at birth was associated with raised serum cholesterol levels as adults. The authors suggest that a small abdominal circumference at birth is an indicator of impaired liver growth, and thus, an impoverished foetal environment.

Associations between the intrauterine environment and morbidity and mortality from cancers have also been found. High birth weight and jaundice have been linked with the risk of breast, prostate and non-seminona cancer, indicating high levels of endogenous pregnancy hormones *in utero* (Ekbom, 1998, Ekbom *et al.* 1996, 1997). Pre-eclampsia, an indicator of low levels of endogenous pregnancy hormones, is associated with decreased risk of these cancers. Severe prematurity and dizygotic twins are also associated with high levels of oestrogens and increase the risk of breast cancer.

Finally, neurodevelopmental disorders have been associated with environmental factors operating during foetal development and at the time of birth. Obstetric complications (particularly, asphyxia at birth associated with a long labour) or a neurodevelopmental disorder in the second trimester strongly predict adult schizophrenia (Murray *et al.* 1988, 1991). Rates of schizophrenia have been linked to maternal infection with the influenza virus between the third and seventh months of gestation, which is a crucial time for the development of the brain. This suggests that the timing of a disturbance is a critical factor for later development of the disease (Barr *et al.* 1990, Mednick *et al.* 1988, Sham *et al.* 1992).

A long term study of records of births and deaths in rural Gambia has demonstrated a clear association between impaired fetal growth and adult survival (Moore *et al.* 1997). The records comprised data on month of birth for 3,102 individuals born between 1949 and 1994, and dates of death of 1,077 individuals from this sample who died before 1995. The study found that adults over the age of fifteen years who were born in the hungry season were 10 times more likely to die in early adulthood than those born in the harvest season. Kaplan Meier survival plots for the two groups diverged at puberty and coincide with the natural onset of thymic involution and post-pubertal decline in the immune system. The main causes of death in the adult sample were infectious disease and pregnancy related conditions.

The long-term consequences of disease during infancy and childhood

A number of studies have examined the link between early respiratory disease and later respiratory disease and associated complications. Acute lower respiratory infection during early childhood has been related to chronic bronchitis in adult life (Barker, Osmond 1989). This study found a geographical association between high mortality rates, chronic bronchitis and emphysema in adults, and infant mortality as a result of bronchitis and pneumonia. Another study has shown that 42% of children who were infected with respiratory syncytial virus as infants (a major cause of bronchiolitis in the first year after birth) experienced recurrent wheezing problems for up to ten years after birth (Pullan, Hey 1982). Recurrent wheezing was most pronounced in the first four years of life and most recurrent wheezing had stopped by the time the child was 6 years of age. It is not clear whether differences in respiratory function between the control group and the children infected during infancy with respiratory syncytial virus are the result of damage caused to the lungs during infection or pre-existing differences in the airway, making some children more susceptible to infection when first exposed to the virus. However, the fact that infection was correlated with maternal smoking and family size (perhaps related to number of children sharing the same bedroom) may indicate that environmental factors play a role in the incidence of this disease. In a controlled follow-up study, Mok, Simpson (1984) found decreased ventilatory function in children seven years after lower respiratory tract infection during infancy. These results were related to three disease categories – bronchitis, bronchiolitis, and pneumonia. Children who had been infected during infancy had increased rates of recurrent wheezing and coughing, and chest problems occurring with colds, as well as increased rates of consultation with general practitioners and absence from school.

The age at which an individual is exposed to infectious disease may have lasting consequences which impinge on adult health and longevity (Alter *et al.* 1986, Martyn 1991). Alter *et al.* (1986) have found that late exposure to a number of infectious diseases, such as rubella, hepatitis A and B, and Espstein-Barr, is associated with an increased risk of developing multiple sclerosis in later life. Martyn, Barker (1988) report a similar relationship between childhood infection with poliomyelitis and later onset of motoneuron disease, based on a geographical association between current mortality patterns from motoneuron disease and incidence of paralytic poliomyelitis in the past in England and Wales. The authors relate these findings to the epidemiology of poliomyelitis, which is a disease that increased as hygiene standards improved prior to the introduction of vaccination. As a result of improved living conditions, exposure to the virus is delayed until the child is no longer an infant protected by maternal antibodies. The study showed that poliomyelitis exposure was later in higher social classes and a similar distribution was reported for the incidence of motoneuron disease.

Early nutrition

Inadequate (insufficient or inappropriate) nutrition is another type of environmental stress which can have long term consequences on an individual's health. Much research has focused on the benefits of breast milk for infant health and development. A study by Reiser, Sidelman (1972) suggests that exposure to high levels of cholesterol early in life in rats facilitates the regulation of cholesterol in later life. This view is supported by Mott *et al.* (1991), who suggest that breast milk, which is higher in cholesterol than formula milk, has an important role in programming later cholesterol metabolism. A study of bile composition in adult baboons showed that breast-fed and formula-fed baboons display differences in biliary lipid composition and in their response to cholesterol and fat during adult life (Mott *et al.* 1990). This has implications for the development of heart disease in adult life.

