

# The Influence of Childhood Circumstances on Adult Health

---

Draft report to the Mitchell Institute

Dr Kim Sweeny  
Victoria Institute for Strategic Economic Studies  
Victoria University  
March 2014

## 1. Social determinants of health and the socioeconomic gradient.

There is considerable evidence that a person's health status is strongly affected by the degree of disadvantage that they suffer, whether this is due to their socioeconomic position measured by factors such as education, income, occupation, or their location or other factors.

Many studies have shown that there is a socioeconomic gradient by which health becomes better the further up the socioeconomic ladder a person is placed. This relationship has been demonstrated in many countries at different levels of development and income and has led to calls for international action (Marmot et al 2008) to address the inequalities arising from these social determinants of health (Wilkinson and Marmot 2003).

In their comprehensive review of the relationship between socioeconomic status (SES) and health, Cutler, Lleras-Muney and Vogl (2008) consider four aspects of SES namely - education, financial resources, rank, and race and ethnicity. They found that socioeconomic status and health are strongly related in most countries regardless of the level of income or the kind of health system. Their conclusions were that the

the mechanisms linking the various dimensions of SES to health are diverse. Some dimensions of SES cause health, some are caused by health, and some are mutually determined with health; some fall into all three categories at once. These differential patterns of causality make a single theory of socioeconomic gradients in health difficult to imagine.

Nonetheless they believe that the best source of the right theory is in the lifecycle, and in particular how childhood circumstances influence adult health.

In Australia a number of studies have shown demonstrated the relationship between disadvantage and mortality (for instance Begg et al 2007, Turrell et al (2007), Korda et al (2007), Kelsall et al (2009)) and between disadvantage and morbidity or poor health (eg Begg et al 2007, Glover, Hetzel and Tennant (2004), Korda et al (2009), Kavanagh et al (2007), Turrell et al (2006)).

As an example, Begg et al (2007) in their study of the burden of disease in Australia calculated various measures of the burden of disease in 2003 by State, socioeconomic group and location. They found clear socioeconomic and location gradients as demonstrated for one of these measures - life expectancy at birth - which provides an estimate of the average years of life a person can expect to live at various ages given current risks of mortality.

Burden of disease studies seek to quantify the amount of disease in a society by combining data about the amount of life lost due to premature mortality with information about the prevalence of non-fatal conditions adjusted for their degree of severity. The resulting estimate of disability adjusted life years (DALYs) lost to disease was calculated by Begg et al (2007) for the year 2003.

They found that the burden of disease was greater for those in the lower socioeconomic quintiles than in the higher quintiles (Table xxx) and for those in remote and regional locations compared to those in the major cities.

**Table 1 Life expectancy at birth by area and sex, Australia, 2003**

	Males	Females	Persons
<b>Socioeconomic quintile</b>			
Low	76.9	82.3	79.6
Moderately low	77.4	82.8	80.0
Average	77.7	82.7	80.2
Moderately high	79.0	83.5	81.2
High	80.9	84.5	82.7
<b>Remoteness</b>			
Major cities	78.8	83.5	81.2
Regional	77.5	82.7	80.0
Remote	75.4	81.5	78.1
Australia	78.3	83.2	80.7

**Table 2 Differentials in burden (DALY rates) by socioeconomic quintile for the 10 leading broad cause groups, Australia, 2003**

Broad cause group	Standardised rate ratio					
	DALYs per 1000	Low	Mod. low	Average	Mod. high	High
<b>Cancer</b>	25.1	1.05	1.05	1.05	0.97	0.88
<b>Cardiovascular</b>	23.8	1.10	1.08	1.05	0.95	0.84
<b>Mental</b>	17.6	1.22	1.05	1.02	0.92	0.80
<b>Neurological</b>	15.7	1.02	1.02	1.03	1.00	0.93
<b>Chronic respiratory</b>	9.4	1.15	1.07	1.01	0.95	0.83
<b>Diabetes</b>	7.2	1.30	1.05	1.09	0.91	0.70
<b>Unintentional injuries</b>	6.3	1.14	1.12	1.12	0.93	0.72
<b>Musculoskeletal</b>	5.3	1.08	1.02	1.05	0.97	0.89
<b>Genitourinary</b>	3.3	1.07	1.02	1.04	0.97	0.92
<b>Intentional injuries</b>	3.0	1.28	1.11	1.00	0.91	0.73
<b>All causes</b>	132.4	1.12	1.05	1.04	0.96	0.85

In 2012, 77.1% of all male deaths occurred in those aged 65 or more. For women the rate was 85.6%. The prevalence of morbidity is also higher for those in older age groups. For instance the percent of people in the ABS National Health Survey for 2007 (ABS 2010) reporting a profound disability is 2.6% for those aged 18-34 rising to 8.7% in those aged 55 and over, similarly, other disability is 24.4% in the younger age group and 53.4% in the highest age group (Table 3).

**Table 3 Disability status, ABS National Health Survey 2007-2008, % of age group**

	Profound or severe activity limitation	Other disability or restrictive long-term health condition
<b>18–34</b>	2.6	24.4
<b>35–54</b>	3.6	34.5
<b>55 and over</b>	8.7	53.4

[Indigenous health in Australia]

## 2. Childhood status and adult health

While it is well established that current socioeconomic status (SES) is related to health there is a growing body of literature that links adult health to a person’s status at critical stages of the life course and in particular to conditions at conception, gestation and early childhood.

In their recent overview of life course epidemiology, Ben-Shlomo, Mishra and Kuh (2014) point out that in the early part of the twentieth century a concern for public health centred on the role maternal and infant health played in the development of child health and subsequent adult health and hence the need for maternal and infant welfare services to improve public health. This emphasis on early childhood tended to be superseded in the middle of the century as more information emerged about the impact of adult risk factors such as hypertension, diet, smoking and alcohol consumption on adult mortality and morbidity, specifically from cardiovascular disease.

