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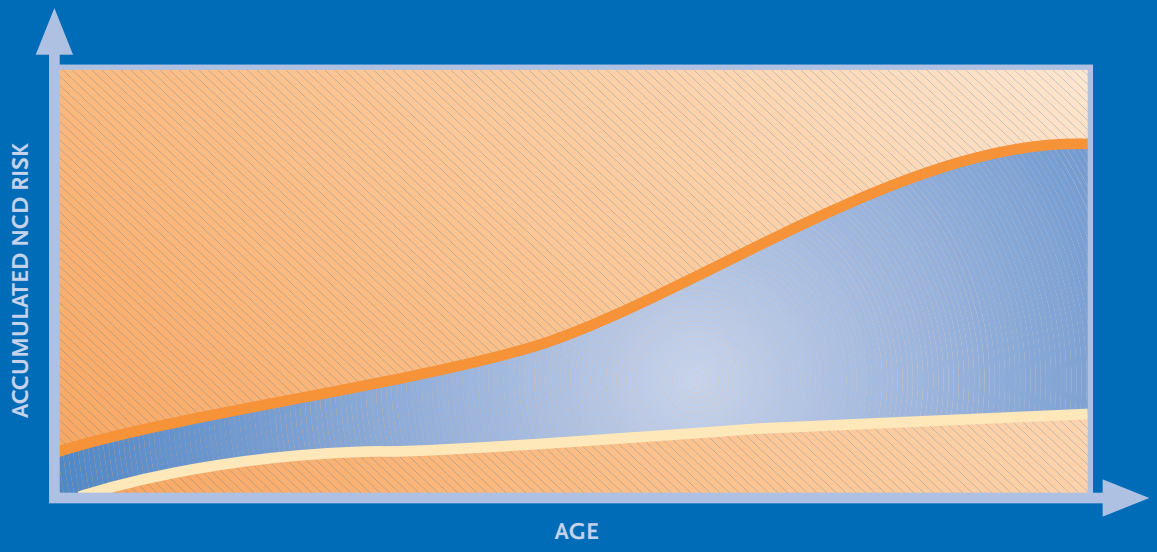
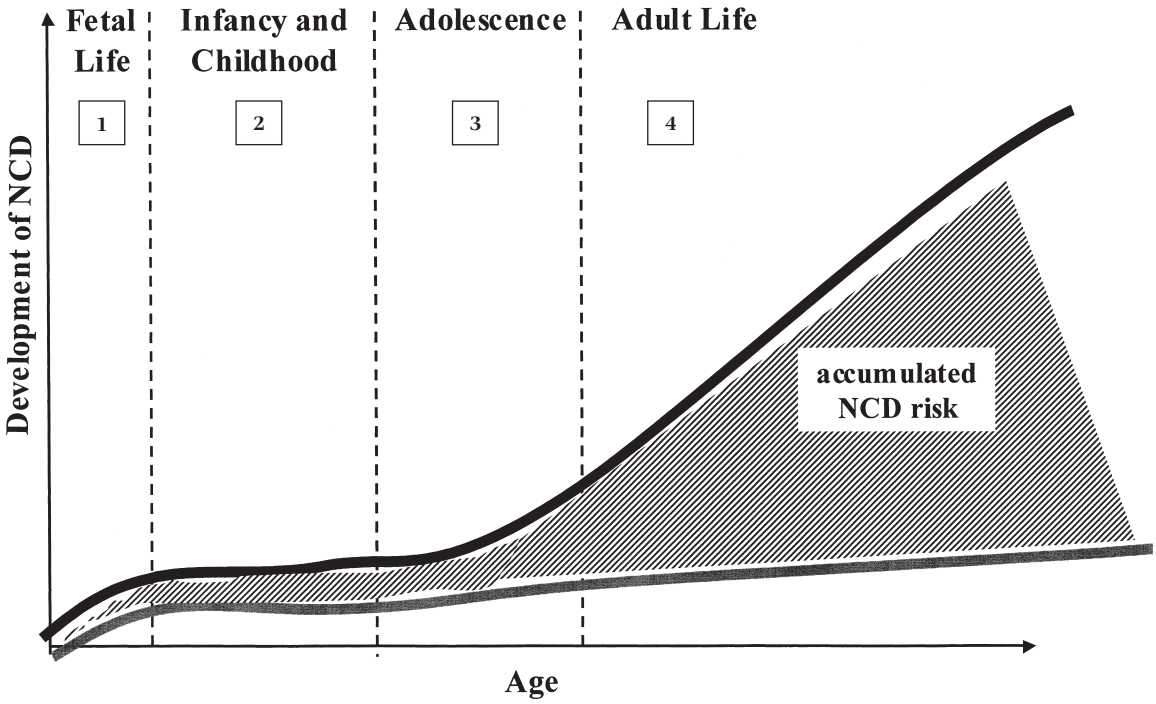
Life course perspectives on coronary heart disease, stroke and diabetes



The evidence and implications for policy and research

Ageing and Life Course
Department of Noncommunicable Diseases Prevention and Health Promotion
Noncommunicable Diseases and Mental Health Cluster
WORLD HEALTH ORGANIZATION

A Life Course Approach to NCD Prevention



The risk of noncommunicable diseases accumulates with age and is influenced by factors acting at all stages of the life span. The main factors at different stages of life include the following:

1 Fetal Life

fetal growth, maternal nutritional status, socioeconomic position at birth

2 Infancy and Childhood

growth rate, breastfeeding infectious diseases, unhealthy diet, lack of physical activity, obesity socioeconomic position

3 Adolescence

unhealthy diet, lack of physical activity, obesity tobacco and alcohol use

4 Adult life

know adult behavioural and biological risk factors

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Contents

Executive Summary

The Life Course and Health Perspective considers chronic disease in terms of the social and physical hazards, and the consequent biological, behavioural and psychosocial processes, that operate across all stages of the life span to cause or modify risk of disease.

This perspective carries a substantial potential for identifying the most appropriate and effective policies for NCD prevention and health promotion—a potential that is yet to be fully realized in public health policy.

Through the preparation for, and the conduct of a meeting of experts on life course and health (2–4 May, 2001), the WHO Department of Noncommunicable Diseases Prevention and Health Promotion (NPH) made a first step towards harnessing the potential of the life course approach for policy.

The meeting has established the state of the art knowledge regarding life course impacts on risk of coronary heart disease, stroke and diabetes and, on the basis of this, has identified emerging agendas for policy and research. The limited initial focus on three diseases was deemed necessary for the task to remain manageable. However, it provides a starting point upon which future assessments of life course and other NCDs can build.

The emerging policy recommendations follow a hierarchy according to the firmness of available evidence. The strongest recommendation, currently, is to continue the focus on the major known risk factors. In doing so particular attention should be paid to primordial/primary prevention strategies to counter the emergence of risk factors and behaviours in childhood or adolescence, particularly in developing countries. Most importantly, such strategies must take into account the varied processes by which urbanisation and 'westernisation' can lead to risk behaviours and factors in different socio-economic contexts and populations. It is important to recognize the cultural, economic and social circumstances within which such behaviours and risks emerge, and that these may be specific to different countries in different stages of economic development. Thus, research to inform the development of such preventive strategies in individual countries is urgently needed.

Despite the high profile of evidence linking early life factors such as reduced fetal growth to later disease, evidence is still insufficient for firm policy recommendations to be made. Further research is urgently needed to establish the relative role and importance of early life exposures, and the mechanisms by which they affect future risk of disease. Key priority areas for research have been identified.

NPH is taking forward the policy and research agendas emerging in light of current evidence on life course, through collaborative work and consultation across departments within WHO, and with outside institutions.

Introduction: Life course as a central part of WHO's work on NCD prevention and health promotion

The WHO initiative on life course and health, the scientific foundation for which was consolidated in a meeting of experts on life course, 2–4 May 2001, is situated within and is a central aspect of the work of the Department of Noncommu-nicable Disease (NCD) Prevention and Health Promotion (NPH). The department's overall goal is to prevent noncommunicable diseases and thus to reduce premature morbidity, mortality and disability caused by them. Particular focus is given to most common NCDs such as cardiovascular diseases (CVD) and diabetes, as they cause much human suffering, pose substantial threats to the economies of individual countries, and are important in the increasing health inequalities between countries and within popu-lations worldwide.

Global trends in CVD and diabetes

Although already high, the burden of CVD and diabetes is expected to rise further in the coming decades—above all in developing countries, i.e. those countries with the least resources to effectively deal with them (see e.g. Murray and Lopez, 1996):

- In developed countries, cardiovascular diseases are and will remain the first cause of death and disability, despite the gradual decline in disease rates experienced in most of them in the last few decades. In 2000, 48.6% of deaths were caused by CVD. By 2020, still 46.4% of all deaths are expected to be attributable to CVD. Meanwhile, the number of those suffering from diabetes will have risen from 51 million in 1995 to 72 million in 2025.
- In the developing world, CVD will soon become the main cause of death and disability: by 2020, a third (33.8%) of all deaths are expected to be due to CVD. The number of those with diabetes will increase more than 2.5 times, from 84 million in 1995 to 228 million in 2025.
- It is projected that by 2020 71% of ischaemic heart disease (IHD) deaths, 75% of stroke deaths and 70% of diabetes deaths will occur in developing countries.
- The current 'epidemic' in adult and childhood obesity, not just in developed but also in many developing countries may indicate even sharper rises in the burden of CVD and diabetes.

Although already high, the burden of CVD and diabetes is expected to rise further in the coming decades—above all in developing countries, i.e. those countries with the least resources to effectively deal with them

The spectre of rising CVD and diabetes underscores the imperative need to develop effective and appropriate prevention policies, especially in poor and marginalized populations. Such policies, as has long been recognized, need to address the major risk factors predisposing to disease (the current focus is on the behavioural risk factors smoking, physical inactivity and unhealthy diet), and take into consideration underlying economic, social, gender, political, behavioural, and environmental factors that foster disease risk.

However, what the most valuable concrete strategies are in different contexts and populations, whom they should be targeted at, when and how, remains to be firmly established and will depend in large part on the cultural, social and economic conditions.

This represents the core charge of NPH's work and is the reason why NPH has adopted the life course as the underpinning perspective of its work. In doing so, WHO recognizes the potential of the life course perspective to enable policymakers to identify the most effective and appropriate prevention strategies and to gain maximum leverage for interventions where prevention resources may be scarce.

The life course perspective—potential and challenge

The current epidemiological focus on a life course approach to chronic disease emerged in the 1980s. However, the notion that experiences in early life shape adult health is not new. It was, in fact, a prominent perspective in public health in the first half of the century, but was superseded by the "life style" model of chronic disease which focused almost exclusively on adulthood risk factors. This was, largely, a result of the success of cohort studies in confirming, for example, smoking or high cholesterol levels as major risk factors for several chronic diseases.

The current revived emphasis on a life course perspective has arisen against a background of increasing evidence, especially from revitalised historical cohorts, maturing birth or child-cohort studies, that the risk of many NCDs such as CVD or diabetes is not just determined by risk factors in mid-adult life, but already begins in childhood or adolescence—and potentially even earlier during fetal development.

Specifically, it has been boosted by prominence given to (a) the increasing evidence on the 'tracking' of conventional risk factors from childhood to adulthood from large and extended cohort studies such as the Bogalusa Heart Study (e.g. Bao *et al*. 1994); (b) the rise of 'programming' as a model of disease aetiology, in particular the fetal origins of adult disease hypothesis (Barker, 2000a); and (c) emerging evidence to indicate that some early risk factors may act across generations thus increasing cardiovascular risk in offspring (Sterne *et al*. 2001; Davey Smith *et al*.2000a).

Whilst consideration of early life factors or exposures is a main focus of the life course perspective, it is much broader than that. Its aim is to transcend the dichotomy between traditional 'adult lifestyle' and 'early origins' models of adult disease, both of which, on their own, are unable to fully explain individual risk as well as geographical, social, and temporal variations in disease patterns (Kuh and Ben-Shlomo, 1998).

Thus, the life course perspective considers the social and physical hazards, and the resulting behavioural, biological and psychosocial processes, that act across ***all*** stages of the life span—gestation, infancy, childhood, adolescence, young adulthood and midlife—to affect risk of disease later on. It considers, in particular, the existence of both "critical" and "sensitive" periods throughout life where exposures are deterministic or especially powerful in predisposing to, or lessening risk of disease later on. The term "critical period" implies exposures that must occur in some specified window(s) of time and often involve exposures that alter normal biological development. "Sensitive period" exposures refer to a broader class of influences that may have greater impact on later outcomes if they occur in certain periods than in others. In empirical terms, both critical and sensitive period exposures imply time by exposure interactions. Better understanding of critical and sensitive period exposures thus offers the potential for identifying the most appropriate and effective interventions or strategies for disease prevention or health promotion. In addition, a life course perspective on NCDs invokes concepts of "accumulation" of both correlated or uncorrelated exposures that over time additively increase the risk of adverse outcomes.

Thus, the life course perspective considers the social and physical hazards; and the resulting behavioural, biological and psychosocial processes, that act across all stages of the life span—gestation, infancy, childhood, adolescence, young adulthood and midlife—to affect risk of disease later on.

The major challenge in harnessing the potential of the life course perspective for public health policy is to fully elucidate the pathways and mechanisms by which, in different populations and at different historical periods, factors or exposures in earlier and later life act to determine subsequent risk of disease. Of particular importance is to identify the relative role of—and interaction between—earlier and later factors, and the critical periods and exposures that may shape chronic disease risk later on.

So far, and on the basis of available evidence, several theoretical models have been advanced to explain the possible ways in which factors over the life course may act to cause chronic disease (Ben-Shlomo and Kuh, 1999)

1. **A critical period model**—where an insult during a specific period of growth or development has a lasting, life long effect on physical functioning or structure thus resulting in disease later on.

2. **A critical period with later effect modifiers**—where later factors may modify such a risk earlier incurred.
3. **Accumulation of risk with independent and uncorrelated results**—where separate and independent risk factors at each stage of life combine to raise disease risk.
4. **Accumulation of risk with correlated results**—where risk factors cluster in socially or biologically patterned ways, and may raise the risk of disease through social and/or biological chains (or pathways) of risk. That is, where one adverse (or protective) experience will tend to lead to another adverse (or protective) experience in a cumulative way.