Cunningham (1995) reviews the evidence supporting the benefits of breastfeeding for health. Breast milk plays an important immunological role in protecting a new-born infant against infection and disease. In infants, it has an important role in reducing morbidity and mortality from gastrointestinal illness, respiratory disease, diseases of the middle ear, as well as bacteremia and meningitis. One protective physiologic mechanism provided by breast milk is in providing secretory immunoglobin (S-IgA), antibodies which defend the body against invasion by pathogens via the respiratory and gastrointestinal tracts. As the secretory immune system, which produces S-IgA, is not fully developed at birth, the infant is reliant on maternal S-IgA, transferred through breast milk, in order to defend against pathogens. There are also a number of other immunological defence mechanisms provided by breast milk. Links between disorders of immune regulation, such as inflammatory bowel disease, celiac disease, juvenile diabetes, malignant lymphanomas, breast cancer, multiple scelerosis, chronic respiratory disease, and coronary artery disease, and method of infant feeding have been demonstrated which emphasise the importance of infant

feeding method for long-term health (Cunningham 1995).

A large body of research has been carried out to look at the short and long term effects of early nutrition on preterm infants. Lucas *et al.* (1990) examined the effect of early diet on allergic reactions in preterm infants randomly assigned to a diet either of breast milk or preterm formula milk (cow's milk formula) for one month. Where there was a family history of allergy, early exposure to cow's milk led to a greatly increased incidence of allergic reactions in comparison to the breast-fed infants who had a family history of atopic disease. Studies investigating differences between breast milk, standard formula and preterm formula have shown that even a short period of dietary manipulation (4 weeks) can have an effect on infant growth. Time taken to regain birth weight is significantly shorter and weight gain in general is more rapid in infants fed a diet of preterm formula and preterm formula in combination with breast milk than in those fed standard formula (Lucas *et al.* 1984). Subsequent research found that, while there were no significant differences in neonatal mortality or respiratory disease in relation to diet, infants fed a diet solely of breast milk had the lowest incidence of necrotizing enterocolitis (Morley, Lucas, 1994).

There are now indications that the effects of early diet persist well into childhood. Morley, Lucas (1994) found that children born preterm whose mothers chose to provide breast milk in the first four weeks of life had higher developmental scores than other preterm at 18 months and a higher intelligence quotient at 7.5 to 8 years. Lucas *et al.* (1998) found that individuals fed standard term formula as neonates had lower cognitive scores at 7.5 to 8 years than preterm infants who had been fed preterm formula fed either as a sole diet or as a supplement to breast milk. This effect was more marked in boys than in girls. The study also found higher rates of cerebral palsy in children who had been fed standard formula. Infants who were small-for-gestational age were also particularly vulnerable to the effects of poor diet in early life. These studies suggest that cognitive function suffers permanent impairment as a result of inadequate nutrition during the neonatal period. Other research has examined variation in bone mineral density in the same sample of children. In a follow-up study of 54 five-year old children, Bishop *et al.* (1996) found that bone mineral content was positively associated with increasing human milk intake in the first four weeks of life. A subsequent study of 244 preterm children measured at 8–12 years found no relationship between early diet and bone mineral content (Fewtrell *et al.* 1999).

EVIDENCE FROM PAST POPULATIONS

The techniques available for investigating the relationship between developmental stress indicators and age at death in past populations are fundamentally different to those used in living populations. A human skeletal sample represents a series of retrospective records of individual experiences of morbidity and mortality. The life history parameters that concern us in this type of analysis are exposure to stress during foetal life, infancy and early childhood and age at death. Apart from exceptional cases, where individual skeletons can be linked to documentary evidence detailing these parameters, they must be inferred from skeletal and dental evidence. The accuracy and completeness with which we can reconstruct these events is therefore limited by a series of filters. It is only possible to infer exposure to extrinsic stress factors during early life if these leave an enduring trace on the skeleton or dentition. Reconstruction of these events also depends on the availability of techniques that can be used to interpret these traces in terms of the frequency, duration, age of occurrence and severity of stress events. Stress indicators that are relevant in this type of analysis are non-specific and as such they cannot generally be used to identify the cause of stress. Similarly, although it is possible to estimate age at death from a variety of skeletal and dental indicators, it is unlikely that the cause of death will ever be known for certain in the majority of cases. A summary of investigations into the relationship between exposure to stress in early life and age at death in past populations is presented in *Table 3*.

Dental evidence

The dentition has several advantages over the skeleton in terms of its value as a retrospective record of environmental stress. Tooth enamel is unique among hard tissues in that it does not remodel. An unaltered record of developmental disruption is preserved for as long as the tooth enamel continues to exist. A number of factors can result in the loss of tooth enamel including dental attrition, pathology, cultural modification and *post-mortem* tooth loss. Another factor that could limit the observation and quantification of dental stress indicators is the presence of heavy calculus deposits (Stodder 1997).

Researchers investigating the relationship between developmental stress and longevity have examined a variety of dental stress indicators, including small tooth crown size, fluctuating asymmetry and enamel defects such as linear and pitting hypoplasia, demarcated and diffuse hypocalcifications, and accentuated striae of Retzius (Rose *et al.* 1978, Cook, Buikstra 1979, Guagliardo 1982, Rudney 1983, Simpson *et al.* 1990, Duray 1996). Enamel defects provide a particularly useful tool for the investigation of developmental stress, because it is possible to establish an approximate chronological framework for events affecting enamel formation by relating the position of an enamel defect to crown formation schedules (Goodman *et al.* 1980, 1984, Blakey, Armelagos 1985, Goodman, Rose 1990, Ensor, Irish 1995). A more exact chronology can be determined by relating the position of enamel defects to incremental growth structures within the tooth enamel (Hillson, Bond 1997, Hillson *et al.* in print).