Over the past 30 years or so, there has been a revival of the earlier emphasis through a more formalised life course approach supported by information from an increasingly broad set of longitudinal and other studies.

According to Ben-Shlomo, Mishra and Kuh, life course epidemiology can be defined as “the study of long-term biological, behavioral, and psychosocial processes that link adult health and disease risk to physical or social exposures acting during gestation, childhood, adolescence, and earlier or adult life or across generations”. This latter aspect extends the influences to the conditions of the mother and father prior to conception.

The development of this life course approach began with a number of studies on the link between early childhood and cardiovascular disease in adulthood. One of the earliest studies was the examination by Forsdahl (1977) of county-level data in Norway on the incidence of heart disease and infant mortality. He found

a significant positive correlation between the county age-adjusted mortality from arteriosclerotic heart disease in people aged between 40 and 69 years and county infant mortality relating to the early years in the same cohorts. The findings suggest that great poverty in childhood and adolescence followed by prosperity is a risk factor for arteriosclerotic heart disease.

Barker (1989) found similar results when examining the outcomes for 5654 men born during 1911-30 in six districts of Hertfordshire, England whose birth weights were known. He found that

Men with the lowest weights at birth and at one year had the highest death rates from ischaemic heart disease. The standardised mortality ratios fell from 111 in men who weighed 18 pounds (8.2 kg) or less at one year to 42 in those who weighed 27 pounds (12.3 kg) or more.

Similar studies by Barker and others which contributed to the development of the “fetal origins” or “developmental origins” hypothesis are reviewed in Barker (2007) and Barker (1998). The hypothesis asserts that chronic diseases in later life are “established by “programming” of processes during embryological development and this in turn was influenced by nutritional influences acting either in pregnancy or prepregnancy through the development of the mother during her childhood or adolescence” (Ben-Shlomo, Mishra and Kuh). Gluckman and Hanson (2004) proposed a more general approach which included the influences of conditions after birth and into childhood as well as those during pregnancy.

### Life course models

As this literature has developed, a number of models have been proposed to explain the influence of status at various stages of life on health outcomes. Ben-Shlomo, Mishra and Kuh describe 7 such models and these are reproduced in the appendix to this paper. Other reviewers such as Pavalko and Caputo (2013), Montez and Haywood (2013) and Pollitt, Rose and Kaufman (2005) have been content with fewer broader classifications. Cohen et al 2010 in their review of childhood SES and adult health propose 3 basic models namely,

#### 1. Timing model

According to the timing model, SES-related factors have the greatest influence on adult health if experienced during specific developmental periods defined as age ranges (e.g., birth to three years) or more broadly as periods of development (e.g., childhood, adolescence). The fit of this model to the actual processes linking early life SES with adult health depends upon the identification of sensitive periods when individuals are most vulnerable to SES exposures.

#### 2. Accumulation model

The accumulation model suggests that the detrimental effects of low SES accrue throughout the life course such that risk for poor adult health increases with increasing intensity of socioeconomic disadvantage and with increasing duration of exposure to such disadvantage. In contrast to the timing model, the accumulation model is indifferent to when during childhood and adolescence the SES-related exposures occur.

#### 3. Change model

The change model suggests that the direction of SES mobility across childhood and adolescence has important implications for adult health outcomes. Predictions of this model include that upward mobility, a change from lower to higher levels of SES, would result in

better adult health. Put differently, it predicts that negative effects of low SES during early childhood would be partly or wholly remediated by higher SES later in childhood or adolescence.

Pollitt, Rose and Kaufman in their influential review of the evidence for life course socioeconomic influences on cardiovascular outcomes further differentiate the timing model into those that emphasise the importance of early sensitive periods and their direct impact on later health and those that focus on pathway effects that place individuals on life trajectories that establish adult risk factors which determine health in later life.

Cohen et al discuss the evidence supporting the link between childhood and adolescent SES and adult health, and explore different environmental, behavioral, and physiological pathways that could explain how early SES would influence adult health. In doing so they differentiate between physical and psychosocial exposures that are related to socioeconomic status

In the home children in lower SES are more likely to experience higher **physical** environmental risk because of greater crowding, exposure to smoking, and poorer housing stock. At school they may have a higher exposure to inadequate facilities, while their neighbourhood may have fewer facilities and amenities such as open areas, and suffer from a greater level of noise and have more polluted air and water.

Adverse **psychosocial** exposures at home that may be experienced by children in lower SES include higher levels of conflict among family members, less supportive family relationships, parental absence and poorer parenting practices. Neighbourhoods with a greater proportion of lower SES are likely to have lower social capital, and higher crime and violence. Schools in such neighbourhoods are more likely to have problems with educational quality, student attendance, classroom behaviour and physical violence.

These exposures singly and in combination during childhood can predispose individuals to anxiety, depression, difficulties in forming relationships, poor emotional regulation and other psychological problems. They can also predispose to risk factors for disease such as reduced physical activity, poor dietary habits, smoking and excessive alcohol consumption. Psychosocial exposures such as chronic stress can create an allostatic load of wear and tear that can contribute to the development of a range of chronic diseases through their impact on the body's nervous, endocrine and immune systems.

Cohen et al note that adult and childhood SES are correlated so they highlight those studies that control for adult SES in examining the link between childhood SES and adult health. They cite the comprehensive review by Galobardes, Lynch and Davey Smith (2004) which looked at 29 studies of childhood SES and adult mortality, most of which were longitudinal prospective or cohort designs. These authors found that

people experiencing poorer socioeconomic circumstances during childhood carry a higher risk of overall mortality, independently of adult socioeconomic position..... The risk associated with lower childhood socioeconomic position was, not surprisingly, partly mediated by adult socioeconomic position and adult risk factors.