Disentangling the ways in which factors at each stage of life act or interact to shape disease risk is, obviously, complex and difficult. This is added to by the fact that explanations are not only disease specific, but may also vary from one cohort, population, or context to another. It is crucial to understand that the effects of early life exposures on later disease risk are likely to be highly contextualized in both time and space. For example, being born into poverty in Bangladesh in 2000 is likely to be associated with very different early life exposures than being born into poverty in the USA in the 1950s. The social meaning of poverty and its life course links to particular types of exposures, as well as the prevailing disease environment will all influence the potential for early life factors to be expressed in different adverse outcomes later in life.

Disentangling the ways in which factors at each stage of life act or interact to shape disease risk is, obviously, complex and difficult.

Despite the complexity and difficulty of the challenge, and despite the fact that work is only in its early stages, a critical mass or body of evidence, in particular from developed countries, has accumulated over the last decade.

The time is thus now ripe for taking a first step towards capturing some of the potential of the life course perspective for policy—by taking stock of what knowledge has accumulated, by considering what policy implications are already emerging, and by pinpointing the key gaps in knowledge that need to be addressed by future research.

Structure of the report

The remainder of this report is divided into two parts:

Part I provides an overview of the state of the art knowledge and evidence regarding life course impacts on risk of CHD, stroke and diabetes, as established at the meeting of experts, 2–4 May 2001. It begins by outlining the associations between early or later life factors and CHD, stroke and diabetes that have been firmly established or are highly suggestive. The subsequent sections examine in detail the nature and factors underpinning these associations. They do this by considering, in turn, each of the key biological or lifestyle related domains discussed, whilst pointing out areas of overlap between them. A final section draws together the emerging key themes, issues, and the main gaps in knowledge regarding the influence of earlier and later life factors on disease risk.

Part II describes the main implications for research and policy that emerge from the current state of knowledge on life course and later disease. Recommendations for public health policy are made and priority areas for future research are identified.

PART I

Life course impacts on risk of CHD, stroke and diabetes – the state of the art evidence

1.1 Introduction

This first part of the report provides an overview of the state of the art evidence on early and later life course impacts on risk of CHD, stroke and diabetes—as established by the experts in the their written comments prior to, and their discussions at the May 2001 meeting. Throughout, the points and issues raised by the experts are substantiated with key references from the literature.

Most of the relevant evidence comes either from historical or retrospective cohort studies, or from ongoing or recently established prospective birth or child cohort studies. A selection of some of the former studies, which are mostly from developed countries, include:

- **UK**—the 1946 and 1950 birth cohorts; the Hertfordshire, Sheffield, and Caerphilly cohorts (see Leon and Ben-Shlomo, 1997); the Glasgow University Students cohort (McCarron *et al*. 1999), and the Boyd Orr cohort (Gunnell *et al*. 1998a)
- **US**—the Harvard Alumni Studies (Paffenbarger and Williams, 1967) or Johns Hopkins Precursor Study (e.g. Klag *et al*. 1993)
- **Finland**—the Helsinki Central Hospital Cohort (Eriksson *et al*. 1999)
- **Netherlands**—the Dutch Famine Cohort (e.g. Ravelli *et al*. 2000)
- **Russia**—the Leningrad Siege Cohort (Stanner *et al*. 1997)
- **Sweden**—the Uppsala cohort (e.g. Leon *et al*. 1996, 1998)

A few such cohorts have, however, also been studied in developing countries, for example in Mysore, India (Stein *et al*. 1996; Fall *et al*. 1998) or Beijing, China (Mi *et al*. 2000).

Prospective child or adolescent cohort studies, too, are predominantly from developed countries, e.g

US—the Bogalusa Heart Study (Berenson *et al*. 1991)
UK—the ALSPAC Study (ALSPAC, 2001)
Finland—the Young Finns Study (Åkerblom *et al*. 1999).

However, several developing country child cohort studies do exist including,

India—the Pune Birth Cohort (Bavdekar *et al*. 1999) and the Pune Maternal Nutrition Studies (Fall *et al*. 1999)

South Africa—the Birth to Ten Study (Yach *et al*. 1991).

A few retrospective child cohort studies, such as for example in Jamaica (Forrester *et al*. 1996), the Gambia (Margetts *et al*. 1991), Zimbabwe (Woelk *et al*. 1998), or the Democratic Republic of Congo (Longo-Mbenza *et al*. 1999), have provided further evidence on early life course risk factors in developing populations.

Additional developing world insights come, moreover, from child health and nutrition surveys such as the CEBU Longitudinal Health and Nutrition Survey in the Philippines (CLHNS) (Cebu Study Team, 1991) or the INCAP Nutrition Supplementation Trial in Guatemala (Martorell, 1995). Whilst these studies did not specifically set out to investigate life course impacts on chronic disease risk, some of their findings are, nevertheless, relevant.

The first of the following sections outlines those associations between life course factors and disease that are firmly established or highly suggestive. Given that these associations have mainly been demonstrated in developed countries it, moreover, considers the extent to which they are generalizable to other populations, particularly in the developing world.

The subsequent six sections, which follow the structure of the discussions at the May 2001 meeting, examine the nature and basis of the observed associations between early or later factors and disease. They do so by exploring in detail the life course determinants and interactions of the main known risk domains: **High Blood Pressure**, **Dyslipidaemias and Impaired Glucose Tolerance**, **Obesity**, **Height**, and **Unhealthy Lifestyles**, and by discussing the potential mechanisms underpinning the association of fetal factors to disease risk.

A final section draws together the main strands emerging from the explorations of the individual domains. It considers the cross-cutting themes and issues, and pinpoints the main gaps in our understanding of how life course factors shape risk of CHD, stroke, and diabetes.

1.2 Established life course factors associated to disease

1.2.1 Factors in adulthood

a. The 'established' risk factors

The most firmly established associations between CVD or diabetes and factors in the life

span are those between disease and the major known 'adult' risk factors—**tobacco use**, **obesity**, **physical inactivity**, **cholesterol, high blood pressure**, and **alcohol**. (see e.g. Godlee, 1999; Elisaf, 2001 for review)

These are the factors confirmed to lead to increased risk of CHD, stroke, and diabetes. Some of the associations are considered causal and reversible:

- high blood pressure for CHD or stroke (e.g. McMahon et al. 1990; Kannel *et al*. 1996)
- high cholesterol (diet) for CHD (e.g.Hu *et al*. 2000; Hooper et al. 2001; Anderson *et al*.1987)
- tobacco use for CHD (e.g. Doll *et al*. 1994; Lopez, 1999)

The most firmly established associations between CVD or diabetes and factors in the life span are those between disease and the major known 'adult' risk factors—tobacco use, obesity, physical inactivity, cholesterol, high blood pressure, and alcohol.

Other associations are robust and consistent, though they have not necessarily been shown to be reversible:

- obesity (physical inactivity) for CHD, diabetes, stroke (e.g. Jousilahti *et al*. 1996; Shaper et al.1997; Davey Smith *et al*. 2000c; Wannamethee et al.1998a)
- heavy and/or binge drinking for CHD and stroke (e.g.Kaukanen *et al*. 1997; Lopez, 1999)

Although most of the evidence establishing the link of these factors to disease is from developed countries, it is generally believed that these associations can be generalized with some confidence to other populations. Supporting evidence from developing countries is beginning to emerge.

This includes the confirmed link in India of tobacco use, history of hypertension, diabetes, and abdominal adiposity to acute myocardial infarction (AMI) (Pais *et al*. 1996); the association of high serum cholesterol levels to CHD in China (Chen *et al*. 1991); as well as the clearly established link of tobacco use to overall and CVD specific mortality in large-scale studies in India (Gupta and Mehta, 2000) and China (Liu *et al*. 1998; Niu *et al*. 1998). Further efforts to determine the major risk factors specifically for CHD in developing countries are being begun by the WHO Interheart Study (Ounpuu *et al*. 2000).

b. Low socio-economic position

In developed countries, various indicators of low socio-economic position (SEP) have clearly been shown to be associated with a higher risk of cardiovascular disease and diabetes (Davey Smith, 1997). Recent evidence from the UK, moreover suggests that although overall CVD rates are falling, these inequalities in disease are persisting or even increasing, (e.g. Harding *et a*l. 1998). However, such rising social inequality in CVD is not necessarily a feature in all developed countries.

The effect of SEP on risk of CVD or diabetes in developing countries is poorly understood, given the paucity of cause-specific mortality and morbidity data. However, what little evidence is available suggests that there has been an initial preponderance of CVD among the higher socioeconomic groups, but that in some populations higher risk of CVD is, in fact, associated with lower SEP (e.g. Gupta *et al*. 1994). The particular nature of the social inequalities in CVD depends upon how lower socioeconomic position within a particular country affects the social distribution of risk factors for CVD, such as smoking, unhealthy diet and physical inactivity.

It is generally assumed, though not as yet verified, that as the 'epidemic' of chronic disease in developing countries advances, the social distribution of adverse risk facors and the burden of disease, as it has done in the West, will progressively shift to the lower social classes.

1.2.2 ***Factors in fetal life***

a. Intrauterine growth retardation (IUGR)

In addition to the major adult risk factors, there is firm evidence, mostly from developed countries, that intrauterine growth retardation (IUGR) is associated with an increased risk of CHD, stroke, and diabetes.

Evidence from revitalized historical cohorts or retrospective studies shows clear associations between retarded fetal growth (indexed by small size at birth), and risk of CHD (Leon and Ben-Shlomo, 1997; Leon *et al*. 1998; Eriksson, *et al*. 1999; Forsén *et al*. 1999); risk of diabetes (Barker *et al*. 1993a; Lithell *et al*. 1996; McKeigue, 1997,

Forsén *et al*. 2000a; Rich-Edwards *et al*. 1999); and risk of stroke (Martyn *et al*.1996; Leon *et al* 1998; Rich-Edwards *et al*. 1997).

Low birth weight, while clearly an imperfect marker, is the most commonly used (and most widely available) indicator for retarded fetal growth. Some research, however, has also investigated the associations of more specific indices of fetal growth, such as birth weight corrected for gestational age (Leon, *et al*., 1998). Other research has examined indicators of in-utero growth retardation such as birth length, head circumference, or 'thinness' i.e. ponderal index (weight/length)^3 with later disease.

The findings of such research show important differences in the strength of associations between disease and different kinds of fetal growth retardation (Barker, 1995), and highlight the limited value of birth weight alone in capturing the range of relevant fetal exposures.

Further evidence for an association between IUGR and later disease comes from 'famine studies' which explore the risk of disease in cohorts exposed to famine during gestation. The Dutch Famine Study exploring the effects of the Dutch Hunger Winter 1944–45, for example, has shown that exposure to famine in early gestation is associated with an increased risk of heart disease (Roseboom *et al*. 2000a). No such effect, however, was found in the Russian famine study examining the impact of the Leningrad Siege 1941–1944 (Stanner *et al*. 1997).

Only two studies in the developing world, both in India, have so far examined the association between fetal growth and disease, and their results suggest similarities and discrepancies with those in the developed world.

Only two studies in the developing world, both in India, have so far examined the association between fetal growth and disease, and their results suggest similarities and discrepancies with those in the developed world. An association between low birth weight and CHD was found in one study (Stein *et al*. 1996). However, diabetes was not found to be related to low birth weight, but rather to fatness (higher ponderal index) at birth (Fall *et al*. 1998).

These diverging findings and possible population differences clearly suggest that there is not sufficient evidence to confirm a link between retarded fetal growth and adult chronic disease across all populations at all times and so can not yet be generalized to developing country populations.

b. Overnutrition *in utero*

Just as there is evidence for an association between small size at birth and later disease, there is also evidence to show that large size at birth (macrosomia), i.e. fetal overnutrition, is associated with increased risk of diabetes and CVD.

In Sweden, for example, birth weight was shown to have an inverse 'J' relationship with CHD, indicating that heavy babies, too, are at increased risk (Leon *et al*. 1998). Among Pima Indians, diabetes was found to have a U-shaped relationship with birth weight, again indicating a greater risk also among those heavy-born (McCance *et al*. 1994).

The role of fetal overnutrition is important to be borne in mind, particularly in view of the general emphasis and prominence currently given to the fetal undernutrition as a determinant of later disease, as encapsulated in the fetal origins hypothesis (Barker, 2000a).

c. Intergenerational factors

There is some evidence of intergenerational transmission of CVD risk associated with fetal growth in humans. For example, several studies have shown low birth weight in offspring to be related to parental cardiovascular mortality (Davey Smith *et al*. 1997, 2000a; Sterne *et al*. 2001).

In some populations, moreover, maternal gestational diabetes (GDM), has been shown to lead to large birth weight and a consequent risk of diabetes as well as gestational diabetes in the offspring (Pettit and Knowler, 1998). Further evidence of such intergenerational transmission of risk, over several generations, comes from animal models. However, the mechanisms for such intergenerational transmission of CVD and diabetes risk remain unclear.

1.2.3 ***Factors in infancy and childhood***

a. Retarded postnatal growth in weight

In addition to showing an association between retarded fetal growth and coronary heart disease, evidence from the developed world also indicates an association between low growth in early infancy (low weight at 1 year) and an increased risk of CHD, irrespective of size at birth.

(Barker *et al*. 1989; Osmond *et al*. 1993; Eriksson *et al*. 2001). This association suggests the importance also of immediate post-natal factors in shaping disease risk.

Again, no research to demonstrate such association has yet been conducted in the developing world, and thus no inferences can be made.

b. Retarded childhood growth in height (short stature)

There is clear evidence from the developed world that short stature or childhood leg length (both indices of socio-economic deprivation in childhood) is associated with an increased risk of CHD, stroke, and to some extent diabetes (e.g. Hart *et al*. 2000; McCarron *et al*. 2000b, 2001a; Marmot *et al*. 1997; Rich-Edwards *et al*. 1997; Njolstad *et al*. 1996; Davey Smith *et al*. 2000b; Wannameethee *et al*. 1998; Jousilahti *et al*. 1998, 2000; Forsén *et al*. 2000b; Gunnell *et al*. 1998a).

There is clear evidence from the developed world that short stature or childhood leg length (both indices of socio-economic deprivation in childhood) is associated with an increased risk of CHD, stroke and to some extent diabetes

Given that short stature, and specifically short leg-length are particularly sensitive indicators of early socio-economic deprivation (Gunnel *et al*. 1998c), their association to disease, very likely reflects an association between poor early SEP and increased risk of disease. (Davey Smith, 1998).

Only indicative data exists so far on the link of stature (or early SEP) to disease risk in developing countries, and firm inferences can hence not yet be made.

1.2.4 *Interactions between early and later factors*

In addition to the robust evidence on independent associations of IUGR, infancy, and adulthood factors with later disease, there are increasing indications that the interaction between some of these early and later factors may lead to a particularly high risk of disease.

a. Interaction between IUGR and adult obesity

Existing evidence from the developed world shows that the *interaction* between retarded fetal growth and obesity in adulthood can be important in raising risk disease.