The deciduous tooth crowns represent a continuous

TABLE 3. Summary of main studies conducted on past populations that indicate an association between stress occurring in early life and adult disease.

Authors	Year	Sample		Stress indicator	Summary of findings
Rose, Armelagos, Lallo	1978	Middle Woodland, Mississippian Acculturated Late Wood'and & Middle Mississippian	Gibson & Dickson Mounds, Illinois	Wilson bands (abnormal striae of Retzius) on the mandibular canine	The mean age of death of adults (over 15 years) with at least one Wilson band was significantly lower than in those without in all three periods.
Cook, Buikstra	1979	Middle Woodland & Late Woodland	Various sites, Illinois	Enamel hypoplasia, hypocalcification and hypoplasia-related caries in the deciduous dentition	The distributions of age at death were significantly different in juveniles with and without enamel defects. Those affected showed relatively higher weaning age mortality than those without defects.
Guagliardo	1982	Late Mississippian	Averbuch site, Tennessee	Mesiodistal and buccolingual dimensions of permanent tooth crowns, fluctuating dental asymmetry	Juvenile lower canines, lower third premolars and lower first molars were significantly smaller than those of adults (over 17 years). Juvenile upper first molars were significantly more asymmetrical than those of adults.
Rudney	1983	Meriotic and X-group	Wadi Halfa, Lower Nubia	Accentuated striae of Retzius on the first molar	In each sample, mean growth disturbance scores were significantly higher in juveniles than in adults (over 15 years).
Clark, Hall, Armelagos, Borkan, Panjabi, Wetzel	1986	Pre-Mississippian & Mississippian	Dickson Mounds, Illinois	Skeletal dimensions	Adults (over 15 years) with small vertebral neural canals had a significantly reduced age at death.
Goodman, Armelagos	1988	Late Woodland, Mississippian Acculturated Late Woodland & Middle Mississippian	Dickson Mounds, Illinois	Enamel hypoplasias developing between 3.5 and 7 years on all permanent teeth except third molars	In the total sample, and in samples from MALW and MM, mean age at death was significantly higher in adults and adolescents with no hypoplasias than in those with one or more hypoplasias.
Simpson, Hutchinson, Larson	1990	Contact Period	Santa Catalina de Guale	Buccolingual dimensions of all permanent tooth crowns except the third molar, hypoplasias on permanent incisors and canines	Juvenile lower canines and premolars were significantly smaller than those of adults (over 18 years). Juveniles showed a tendency towards a higher frequency of enamel hypoplasias but the difference was not significant.
Duray	1996	Late Woodland	Libben, Ottawa County, Ohio	Enamel defects on at least six permanent teeth in each individual	Individuals with each type of enamel defect had a significantly lower mean age at death than those without.
Goodman	1996	Births occurred between 1852 and 1912	Hammon-Todd, Cleveland area	Linear enamel hypoplasias on at least four permanent anterior teeth	Mean age at death was significantly lower in adults with hypoplasias than in those without. The frequency of hypoplasias forming between 2 and 4 years was significantly higher in adults who died before 30 years of age than in those who survived beyond this age.
Stodder	1997	Latte Period	Guam, Mariana Islands	Linear enamel hypoplasias on all permanent tooth crowns except the third molar	Juveniles had higher frequencies of permanent teeth with hypoplastic defects than adults (over 16 years). Adults over 21 years had a significantly lower number of defects per tooth than younger individuals.

sequence of enamel formation starting at about 14–16 weeks after fertilisation and continuing until approximately 11 months after birth (Hillson 1996). Sequential loss of the deciduous teeth, starting at about six years of age, limits their value as retrospective stress indicators, but they can be used to examine childhood experience of mortality and morbidity in relation to differential exposure to stress during foetal life and infancy. Cook, Buikstra (1979) documented enamel defects in the deciduous teeth of juveniles under 6 years from Middle and Late Woodland skeletal series from the Lower Illinois Valley. Children with enamel defects were found to suffer a higher level of mortality during the weaning period than those without. This suggests that individuals who had suffered stresses severe enough to result in enamel defects either prenatally or in the first year after birth were more susceptible to the effects of subsequent environmental stress than the population as a whole.

The permanent tooth crowns represent a continuous sequence of enamel formation from about 30 weeks after fertilisation until approximately 7 years of age (Hillson 1996). Development of the third molar is highly variable and crown initiation may not take place until after the crowns of the other permanent teeth are complete (Hillson 1996). As a result it cannot reliably be used to extend an otherwise unbroken sequence of enamel formation, and it is frequently omitted from dental stress analyses. The study of permanent tooth crowns provides a retrospective method of evaluating exposure to stress during the period of tooth crown formation that can be studied in both juveniles and adults.