The evidence from individual-level studies suggests that childhood socioeconomic circumstances contribute to a variety of different causes of death. In particular, childhood conditions appear strongly related to mortality from stomach cancer and hemorrhagic stroke. Childhood circumstances, together with adulthood socioeconomic position, contribute to mortality from coronary heart disease, lung cancer, and respiratory-related diseases. Poorer childhood conditions are not generally associated with mortality from non-smoking related cancers and prostate cancer, but they may contribute to external and alcohol-related causes of death...

The findings relating childhood social circumstances to cause-specific mortality are congruent with data from studies relating height and mortality. Adult height is determined early in life, so shorter stature is partly a marker for an unfavorable profile of socially patterned exposures acting during the growing period (from the intrauterine period until final height is achieved). Height is negatively associated with risk of hemorrhagic stroke, stomach cancer, coronary heart disease, and chronic obstructive pulmonary disease, and it is either not associated or positively related to mortality from site-specific cancers, such as breast cancer.

The association between childhood social circumstances and mortality probably comes about through a variety of processes ...Infection with *Helicobacter pylori* during infancy and childhood offers a plausible mechanism to explain the association between poor childhood circumstances and stomach cancer and possibly illustrates a critical period model during early life when individuals are most susceptible to acquiring this infection. Moreover, the similarity of associations of stomach cancer and hemorrhagic stroke with poor childhood circumstances, together with similarities in their association with height, and the cross-national relation between hemorrhagic stroke and stomach cancer risk raise, speculatively, the possibility that an early life infection—or a factor related to early life infection such as dehydration due to childhood diarrhea—is associated with hemorrhagic stroke risk. On the other hand, coronary heart disease, ischemic stroke, lung cancer, and chronic obstructive pulmonary disease appear to be influenced by factors acting across the entire life course and therefore may conform more to a cumulative risk model. For example, poor childhood and adult social circumstances could independently influence lung cancer risk via increased probability of initiation, earlier age of initiation, lower probability of quitting, and higher age of quitting smoking. Similarly, an accumulation of adverse exposures over the life course may result in higher risk of coronary heart disease.

This review was updated by the authors in 2008 with a further 11 studies and 5 updates of previous studies and confirmed most of their original findings.

In summary, the newer evidence available from this update allows us to more strongly affirm that poor socioeconomic circumstances during childhood are associated with higher mortality among men and women and that this association persists among younger cohorts. The new evidence highlighted the difficulty in establishing a particular life course model to explain this association, but several studies established the importance of education as mediator between early life SES and adult mortality.

An interesting study cited here is that of Osler et al (2006) which examined a study of 12 608 children born 1924–47 in Denmark who were placed early in life with adoptive parents. The found that

Adoptees with biological fathers from higher social classes had a lower rate of mortality after their fifth decade of life, mainly due to a lower risk of cardiovascular, infectious, and respiratory diseases. Adoptive father's social class showed no clear relation with adoptee's mortality risk. The risk estimates for paternal social class were slightly attenuated after adjustment for adoptee's adult social class, which as expected was inversely related to mortality from both natural and external causes.

Genetic and/or prenatal environmental factors contribute to the development of the relation of paternal social class to mortality from natural causes later in adult life independently of the effect of own social class, whereas there is no evidence for such long-term effect of the rearing environment

Pollitt, Rose and Kaufman come to conclusions similar to those of Galobardes, Lynch and Davey Smith:

Study results suggest that low SES throughout the life course modestly impacts CVD risk factors and CVD risk. Specifically, studies reviewed provided moderate support for the role of low early-life SES and elevated levels of CVD risk factors and CVD morbidity and mortality, little support for a unique influence of social mobility on CVD, and consistent support for the detrimental impact of the accumulation of negative SES experiences/conditions across the life course on CVD risk.

They also draw attention to the limitations of studies to date and the difficulties of clearly delineating models

The wide range of populations, analysis designs, exposures, and outcomes used in the life course studies reviewed precludes a simple, quantitative analysis of the impact of life course SES on CVD risk. Nevertheless, the results thus far modestly support the existence of life course SES effects on risk of adult CVD. The cumulative life course model is more consistently supported by extant studies than other models.

Cohen et al 2010 are also cautious in their conclusions:

The models we examined present alternative and sometimes complimentary hypotheses about the ages at which childhood and adolescent SES matter most for adult health, and how long SES exposures of specific types need to last to influence health. To date, there are few empirical data testing the models against one another in the prediction of physical health. There are practical, conceptual, and analytical explanations for this lack of data...

[In addition] more than one model could apply at the same time. For example, it is possible that there are cumulative effects of early SES exposure across childhood and adolescence (accumulation model), but that exposures at specific developmental periods are more impactful than those at others (timing model)...

Another conceptual issue concerns the possibility that both the mechanisms linking early SES with adult health outcomes and the models describing when during childhood and adolescence these mechanisms are most influential, vary across diseases or disease stages. For example, disease processes that are progressive, such as atherosclerosis, may fit the accumulation model, whereas those that involve exposure to a critical triggering event, such as early viral or antigen exposures associated with increased risk for adult respiratory disease, may fit the timing model.

### 3. Epigenetic mechanisms linking early life to adult health

There is growing evidence linking variants in a number of genes to both birth weight and adult height and metabolism. The Early Growth Genetic Consortium has recently published the results of an expanded genome-wide association study of birth weight in some 69,308 people and specific genes (Horikoshi 2013). They identified or confirmed that 7 loci in the genome are associated with birth weight and explain a similar proportion of variance to that explained by maternal smoking in pregnancy. Further

The associations between five of the loci and adult traits (i) highlight biological pathways of relevance to the fetal origins of type 2 diabetes; (ii) reveal complexity, in that type 2 diabetes risk alleles can be associated with either higher or lower birth weight; (iii) illuminate a new genetic link between fetal growth and adult blood pressure and (iv) show substantial overlap between the genetics of prenatal growth and adult height.