For example, IUGR (low birth weight), followed by subsequent adult *obesity* has been shown to impart a particularly high risk of CHD (Frankel *et al*. 1996), as well as of diabetes (e.g. Lithell *et al*. 1996).

Only indicative evidence of such an effect exists as yet for the developing world, and firm generalization can not yet be made.

b. Interaction between IUGR and enhanced growth in weight in childhood/adolescence

Further evidence for an interactive effect between IUGR and post-natally gained weight is provided by studies in developed countries, showing an interaction between rapid catch-up growth in weight and IUGR in raising risk of disease.

In Finland, for example, among men and women, the highest risk of CHD or metabolic syndrome was found to be associated to IUGR (small size at birth) followed by rapid growth to above average weight in childhood. (Eriksson *et al*., 1999, 2001; Forsén *et al*. 2000a). The precise period during childhood in which rapid weight growth is detrimental is yet unclear. Evidence so far would seem to give conflicting indications.

Considerable, but only indicative evidence on such an effect of catch up growth on disease is available from the developing world, suggesting that no firm generalizations can yet be made.

c. Interaction between IUGR and enhanced growth in height in childhood/adolescence

In addition to evidence of an interaction between enhanced IUGR and enhanced growth in weight, there are indications of such an effect also for rapid growth in height in raising disease risk.

In Finland, for example, short length at birth followed by enhanced growth in height to become average or tall, was found to be associated with an increased risk of CHD in women (in contrast, tallness in girls with long birth length was associated with lower risk) (Forsén *et al*. 1999). Similarly, among men and women, increased stroke risk was shown to be associated with small size at birth followed by accelerated growth in height to reach average levels in later childhood (Eriksson *et al*. 2000a).

Very little indicative evidence on such an effect of enhanced growth in height on CVD or diabetes risk factors is present from the developing world, and generalizations can not yet be made.

d. Possible interpretations of the interaction between IUGR and later growth

The apparent detrimental interaction between IUGR and enhanced later growth in weight or height—which, as the subsequent sections will discuss, has also been shown to be linked to raised blood pressure, dyslipidaemia and IGT, is not yet fully understood. However, four (not mutually exclusive) interpretations are possible:

i. It represents a negative effect of enhanced growth in childhood or adolescence *per se*. In other words, accelerated growth in weight (or height) itself could have negative consequences.

ii. It is the *difference* in size between birth and the later stage that better defines detrimental impaired early growth: the higher the difference, the higher the risk. (see e.g. Lucas *et al*. 1999)

iii. Obesity reveals/activates underlying susceptibility induced by impaired early growth and, vice versa, low birth weight enhances the risk associated to obesity. I.e. obesity is particularly harmful in those with early growth retardation.

iv. The effect of enhanced growth in height in IUGR babies may reflect a failure of the fetus to realize its genetic growth potential in utero, possibly due to placental failure. It may be this insult on fetal growth, not an effect of post-natal growth, that underlies the increased risk of disease (e.g. Leon *et al*. 1996)

Whilst the particular interpretation may depend on the specific disease or risk factor concerned, each indicates the importance of an adequate post-natal nutritional environment in bringing to the fore a risk associated with fetal growth retardation.

There are increasing indications that the *interaction* between some of these early and later factors may lead to a particularly high risk of disease.

1.2.5 ***Developing a deeper understanding of the associations of life course factors to adult disease: individual risk domains and potential mechanisms***

The established or highly suggestive associations described above demonstrate the undoubted clear importance of early life—as well as adulthood factors in influencing risk of CHD, stroke and diabetes.

What is less clear however, is the nature and basis of these associations. What is the basis of the association between retarded fetal or infant growth and later disease? What is the nature and the basis of the apparent interaction between retarded fetal growth and high weight (or height) gained postnatally in raising risk of disease? What are the biological mechanisms underpinning these associations and interactions? What is the influence of socio-economic conditions? What is the relative importance of earlier versus adulthood risk factors in causing disease?

The following sections will examine what is known in relation to these complex questions. They do this, first, by exploring in detail the life course determinants of the five main risk domains:

> High blood pressure, dyslipidaemias and impaired glucose tolerance, height, obesity, and unhealthy lifestyles (tobacco use, physical activity, and unhealthy diet).

Discussion of each risk domain, as indicated earlier, will specifically assess the following two aspects:

- the global, secular trends in both developed and developing countries, and what is known on the prevalence patterns with respect to gender, ethnicity and socio-economic status.

  Particular attention is paid to examining the extent to which prevalence patterns follow the classically assumed distribution, i.e. that higher risk levels are associated with low socio-economic status in industrialized countries, and with high socio-economic status in developing populations.

- what is known of the determinants of each biological/lifestyle related factors in:

— fetal life
— infancy
— childhood
— adolescence
— intergenerationally

Of the four biological risk factor domains discussed, obesity will be discussed last, because of the central importance of obesity in the development of the other biological risk factors (Berenson *et al*. 1991; Pi-Sunyer, 1991); because of its apparent importance in raising the disease risk related to impaired fetal growth; and because of the growing global health burden related to obesity.

Following the examination of the individual risk domains, the discussion will turn to exploring what is known about the potential mechanisms that underpin the associations of fetal factors to later disease risk. This includes questions regarding:

- the relative role of genetic versus 'environmental' factors as the basis of the associations between fetal growth and later disease
- the specific role of intergenerational and intrauterine factors (e.g. maternal or fetal nutrition) in the association between fetal growth and later disease
- the role of programming of endocrine, insulin or stress (HPA) pathways in the association between early growth and later disease
- the role of post-natal factors such as infections or childhood diet in underpinning associations, for example, between childhood socio-economic position and later disease

The final section will draw together the main strands emerging from the individual domain and mechanism discussions. It will highlight the cross-cutting themes and issues, and pinpoint the main gaps that remain in our understanding of the life course impacts on disease risk.

1.3 Life course perspectives on blood pressure

1.3.1 Blood pressure over the life course as a risk factor for CVD

High blood pressure—usually measured in mid or later life—has been established as a main risk factor for cardiovascular diseases—stroke and coronary heart disease. (e.g.Psaty *et al*. 2001).

No serial data exists, however, on the relationship of blood pressure at different points of the life span to later disease, including blood pressure at one year prior to the disease outcome. Such data, however, would be necessary to determine whether long term average exposure to raised blood pressure is important or, perhaps, simply an acute high transient level.

Nevertheless, some long-term cohort studies (e.g. the Harvard Alumni Study, the Chicago Heart Association Detection Project or the Glasgow University Students Study) have shown that high blood pressure already in adolescence or young adulthood is strongly related to risk of stroke or CHD, *independently* of blood pressure in mid life (Paffenbarger and Wing, 1969, 1971; Paffenbarger and Williams, 1967; Thorne *et al*. 1968; Miura *et al*. 2001; McCarron *et al*. 2000a). In other words, risk of CVD through high blood pressure already starts well before middle age.

Cohort studies have shown that high blood pressure already in adolescence or young adulthood is strongly related to risk of stroke or CHD, *independently* of blood pressure in mid life. In other words, risk of CVD, through high blood pressure already starts well before middle age.

Whether, however, elevated blood pressure in early life is a stronger predictor of disease than high blood pressure in mid adulthood has not yet been established, with existing evidence being sparse and conflicting. Data from the Harvard Alumni study point to high blood pressure in midlife as a stronger indicator of risk of non-fatal stroke than high blood pressure in youth. Other evidence, however, suggests an equally important effect of high blood pressure in earlier life (Navas-Nacher *et al*. 2001).

Indirect evidence for the importance of exposure to high blood pressure from early life comes, moreover, from the Bogalusa Heart Study which shows that high blood pressure, tracking from childhood to adulthood, is related to the onset of early atherosclerosis (e.g. Bao *et al*. 1995; Berenson *et al*. 1998a). More evidence on the actual strength of the association between early and prolonged high blood pressure and later CHD or stroke will emerge as study cohorts, such as in the Bogalusa study, continue to age.

1.3.2 ***Global trends in blood pressure***

a. A word of caution

A word of caution is necessary prior to outlining the trends and patterns in blood pressure. This concerns the current limitations in methodology and measurement of blood pressure which make international comparisons difficult, and limit the accuracy of blood pressure estimates within populations. The particular limitations include:

i. differences in measurements and methodology between national surveys

ii. a lack of data on blood pressure levels especially from developing countries

iii. fundamental difficulties in the accurate measurement of blood pressure and hypertension due to the acute variability of blood pressure. Experience from the Bogalusa Heart Study, for example, has shown that estimates of hypertension can yield up to 10–20% false positives. Ambulatory measures have, moreover, revealed the inadequacy of single measurements as an index of 'typical blood pressure' (Berenson, *personal communication*).

iv. indications that 'normal' levels of blood pressure may differ between populations or age groups. In India, for example, levels appear to be lower than in other countries, and levels among children are lower than among adults. Correct identification of hypertension in populations thus requires the establishment of appropriate population norms of blood pressure.

These limitations not withstanding, several broad patterns and trends in blood pressure are identified.

b. Secular trends in blood pressure

Developed world

Evidence from multi-country studies such as WHO MONICA show that in most developed countries, mean population blood pressure levels have decreased over the past decades (e.g. Dobson *et al*. 1998; Kuulasmaa *et al*. 2000). Many surveys from individual countries further support this general picture. In Denmark, for example, blood pressure levels shifted towards lower values between 1964 and 1991 (Sjol *et al*. 1998). In Finland, similar shifts at least in systolic blood pressure were observed between 1982 and 1997 (Kastarinen *et al*. 2000), and in the U.K. between 1984 and 1993 (Bartley *et al*. 2000).

However, not all countries show this general trend. In Japan, for example, more complex trends have been observed. Whereas systolic and diastolic blood pressure levels had decreased until the early 1990s, they have plateaued during the last ten years, showing cyclical oscillations (Hasegawa and Oshima, 2001).

Developing world

In contrast to the largely declining trends in blood pressure in the developed world, the little available evidence suggests that blood pressure levels in developing countries are rising. In China, for example, WHO MONICA and other studies have found significant increases in both diastolic and systolic blood pressure over the past decades (Dobson *et al*. 1998; Gao *et al*. 1999), one study documenting such adverse trends particularly in the younger population (aged 15–34) (Yu *et al*. 1999).

In contrast to the largely declining trends in blood pressure in the developed world, the little available evidence suggests that blood pressure levels in developing countries are rising.

In general, the prevalence of hypertension seems to rise with GNP, i.e. the higher the level of economic 'development' the higher the prevalence of hypertension (Fuentes *et al*. 2000).

Hypertension—though recognized as a public health problem since the 1970s in some nations—is now, clearly, a problem in most developing countries (Fuentes *et al*. 2000). High blood pressure is particularly found to be a problem in Sub-Saharan Africa, consonant with the higher rates of stroke and susceptibility to hypertension observed among black populations (Pickering, 2001).

1.3.3 ***Social patterns of blood pressure***

Developed countries

In developed countries, the prevalence of high blood pressure and other cardiovascular risk factors has generally been found to have a social gradient, with higher prevalence among those with lower socio-economic positions (Bartley *et al*. 2000; Marmot 1989; Luepker *et al*. 1993; Lynch *et al*. 1996; Myllykangas *et al*. 1995, Manhem *et al*. 2000; Colhoun *et al*. 1998).

Apart from low adult socio-economic position, low childhood socio-economic position, too, has often but not always been found to be associated with higher blood pressure in later life (Blane *et al*. 1996; Lynch *et al*. 1997; Brunner *et al*. 1999). Evidence suggests, however, that its effect is weaker than that of adult socio-economic position (Blane *et al*. 1996).

Despite applying overall, it is important to bear in mind that the generally observed social gradient pattern may not apply to all ethnic or population groups. For example, among blacks in the US no significant differences in blood pressure levels were found between socio-economic groups (Resnicow *et al*. 2001).

Developing countries

In developing countries, blood pressure patterns are usually assumed and typically found to show marked rural/urban differences with levels considerably higher in urban populations, and among higher socio-economic groups (e.g. Colhoun *et al*. 1998)

In India, for example, the CRISIS study (Coronary Risk of Insulin Sensitivity in Indian Subjects) found hypertension prevalence to be highest among urban middle class population (12.4%), much lower prevalence in urban slum dwellers (3.8%), and the lowest prevalence in rural populations (2.4%) (Lubree *et al*. 2001). Similar urban-rural and socioeconomic group differences in blood pressure and hypertension levels have been found in China (Gao *et al*. 1999; Yu *et al*. 2000).

Low childhood socio-economic position too, has often but not always been found to be associated with higher blood pressure in later life.

Evidence from Nigeria, Tanzania and the Gambia, similarly shows significantly higher levels of hypertension in urban compared to rural areas (Kaufman *et al*. 1999; van der Sande *et al*. 2000; Ministry of Health Tanzania, 1997). In urban Nigeria and in Tanzania, moreover, the highest rates of hypertension were found in the higher socioeconomic groups (Olatunbosun *et al*. 2000; Ministry of Health Tanzania, 1997).

Although this general pattern prevails in many cases, it is again important to bear in mind that it may not always hold. In urban China, for example, blood pressure was found to be highest among those with lowest socio-economic positions (Yu *et al*. 2000). In South Africa, similarly, blood pressure levels were not found to simply rise with degree of urbanization. Rather, the highest levels were found among newcomers to cities living in informal settlements. The lowest levels were, in fact, found in the most urbanized group (van Rooyen *et al*. 2000).

1.3.4 ***Factors in childhood and adolescence and blood pressure***

a. High blood pressure origins in childhood

High blood pressure and essential hypertension can emerge in childhood.

Contrary to the long held assumption that high blood pressure emerges in mid adulthood, evidence from the developed world (e.g. the Bogalusa Heart Study) shows that it is already present in children. Some evidence also shows that blood pressure 'tracks' from childhood to predict hypertension in adulthood, though the strength of tracking to adulthood varies depending on age, with stronger tracking seen at older ages in childhood or adolescence (see Whincup and Cook, 1997). Virtually no evidence exists yet on the emergence and development of high blood pressure in children in developing countries.

As the developed world evidence further shows, high blood pressure in childhood (in combination with other risk factors), moreover, causes target organ and anatomical changes associated with cardiovascular risk, such as reduction in artery elasticity, increased left ventricular size and mass, haemodynamic increase in cardiac output, and peripheral resistance. These effects are seen already at levels lower than the conventional 140/90 cut-off point used to define adult hypertension (Berenson *et al*. 1991, 1998a; Bao *et al*. 1995).