One method that has been used to study the relationship between developmental stress and longevity is a comparison of the incidence of enamel defects in individuals who died during childhood and those who survived into adulthood (Rudney 1983, Simpson *et al.* 1990). A study of two skeletal samples from Lower Nubia found that juveniles had significantly higher levels of growth disturbance in their teeth than adults, indicating that individuals displaying evidence of exposure to stress during the period of tooth crown formation suffered higher mortality in the juvenile period than the population as a whole (Rudney 1993). Another study of juvenile and adult dentitions from Santa Catalina de Guale found a higher frequency of enamel defects in juveniles than adults but the difference between the juvenile and adult sample was not significant (Simpson *et al.* 1990). An alternative strategy for investigating the relationship between developmental stress and longevity is to compare the incidence of enamel defects among adults in different age groups (Goodman 1996), or to compare the mean age at death of adults with and without enamel defects (Rose *et al.* 1978, Goodman, Armelagos 1988, Duray 1996, Goodman 1996). Several such studies have found significantly lower mean ages at death among adults exhibiting enamel defects than in unaffected adults (Rose *et al.* 1978, Goodman, Armelagos 1988, Duray 1996, Goodman 1996). Stodder (1997) carried out a detailed analysis of the relationship between the occurrence of dental enamel defects and age at death for individuals from Latte Period sites on Guam. In this sample juveniles (under 16 years) had a lower incidence of enamel hypoplasia than adults, and adults over 21 years had fewer hypoplasias than young adults. An interesting new research direction is the examination of differences between males and females in the relationship between stress and longevity. This method of analysis is more appropriate for comparisons between adult samples since an unbiased result depends on accurate sex determination. In an analysis of the relationship between age at death and developmental enamel defects among adults from the Libban population of prehistoric native Americans, Duray (1996) noted that the difference between the means age of death of females (7.14 years) with and without linear enamel hypoplasia, was greater than that in males (5.02 years), but the difference between males and females was not statistically significant in this study.

Variation in tooth crown size is influenced by environmental parameters (Garn *et al.* 1979, Fearne, Brook 1993). As a result, tooth crown dimensions can also be used as an indicator of differential exposure to environmental stress during the period of tooth crown formation. Guagliardo (1982) analysed tooth crown dimensions of a prehistoric native American sample from Tennessee and found that the lower permanent canine, first molars and third premolars were significantly smaller in juveniles than in adults. A similar analysis of tooth crown dimensions of 17th century human remains from Mission Santa Catalina de Guale found that juveniles had significantly smaller mandibular canine and premolar tooth crowns than those who survived into adulthood (Simpson *et al.* 1990). Both these studies suggest that individuals who had failed to meet their genetic size potential for tooth crown size were more likely to die prematurely than those who had achieved their genetic potential and support the hypothesis of a relationship between developmental stress and subsequent mortality. In an earlier study, Perzigian (1975) compared permanent tooth dimensions of juveniles aged between six and 15 years and adults aged between 16 and 30 years in an Arikara population from South Dakota, and found that juveniles had significantly smaller upper and lower first permanent molars than adults. Perzigian suggested that individuals with small teeth were at a selective disadvantage compared to those with larger teeth because they were less able to resist a high level of dental attrition. Guagliardo (1982) considered this interpretation unlikely, because the site was occupied for a short period and the teeth of many of the juveniles who died were not heavily worn. Simpson *et al.* (1990) also criticised the original interpretation of these data, noting that there was substantial overlap in tooth crown size between the adult and juvenile group. The data were reinterpreted by Guagliardo (1982) as further evidence of a relationship between developmental stress, as indicated by tooth crown size, and subsequent longevity in a past population.

An alternative interpretation of studies that reveal significantly smaller tooth crowns in juveniles compared to adults is that the juvenile samples include a disproportionately large number of females, since females have smaller tooth crown dimensions than males (Perzigian 1975, Guagliardo 1982, Simpson *et al.* 1990). It may be possible to recognize this type of biased sex ratio from the pattern of tooth dimensions showing a significantly smaller size in juveniles than in adults. If the affected dimensions are those that exhibit the highest magnitude of sexual dimorphism in the adult sample, it is possible that the juvenile sample appear to smaller teeth as a result of a pronounced bias in favour of smaller toothed females. In the absence of this pattern, it is unlikely that the differences in juvenile and adult tooth size reflect sex-specific mortality rates. One area of research that has not yet been investigated is whether it would be possible to infer an age range at which exposure to developmental stress occurred from the pattern of tooth dimensions that vary significantly with age at death. Such an analysis could be carried out by examining the age of formation of tooth crowns whose dimensions were significantly smaller in juveniles than in adults.

A further of dental indicator of developmental stress is fluctuating asymmetry. This has been related to exposure to a variety of intrinsic and extrinsic stress factors in early life including cardiovascular and respiratory disease in infants, maternal obesity, smoking and infectious disease during pregnancy, and maternal exposure to noise and heat stress (Doyle, Johnston 1977, Livshits, Kobyliansky 1991, Kieser *et al.* 1997). Population differences in fluctuating asymmetry have been related to differential exposure to stress (e.g. Bailit *et al.* 1970, Kieser 1990), but the results have not always supported anticipated differences, suggesting that the underlying causes of variation in fluctuating asymmetry are complex and not fully understood. In a study of age related differences in the occurrence of fluctuating asymmetry within a past population, Guagliardo (1982) found that the upper first molars of juveniles from a Late Mississippian site in Tennessee were significantly more asymmetrical than those of adults from the same population.