A person's genetic material is contained in 23 chromosomes each of which consists of a long strand of DNA built from 4 nucleobases. The genes consist of sections of DNA which serve as the basis for production of proteins that are the building blocks of the body. Genetic material inherited from the parents is largely unchanged throughout a person's life.

Each cell in the body contains all a person's genes which are replicated in each cell division. However the particular function of a cell is controlled by the differential silencing of genes through processes such as DNA methylation and histone modification. These are known as epigenetic processes and also include chromatin remodelling and microRNA. In the early stages of the embryo, the genome is "wiped clean" of most epigenetic modifications which are progressively re-established during embryonic development (Gluckman et al 2009). The epigenome changes as the organism develops and reflects the environmental and other influences on its development.

The fact that the epigenome can change while the underlying genetic material is unchanged enables the organism to have some plasticity during its development so that it can respond to changing circumstances. However there may arise a mismatch between the circumstances in which the epigenome developed and the circumstances faced by the organism at later stages. This mismatch in the development of humans in pregnancy and early childhood has been investigated as the source of increased risk of chronic non-communicable disease in adulthood.

Most of the scientific research on epigenetic processes has been carried out in animal models such as rats and mice although there is a growing evidence base from research in humans.

Lillycrop and Burdge (2012) reviewed a number of studies that looked at the role of epigenetic mechanisms in the impact of early nutrition on long term health. They asserted that

Traditionally it has been widely accepted that our genes together with adult lifestyle factors determine our risk of developing noncommunicable diseases such as type 2 diabetes mellitus, cardiovascular disease and obesity in later life. However, there is now substantial evidence that the pre and early postnatal environment plays a key role in determining our susceptibility to such diseases in later life. Moreover the mechanism by which the environment can alter long term disease risk may involve epigenetic processes. Epigenetic processes play a central role in regulating tissue specific gene expression and hence alterations in these processes can induce long-term changes in gene expression and metabolism which persist throughout the lifecourse. This review will focus on how nutritional cues in early life can alter the epigenome, producing different phenotypes and altered disease susceptibilities.

They found that

There is now a considerable body of evidence to suggest that our genotype is not the sole determinant of disease risk but that variations in the quality of the early life environment affects future disease risk through the altered epigenetic regulation of genes. The demonstration of a role for altered epigenetic regulation of genes in the developmental induction of NCD together with the identification of potential epigenetic biomarkers of future disease risk suggest the possibility that individuals at increased risk could be identified at an early stage of the lifecourse and their long term risk of NCD modified either through nutritional or lifestyle interventions. However further understanding of the mechanism by which nutrition can modify the epigenome, the periods of epigenetic susceptibility, the nutritional factors that induce epigenetic changes and the stability of the induced changes are all critical for both the robust identification of individuals at risk and for the development of novel intervention strategies, to reverse this current epidemic of NCD.

Although the research is in its early stages, there is some limited evidence linking epigenetic modifications to early life socioeconomic circumstance. Tehranifar et al (2013) using data from a study of a cohort of New York women born between 1959 and 1963 found that low family income and single parent family at birth was associated with higher white blood cell methylation in adulthood.

#### **4. The impact of birthweight and other factors on health in later life**

Many of the earlier studies linking childhood status to adult health have examined the relationship between birthweight and health outcomes. Initially this concentrated on the negative effects of low birthweight and undernutrition but more recent studies now also consider high birthweight and overnutrition.

Important early studies were those by Forsdahl and Barker mentioned earlier and the study of people exposed to famine in pregnancy such as those in the Dutch Winter Famine in 1944-45 and the famine in China in 1959-61 associated with the Great Leap Forward.

An analysis by Painter, Roseboom and Bleker (2005) of the Dutch Winter Famine showed that individuals whose mothers were exposed to the famine around the time of conception and in the first trimester of pregnancy did not have reduced birth weights compared to unexposed individuals, but as adults exhibited an increased risk of obesity and CVD, whereas individuals whose mothers were exposed in the later stages of gestation had reduced birth weights and showed increased incidence of insulin resistance and hypertension.

Further analysis by Roseboom, de Rooij and Painter (2006) found that women exposed to famine in early gestation had an increased risk of breast cancer and people exposed to famine in mid gestation had more obstructive airways disease.

A recent systematic review and meta-analysis by Risnes et al (2011) considered the results from 10 studies that assessed the association between birthweight and adult mortality from all causes, CVD or cancer. They found

an inverse but moderate association of birthweight with adult mortality from all-causes and a stronger inverse association with cardiovascular mortality. For men, higher birthweight was strongly associated with increased risk of cancer deaths.

Rainkokonen et al (2012) reviewed the evidence on the early determinants of **mental health**. They noted the findings of studies of the Dutch Winter Famine and the Chinese Famine which found that those exposed to these events had twice the rate of schizophrenia of similar populations. In addition there was evidence of higher rates of antisocial personality disorders, affective psychoses, depression and addictive disorders among the Dutch Winter Famine cohort. From the results of these and other studies of low birthweight children, the authors concluded that

Environmental adversities in early pre- and postnatal life seem to have widespread consequences on mental health outcomes later in life.

They further assert that, although the evidence is still limited

Epigenomic mechanisms influencing gene expression at the level of the placenta and the offspring may play key roles

In their review of studies concerned with the early determinants of **type-2 diabetes (T2D)**, Berends and Ozanne (2012) cite the results of numerous animal and human studies, including those of the Dutch Winter Famine which showed that low birth weight was associated with impaired glucose tolerance and type-2 diabetes in later life. More recent studies however have demonstrated a U-shaped relationship in which risk of diabetes increase with both low birthweight and high birthweight. In addition,

Over more recent years it has become apparent that a variety of expositions, including maternal obesity and/or maternal diabetes, can have a significant effect on offspring health outcomes. Further complicating matters, paternal and transgenerational transmission of T2D can occur thus mediating a perpetuating cycle of disease risk between generations.