High blood pressure in children is strongly associated to obesity, in particular central obesity. It moreover clusters and tracks with an adverse serum lipid profile (especially LDL-c) and glucose intolerance (Berenson *et al*. 1991, Tershakovec *et al*. 1998). Such clustering and tracking has also been shown in non-western industrialized populations, for example in Japan (Tan *et al*. 2000).

Within this general picture, however, some racial differences have also been observed in some studies. These include the higher blood pressure rates and rises found in black children, especially boys; and the stronger relationship

of blood pressure to obesity in white children (Berenson *et al*. 1991). In a recent cross-sectional study of more than 47,000 children and adolescents in the US, few substantive differences in blood pressure were observed between African-Americans and Whites. The racial differences in blood pressure that did emerge were often explained by differences in BMI. Interestingly, at lower levels of BMI black children and adolescents tended to have higher blood pressure and more hypertension, but at higher levels of BMI, the reverse was true (Rosner *et al*. 2000).

The presence and tracking of blood pressure in children and adolescents occur against a background of unhealthy lifestyles. These include excessive intake of total and saturated fat, cholesterol and salt, inadequate intake of potassium, and reduced physical activity, often accompanied by high amounts of television viewing. In older children habitual alcohol and tobacco use moreover contributes to blood pressure (Berenson *et al*. 1991; Okasha *et al*. 2000).

Just as diet in childhood is important, there are indications that breastfeeding in infancy too has an effect on later blood pressure levels.

Breastfeeding and blood pressure

Just as diet in childhood is important, there are indications that breastfeeding in infancy too has an effect on later blood pressure levels.

There is specific evidence from recent prospective studies and trials, for example in the UK, showing that among term and pre-term infants, breastfeeding was associated with significantly lower blood pressure levels in childhood (Wilson *et al*. 1998; Singhal *et al*. 2001).

Other studies on older cohorts, however, for example in the UK (Fall *et al*. 1998) or the Dutch Famine Study (Ravelli *et al*. 2000) have shown no such association, possibly reflecting cohort or population variations relating to modes or duration of breast feeding.

The mechanisms that may underlie a beneficial effect of breastfeeding on blood pressure are not yet understood. Virtually no evidence exists, moreover, on the effects of breast feeding on blood pressure in developing country populations.

1.3.5 ***Fetal factors and blood pressure***

a. IUGR and high blood pressure

In addition to its determinants in childhood, there is consistent evidence that high blood pressure, in particular high systolic blood pressure in adulthood is associated with retarded fetal growth (as measured by low birth weight) (Huxley *et al*. 2000; Eriksson *et al*. 2000a; Leon *et al*. 2000). It is not yet clear, however, whether this association mediates the link between IUGR and CVD.

Most of the evidence showing this association comes from studies in developed countries, though some also comes from the developing world, for example from China (Mi *et al*. 2000) or South Africa (Levitt *et al*. 2000).

Blood pressure in childhood has equally been found to be associated to low birth weight. The evidence comes from studies on child cohorts in both the developed and developing world, for example in Sweden, Chile, Guatemala, China (Law *et al*. 2001); the UK (Whincup *et al*. 1999); Zimbabwe (Woelk *et al*. 1999); South Africa (Levitt *et al*. 1999); the Democratic Republic of Congo (Longo-Mbenza *et al*., 1999); Jamaica (Walker *et al*. 2001); and India (Bavdekar *et al*. 1999).

In contrast to the bulk of evidence, some developing country studies, among children in Jamaica (Gaskin *et al*. 2000) and Nigeria (Law *et al*. 2001), and among adults in India (Kumaran *et al*. 2000) and Hong Kong (Cheung *et al*. 2000) do not find an association between small size at birth and higher blood pressure. The latter, rather, find greater length at birth to be associated to higher blood pressure.

Similarly, findings from the two natural 'famine' studies—the Leningrad Siege Study, and the Dutch Famine Study, show no association between exposure to famine at any stage in gestation and higher blood pressure in adulthood (though in the Dutch cohort, exposure late in gestation was associated with lower birth weight) (Stanner *et al*. 1997; Roseboom *et al*. 2001).

These divergent findings clearly highlight two important points:

- First, they indicate the possible existence of population and cohort differences in the relationship of fetal growth to blood pressure. It has been suggested that this relationship may be specifically different in black populations.
- Second, they indicate that the association with higher blood pressure may depend on

the type of growth retardation or impairment experienced *in utero*, with birth weight too crude an index to distinguish between such different factors

b. Issues relating to the link between IUGR and high blood pressure

A mediating effect of obesity or enhanced weight gain in childhood/adolescence?

Just as evidence has indicated a possible interacting effect of obesity or gained weight in enhancing the risk of CHD or diabetes associated with impaired fetal growth, several indications also point to such a possible effect for blood pressure:

Just as evidence has indicated a possible interacting effect of obesity or gained weight in enhancing the risk of CHD or diabetes associated with impaired fetal growth, several indications also point to such a possible effect for blood pressure.

i. A mediating effect of obesity (high BMI)

Some evidence on the association between low birth weight and adult blood pressure, for example from Sweden, demonstrates an apparent mediating effect of obesity (high BMI). It shows that the effect of low birth weight on higher blood pressure increased with rising adult BMI, being significantly stronger in the highest than in the lower tertile of BMI (Leon *et al*. 1996). Conversely, the association of current BMI to blood pressure was enhanced in those with low birth weight.

Such an effect of fatness has been replicated in other studies though not in all. In the study among 11–12 year old children in Jamaica, for example, blood pressure levels were found to be highest in those with retarded fetal growth and greater weight gain between the ages of 7 and 11 (Walker *et al*. 2001). Similarly, in the child cohort study in India (Bavdekar *et al*. 1999), blood pressure was highest in those with low birth weight and highest fat mass at age 8, though the interaction term was not statistically significant. These children also had the highest central adiposity.

Further studies on the body composition of low birth weight Indian babies have revealed that these, e.g. in contrast to newborns in the UK, these have a distinct phenotype characterized by poor muscle but high fat preservation. It is this 'thin-fat' phenotype, which persists through the post-natal period and is associated with increased central adiposity in childhood, and the higher risk of raised blood pressure (Fall *et al*. 1999; Yajnik, 2000, 2001).

ii. Adjustment for current size (BMI)

In most studies, the association between low birth weight and high blood pressure has been found to be particularly strong if adjusted for current size (BMI), suggesting the importance of weight gain after birth on the association (Lucas *et al*. 1999).

As discussed in the previous section, the apparent effect of post-natally gained weight is as yet poorly understood, and several possible interpretations exist. What is clear, however, is that it signals the importance of the postnatal context of nutrition and growth in shaping the association between impaired fetal growth and higher blood pressure later in life.

A mediating effect of enhanced growth in height in childhood/adolescence?

In addition to the possible mediating effect of obesity, there is evidence to suggest an interaction between small size at birth and accelerated growth in height in raising risk of disease.

In Sweden, for example, low birth weight followed by enhanced growth in height to become tall in adulthood was found to be associated with highest blood pressures (Leon *et al*. 1996). In Finland, similarly, shortness and thinness at birth combined with accelerated growth in height (as well as weight) to reach average levels was associated with increased risk of hypertension (Eriksson *et al*. 2000b).

The nature and factors underlying this effect of height growth are not yet fully understood. However, again, they point to the importance of the post-natal (nutritional) environment in shaping the association between retarded fetal growth and blood pressure.

Underlying mechanisms—genetic? environmental?

The mechanism underpinning the observed association between retarded fetal growth (low birth size) and higher blood pressure remains poorly understood. The most important question concerns the relative role played by genetic traits as opposed to environmental exposures *in utero*.

As has been proposed for insulin resistance (IR), the association may reflect the action of genetic feature that simultaneously affects birth weight (fetal growth) as well as physiological components predisposing to high blood pressure (Hattersley *et al*. 1998; Hattersley and Tooke, 1999). Alternatively, the association may reflect the effect of exposures *in utero*, for example as a result of maternal nutrition or stress, which lead to fetal adaptations which in turn lead to higher blood pressure later on.

Although several twin studies have explored the relationship between impaired fetal growth and blood pressure, they have failed to produce a particularly clear picture, perhaps partly as a result of methodological problems.

Their findings as they stand have not produced particularly convincing evidence for an environmental effect (Dwyer *et al*. 1999; Poulter *et al*. 1999; Ijzerman *et al*. 2000; Baird *et al*. 2001; Rassmussen (unpublished).

Little support for the role specifically of maternal undernutrition in causing high blood pressure comes, moreover, from the famine studies. (Roseboom *et al*. 2001 ; Stanner *et al*. 1997)

Inadequacy of low birth weight as an index of IUGR

The Dutch famine study's finding of an association between high blood pressure and exposure to famine in early gestation (an exposure that was *not* associated with low birth weight) clearly indicates the limitation of low birth weight in capturing the range of potentially important exposures *in utero*.

Some recent evidence from the UK suggests a possible intergenerational effect on risk of blood pressure associated with maternal fetal growth

1.3.6 *Intergenerational factors and blood pressure*

a. Maternal birth weight

Some recent evidence from the UK suggests a possible intergenerational effect on risk of blood pressure associated with maternal fetal growth. The data shows that blood pressure levels in adult offspring were inversely related to maternal fetal growth, i.e. low maternal birth weight was associated with higher blood pressure levels in the offspring, independent of the relation between offspring's own birth weight and blood pressure (Barker *et al*. 2000b). The mechanisms underlying such an intergenerational association are as yet poorly understood.

1.4 Life course perspectives on dyslipidaemias and impaired glucose tolerance (IGT)

1.4.1 *Dyslipidaemias and IGT over the life course as risk factors for CVD and diabetes*

Dyslipidaemias and impaired glucose tolerance (IGT) are commonly considered together as elements of the metabolic syndrome or 'syndrome X'. Syndrome 'X'—the clustering in the population of physiological disturbances associated with insulin resistance, i.e. hyperinsulinaemia, IGT, hypertension, elevated plasma triglyceride and low high density lipoprotein cholesterol (HDL-c)—is considered a distinct condition that is related to diabetes and atherosclerotic cardiovascular disease (Reaven, 1988; De Fronzo *et al*. 1991).

The clustering of these risk variables already occurs in childhood and adolescence and is associated with atherosclerosis in young adulthood, and thus risk of later cardiovascular disease (Bao *et al*. 1994; Berenson *et al*. 1998a). In some though not all cases, moreover, such clustering of risk factors in childhood is shown to lead on to diabetes, suggesting that there may be several different subtypes of 'syndrome X' (Berenson, *personal communication*).

Raised serum cholesterol levels on their own in middle age have also been established as a clear risk factor for cardiovascular disease (e.g. Davey Smith *et al*. 1992; Neaton and Wentworth 1992).

Raised serum cholesterol in early life, too, is shown to be already associated with an increased risk of disease later on. The Johns Hopkins Precursor Study, for example, has shown that among white males serum cholesterol levels in adolescence or young adulthood were strongly related to subsequent risk of CVD morbidity and mortality. An increased risk of CVD, especially for CHD, was found even for higher cholesterol levels in the 'normal' range, indicating that serum cholesterol levels in healthy young adults are a strong predictor of disease in mid-life (Klag *et al*. 1993).

1.4.2 *Global trends in dyslipidaemias and IGT*

a. Secular trends in serum lipid levels

Developed countries

Evidence from multi-country (e.g. WHO MONICA) and national surveys suggest favourable trends in serum lipid levels in most developed countries over the past decades. Whilst WHO MONICA found little overall change in population cholesterol levels in most of the 20 developed world countries studied during the 1980s (Dobson *et al*. 1998), national surveys, for example in the US or Finland have shown consistent reductions as well as reductions in the incidence of hypercholesterolaemia (e.g. Szklo *et al*. 2000; Johnson *et al*. 1993; Kastarinen *et al*. 2000).

In addition, adverse lipid levels have sometimes but not always been shown to be linked to poor childhood socio-economic position.

Developing countries

Very little evidence is available on trends in lipid levels in developing countries, in particular in Africa, Latin America and South Asia. The little evidence that is available suggests an unfavourable trend, contrasting with the situation in the developed world.

Secular increases in dyslipidaemia have been indicated for several developing country populations. In China, for example, Sino-MONICA has shown rises in cholesterol levels in mid aged adults between 1984/86 and 1988/89 (Yao *et al*. 1993; Dobson *et al*. 1998). Similar rises have been observed in other Chinese populations with one study finding them in particular among younger age groups (e.g. Gao *et al*. 1999).

b. Secular trends in impaired glucose tolerance

Whilst comprehensive data on global trends and patterns in IGT is sparse, some data and projections on diabetes prevalence as measured by venous post-load plasma glucose are available. (King *et al*. 1998) These data show that prevalence of diabetes is currently higher in developed and than in developing countries, and will remain so by 2025. However, the proportional increase will be greater in the developing world, greatest in China and India.

1.4.3 *Social patterns in dyslipidaemias and impaired glucose tolerance*

a. Social patterns in serum lipid levels

Developed countries

Adverse lipid levels, as most other cardiovascular risk factors are, currently, generally shown to have a social gradient, with higher prevalence among those with lower socio-economic position. (Bartley *et al*. 2000; Brunner *et al*. 1999; Marmot 1989; Luepker *et al*. 1993; Lynch *et al*. 1996; Myllykangas *et al*. 1995; Perova *et al*. 2001). An opposite gradient, interestingly, was found a few decades ago in the UK, highlighting the fact that socio-economic patterns of disease risk factors may be cohort specific. The Whitehall I study in the late 1960s, for example, found higher adverse lipid levels among higher ranking UK civil servants (Smith *et al*. 1992), indicating that a social gradient reversal in dyslipidaemia levels has occurred over the past three decades. A similar reversal is predicted for non-industrialised countries as they progressively develop and urbanize.

In addition, adverse lipid levels have sometimes but not always been shown to be linked to poor childhood socio-economic position. In the West of Scotland Collaborative Study among a cohort of employed men, for example, serum cholesterol was related to poor adult and poor childhood SEP, though the effect of the latter was weaker (Blane *et al*. 1996). The Whitehall II study, however, only found childhood SEP to be linked to adverse HDL-c levels in women (Brunner *et al*. 1999). A recent study of men in Eastern Finland similarly found a detrimental impact of low childhood SEP. Compared to men who had been born into advantaged childhood circumstances and had gone on to high income positions later in life, men who had come from poorer backgrounds but achieved the same level of adult income had significantly higher LDL-c levels. However, no socio-economic differences in HDL-c were observed (Lynch, 2000).