Skeletal evidence

Potential skeletal indicators of childhood stress are numerous, and include growth attainment in different skeletal dimensions, cranial base height, pelvic and long bone morphology, skeletal changes associated with iron deficiency anaemia, and Harris lines (Larsen 1997). Harris lines (lines of arrested growth) might at first glance appear to be the most promising retrospective stress skeletal indicator. Such lines result from the resumption of growth following a period of growth arrest and have been related to a variety of environmental parameters including nutritional deficiency, psychological stress, disease and immunisations (Sontag, Comstock 1938, Acheson 1960, Park 1964). They have been widely used as an indicator of developmental disturbance in living populations (Dreizen *et al.* 1964, Blanco *et al.* 1974) and skeletal samples (Clarke 1980, Mays 1985, Mays 1995, Ribot, Roberts 1996, Hughes *et al.* 1996). It is also possible to establish an approximate chronology for the formation of Harris lines from their location on a long bone (Maat 1984, Byers 1991). Unfortunately Harris lines cannot provide a reliable retrospective record of childhood growth disturbance because they are affected by bone remodelling throughout life and are gradually obliterated with age. Observations suggest that very few lines formed during infancy and early childhood are still present in adults (Hummert, Van Gervan 1985). Furthermore, inter and intra-observer recording consistency may be poor (Macchiarelli *et al.* 1994).

An alternative skeletal indicator of differential childhood exposure to stress is skeletal size. Final growth attainment reflects genetic endowment and the cumulative effects of environmental parameters impacting on the growing infant and child (Eveleth, Tanner 1990). Impoverished environmental circumstances can prevent the full attainment of potential skeletal size due to the disturbance of normal growth. The most common causes of poor growth are inadequate nutrition and exposure to infectious disease, or the synergistic interaction of poor nutrition and infection, but many other factors could be implicated including, for example, exposure to toxins and psychological stress (Bogin 1988). Small size of an individual is not necessarily indicative of stunted growth due to impoverished environmental circumstances, but within a skeletal sample, there is likely to be a higher proportion of stunted individuals occurring at the lower end of the size range. As a result, the relationship between skeletal size and age at death among a sample of fully-grown individuals from a single population can be used to investigate the long-term consequences of childhood stress.

Different parts of the cranial and post cranial skeleton complete their growth at different ages, and may be differentially affected by exposure to stress at different stages of development. The timing of growth may also affect the potential for catch up growth to take place. Parts of the skeleton that grow rapidly in the prenatal and early postnatal stage and complete their growth in the first few years of life may be particularly susceptible to permanent stunting as a result of severe growth disruption during gestation, infancy and early childhood (Clark *et al.* 1986). Conversely, early growing skeletal elements may escape the effects of severe developmental disruption during late childhood and early adulthood. A pattern of rapid early growth is typical of neural and lymphatic structures (Scammon 1930) and is exhibited by parts of the skeleton that protect and support these structures (Humphrey 1998). Clark and colleagues (1986) examined the relationship between age at death and skeletal size using adult skeletons (over 15 years) from Dickson Mounds. Measurements of the antero-posterior and transverse diameters of the vertebral neural canals, vertebral body height and tibial length were evaluated in four age groups. Small vertebral

neural canals were significantly associated with reduced life span, but there was no relationship between tibial length or vertebral body height and age at death in adults. The authors identified two different factors that might contribute to this difference. First, the early developing neural structures may be particularly susceptible to the effects of systemic growth disruption during prenatal and early postnatal life because of their rapid growth rate. Second, these structures may not experience catch-up growth because of their early maturation, particularly if the disruption continues beyond the normal period of maturation. These data supported the hypothesis that poor early growth should result in decreased lifespan (Clark *et al.* 1986).

Flattening of the bony pelvis is caused by poor nutrition in early childhood. Martyn and colleagues (1996) found that women exhibiting this type of pelvic deformation have a tendency to give birth to children with low birth weight and low placental weight in relation to head diameter, because of an impaired ability to sustain the growth of the placenta and foetus in late pregnancy. Interestingly, this follow-up study of 13,249 British men which looked at pelvic size of the mother, foetal growth and death from stroke and coronary heart disease, found that the children of women exhibiting a flat bony pelvis had a substantially higher risk of stroke in later life as a result of growth impairment in foetal life. This study suggests that the effect of childhood malnutrition, as indicated by pelvic deformation, on mortality manifests itself in the succeeding generation. This link would not be easy to investigate in most past populations because of the difficulty in identifying mother-offspring associations. It would be an possible avenue of investigation in samples, such as the one from Christ Church, Spitalfields (Molleson, Cox 1993) for which these relationships can be determined from documentary sources.

CAUSES OF THE ASSOCIATION BETWEEN STRESS IN EARLY LIFE AND LONGEVITY

Several explanations for the association between childhood stress indicators and early mortality have been proposed (Clark *et al.* 1986, Goodman, Armelagos 1988, Duray 1996) and these can be divided into three broad categories. Although there has been a tendency for researchers to favour one explanation over another, it should be remembered that these mechanisms are not necessarily exclusive of one another (Goodman, Armelagos 1988, Duray 1996).

1. Individuals who are exposed to prenatal or early childhood stress may be "biologically weakened" in such a way as to reduce their ability to cope with stress episodes in later life (Clark *et al.* 1986, Goodman, Armelagos 1988, Goodman *et al.* 1988, Duray 1996).