In their review of the epigenetic and other mechanisms involved in the early determinants of **cardiovascular and kidney disease**, Santos and Joles (2012) discuss the role of development

plasticity or programming in the adaptation of the organism during pregnancy and early childhood to environmental insults. Drawing upon studies using animal models, they assert however that these mechanism can be reprogrammed.

Potentially a genetic predisposition or known deleterious environmental factors acting in the early life can be counterbalanced during gestation and lactation through provision of nutritional supplements or pharmaceuticals, such as citrulline, to pregnant women with hypertension, preeclampsia, diabetes, etc. where the fetus is at risk to develop CV disease later in life. Thus, we may be able to reprogram CV health and prevent or delay the onset of a CV disease. Epigenetics offers exciting opportunities, such as perinatal and personalized administration of supplements such as folate, acting on DNA methylation, compounds such as butyrate, with HDAC inhibitory activity, or the soy isoflavone genistein, to alter miRNAs, to repress or derepress gene expression according to the genetic or programmed predisposition to develop CV disease.

These findings have lead to the concept of an “epigenetic diet” which is discussed further below.

There are a number of studies in Australia that have provided evidence on the link between childhood circumstances and later health.

In Australia the Mater-University of Queensland Study of Pregnancy (MUSP) is a large, prospective, pre-birth cohort study which enrolled 8556 pregnant women at their first clinic visit over the period 1981–1983. These mothers (and their children) were followed up at intervals until 14 years after the birth. A number of publications have looked at the relationship between socioeconomic status and a variety of outcomes for mothers and children. As examples, Morrison et al (1989) examined the relationship to pregnancy outcomes, while Najman et al (2004) assessed the impact on child cognitive development (CD) and emotional health (EM). This latter study found that

Family income was related to all measures of child CD and EH and smoking, independently of all other indicators of the socioeconomic status of the child. In addition, the grandfathers’ occupational status was independently related to child CD (at 5 and 14 years of age). Children from socioeconomically disadvantaged families (previous generations’ socioeconomic status as well as current socioeconomic status) begin their lives with a poorer platform of health and a reduced capacity to benefit from the economic and social advances experienced by the rest of society.

Similarly, Raposa et al (2013) exploring using the same data set found that

Early adverse conditions have lasting implications for physical health, and that continued exposure to increased levels of both social and nonsocial stress in adolescence, as well as the presence of depression, might be important mechanisms by which early adversity impacts later physical health.

Raposa et al (2014) looking specifically at maternal depression found that

prenatal maternal depressive symptoms predicted worse physical health during early childhood for offspring, and this effect was partially explained by ongoing maternal depression in early childhood. Offspring poor physical health during childhood predicted increased

health-related stress and poor social functioning at age 20. Finally, increased health-related stress and poor social functioning predicted increased levels of depressive symptoms later in young adulthood. Maternal depression had a significant total indirect effect on youth depression via early childhood health and its psychosocial consequences

Hoy and Nichols (2010) report on a longitudinal cohort study of 995 people with recorded birthweights who were born between 1956 and 1985 to an Aboriginal mother in a remote Australian Aboriginal community. Participants were followed through to the end of 2006. The authors found that low birthweight was associated with a 2-3 times higher risk of death among adults from all causes and for cardiovascular and renal disease in particular.

## 5. Childhood health and future socioeconomic status

Currie (2009) examines the link between a parents' socioeconomic status and the child's level of income and wealth in later life. She makes the obvious connection that income is strongly determined by level of education so extends the question into one linking parental SES to both educational and labour market outcomes. In doing so she is concerned to see if this occurs because of the effect of parental SES on child health.

Partly because she draws on the same studies that have been reviewed earlier, Currie finds a strong relationship between parental SES and child health, and between child health and future outcomes. On important study cited is that of Smith (2007) who used data from the US Panel Study of Income dynamics to show that better health in childhood is related to higher incomes, higher wealth, more weeks worked, and a higher growth rate in income. The estimates imply that within families, a sibling who enjoyed excellent or very good health in childhood earns 24 percent more than a sibling who was not in good health.

Case and Paxson (2010) examine the literature on the relationship between child health and economic and health outcomes in Adulthood, using height as the measure of child health.

They conclude that taller individuals attain higher levels of education and height is positively associated with better economic, health, and cognitive outcomes.

Drawing upon a UK longitudinal study of 12,686 young men and women who were 14-22 years old when they were first surveyed in 1979, Case and Paxson show that

Even among children with the same mother, taller siblings score better on cognitive tests and progress through school more quickly. Part of the differences found between siblings arises from differences in their birth weights and lengths attributable to mother's behaviors while pregnant. Taken together, these results support the hypothesis that childhood health influences health and economic status throughout adulthood.

## 6. Policy and research implications

A recent study by the Center on the Developing Child at Harvard University (2010) aimed at policies and programs for strengthening lifelong health argued that health promotion and disease prevention policies focused on adults would be more effective if evidence-based investments were also made to strengthen the foundations of health and mitigate the adverse impacts of toxic stress in the prenatal and early childhood periods

The study identifies three critical areas in which programs should be developed:

- Creating a stable and responsive environment of relationships
- Safe and supportive chemical, physical and built environments
- Sound and appropriate nutrition

### a. Creating a stable and responsive environment of relationships

The first of these categories encompasses a range of different programs to (i) strengthen the ability of parents and other caregivers to provide a stable responsive and nurturing environment for children to develop, for example through enabling more secure attachments between children and caregivers, and through the development of consistent and predictable sleeping patterns and other aspects of daily routine.