Despite the broad overall pattern of more adverse lipid profiles among the lower social strata, it is clear that this social gradient may not hold in all developed countries. In Russia and Poland, for example, an opposite gradient was found, with adverse lipid levels increasing directly with years of education (Perova *et al*. 2001).

Furthermore, the expected social gradient may not apply in specific ethnic groups. Among blacks in the US, for example, no significant differences in cholesterol levels were found between socio-economic groups (Resnicow *et al* 2001).

Developing countries

In the developing world, the prevalence of dyslipidaemias is generally assumed to follow an opposite pattern to that in the developed world, i.e. levels are assumed to increase with socio-economic position and to be highest in the affluent, urban population.

The little evidence available from developing countries suggests that in most cases levels follow this general pattern. In China, for example, the prevalence of adverse lipid profiles among men was found to increase directly with years of education (Perova *et al*. 2001). Dyslipidaemia prevalence in Taiwan has similarly been shown to be higher in higher socio-economic groups (Lee *et al*. 2000).

In Jamaica, serum cholesterol levels among children and adolescents were found to show a similar social gradient with higher levels in those of higher socio-economic back ground (Forrester *et al*. 1996).

Evidence suggests, however, that the prevalence of dyslipidaemias does not always follow the expected pattern or gradients.

In India, as expected, cholesterol and triglyceride levels have been found to be highest among middle class urban populations, followed by urban slum dwellers, and lowest in rural samples (Lubree *et al*. 2001). Similar rural-urban distributions in hyperlipidaemia were found in the Gambia (van der Sande *et al*. 2000).

Evidence suggests, however, that the prevalence of dyslipidaemias does not always follow the expected pattern or gradients. In Tanzania, for example, cholesterol levels were found to be significantly higher in affluent rural areas than in urban areas (Ministry of Health Tanzania, 1997). Blood cholesterol concentrations in South Africa, similarly, were found not to rise with degree of urbanization (Steyn *et al*. 1997).

b. Social patterns in impaired glucose tolerance

Developed countries

In developed countries, impaired glucose tolerance, just as dyslipidaemias, is generally found to be higher among the poor socio-economic strata. However, it has not so far been found to be associated to poor childhood socioeconomic position (e.g. Brunner *et al*. 1999; Wannamethee *et al*. 1996).

Developing countries

Very little data exists on the social patterns of impaired glucose tolerance or diabetes in developing countries. However, diabetes or IGT, just as the other risk factors, are again assumed to be higher among the more affluent, urban, 'westernised' population.

The little information available suggests that in many cases this pattern holds.

In India (Lubree *et al*. 2001) and the Gambia (van der Sande, 2000), for example, diabetes prevalence has been shown to be considerably higher in urban than in rural areas and, in the case of India, has also been found to be significantly higher among the more affluent population.

Despite the rural urban differentials, however, it is important to note that in many cases diabetes or IGT prevalence in the rural population is already substantial. In India, for example, rural prevalence was found to stand at almost 10%.

In China, similarly, rural levels are found to be almost as high as those in the urban population (van der Sande, 2000).

1.4.4 ***Factors in childhood/adolescence and dyslipidaemias and IGT***

a. Origins of IGT and dyslipidaemias in childhood

Developed country evidence, for example from the Bogalusa Heart Study, the Young Finns Study, and Japan, shows that impaired glucose tolerance and an adverse lipid profile already emerge in childhood or adolescence, where they typically appear clustered together with higher blood pressure and relate strongly to obesity, in particular central obesity (e.g. Berenson *et al*. 1991; Raitakari *et al*. 1994 a,b; Twisk *et al*. 1999; Tan *et al*. 2000). Virtually no evidence exists yet on the emergence and development of these factors in children in the developing world.

Evidence moreover shows that obesity in childhood is the driving force behind the emergence of both IGT and dyslipidaemias, and their

tracking through adolescence into early adulthood (e.g. Berenson *et al*. 1991).

Within this broad pattern, race and gender differences have been observed in the emergence and development of obesity. These include the development of a markedly more adverse profile of triglycerides and HDL-c in white boys, and the weaker relationship of obesity to dyslipidaemia in black girls (Berenson *et al*. 1991).

As is the case with blood pressure, IGT and dyslipidaemia in children and adolescents is accompanied by unhealthy lifestyles, including the excessive intake of total and saturated fat, cholesterol and salt, inadequate intake of potassium or fibre, as well as lack of exercise, often due to television viewing. In older children habitual alcohol and tobacco use moreover contributes to blood pressure (Berenson *et al*. 1991; Raitakari *et al*. 1994c; 1997; Boulton, *et al*. 1995; Ludwig *et al*. 1999).

Current evidence on the relationship between fetal growth and serum lipid levels is somewhat conflicting and difficult to interpret.

The importance of a low saturated fat diet in lowering cholesterol levels in children has recently been demonstrated in a recent randomized controlled trial in Finland (Simell *et al*. 1999).

b. Breastfeeding and dyslipidaemias and IGT

In contrast to the relatively solid evidence for a beneficial effect of breastfeeding on blood pressure, evidence on its effects on dyslipidaemias and IGT is conflicting (Berenson *et al*. 1991).

Whilst data from the Dutch Famine Study showed exclusive breastfeeding in the first few weeks to be associated to a lower risk of IGT and a more favourable lipid profile (Ravelli *et al*. 2000), studies on younger cohorts, for example in the Bogalusa Heart Study, or a recent study in the UK (Leeson *et al*. 2001) as well as on a historical cohort (Fall *et al*. 1995), find no such beneficial effect of breastfeeding on dyslipidaemias (Leeson *et al*. 2001).

Virtually no evidence exists on the long term effects of breastfeeding on lipid levels and IGT in developing country populations.

1.4.5 ***Fetal factors, dyslipidaemia and IGT***

In addition to its determinants in childhood, evidence in western populations has shown a strong association between reduced fetal growth and increased risk of metabolic syndrome (measured as an aggregate of all components taken as a single binary trait) in middle life (Barker *et al*. 1993b).

However, the association of fetal growth to IGT or those dyslipidaemias most strongly associated to CVD risk (i.e. high triglyceride and low HDL-c levels) is less clear cut.

a. Fetal factors and dyslipidaemias

Current evidence on the relationship between fetal growth and serum lipid levels is somewhat conflicting and difficult to interpret.

In developed countries, several studies have found relationships between small size at birth and adverse serum total cholesterol (TC) or LDL-c levels (Barker *et al*. 1993b; Tenhola *et al*. 2000). Some have, moreover, found associations between small size at birth and triglyceride levels in youth (Donker *et al*. 1997; Morley *et al*. 2000). Others, however, have found no association between reduced fetal growth (small size at birth) and adverse triglyceride (TG) or HDL-c levels (Lithell *et al*. 1996; Phillips *et al*. 1995; Valdez *et al*. 1994).

Data from the Dutch Famine Study similarly fails to show a significant association between exposure to famine *in utero* and adverse HDL or TG levels. However it does show a significant association between exposure to famine in early pregnancy (not related to lower size at birth) and a more adverse lipid profile (a higher LDL:HDL ratio) (Roseboom *et al*. 2000b).

The finding of the Dutch study conflicts with that of the Russian Famine Study which found no effect of exposure to famine *in utero* on lipid levels (Stanner *et al*. 1997).

In contrast to the developed world, evidence from developing countries so far has consistently shown an association between small size at birth and adverse lipid levels. In China, for example, an association has been shown between low birth weight and higher triglyceride levels in adults (Mi *et al*. 2000).

In Jamaica, among 6–16 year olds, a relationship was found between length at birth and total cholesterol levels (Forrester *et al*. 1996). Similarly, the recent child cohort study in India has found a link between low birth weight and adverse total serum cholesterol and LDL-c levels in 8 year old children (Bavdekar *et al*. 1999).

b. Fetal factors and impaired glucose tolerance

Developed countries

In contrast to the limited evidence regarding a link between reduced fetal growth and lipid levels, considerably clear evidence shows an association between IUGR and IGT—at least in western populations that are at comparatively low risk of diabetes.

A consistent association between small size at birth and IGT in adulthood has been found in historical cohort studies. Typically this relationship has been found more strongly with ponderal index ('thinness') at birth than with birth weight (Hales, *et al*. 1991; Phipps *et al*. 1993). An association between low ponderal index and IGT in children has been shown, for example, in the UK (Law *et al*. 1995).

Further evidence for an association between IUGR and IGT comes from the Dutch Famine Study. This has shown an increased risk of IGT in those adults who were exposed to famine in late gestation. The highest risk was found in those who had become obese as adults (Ravelli *et al*. 1998).

The Dutch finding again conflicts with that of the Russian Famine Study which found no effect of exposure to famine *in utero* on risk of impaired glucose tolerance (Stanner *et al*. 1997).

Developing countries

Much of the sparse evidence from developing countries also indicates an association between retarded fetal growth and impaired glucose tolerance.

In China, for example, an association between low birth weight and IGT was found among a cohort of adults (Mi *et al*. 2000).

Much of the sparse evidence from developing countries also indicates an association between retarded fetal growth and impaired glucose tolerance.

Child cohort studies in developing countries, for example in India and South Africa, have shown a similar association between IGT and small size at birth, with the link being strongest in those who had become fat or tall in childhood (Yajnik *et al*. 1995; Bavdekar *et al*. 1999; Crowther *et al*. 1998). In Jamaica an association to IGT was found only with short length at birth among prepubertal children (Forrester *et al*. 1996).

No clear association between IUGR and IGT, however, has been found among adults in some ethnic populations, such as Indians or Pima Indians who are at high risk of diabetes.

In India, among adults (and in contrast to the relationship found among children) an association was found between IGT and *high* ponderal index (i.e. fatness) at birth (Fall *et al*. 1998). In Pima Indians, a U-shaped relationship to birth weight was found; among Mexican Americans the relationship was found to be flat (McCance *et al*. 1994; Valdez *et al*. 1994).

A possible interpretation has been that these divergent results reflect a high prevalence of maternal gestational diabetes (GDM) in these populations which, in turn, leads to macrosomia (large size at birth), hyperinsulinaemia and changed glucose metabolism in the fetus, in turn predisposing to diabetes in later life (McKeigue, 1997).

c. Issues relating to the relationship between fetal growth and IGT

The current findings regarding the association between fetal growth and IGT highlight several important issues regarding the role, nature of the relationship, and the mechanisms that underpin it.

Insulin resistance or insulin deficiency?

Evidence is as yet unclear as to whether the observed association between fetal growth and later impaired glucose tolerance in many populations is underpinned by insulin resistance or insulin sensitivity (insulin deficiency).

In the developed world, most evidence so far suggests that insulin resistance rather than insulin deficiency is involved (McKeigue, 1997; Phillips *et al*. 1994; Lithell *et al*. 1996; Ravelli *et al*. 1998), although some studies find no indication of insulin resistance (Robinson *et al*. 1992; Law *et al*. 1995).

In the developing world, too, most evidence points to the involvement of insulin resistance (Bavdekar *et al*. 1999; Valdez *et al*. 1994; Mi *et al*. 2000). However, the study among Indian adults showing an association between fatness and IGT, implicates insulin sensitivity as the underpinning process, indicating, perhaps a very different kind off association.

Population differences?

The conflicting evidence regarding the association between fetal growth and serum lipid

levels, especially for triglyceride levels suggests that there may be important population differences in the way fetal growth relates to or impacts on lipid metabolism.

Evident population differences are shown in the association between small size at birth and IGT. As mentioned, these are thought to perhaps reflect the effect of a high population prevalence of maternal gestational diabetes.

Cohort differences—importance of the post-natal environment?

The conflicting findings regarding the relationship between IUGR and IGT among children and adults in India may indicate the existence of important cohort differences in the impact that reduced fetal growth has on subsequent risk. These differences may reflect changes in the post-natal environment for the two cohorts, as a result of rapid social change in India.

A mediating effect of obesity or enhanced weight gain in childhood/adolescence

As in the case of blood pressure, there are indications that the relationship of IUGR to IGT or dyslipidaemia may be mediated by the degree of weight gained post-natally:

i. A mediating effect of high BMI

One study in the developed world has shown that the adverse effect of reduced fetal growth on risk of IGT was largest in those with highest adiposity. At the same time, the IUGR and later adiposity showed a significant interaction such that the risk of IGT was highest in those who had low birth weight but who had become obese as adults (Lithell *et al*. 1996).

A similar effect of IUGR and fatness gained on IGT risk has been shown in child cohorts in South Africa (Crowther *et al*. 1998) and India (Bavdekar *et al*. 1999). In the latter, insulin resistance and dyslipidaemia were highest in those who had low birth weight but had highest fat mass at 8 years, though the interaction between IUGR and current size was only significant for IR (Bavdekar *et al*. 1999). As in the case of blood pressure, the raised risk of IR and dyslipidaemia in these children was linked to their increased central adiposity driven by the distinct thin-fat phenotype of IUGR Indian babies (Fall *et al*. 1999; Yajnik, 2000, 2001).

As is the case for blood pressure, the mechanisms underpinning the observed association between retarded fetal growth (low birth size) and risk of impaired glucose tolerance or dyslipidaemia remain poorly understood.

ii. Adjustment for current BMI

In addition to the observed effect of obesity, the apparent role of weight gained in mediating the link between IUGR and disease risk is indicated by the fact that most studies find a significant or strong link only *after* adjustment for current weight or BMI (Yajnik *et al*. 1995; Bavdekar *et al*. 1999, Crowther *et al*. 1998).

A mediating effect of high post-natal growth in height?

Some indicative evidence of a mediating effect also of height gained post-natally, as has been suggested for blood pressure, comes from the Indian child cohort study.

This shows that highest insulin resistance levels were found in children who had low birth weight but had subsequently grown tall at 8 years. Among these children, insulin resistance was highest in those who had short parents (Bavdekar *et al*. 1999).

As in the case of blood pressure, the apparent effect of post-natally gained weight or height on the link between IUGR and risk is as yet poorly understood. However, it again signals the importance of the post-natal nutritional context in shaping the association between impaired fetal growth and higher blood pressure.

Differential effect of starvation in utero: importance of the post-natal nutritional environment

A final strand of evidence indicating the importance of the post-natal nutritional environment in bringing out the risk attached to reduced fetal growth, are the discrepant findings between the Dutch and the Russian Famine studies.