According to this argument individuals who survive an episode of stress may be damaged or weakened in such a way as to increase their susceptibility to certain diseases and the effects of other stress factors in later life. It is this hypothesis for the association between early exposure to stress and reduced life span that invokes the concept of biological programming, whereby an early insult at a critical time can have a number of lasting effects in terms of health and longevity. Lucas (1991) emphasises two processes through which programming can have long-term effects. The first is the impairment of a permanent somatic structure as a result of an insult occurring at a sensitive period. The second process occurs when an insult at a critical time causes a physiological "setting" resulting in lasting consequences for function.

The long-term effects of retarded growth in gestation or infancy can be related to reduction in growth of organs leading to permanent changes in their metabolism or function (Desai, Hales 1997). Experimental work has demonstrated that visceral organ size can be altered by dietary manipulation, and has shown that in humans the period between birth and the first few years of life may be most sensitive to nutritional deprivation (Henry 1996, Desai, Hales 1997). Desai and co-workers (1996) demonstrated that, in rats, a low-protein diet during pregnancy has an effect on postnatal growth of the offspring. Relative to reduction in body weight, the lungs and brain exhibited the smallest decrease in weight indicating that they were protected. The heart, kidney and thymus decreased in proportion to body weight and the pancreas, spleen, muscle and liver exhibited a greater reduction in weight. Two follow-up studies using hospital records have shown that small abdominal circumference at birth, reflecting foetal growth retardation, is associated with impaired liver growth (Barker *et al.* 1993b, Martyn *et al.* 1998). Another study has shown that foetal growth retardation can affect the development of the endocrine pancreas (Phipps *et al.* 1993). A follow up study of preterm infants fed on different combinations of breast and formula milk in the first 4 weeks of life has shown that postnatal nutrition can have a major impact on subsequent brain growth and bone mineralisation and that these effects can last into mid-childhood (Morley, Lucas 1994).

Researchers examining the relationship between stress experience in early life and longevity in past populations have focused on the possible effects of an early developmental insult on the growth and function of the immune system (Clark *et al.* 1986, Duray 1996). Clark *et al.* (1986) have developed a model based on impaired immune function to explain the relationship between small (stunted) vertebral neural canals and early mortality in adult skeletons from Dicksons Mounds. This model relies on the principle that stress suffered during early life can have a lasting effect on organ size and in the size of skeletal structures that support and protect affected organs. Clark and co-workers note that the thymolymphatic tissues show a similar pattern of rapid early growth to the neural tissues. Small size in the neuro-osseous structures may reflect systemic stress-related growth disruption during this early

stage of development, such that adults with small vertebral neural canals would also have experienced poor thymic development (Clark *et al.* 1986). The reduced life expectancy of individuals with small vertebral canals could be the result of impaired neural and immune functions caused by developmental disturbance during the critical period of rapid growth in prenatal and early postnatal life.

Duray (1996) has argued that prenatal activation of the stress response could be one of several possible causal mechanisms underlying the association between developmental stress and subsequent morbidity and mortality. Experimental evidence suggests that prenatal exposure to stress can biologically alter an organism in such a way that subsequent exposure to stress factors elicits an exaggerated corticosteroid response. This can lead to increased immune suppression and an increased risk of infection and mortality.

Environmental factors in early life have a direct impact on the development and long-term functioning of the immune system. Foetal malnutrition, resulting in small for gestational age low birth weight infants, can cause pronounced and prolonged impairment of several aspects of immunocompetence (Chandra 1991). Chandra (1975a) investigated the effect of nutritional deprivation on rats. Deprived rats had lower body weights and a marked involution of the thymus and spleen together with a significant decrease in the number of lymphocytes in the blood and tissues. Importantly, the study showed that there was reduced antibody-forming cell response in first and second generation offspring even though they had free access to food. Chandra (1975b) examined immune system function in infants who had undergone foetal growth retardation. The postnatal immunocompetence of 26 low birth weight infants who had been diagnosed with foetal growth retardation was examined using a number of indicators. Results show that immunoglobin (IgG) in umbilical cord blood was positively correlated with birth weight up to a weight of 2,500 g and a greater physiologic decrease in IgG levels was seen between 3 and 5 months after birth in low birth weight infants. These infants had an impaired antibody response to the poliovirus vaccine. Low birth weight infants also had a significantly lower number of peripheral T lymphocytes during the first three months after birth indicating that phagocyte function was impaired. In another study antibodies to several food proteins were found in the serum of children who had undergone foetal growth retardation (Chandra 1975c). This is the result of alteration to the structure function and immune system of the intestine allowing antigen access to the lymphoid tissue.

The impaired immunocompetence suffered by low birth weight infants is reflected in an increased incidence of infection in early life. Xanthou (1985) found that full-term low birth weight babies had an increased rate and severity of infections compared to normal birth weight full-term infants. Postnatal experience of disease can also affect the development of the thymus. Dutz *et al.* (1975) found that atrophy of the thymus, resulting from severe gastroentiritis in infants up to six months old, persisted for up to five years after birth. A similarly severe stress after six months of age did not result in atrophy of the thymus. Prolonged immunosupression in some small-for-gestational age children has also been linked to exposure to infectious disease after birth (Chandra 1986). Interestingly, in their study of mortality in rural Gambia, Moore *et al.* (1997) found that differences in mortality between individuals born in the harvest season and those born in the hungry season coincided with the onset of thymic involution at puberty, indicating a long-term effect of malnutrition during the development of the immune system.