Examples of policy responses include parenting education and home visiting programs and expanded professional development for early care and education providers

### b. Safe and supportive chemical, physical and built environments

The second category of programs are those aimed at reducing exposures to harmful chemicals and improving the physical and built environment at home, at school and in neighbourhoods.

### c. Sound and appropriate nutrition

The third category consists of programs to provide sound and appropriate nutrition over the lifecourse beginning with the mother's pre-conception nutritional status, extending through pregnancy to early infant feeding and weaning, and continuing with diet and activity throughout childhood and into adult life. The importance of adequate intake of folate, iron, and vitamins A and D during pregnancy is acknowledged but nutrition is critically important for the developing fetus and in early childhood.

Examples include policies and programs that support breastfeeding at home and at work, and supplemental nutrition programs for mothers and infants.

As mentioned earlier there is increasing interest in the "epigenetic diet" as a way of preventing or reversing adverse epigenetic modifications during pregnancy and postnatally.

Park, Friso and Choi (2012) in their paper on nutritional influences on epigenetics and age-related disease, such as cancer, CVD and neurodegenerative disorders, identified a number of agents that can modify the epigenome beneficially

Nutrients involved in onecarbon metabolism, namely folate, vitamin B12, vitamin B6, riboflavin, methionine, choline and betaine, are involved in DNA methylation by regulating levels of the universal methyl donor S-adenosylmethionine and methyltransferase inhibitor S-adenosylhomocysteine. Other nutrients and bioactive food components such as retinoic acid, resveratrol, curcumin, sulforaphane and tea polyphenols can modulate epigenetic patterns by altering the levels of S-adenosylmethionine and S-adenosylhomocysteine or directing the enzymes that catalyse DNA methylation and histone modifications

Similarly, Hardy and Tollefsbol (2011) in discussing the role of epigenetic diet and cancer find that

A growing body of evidence suggests that dietary agents as well as non-nutrient components of fruits and vegetables can affect epigenetic processes and are involved in processes, including the reactivation of tumor suppressor genes, the initiation of apoptosis, the repression of cancer-related genes and the activation of cell survival proteins in different cancers. Dietary phytochemicals such as tea polyphenols, genistein, sulforaphane (SFN), resveratrol, curcumin and others have been demonstrated to be effective agents against cancer and to act through epigenetic mechanisms that affect the epigenome.

In their report to the WHO on the policy and research implications of the life course perspectives on coronary heart disease, stroke and diabetes, Aboderin et al (2002) recommend that because scientific understanding of the pathways of life course impacts on disease is still evolving, policies should concentrate on prevention policies addressing risk factors such as tobacco use and obesity. In addition there is a need for school-based and other public health programs aimed at promoting health diets and exercise.

Almost all authors cited in this report have cautioned that more evidence and research is needed to strengthen and confirm their findings and to further elucidate pathways between childhood circumstances and adult health, particularly for different disease states.

Echoing this Aboderin et al have called for more well-designed prospective maternal and birth (or child) cohort studies, and the development and greater use of historical cohort studies and multi-generational studies.

Some of the research questions to which they give priority are

- a. The nature of the effects of fetal and post-natal growth on later disease risk.
- b. The influence of maternal factors on fetal growth and offspring's risk of disease.
- c. The biological mechanisms underlying the association of fetal growth to later disease risk.
- d. The association of infectious disease to chronic disease risk.
- e. The social, psychological, economic and biological processes leading to unhealthy lifestyles and risk factors in different populations.
- f. The relative importance of early vs. later life exposures on risk of disease at individual and population level.

## References

- Aboderin, I., Kalache, A., Ben-Shlomo, Y., Lynch, J.W., Yajnik, C.S., Kuh, D., Yach, D. (2002) Life Course Perspectives on Coronary Heart Disease, Stroke and Diabetes: Key Issues and Implications for Policy and Research. Geneva, World Health Organization
- ABS 2010, 43640DO010\_20072008 National Health Survey: Summary of Results, 2007–2008 (Reissue), [http://www.abs.gov.au/AUSSTATS/abs@.nsf/DetailsPage/4364.02007-2008%20\(Reissue\)?OpenDocument](http://www.abs.gov.au/AUSSTATS/abs@.nsf/DetailsPage/4364.02007-2008%20(Reissue)?OpenDocument)
- Barker DJ, Winter PD, Osmond C et al. Weight in infancy and death from ischaemic heart disease. *Lancet* 1989 Sep 9; 2(8663): 577–580.
- Barker D J P 1998, In utero programming of chronic disease, *Clinical Science* (1998) 95, 115–128
- Barker D J P 2007, The origins of the developmental origins theory, *Journal of Internal Medicine* 261; 412–417
- Begg S, Vos T, Barker B, Stevenson C, Stanley L, Lopez AD, 2007. The burden of disease and injury in Australia 2003. PHE 82. Canberra: AIHW.
- Ben-Shlomo Yoav, Gita Mishra and Diana Kuh 2014, Life Course Epidemiology, Chapter 40 in W. Ahrens, I. Pigeot (eds.) *Handbook of Epidemiology*, 2nd edition, Springer Science+Business Media New York
- Berends L.M. and S.E. Ozanne 2012, Early determinants of type-2 diabetes, *Best Practice & Research Clinical Endocrinology & Metabolism* 26 (2012) 569–580
- Center on the Developing Child at Harvard University (2010). The Foundations of Lifelong Health Are Built in Early Childhood. <http://www.developingchild.harvard.edu>
- Cohen Sheldon, Denise Janicki-Deverts, Edith Chen, and Karen A. Matthews 2010, Childhood socioeconomic status and adult health, *Ann. N.Y. Acad. Sci.* 1186 (2010) 37–55
- Currie Janet 2009, Healthy, Wealthy, and Wise: Socioeconomic Status, Poor Health in Childhood, and Human Capital Development *Journal of Economic Literature* 2009, 47:1, 87–122
- Cutler David M., Adriana Lleras-Muney and Tom Vogl 2008, Socioeconomic Status and Health: Dimensions and Mechanisms, NBER Working Paper No. 14333, September 2008
- Forsdahl A. Are poor living conditions in childhood and adolescence an important risk factor for arteriosclerotic heart disease? *British Journal of Preventive & Social Medicine* 1977 Jun; 31(2): 91–95
- Galobardes Bruna, John W. Lynch, and George Davey Smith 2004, Childhood Socioeconomic Circumstances and Cause-specific Mortality in Adulthood: Systematic Review and Interpretation, *Epidemiol Rev* 2004;26:7–21
- Galobardes B, J W Lynch, G Davey Smith 2008, Is the association between childhood socioeconomic circumstances and cause-specific mortality established? Update of a systematic review, *J Epidemiol Community Health* 2008;62:387–390.