The fact that the Russian study has failed to find any effect of exposure to famine on later risk of disease, whereas the Dutch study has, may suggest that nutritional deprivation *in utero* may *only* be detrimental if it is followed by adequate or plenty nutrition after birth. This was the case in the Dutch famine which ended abruptly after 5–6 months and was followed by a period of adequate nutrition and increasing affluence. In contrast, the Leningrad siege lasted 28 months (1941–1944) with extreme undernutrition lasting from July 1941 through 1942. Thus, children exposed to undernutrition *in utero* continued to be inadequately nourished.

In this context, exposure to undernutrition *in utero* did not confer an increased risk of IGT or dyslipidaemia.

Underlying mechanisms—genetic? environmental?

As is the case for blood pressure, the mechanisms underpinning the observed association between retarded fetal growth (low birth size) and risk of impaired glucose tolerance or dyslipidaemia remain poorly understood. The most fundamental question concerns the relative role played by genetic traits as opposed to environmental exposures *in utero*.

Several strands of existing evidence suggest that risk of IGT related to fetal growth may be transmitted intergenerationally.

Some evidence and a specific hypothesis have been advanced to argue for a genetic base, related to glucokinase deficiency, of the association between retarded fetal growth and IGT (Hattersley *et al*. 1998; Hattersley and Tooke, 1999).

Results from the few twin studies conducted so far as well as from migrant studies also provide no particularly convincing evidence for an environmental effect (Baird *et al*. 2001; McKeigue, 1997; Poulsen *et al*. 1997).

In contrast, the link found between exposure to famine and IGT in the Dutch Famine Study would seem to point to a role of intrauterine exposures (Stanner *et al*. 1997).

1.4.6 ***Intergenerational factors and IGT***

Several strands of existing evidence suggest that risk of IGT related to fetal growth may be transmitted intergenerationally.

a. Maternal gestational diabetes mellitus (GDM)

Evidence from animal models suggests that exposure to maternal gestational diabetes or hyperglycaemia *in utero* results in IGT in the offspring, and that this effect is transmissible from one generation to the next (see McKeigue, 1997)

Among Pima Indians, a similar effect is observed. Findings suggest that exposure to maternal gestational diabetes is associated to a higher risk of IGT in the offspring, as well as a higher risk of developing GDM, independently of offspring's weight (Pettit and Knowler, 1998).

Evidence from other populations indicates that the risk of developing GDM is enhanced by maternal obesity (Martorell *et al*. 2001) as well as by short stature (Kousta *et al*. 2000; Anastasiou *et al*. 1998; Jang *et al*. 1998) which in turn may be linked to intergenerational processes of risk transmission.

The possible mechanisms that underpin the development of GDM and its association to fetal growth and later risk of offspring across generations are not understood. A fundamental question relates again to the relative influence of genetic traits as opposed to factors associated to the uterine environment.

1.5 **Life course perspectives on height**

1.5.1 ***Short stature as a risk factor for disease***

a. Developed countries

Adult Height

As mentioned in section 2.1, evidence from developed countries has consistently shown short adult height to be associated to a higher risk of CHD, stroke, and probably also of adult onset diabetes. In addition, short stature has been linked to a higher risk of stomach cancer, suicide, and respiratory disease (e.g.McCarron *et al*. 2000b; Marmot *et al*. 1997; Rich-Edwards *et al*. 1997; Njolstad *et al*. 1996; Davey Smith *et al*. 2000b; Wannameethee *et al*. 1998b; Jousilahti *et al*. 1998, 2000; Forsén *et al*. 2000b).

In contrast, adult height has been found to have a positive relationship with some diseases such as the sex-hormone dependent cancers (prostate, colorectal and breast cancer), possibly through processes involving growth factor levels (e.g. Gunnell *et al*. 1998b; Davey Smith *et al*. 1998).

The association off short adult stature to stroke is particularly strong for haemorrhagic stroke suggesting that the relationship of height to disease is not just disease specific but also differs with respect to subtypes of disease (McCarron *et al*. 2001a).

Little is known about the association of adult height to disease in eastern developed countries, such as Japan, though research is currently ongoing (Hasegawa, *personal communication*).

Height in childhood

In addition to its association with short adult height, CHD has also been found to be linked to shorter height in childhood, for example in two

historical cohorts from the UK and Finland (Gunnell *et al*. 1998a; Eriksson *et al*. 2001). Cancer, in contrast, was found to be positively related to childhood leg length (Gunnel *et al*. 1998b).

b. Developing countries

Adult height

Very little evidence exists on the relationship of adult stature to chronic disease in developing countries. However, emerging indications are that the relationships may be similar to those found in the West.

Very recent research in Korea, for example, has found short stature to be associated with an increased risk of haemorrhagic stroke, though not with ischaemic stroke. No association however has been found with CHD (of which levels are very low in Korea), suggesting perhaps that the association may be dependent on the presence of other factors (Davey Smith, *personal communication*).

A few other developing country studies investigating the relationship of stature to blood pressure and impaired glucose tolerance, e.g. in Brazil and Nigeria, have found some, though not compelling indications of an association with short stature (Sichieri *et al*. 2000; Olatun-bosun and Bella, 2000).

Finally, short adult height is also indicated to have an adverse effect on disease risk in the ***next generation***. In India, shorter parental height was associated with a significantly higher risk of insulin resistance in children—especially in those children who has themselves grown tall, i.e. who had a high growth velocity (Bavdekar *et al*. 1999).

In addition to its association with short adult height, CHD has also been found to be linked to shorter height in childhood.

Childhood height

Virtually nothing is known about the relationship of childhood height or leg length to chronic disease in developing countries. However, indirect evidence for an association comes from the earlier described observed relationship between childhood stunting and risk of adiposity in several developing countries. A relationship of short stature to risk of IGT and raised cholesterol levels was moreover found among children in Jamaica (Forrester *et al*. 1996).

1.5.2 *Secular trends in height*

a. Developed countries

In industrialised countries, height has generally shown clear secular increases over the past century. Generally these increases are thought to reflect improvements in nutrition and hygiene.

In most populations the increases in height seem to have slowed down or even stopped in the last decade or so. In some countries however, such as in the Netherlands or the US, indications are that height is continuing to increase, in the US specifically among middle class subjects. In Japan, height is, and has been increasing particularly strongly from 1975 onwards, mainly due to increases in leg length. (Eveleth and Tanner, 1990)

The secular increases in height in the developed world seem to be consistent with the trends in disease that have occurred over the past decades. Those diseases related to short stature—CVD, respiratory disease etc.—have shown declines, whereas those positively associated to height—i.e. breast, prostate and colorectal cancer—are increasing.

b. Developing countries

The little data that exists suggests that secular increases in height have also occurred in many developing countries mainly in Latin America and East Asia. As in industrialised countries, these increases are attributed to economic and dietary improvements. In other parts of the developing world however, particularly in Sub-Saharan Africa, height levels seem not to have increased, possibly reflecting the persisting economic and nutritional deprivation (Eveleth and Tanner, 1990; Davey Smith, personal communication).

1.5.3 *Height as a marker of early life factors*

The significance of the association between short stature and CVD or diabetes lies in the fact that short stature in childhood and adulthood is a marker of socio-economic (and psychosocial) circumstances in childhood, as well as of fetal growth (Peck and Lundberg, 1995). In other words, the association between short stature and disease illustrates the potential importance of factors acting in early life that may

affect attainment of the full genetic potential for adult height.

a. Short stature as a marker for early childhood deprivation

Most importantly short stature in childhood and adulthood, in particular short leg length, indicates socio-economic (or psychosocial) deprivation in childhood. (Peck and Lundberg, 1995). Thus, among children today, for example, slow growth and short stature is found most often in children living in long-term poverty (Miller and Korenman, 1994)

The association between short stature and disease is thus consistent with the inverse association that has been found between early socio-economic position and later disease or mortality (Kuh *et al*. 1997; Davey Smith, 1997, Dedman *et al*. 2001)

Short stature in childhood and adulthood is a marker of socio-economic (and psychosocial) circumstances in childhood, as well as of fetal growth.

A marker of nutritional deprivation and infectious load

Height or leg length, much more than trunk length is thought to be an especially sensitive indicator of childhood socioeconomic circumstances, because of the specific effect of undernutrition on long bone growth. (Gunnell *et al*. 1998c). Though it may also reflect aspects such as housing conditions, it is considered mainly as an index of early nutritional deprivation and of infectious load. Infection in early childhood, as for example measles, slows down the rate of growth in height.

If, following infection, nutrition is adequate, subsequent catch-up growth rapidly restores the child to its normal growth curve. If the available nutrition is unable to meet the high energy intake needed to sustain catch-up growth, stunting occurs. (Eveleth and Tanner, 1990) Moreover, poor nutrition in general causes a reduced growth in height. No conclusive evidence exists yet on which nutrients are of particular relevance to height growth, however it is clear that more calories alone are insufficient.

A marker for psychosocial deprivation

In addition to reflecting nutrition and infectious load, short stature is assumed to be an indicator of psychosocial deprivation in childhood. Evidence has shown fairly severe psychological stress to cause a failure to grow among some children (e.g. Peck and Lundberg, 1995; Zimet *et al*. 1997) and it is generally assumed that psychological deprivation causes a failure to grow, possibly through affecting growth hormones.

b. Fetal growth and height

In addition to being an indicator of childhood conditions, height is also a reflection of fetal growth. Short stature has consistently been shown to be related to low birth weight and height (regardless of SEP, gender, or race). Thus, most low birth weight and length babies remain short into adult life. (Martorell *et al*. 1998, 2001, Adair, 1998, Bavdekar *et al*. 1999; Sørensen *et al*. 1999).

Moreover, evidence suggests that where low birth weight babies grow up in good nutritional conditions they may catch up in height in childhood, but this may be a reflection of earlier maturation rather than overall increase in height. In girls it has been observed to lead to earlier onset of menarche (e.g. Cooper *et al*. 1996).

c. Genetic influences

Genetic factors undoubtedly influence early growth and stature. The nature and role of possible genetic determinants is not yet well understood, but evidence indicates that their relative influence (as opposed to environmental factors) depends on the general socio-economic conditions in the population. As evidence suggests, the role of genetic factors in shaping differences in height is likely to be greater, the higher and more evenly distributed the living standards are (Silventoinen *et al*. 2000).

Thus, the importance of height as an indicator of childhood living conditions is likely to vary between cohorts and populations, depending on the prevailing level of 'development'.

1.5.4 ***Possible factors mediating the association of short stature to disease***

The association between short stature and risk of disease may reflect an effect of early socio-economic conditions in childhood, of retarded fetal growth, or of short stature itself.

However, what the relative importance or role of each of these is, or what the factors are that mediate the association between height (or the early exposures it is a marker for) and later dis-

ease or, indeed, to disease risk in offspring are not yet fully understood.

The involvement of several factors or processes, however, is indicated by the available evidence.

a. Short stature as a reflection of the effects of child socioeconomic deprivation

i. Poor childhood SEP and risk behaviours

To some extent the association between short stature (as a marker for poor childhood socioeconomic position) and later disease may be mediated by the relationship between childhood deprivation and higher risk behaviour discussed in the previous section. However, it is clear that this relationship can not fully explain the association between short stature or child SEP to disease.

Like adult obesity, obesity in childhood and adolescence is already related to risk of later CHD or diabetes.

ii. Childhood infections and disease

The relationship of short stature to disease may possibly reflect the effect of exposure to infectious agents in early childhood.

Two specific bacterial pathogens, *Helicobacter pylori* and *Chlamidia pneumoniae*, which are associated with poorer conditions, have been indicated to possibly play a role in causing long term risk of CVD. *C. pneumoniae*, for example, has been shown to be present in atherosclerotic lesions, and there has been a preliminary successful antibiotic prevention trial. However, evidence so far is difficult to interpret and far from conclusive (Leon and Ben-Shlomo, 1997; Leinonen and Saikku, 2000; Danesh *et al*. 1997).

A further, possibly infectious but yet unidentified factor may explain the particularly consistent association that is seen between poor childhood SEP and haemorrhagic stroke.

iii. Nutritional stunting and risk of obesity

A possible, though probably less important way in which short stature may, to some extent, mediate the association between early nutritional deprivation and later disease, especially in developing countries, may be through the earlier discussed higher risk of (abdominal) adiposity associated to stunting, particularly severe stunting.

b. Adverse outcomes of short stature itself

i. Short stature and adverse body function

The association of short stature to disease could be an outcome simply of body function. Height correlates with lung function and coronary artery size, and thus shorter height means reduced lung function and smaller arteries. However, though there is still debate, growing indications are that lung function is not involved in the link between short height and CVD.

An important role of lung function, for example, is not easily reconcilable with the fact that the association between short stature and CHD is much stronger than that with respiratory disease. Moreover, it is leg length (not trunk length) that is shown to be particularly strongly related to heart disease. Lung function however, shows a greater correlation with trunk length (Davey Smith *et al*. 2001a).

ii. Short stature and poor social outcomes

Short stature itself, just like obesity, has been shown in developed countries to be associated with a poorer socio-economic trajectory and it may be this that links it to disease. For example, short stature is linked with downward social mobility, a higher risk of adult unemployment, and lower educational achievement, which in turn are associated with higher rates of disease (Peck, 1992; Montgomery *et al*.1996; Power and Matthews, 1997).

In contrast, larger height, together with being healthier and of higher intelligence, has been shown to be associated with upward social mobility.

In addition, short stature among men is associated with a reduced chance of getting married, which again is associated to poorer health outcomes.

In developing countries short children have been shown to have both lower intellectual functioning and work capacities (Martorell, 1995). Short stature is moreover associated with low educational attainment.

c. Short stature as a reflection of retarded fetal growth

The association of short stature to disease may be an expression of the effect of retarded fetal growth. Since short stature correlates with low birth weight (as well as ponderal index and birth

length), its link to disease could reflect the well documented and earlier discussed association between intra-uterine growth retardation and later CVD and diabetes.

However, indications are that this may not be the case. The fact that size at birth is equally strongly related to both leg and trunk length, but only leg length is closely linked to disease (Gunnel *et al*. 1999), indicates that fetal factors may not underlie the association between short stature and disease. Rather, factors affecting post-natal growth may be more important in understanding the link between short stature and disease.

d. Genetic determinants

Finally, the association between short adult height and later disease may reflect the action of genetic traits. However, virtually nothing is yet known about the extent or role of such a genetic influence. Evidence from some research among dizygotic and monozygotic twins, so far, indicates that the relationship of shorter height to later disease may not be genetically determined (e.g. Vagero and Leon, 1994). More twin studies are required to provide more solid insights.

e. Factors mediating the association of adult short stature to risk of disease in offspring

As discussed in the earlier section, the factors mediating the indicated intergenerational effect of parental short stature on the risk of insulin resistance in offspring are not yet understood at all, but are thought to possibly involve either genetic mechanisms related to the function of insulin as a growth hormone; or to reflect intrafamilial environmental factors relating to poor nutrition and acting on fetal growth and development (Bavdekar *et al*. 1999). The observed association (discussed above) between short maternal stature and increased risk of developing GDM (which in turn is linked to a higher risk of obesity and related disease risk in offspring), may speak to this.