Deficiency of single nutrients influences the development and function of the immune system. Iron deficiency in the prenatal and early postnatal period has been shown to result in long-term impairment of the immune system that cannot be corrected by subsequent supplementation (Dallman *et al.* 1980, Duray 1996). Deficiency in zinc, vitamin B-6, vitamin A, copper and selenium have also been related to impaired immune system function (Chandra 1992). Duray (1996) concluded that iron deficiency could have played an important role in the association between developmental enamel defects and early adult mortality in the Libben population. Infants and young children aged between 6 and 24 months had a high incidence of porotic hyperostosis, a possible indicator of iron-deficiency anaemia, and periosteal reactions, indicating that infectious disease may have been a cause of nutrient depletion.

2. Certain individuals within a population are exposed to a lifelong pattern of deprivation due to the persistence of poor environmental circumstances throughout their lifetime, and this affects both the incidence of developmental stress indicators and longevity.

Differential lifetime exposure to environmental deprivation between individuals within a living population or in a past population represented by a skeletal sample could arise in several different ways. Groups of individuals within a population may have been subjected to a culturally determined pattern of differential exposure to stress, caused for example by differences in social status (Goodman, Armelagos 1988, Goodman *et al.* 1988, Duray 1996). High social status is likely to be associated with access to better nutrition and living accommodation than is available for the population as a whole, and these factors could help to provide a cultural buffer against stress factors that are associated with inadequate nutrition, overcrowding and poor sanitation. In the context of a past population, it may be possible to examine the possibility that short lifespan and the presence of developmental stress indicators are both associated with social status by reference to archaeological evidence. One possibility would be to use burial circumstances or grave goods as an indicator of social status (Goodman *et al.* 1983). However, Goodman, Armelagos (1988) have argued that evidence of differential

cultural buffering may be absent or ambiguous in many past populations, and that the inability to find a link between archaeological evidence of social inequality and differences in morbidity and mortality should not be used as evidence of the absence of such a relationship.

An analogous situation may arise with the study of a past population represented by a sample spanning several generations. Individuals showing evidence for childhood stress and suffering early mortality may be those who lived through a period of resource scarcity (Duray 1996). This factor can be investigated by reference to whatever chronological framework is available, including absolute or relative dating indicators, stratigraphic evidence and occasionally documentary sources. Systematic biases in the period in which affected individuals were buried could alert researchers to this possibility, but we are not aware of any examples of this type of bias in published studies of the relationship between developmental stress and subsequent mortality in archaeological samples.

The possibility that socio-economic inequalities contribute to mortality and morbidity patterns in living populations has been raised as a criticism of studies that attempt to correlate past and present experience of these factors in order to infer a causal relationship between conditions impacting on early life and subsequent morbidity and mortality. Geographic correlations between present adult mortality rates and past infant mortality rates could be the result of socio-economic differences between geographic regions that have persisted through time (Ben-Shlomo, Davey Smith 1991). Follow-up studies of individuals whose early life circumstances are known and which are able to control for socio-economic differences are an important means of countering this argument.

3. Individuals within a population may differ in their susceptibility to the effects of certain types of stress factors, with more susceptible individuals suffering a lifelong pattern of poor health that results in both early mortality and the presence of developmental stress indicators (Goodman, Armelagos 1988, Simpson *et al.* 1990, Duray 1996).

According to this argument, individuals within a population must vary in their ability to mitigate the effects of environmental stress. Individuals who are less able to withstand the effects of extrinsic stress factors exhibit a higher frequency of developmental stress indicators and a shorter lifespan than individuals within the same population who are able to withstand comparable stress loads. Such individuals can be described as having a "weaker constitution" (Goodman, Armelagos 1988). This mechanism differs from the biological damage hypothesis discussed above in that the differential ability of individuals to resist the effects of stress is considered to result from genetically caused lack of resistance rather than biological damage caused by premature exposure to stress. Simpson *et al.* (1990) have proposed that the relationship between small tooth crowns and reduced age at death in the human remains from Mission Santa Catalina de Guale could b caused by the differential ability of individuals within tha population to withstand the "rigors of life". Since they d not discuss the possible impact of exposure to stress i early life, it would appear that their argument depends o genetic variability in the ability of individuals to mitigat stress. Duray (1996) has argued that a genetic explanatio is unlikely since traits that have a high correlation wit fitness generally have low heritability.

One way in which a genetically caused difference i susceptibility to extrinsic stress factors might manifest itsel is as a difference in the morbidity and mortality of male and females within a population. The idea that males ar less well buffered against environmental stress than female during the developmental period is pervasive (Stinson 1985). Stinson (1985) carried out an extensive review o studies on sex differences in growth, maturation, morbidity and mortality during the prenatal and postnatal periods tha occur under stressful circumstances in order to examine the evidence for this hypothesis. She concluded that the evidence available gave only weak support to the hypothesis that males are less well buffered against the effects of environmental stress. The strongest support came from studies of prenatal mortality and growth, which suggest that male mortality is higher and male growth is more severely retarded under conditions of environmental stress. The evidence for a difference in male and female sensitivity to environmental stress during the postnatal period was less consistent and may reflect cultural biases in the treatment of male and female infants and children. Several studies have reported differences between males and females in the frequency and age of onset of enamel hypoplasia in present and past populations. The results of these studies do not consistently support the hypotheses that males are less well buffered than females, and may be influenced by cultural preference for male children (Rathbun 1987, Van Gerven *et al.* 1990, Lukacs 1992, May *et al.* 1993, Lukacs, Guatelli-Steinberg 1994). In studies of past populations it may in fact be difficult to escape from the tendency to assign an outcome that is more favourable for females to differential buffering and an outcome that is more favourable for males to cultural bias. The possibility that males and females exhibit a differential relationship between childhood stress and longevity is an area that could be further explored.