Glover John D, Diana MS Hetzel and Sarah K Tennant 2004, The socioeconomic gradient and chronic illness and associated risk factors in Australia, *Australia and New Zealand Health Policy* 2004, 1:8

Gluckman PD, Hanson MA 2004, Living with the past: evolution, development, and patterns of disease. *Science* 305:1733–1736

Gluckman Peter D., Mark A. Hanson, Tatjana Buklijas, Felicia M. Low and Alan S. Beedle 2009, The development of the epigenetic mechanisms that underpin metabolic and cardiovascular diseases, *Nat. Rev. Endocrinol.* 5, 401–408 (2009)

Hardy Tabitha M and Trygve O Tollefsbol 2011, Epigenetic diet: impact on the epigenome and cancer, *Epigenomics*. 2011 August 1; 3(4): 503–518.

Horikoshi Momoko 2013, New loci associated with birth weight identify genetic links between intrauterine growth and adult height and metabolism, *Nature Genetics* 45:1, January 2013, 76-82

Hoy Wendy E and Jennifer L Nicol 2010, Birthweight and natural deaths in a remote Australian Aboriginal community, *MJA* 2010; 192: 14–19

Kavanagh A, Thornton L, Tattam A, Thomas L, Jolley D and Turrell G. Place does matter for your health: A report of the Victorian Lifestyle and Neighbourhood Environment Study. University of Melbourne, May 2007.

Kelsall Helen L., Laura Baglietto, David Muller, Andrew M. Haydon, Dallas R. English, Graham G. Giles 2009, The effect of socioeconomic status on survival from colorectal cancer in the Melbourne Collaborative Cohort Study, *Social Science & Medicine* 68 (2009) 290–297

Korda Rosemary J., Emily Banks, Mark S. Clements and Anne F. Young 2009, Is inequity undermining Australia's 'universal' health care system? Socio-economic inequalities in the use of specialist medical and non-medical ambulatory health care, *Aust N Z J Public Health*. 2009; 33:458-65

Korda Rosemary J, James RG Butler, Mark S Clements and Stephen J Kunitz 2007, Differential impacts of health care in Australia: trend analysis of socioeconomic inequalities in avoidable mortality, *International Journal of Epidemiology* 2007;36:157–165

Lillycrop Karen A., and Graham C. Burdge 2012, Epigenetic mechanisms linking early nutrition to long term health, *Best Practice & Research Clinical Endocrinology & Metabolism* 26 (2012) 667–676

Marmot Michael, Sharon Friel, Ruth Bell, Tanja A J Houweling, Sebastian Taylor, on behalf of the Commission on Social Determinants of Health 2008, Closing the gap in a generation: health equity through action on the social determinants of health, *Lancet* 2008; 372: 1661–69

Montez Jennifer Karas & Mark D. Hayward 2013, Cumulative Childhood Adversity, Educational Attainment, and Active Life Expectancy Among U.S. Adults, *Demography*. 2013 Nov 27. [Epub ahead of print]

Osler Merete, Liselotte Petersen, Eva Prescott, Thomas W Teasdale and Thorkild I A Sørensen 2006, Genetic and environmental influences on the relation between parental social class and mortality, *International Journal of Epidemiology* 2006;35:1272–1277

- Painter Rebecca C., Tessa J. Roseboom and Otto P. Bleker 2005, Prenatal exposure to the Dutch famine and disease in later life: An overview, *Reproductive Toxicology* 20 (2005) 345–352
- Park Lara K., Simonetta Friso and Sang-Woon Choi 2012, Nutritional influences on epigenetics and age-related disease, *Proceedings of the Nutrition Society* (2012), 71, 75–83
- Pavalko Eliza K. and Jennifer Caputo 2013, Social Inequality and Health Across the Life Course, *American Behavioral Scientist*, 57(8) 1040–1056
- Pollitt Ricardo A, Kathryn M Rose and Jay S Kaufman 2005, Evaluating the evidence for models of life course socioeconomic factors and cardiovascular outcomes: a systematic review, *BMC Public Health* 2005, 5:7
- Räikkönen Katri, Anu-Katriina Pesonen, Tessa J. Roseboom and Johan G. Eriksson 2012, Early determinants of mental health, *Best Practice & Research Clinical Endocrinology & Metabolism* 26 (2012) 599–611
- Raposa, Elizabeth B.; Hammen, Constance L.; Brennan, Patricia A.; O'Callaghan, Frances; Najman, Jake M. 2013, Early Adversity and Health Outcomes in Young Adulthood: The Role of Ongoing Stress. *Health Psychology*, Jun 3 , 2013
- Raposa Elizabeth, Constance Hammen, Patricia Brennan, and Jake Najman 2014, The Long-Term Effects of Maternal Depression: Early Childhood Physical Health as a Pathway to Offspring Depression, *Journal of Adolescent Health* 54 (2014) 88e93
- Roseboom Tessa, Susanne de Rooij and Rebecca Painter 2006, The Dutch famine and its long-term consequences for adult health, *Early Human Development* (2006) 82, 485— 491
- Smith, James P. 2007, The Impact of Socioeconomic Status on Health over the Life-Course, *Journal of Human Resources*, 42(4): 739–64.
- TehraniFar Parisa, Hui-Chen Wu, Xiaozhou Fan, Julie D. Flom, Jennifer S. Ferris, Yoon Hee Cho, Karina Gonzalez, Regina M. Santella and Mary Beth Terry 2013, Early life socioeconomic factors and genomic DNA methylation in mid-life, *Epigenetics* 8:1, 23–27; January 2013
- Turrell Gavin, Anne Kavanagh, Glenn Draper, S V Subramanian, Do places affect the probability of death in Australia? A multilevel study of area-level disadvantage, individual-level socioeconomic position and all-cause mortality, 1998–2000, *J Epidemiol Community Health* 2007;61:13–19
- Turrell G, Stanley L, de Looper M & Oldenburg B 2006. Health Inequalities in Australia: Morbidity, health behaviours, risk factors and health service use. Health Inequalities Monitoring Series No. 2. AIHW Cat. No. PHE 72. Canberra: Queensland University of Technology and the Australian Institute of Health and Welfare.
- Wilkinson, Richard and Michael Marmot (ed) 2003, *Social determinants of health: the solid facts*. 2nd edition, WHO, 2003