Obesity early in life may also have long-term indirect impacts on disease, by leading to poorer socio-economic trajectories which in turn are linked to an increased risk of CVD incidence and mortality.

1.6 Life course perspectives on obesity in relation to CVD and diabetes

1.6.1 Obesity over the life course as a risk factor for CVD and diabetes

Obesity, in particular abdominal obesity in adults is one of the main risk factors for CHD, stroke, and diabetes (WHO, 2000).

The adverse health consequences of obesity in adults are influenced by the degree of overweight, the location of body fat, (with higher risk associated to abdominal fat rather than fat in thigh and hips), the magnitude of weight gain during adulthood, and a sedentary life style (Bray, 1996)

Like adult obesity, obesity in childhood and adolescence is already related to risk of later CHD or diabetes (Freedman *et al*. 1999; WHO, 2000).

Evidence from the Harvard Growth Study, for example, shows that obesity in adolescence significantly increases (2 fold) the risk of CHD death, independently of weight in adulthood. The risk associated to adolescent obesity is, moreover, found to be even stronger than that associated to obesity in adulthood (Must *et a.* 1992).

The link of obesity in childhood to diabetes is illustrated by the fact that it has been a major factor underpinning the recent 10-fold rise in the incidence of diabetes among adolescents (Pinhas-Hamiel *et al*. 1996).

Social consequences of obesity

Obesity early in life may also have long-term indirect impacts on disease, by leading to poorer socio-economic trajectories which in turn are linked to an increased risk of CVD incidence and mortality. Data from the Bogalusa Heart Study has shown overweight in adolescence to be associated with lower levels of socioeconomic attainment seven years later, especially in women. The US National Longitudinal Survey of Youth found obesity in late adolescence to be related to lower rates of marriage, fewer years of education completed, lower family incomes and higher rates of poverty (Gortmaker *et al*. 1993).

Which carries a greater risk? Childhood or adult obesity?

Evidence on whether childhood or adult obesity is more important in developing disease is inconclusive and the relative importance of early vs. later obesity may be disease specific.

The Harvard Growth Study findings, for example, indicate that for CHD, earlier obesity may be more important. In contrast, evidence from Finland regarding the risk of insulin resistance syndrome, suggests that childhood obesity, on its own, has little effect. If persisting into adulthood, however, (thus causing longer periods of insulin resistance) it has an important enhancing effect on the risk associated with the adult obesity (Vanhala *et al*. 1998).

1.6.2 *Global trends in obesity*

a. A note of caution

At the outset, before describing the global trends of obesity, a word of caution is necessary. This relates to several methodological constraints that seriously hamper the estimation of comparable trends and patterns on obesity.

These constraints include the dearth of nationally representative, especially secular data, particularly from developing countries; a lack of standardisation in age groups, periods of data collection, and measurements of obesity (WHO, 2000).

An additional limitation exists because BMI, the most commonly used index of obesity, does not adequately measure adiposity and related disease risk (see WHO, 2000; Guo and Chumlea, 1999). BMI does not distinguish between weight associated with muscle and with body fat; thus a given BMI may not correspond to the same degree of fatness across populations. For example blacks tend to have a lower fat percentage than whites. In contrast, people of South Asian descent have a higher percentage especially of abdominal fat for a given level of BMI (WHO, 2000, McKeigue, 1996).

The estimation of obesity in childhood or adolescence is limited by an even greater lack of agreement regarding its classification and measurement, as well as by serious technical and biological problems in the reference populations and charts used so far.

Despite these limitations, several trends and patterns are clearly emerging.

A global epidemic of obesity is currently underway. Obesity in both children and adults is increasing at an alarming rate in many developed and developing countries.

b. A global 'epidemic' in obesity

A global epidemic of obesity is currently underway. Obesity in both children and adults is increasing at an alarming rate in many developed and developing countries (WHO, 2000, Mokdad *et al*. 2001; Dietz, 2001). In the US for example, adult obesity has increased from 12.0% in 1991 to 18.9% in 1999—a 57% increase in just 8 years (Mokdad *et al*. 2001). Among pre-school children in the UK, obesity has increased by 70% in just 9 years from 1989 to 1998 (Bundred *et al*. 2001). Data from the US also show important race/ethnic and gender differences in obesity trends among children and adolescents, with the temporal increases being especially large among young black girls (NCHS, 2000).

In the developing world, obesity, especially in women, but also in children, is already becoming a serious problem in many of the more affluent countries in Latin America and the Caribbean, the Middle East and North Africa, though levels are still relatively low in Sub-Saharan Africa and Asia (see WHO, 2000; Martorell *et al*. 2000a, b; de Onis and Bloessner, 2000). It is assumed that as GNP and 'westernisation' increase, with its attendant changes in diet and physical activity, obesity will become a problem also in the poorer countries (Martorell *et al*. 2000a).

The epidemic increase in obesity threatens even higher than expected future increases in CVD and diabetes in the developing world. In the developed world, the rise in obesity threatens to undermine some of the progress that has been made in reducing the rates of other risk factors. Indeed, the growth in obesity prevalence is seen as a main factor underpinning the recent slow-down in the reduction of CVD rates in developed countries.

The reason for the recent drastic rise in obesity is unlikely to be related to changes in the gene pool. Rather, it is most likely a result of environmental and cultural changes (in the developing world termed 'nutrition transition') related to physical inactivity and shifts towards a diet high in saturated fats, sugar and refined foods which, possibly in interaction with genetic susceptibilities, promote the development of obesity (see Dietz, 2001a; Popkin 1994, 2001; Martorell *et al*. 2000a).

1.6.3 ***Social patterns of obesity***

In both developed and developing populations, the prevalence of obesity and overweight shows some clear socio-economic and ethnic patterns.

Developed countries

In industrialised countries obesity is generally shown to be associated with lower socio-economic position (e.g. Sobal and Stunkard, 1989; Braddon *et al*., 1986; Power *et al*. 1988; Kimm *et al*. 1996; Greenlund *et al*. 1996; Croft *et al*. 1992).

However, such a straightforward relationship clearly does not hold in all cases. Among many ethnic groups, for example African, Mexican or Cuban Americans, no such social gradient has been demonstrated (e.g. Crawford *et al*. 2001; Stettler *et al*. 2000, Maurer *et al*. 1985).

Racial differences moreover exist in the prevalence rates of obesity. In the US, for example, child, adolescent, and adult obesity is higher in African Americans than it is in white or Hispanic Americans (e.g. Troiano *et al*. 1995; Flegal *et al*. 1998; Srinivasan *et al*. 2001; Kimm *et al*. 2001; Crawford *et al*. 2001).

Developing countries

The relationship between obesity and SEP especially in poorer developing countries is generally assumed, and in most cases found to be opposite to that in the developed world: i.e. obesity is higher in the more affluent, urban populations (Sobel and Stunkard, 1989, Martorell *et al*. 2000a, 2000b, Bavdekar *et al*. 1999). In richer developing countries, obesity prevalence is higher and more equally distributed in the population. These patterns are assumed to reflect the influence of increasing urbanisation, westernisation and rising national income on life styles.

In both developed and developing populations, the prevalence of obesity and overweight shows some clear socio-economic and ethnic patterns.

Urbanisation and national economic development, however, do not always have the same uniform impact on social patterns of obesity. Rather, the patterns vary depending on the particular macro-structural context—the prevailing economic, market, social and cultural forces that determine, amongst others, cost and meaning of unhealthy diet and exercise.

For example, in many Latin American developing countries, against a context of increasing income inequality, obesity is emerging as a serious disease specifically among the poor. Poor people, in these countries, simply cannot afford a 'healthy' diet, but must choose low cost, high-fat, high-sugar, high-calorie foods. At the same time they have less access to the necessary resources, health promotion messages and scope for systematic physical exercise (Pena and Bacallao, 2000). At the same time, obesity among higher socioeconomic classes, for example among women in Brazil, has shown some reductions, possibly as a result of intensive media driven health promotion programmes (Monteiro *et al*. 2000).

1.6.4 ***Factors in childhood and adolescence and obesity***

a. Emergence of obesity in childhood and tracking through to adulthood

Evidence from the developed world clearly shows that obesity, and the related disease risk, already emerge in childhood. Comprehensive developing country evidence on the development of obesity in childhood is virtually non-existent.

In developed countries, as the Bogalusa Heart study has demonstrated, obesity, especially abdominal obesity in childhood drives the development of high blood pressure, dyslipidaemia and impaired glucose tolerance in children, adolescents and through to adulthood (Freedman *et al*. 1999, 2001; Mahoney *et al*. 1991). The higher the rate of increase in adiposity during childhood and adolescence, the more adverse the changes in cardiovascular risk factor profiles (Srinivasan *et al*. 2001).

Within this broad picture, however, some race and gender differences exist. The association of obesity to development of other risk factors is stronger in white than in black children, and is strongest in white boys. The weakest association is seen in black girls (Berenson *et al*. 1991).

The presence of obesity in children is linked to their dietary and physical activity patterns, with the recent rise in obesity being underpinned by growing total and saturated fat, salt and sugar intake, excess calorie intake and lack of physical activity (Berenson *et al*. 1991, 1998b; Muller *et al*. 1999; Burke *et al*. 2001). In the US, for example, childhood obesity has been shown to be specifically related to decreased physical

activity due to television viewing, as well as increased consumption of sugar-sweetened drinks (Gortmaker *et al*. 1996, Robinson, 1999, 2001; Ludwig *et al*. 2001).

Recent developing country evidence, e.g. from Thailand and Mexico, has similarly found obesity in children to be linked to physical inactivity. In Mexico, specifically TV viewing was found to be a risk factor (Hernandez *et al*. 1999; Mo-suwan *et al*. 2000).

Obesity that emerges in childhood or adolescence generally tracks into adulthood, with all the associated health risks. Tracking is especially likely if obesity is present by late childhood or adolescence—the odds ratio is found to rise linearly with age (Guo *et al*. 1994; Guo and Chumlea, 1999).

In fact, adolescence is a critical period for development of obesity that persists into adulthood, especially in girls. The reasons for this are not yet fully understood, but are thought to relate to changes in the location of body fat during puberty, with particular risk associated to earlier menarche (Dietz, 1997, Kimm *et al*. 2001).

A second period in early life that is indicated to be critical in the development of obesity that persists into adulthood is the 'adiposity rebound' (AR)—i.e. the age at which BMI increases after its nadir in early childhood (6–8yrs). An early adiposity rebound has been shown to be associated with higher BMI in childhood, adolescence, and young adulthood, and a substantially increased risk of adult obesity (as defined by BMI) (Dietz, 1997).

There is increasingly strong evidence from studies in developed countries to suggest that breastfeeding is associated with a lower risk of developing obesity.

The mechanisms of, reasons for, and significance of the effect of AR are still unclear (questions remain, for example, regarding the extent to which the higher BMI reflects increases in body fat), as are the determinants of an earlier adiposity rebound (Dietz, 2000).

There are conflicting findings regarding the influence of high protein or dietary intakes on the timing of AR, nor has any evidence demonstrated an association with SEP. However, there is evidence to suggest that parental obesity, as well as exposure to maternal gestational diabetes *in utero* are associated with an earlier adiposity rebound (Dorosty *et al*. 2000).

b. Stunting and obesity

Increasing evidence from several developing countries suggests that stunting, especially severe stunting in childhood (a result of nutritional deprivation) may be associated with an increased risk of developing obesity (high BMI) or abdominal fatness, especially in rural-urban migrants (Sawaya *et al*. 1995,1999; Popkin *et al*. 1996, Sichieri *et al*. 2000; Schroeder *et al*. 1999; Bénéfice *et al*. 2000).

It s thought, though not yet fully understood, that stunting may increase people's susceptibility (in terms of weight gain) to high-fat 'urban' diets, possibly through mechanisms related to inefficient fat oxidation (Sawaya *et al*. 1999; Hoffman *et al*. 2000).

Such an increased susceptibility is potentially of great concern to developing world populations where malnutrition is common but coexists with rapid socio-economic development (i.e. ongoing nutritional transition) and urban migration (Schroeder *et al*. 1999).

c. Breast feeding and obesity

There is increasingly strong evidence from studies in developed countries to suggest that breastfeeding is associated with a lower risk of developing obesity (e.g. Kramer *et al*. 1981; von Kries *et al*. 2001; Gillman *et al*. 2001). Indications are that the magnitude of this protective effect may be directly related to the length of exclusive breastfeeding; and that it does not become evident until after a certain age (Dietz, 2001b).

The mechanisms underpinning the apparently protective effect of breastfeeding on obesity are not yet understood and there is no evidence on the long term effects of breastfeeding on obesity from the developing world.

1.6.5 ***Fetal factors and obesity***

a. Interactions of obesity and IUGR and risk of disease

In many cases, as described in previous sections, obesity (or fatness) in adults or children has been found to mediate or enhance the risk of disease or risk factor prevalence associated with retarded fetal growth. In addition obesity has been shown to interact with retarded fetal growth to create a particularly high risk of disease.

b. IUGR and risk of obesity

In view of the apparent importance of obesity in influencing the risk of disease associated to IUGR, the question of whether IUGR enhances the risk of obesity itself is crucial.

The available evidence so far, however, is conflicting and difficult to interpret (Dietz, 1997; Whitaker and Dietz, 1998; Martorell *et al*. 2001).

Most studies in developed and developing countries show ***no*** association between IUGR (low birth weight) and later risk of high BMI (or in one study % body fat). Instead, they find a consistent, often linear, positive relationship of BMI with birth weight (Martorell *et al*. 2001), i.e. a particularly high risk of obesity in those with large birth weights (macrosomic babies).

In contrast, a few studies do find a link between low birth weight (or exposure to famine in early gestation) and BMI. Others, again in both developed and developing countries, find a relationship between small size at birth and central adiposity (WHR or SS:TR), though only after adjustment for current size (Martorell *et al*. 2001; Bavdekar *et al*. 1999). Recent evidence from the ALSPAC study in the UK, moreover, has shown lower size at birth to be associated to higher catch-up growth between birth and two years, and higher fatness at age five (Ong *et al*. 2000)

Most studies in developed and developing countries show *no* association between IUGR (low birth weight) and later risk of high BMI (or in one study % body fat).