SUMMARY

The concept of biological programming provides an appropriate theoretical framework in which to examine evidence from past and present populations for a relationship between the circumstances of early life and subsequent experience of mortality and morbidity. The biological indicators and methods that have been used to investigate the long-term effects of early life circumstances differ between living populations and those that are

represented by skeletal samples. Studies of living populations have concentrated on the association between foetal malnutrition and the occurrence of disease in adult life, with particular emphasis on late onset diseases. Conditions that have been linked to foetal development in particular, and to the perinatal period include ischaemic heart disease, stroke, non-insulin-dependent diabetes, and neurodevelopmental disorders such as schizophrenia. Several factors that predispose individuals to disease in later life, such as hypertension, a tendency to store fat abdominally, and alterations to the programming of cholesterol metabolism can also be related to an impoverished foetal environment. These studies demonstrate the importance of the intrauterine environment in programming later growth and development and its consequences for subsequent disease experience. Postnatal factors including nutritional intake in early life, infection of the lower respiratory tract, and the timing of exposure to childhood infection have also been shown to impinge upon subsequent health and development. Follow-up studies indicate that these effects occur independently of social class and adult lifestyle. In order to convince sceptics, long-term prospective data that follow individuals throughout the course of their lifetime will be necessary. Until recently, understanding of the causes of adult onset diseases has focused on lifestyle differences including smoking, diet, exercise and alcohol abuse. Hypotheses implicating exposure to stress in early life and those that emphasise lifestyle and socio-economic status are not mutually exclusive and the relationship between these factors is one that is worthy of investigation.

Studies of the long-term consequences of exposure to stress in early life in past populations have concentrated on the association between skeletal and dental markers of developmental stress and longevity. Taken together, these studies which rely on a range of different stress indicators and encompass geographically and temporally diverse populations, give considerable support to the hypothesis that there is an association between developmental disruption suffered prenatally or during infancy and early childhood and subsequent early mortality. In studies of past populations, it may be difficult to conclude unambiguously that this association is causal, since other factors that could be implicated cannot be statistically controlled. Socio-economic status and lifestyle differences can be difficult to determine from archaeological evidence, and even if these have been shown to exist within a past population, it may be difficult to identify the status of a particular individual from their burial circumstances.

We have identified a number of research issues relating to the investigation of environmental stress in early life in past populations that are worthy of further research, and these are briefly reviewed below. One area that has not been explored is whether different developmental systems in the skeleton and dentition vary in their sensitivity to impoverished environmental circumstances. Skeletal evidence for growth disruption could be a more sensitive indicator of childhood stress than the evidence recorded by the teeth since skeletal growth and maturation are generally held to be more susceptible to disruption caused by environmental stresses than dental development (Garn *et al.* 1965, Edler 1977, Demirjian 1986). However, the evidence for differential susceptibility of different developmental systems to environmental stress is inconsistent. A study of the response of bone and enamel formation to nutritional supplementation among malnourished Guatemalan children found that children given nutritional supplementation exhibited lower levels of linear enamel hypoplasia compared to children who were not given nutritional supplementation, but there was no difference in hand wrist ossification (May *et al.* 1993). Further work will be required to establish whether there is a hierarchy in the extent to which different developmental systems exhibit developmental stress indicators.

A second and related problem is whether the techniques available for quantifying early stress in past populations will allow us to identify developmental periods during which an insult would be particularly critical in terms of its effect on subsequent development. This line of investigation will depend on our ability to estimate the age of occurrence of developmental stress events. We have suggested that if stress is inferred from a failure to meet genetic size potential, the timing of tooth crown development and skeletal growth could be used to broadly identify the period in which an insult occurred. The best chronological framework of exposure to stress in early life can be achieved by studying enamel defects. Most previous attempts to establish the chronology of growth disruption events in the teeth have done so by relating the position of a hypoplastic event on the enamel surface to tooth formation chronologies. The standard method involves using population averages for the age of onset and completion of tooth crown calcification to determine the age range during which an enamel defect forms, but this technique relies on a number of assumptions that are difficult to justify (Hillson 1996). The use of scanning electron microscopy (SEM) for the examination of enamel defects on the surface of a tooth crown is a powerful new technique, which avoids many of the problems associated with the standard methodology. Hillson, Bond (1997) have shown that it is possible to relate linear enamel hypoplasia to the incremental growth structures on the surface of a tooth crown. This provides an accurate chronological framework in which to quantify the frequency of enamel hypoplasia and the duration and age of occurrence of each stress episode.

A third area that has received relatively little attention by researchers studying past populations is whether there are differences between males and females in the relationship between exposure to stress in early life and longevity. Studies of differences in male and female buffering to environmental stress factors have been plagued by the difficulty of distinguishing between differential susceptibility in males and females and differential

treatment of male and female offspring by their families. Analysis of the long-term consequences of early stress in males and females will not necessarily help to resolve this problem but it will help us to understand the different experiences of men and women in past populations.

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