## Appendix Life Course Epidemiology Models

The life course approach has evolved a number of different models to explain the influence of status at various stages of life on health outcomes. According to Ben-Shlomo, Mishra and Kuh 2014 there are 7 models as follows:

### 1. Critical Period Model.

In this model, it is assumed that an exposure, e.g. a specific viral infection, acting within a predefined time window, e.g. first trimester of pregnancy, may result in a specific disorder, e.g. schizophrenia. This model does not preclude other causes of schizophrenia that are unrelated to viral infection, e.g. genetic factors, or that other exposures, e.g. expressed familial hostility, cannot also increase risk of schizophrenia. It does assume that maternal exposure after the first trimester or if a subject is exposed postnatally is not associated with any increased risk compared to an unexposed subject.

### 2. Sensitive Period Model.

An obvious variant of the above scenario is that exposure in the second trimester is associated with a milder form of the disease and that exposure in the third trimester is associated with a schizophreniform type of personality but not overt clinical disease. This is what is meant by a sensitive rather than a critical period model, namely, that exposure within specific time windows has a greater or lesser risk of disease.

### 3. Critical/Sensitive Period Model with Later Effect Modification.

Even though the timing of an exposure may be essential to have any effect or a stronger effect on a disease outcome, this does not mean that it is inevitable that disease will always emerge. Unrelated exposures in later life that are not themselves secondary to the initial insult could still modify disease risk either through independent or interactive effects. For example, if maternal undernutrition in pregnancy, as seen in the Dutch Hunger Winter (Stein et al. 1975), was associated with a permanent reduction in the number of muscle cells at birth, this could be compensated by increased physical activity in later life resulting in muscle hypertrophy.

### 4. Accumulation of Risk with Uncorrelated Exposures.

We live in an associational world whereby many non-genetic exposures are correlated to varying degrees due to social patterning of exposures. It is therefore rare to have environmental associations that are truly randomly distributed. In such a scenario, the risk of being exposed to A is unrelated to B and C so that unexposed individuals are equally as likely to be exposed to B and C. For example, the risk of depression may be associated with a genetic variant (A), death of a father due to military conflict, and unemployment in adult life (C) due to the subject's employer going bankrupt. In this example, there is no reason to believe any of these exposures are correlated with each other. If each exposure increases risk (though this may be to varying degrees), then individuals exposed to more than one factor will have a greater risk than those exposed to fewer factors. In this case, we are assuming that these exposures do not interact with each other and the effects are additive.

#### 5. Accumulation of Risk with Correlated Exposures.

Exposures are more commonly correlated because of risk clustering. For example, living in a poor neighborhood may be associated with being exposed to a less healthy diet, reduced opportunities to exercise, and greater peer influences on smoking. Each of these factors may additively increase risk of coronary heart disease, but in this case, one exposure will be associated with the others due to the common factor of neighborhood poverty which is an upstream determinant of the other mediating factors.

#### 6. Chain of Risk Additive Model.

In this scenario, each exposure increases risk, but A is itself a determinant of B which in turn increases the risk of C. Hence, a chain effect may be established whereby an exposure may only have a modest effect directly on outcome, but its overall effect, including the indirect pathways, may be much larger. For example, smoking may directly result in subclinical atherosclerosis through an inflammatory effect on the arterial wall, but it also reduces exercise behavior due to respiratory symptoms. This in turn results in reduced aerobic capacity but also increases obesity. This in turn results in insulin resistance syndrome and is a risk factor for coronary heart disease. In this case, intervening on obesity alone would have health benefits, but obese individuals who have followed this pathway would still be at increased risk due to their life course history compared to non-obese individuals.

#### 7. Chain of Risk Trigger Model.

In contrast to the previous model, the trigger model is only associated with risk due to the last exposure in the chain. For example, poor childhood socioeconomic environment results in overcrowding which in turn increases exposure to *Helicobacter pylori*, and this is associated with peptic ulcer. In this scenario, eradication of *H. pylori* will eliminate the risk, and there will no longer be any residual risk associated with the socioeconomic environment. Such pathways are interesting as they may explain why some epidemiological studies show marked heterogeneity of effects (assuming this is not due to random variation). In these pathways, variations in temporal or cultural differences can abolish associations. So, for example, the association of socioeconomic conditions with any smoking-mediated disease can legitimately vary by time and place due to cultural or temporal changes in smoking behavior.