The consistent positive, often linear relationship between birth weight and later BMI (and thus, presumably, increased risk of disease) on the one hand, and the association between low birth weight and risk of central adiposity and disease on the other, seemingly present a paradox.

This paradox may be explained by the inability of BMI to adequately measure adiposity. Recent evidence has shown that the larger BMI associated with larger birth weight is due to increments in muscle rather than fat. Conversely, the lower BMI linked with low birth weight is associated with lower muscularity, but a higher percentage of body fat.

This is assumed to lead to lower expenditure of energy, a consequent higher risk of a positive energy balance and development of adipose tissue, and a reduced responsiveness to insulin (insulin resistance) (Kahn *et al*. 2000; Hediger *et al*. 1998). Thus, the lack of an association between low birth weight and high BMI may disguise an important relationship between low birth weight and greater risk of body fat, perhaps especially central body fat. In the case of Indian low birth weight babies such a link has been demonstrated. This is mediated by the distinct poor muscle-high fat phenotype of IUGR infants that persists through the poast-natal period and is associated with increased central adiposity (Yajnik, 2001).

1.6.6 ***Intergenerational factors and obesity***

There are clear indications that parental factors may have a significant impact on the risk of obesity of their offspring.

a. Parental obesity

Growing evidence from developed countries suggests that parental body composition, in particular parental adiposity is an important predisposing factor for the development of obesity in children (Whitaker *et al*. 1997; Stettler *et al*. 2000; Burke *et al*. 2001; Magarey *et al*. 2001; Parsons *et al*. 2001). One study in the US, for example, found parental obesity to lead to a 4-fold increase in the risk of obesity in children aged 3–5 (Hediger *et al*. 2001). In Australia, maternal obesity was found to be associated with an independent eight-fold risk of obesity in adolescent daughters (Burke *et al*. 2001). A further study, finally, indicates that parental obesity may be even more important than large birth weight in predicting risk of obesity in adolescents (Frisancho, 2000). Little is known about the effects of parental obesity in developing countries.

The mechansims underpinning the effect of parental obesity are poorly understood but are though to involve both genetic, environmental, and behavioural influences. One possible mechanism may be through the development of gestational diabetes. Obese women have a higher risk of developing GDM, and this in turn is associated with a higher risk of obesity in offspring (Martorell *et al*. 2001).

b. Maternal gestational diabetes mellitus (GDM) and obesity

Evidence from developed countries clearly shows that fetal exposure to GDM (though only insulin requiring GDM), increases the off-

spring's risk of developing obesity in childhood and adolescence (Weintrob *et al*. 1996). Again, little is known about the impact of GDM in developing countries.

GDM is known to lead to fetal overnutrition, hyperglycaemia, hyperinsulinaemia and thus a large size at birth. It may thus partly explain the consistent relationship between large birth weight and obesity (Whitaker and Dietz, 1998; Martorell *et al*. 2001). Moreover, GDM is indicated to be associated to an earlier adiposity rebound, which as described above is clearly associated to a higher risk of obesity. (see Dorosty *et al*. 2000)

The precise mechanisms, however, by which GDM leads to an increased obesity risk in offspring remain poorly understood. Some evidence suggests that its effect is independent of maternal fatness but is a function of the metabolic intrauterine experience associated with diabetes. Other evidence, however, throws doubts on the importance of the uterine environment pointing instead to the role of genetic determinants (Velho *et al*. 2000).

What leads to GDM?

As the previous sections have discussed, the determinants of GDM are not yet well understood. However, several factors have been shown to be linked to GDM, at least in some populations. These include obesity, own exposure to GDM, and short stature.

a. Maternal birth weight

Recent evidence also points to a possible intergenerational effect on risk of obesity associated with maternal birth weight. For example, findings from the ALSPAC birth cohort study in the UK found that low maternal birth weight was associated with lower size at birth, heightened post-natal catch-up growth, and subsequently higher fatness, i.e. risk of obesity at age 5 in offspring. The genetic or environmental mechanisms underlying these associations are as yet poorly understood (Ong *et al*. 2000).

Whilst most of the evidence establishing these risk factors so far comes from developed countries, evidence demonstrating their association to disease in developing country populations is accumulating.

1.7 Life course perspectives on unhealthy lifestyles

1.7.1 Unhealthy lifestyles of the life course as risk factors for disease

The lifestyle behaviours of ***unhealthy diet***, in particular a diet high in saturated fat, refined foods, salt and sugar, ***physical inactivity***, and ***tobacco use*** are some of the most firmly established adult risk factors for obesity, high blood pressure, dyslipidaemia and IGT and, consequently CHD, stroke, and diabetes in adults. They are shown to be significant at both the individual and population level.

Whilst most of the evidence establishing these risk factors so far comes from developed countries, evidence demonstrating their association to disease in developing country populations is accumulating. The clear link of tobacco use to CVD specific and overall mortality, for example, has been demonstrated in large-scale cohort and case-control studies in China (Liu *et al*. 1998; Niu *et al*. 1998) with similar evidence emerging from India (e.g. Gupta and Mehta, 2000).

Changes in lifestyles—especially towards unhealthy diet (what has been termed the 'nutritional transition') in the developing world and physical inactivity in the West—are believed to underpin the recent alarming global rises of obesity and related disease risk among adults and children (Dietz, 2001a; Popkin, 1994; Fung *et al*. 2000).

Similarly, differences in lifestyles are shown to be responsible for differences in risk factor prevalence between more and less 'westernised' populations—for example, between blacks in Africa, the Caribbean and the USA (Okosun *et al*. 1999).

Early uptake of unhealthy lifestyles

Unhealthy lifestyles do not just emerge in adulthood. They are already taken up in childhood and adolescence and, as for example the Bogalusa Heart Study has shown, drive the early development of obesity, dyslipidaemia, high blood pressure, impaired glucose tolerance and associated disease risk (Berenson *et al*. 1991, 1998b; Yang *et al*. 1999; Twisk *et al*. 2000). In the US, for example, much of the rise in obesity has been specifically related to decreased physical

activity due to television viewing (Gortmaker *et al*. 1996).

Unhealthy lifestyles in early life, e.g. physical inactivity or smoking, have also been shown to independently predict CHD and stroke in later life, regardless of their presence in mid adulthood (Lee and Paffen-barger, 1998; Paffenbarger and William, 1967; Thorne *et al*. 1968; Paffenbarger and Wing, 1969, 1971; Deckers *et al*. 1990; McCarron *et al*. 2001b).

In addition, unhealthy lifestyles, in particular smoking, have a direct effect also on the health of the next generation. Smoking in pregnancy, for example, has been shown to be strongly linked to low birth weight, and the associated morbidity and mortality risk in offspring. Parental smoking, moreover, by exposing children to environmental tobacco smoke and reducing the amount of breastfeeding, has been found to increase children's disease risk. It specifically causes reduced lung functioning, asthma, and risk of infections in offspring (see WHO, 2001a).

In the developed world, indications are that physical inactivity is on the increase, especially among the young.

Children and adolescents take up unhealthy behaviours largely as a result of massive marketing and media pressures which are reinforced through peer pressure as well as through parents' own health behaviours.

Parents' physical inactivity, for example, has been shown to be strongly linked to children's lack of physical activity and consequent obesity (Fogelholm *et al*. 1999). Likewise, unhealthy parental diet has been found to be linked to unhealthy dietary intake and overweight in children (e.g. Cutting *et al*. 1999; Burke *et al*. 2001). Parental tobacco use and quitting have an important influence on the uptake of smoking especially by younger children (see WHO, 2001a,b).

Little is so far known about the processes leading to early adoption of unhealthy diet and physical inactivity in developing countries. However, the alarming exposure of the young to tobacco advertising and their consequent uptake of tobacco use in many developing countries is beginning to be documented by the WHO/UNICEF supported Global Youth Tobacco Survey (GYTS) (e.g. Warren *et al*. 2000).

1.7.2 ***Global trends in unhealthy life styles***

As with the biological risk factors, perhaps even more so, quality data on trends and patterns in unhealthy lifestyles is seriously lacking—in particular in the developing world. The little data that is available from developing countries is usually from scattered, non representative surveys on selected populations. Nevertheless, some very broad features are discernible.

Developed world

Physical inactivity

In the developed world, indications are that physical inactivity is on the increase, especially among the young. In the US, for example, participation in physical activity classes among high school students has declined over the past decade (YBRFSS, 2000). In leisure time, too, as indicated above, physical activity has declined mainly due to increased television viewing (Gortmaker *et al*. 1996).

Unhealthy diet

Intake of unhealthy foods, too, is showing rising trends, particularly among the young.

Among 18–29 year olds in the U.S. for example, there has been a sharp increase in the consumption of hidden high fat foods such as pizza, French fries, burgers, Mexican and Chinese fast food (Popkin *et al*. 2001). Similarly, between 1977 and 1996, there has been a significant rise in snacking (high fat and high sugar snacks) among 2–18 year olds (Jahns *et al*. 2001).

Smoking

In contrast to the adverse trends in diet and physical activity, smoking in many developed countries, including the US, UK, Finland and Australia, has declined over the past decades, particularly among adults. In other countries however, adverse trends are seen. These include, for example, the rising prevalence of smoking among women in Germany or Japan, and in many countries the alarming rise in smoking among teenagers, especially girls. Whereas in the past smoking rates among girls were always considerably lower, in several countries they now exceed those of boys (HBSC, 1998, Corrao *et al*. 2000).

The most worrying trends are currently seen in Central and Eastern European countries where smoking rates are rising among both men and women with prevalence rates higher than 45% in some countries (Corrao *et al*. 2000).

Developing world

Physical inactivity

Virtually no information exists on the trends in physical activity patterns in the developing world.

Virtually no information exists on the trends in physical activity patterns in the developing world.

Diet

The scanty information that exists on trends in diet suggests that they are unfavourable. In Asia overall there has been a fall in the percentage of diet energy derived from complex carbohydrates and an increase in the proportion contributed by fat (Lang, 1997). In China the percentage of households consuming a relatively high fat diet has been found to have increased sharply from 1989 to 1993 (Peto, 1996).

Similar increases in the intake of dietary fat have been observed in Latin American Countries as for example in Brazil (WHO, 1990). Virtually no information on diet trends is available from Africa.

Smoking

The data that exists on smoking the developing world shows very divergent trends depending on region and country. In some regions like South East Asia, Latin America, the Caribbean, and some Middle Eastern countries tobacco use is generally high and in many countries, for example China, is on the increase. In others, however, such as India or Hong Kong, rates are shown to be falling (Corrao *et al*. 2000; Shah, personal communication). In Africa and some Middle Eastern countries, in contrast, smoking prevalence is generally low, and in some countries, for example South Africa, Ghana, Zimbabwe or Kuwait, is falling.

A particularly worrying trend especially in many Asian countries is the increase in the traditionally low rates of tobacco use in women. In some Caribbean countries, alarmingly high rates of smoking are also seen among youth. In the Dominican Republic, for example, rates stand at 35% (Corrao *et al*. 2000).

1.7.3 ***Socio-economic patterns of unhealthy life styles***

Unhealthy lifestyles are directly influenced by individuals' motivations and attitudes which in turn are shaped, to greater or lesser extents, by family, friends, peer groups, the school, and broader social environment.

In addition, the prevalence of unhealthy lifestyles shows clear variations between race, gender, and socio-economic groups, indicating the important influence that social or economic determinants have on the choice of diet, smoking and the extent of physical activity.

a. Patterns in developed countries

Current SEP and unhealthy lifestyles

In developed countries the prevalence of unhealthy lifestyles generally shows a clear social gradient with higher rates in those of poorer socio-economic position.

For example, studies in many countries have shown physical inactivity among adults and youth to be highest in poor income or occupational strata (Luepker *et al*. 1993; Lynch *et al*., 1997; NCHS, 1998; NLSCY, 2000; Brunner *et al*. 1999). Smoking and unhealthy diets are similarly found to be associated to lower occupational or income level (Blane *et al*. 1996; Brunner *et al*. 1999). In Finland, for example, salt consumption, binge drinking, total calorie and saturated fat intake, and little intake of fresh fruit and vegetables have all been shown to be highest in the poorer socio-economic strata (Lynch *et al*. 1997).

This clustering of unhealthy behaviours in the lower socio-economic groups is consistent with, but does not fully explain, the observed inequalities in health and disease rates in developed countries (Lynch *et al*. 1997).

Earlier SEP and unhealthy lifestyles

At the same time as they are related to current SEP, unhealthy lifestyles in adults in developed countries are often also related to their earlier socio-economic position—i.e. to lower levels of education and poorer background in childhood.

In Finland, for example, unhealthy diet has been shown to be linked not just to adult but to low childhood SEP (Lynch *et al*. 1997). Risk of smoking, similarly, and less successful smok-

ing cessation has been linked to lower educational level in many countries (Lynch, *personal communication*) (NCHS, 1995). A similar link has been shown between lower education and increased physical inactivity (Luepker *et al*. 1993).

This influence of early SEP suggests that early disadvantage may increase risk of later disease through development processes where children adopt particular detrimental behaviours and attitudes.

Important variations in the influence of SEP over the life course

It is crucial to bear in mind that the impact of early and later SEP on risk behaviours clearly does not always follow the general social gradients described above. Rather, different relationships are found in different populations and the nature and extent of associations varies depending on cohort, gender, race, or the life trajectories involved.

The impact of subsequent life trajectory is illustrated, for example, by the effect of childhood SEP on physical activity in Finnish men. The risk of physical inactivity among high income men, was highest if they had had a low childhood SEP. In contrast, among low income adult men, a high childhood SEP conferred an increased risk, perhaps indicating an effect of downward social mobility (Lynch *et al*. 1997; Lynch 2000).

The influence of life trajectory and cohort is illustrated, for example, in the effects of child and adult SEP on smoking in the Alameda County cohort in the U.S. In 1965, the greatest cumulative life course disadvantage with respect to smoking was in adults in high income strata whose fathers had been manual workers, i.e. who had moved upwards. In 1994, by contrast, the highest cumulative risk was in those who came from low occupational class origins and had remained in a low income strata as adults (Davey Smith *et al*. 2001b).

At the same time as they are related to current SEP, unhealthy lifestyles in adults in developed countries are often also related to their earlier socio-economic position—i.e. to lower levels of education and poorer background in childhood.

Cohort differences are also illustrated in the impact of family income on 'snacking' in young US adults. Whereas in 1977, low income family background was protective of snacking among 18–29 year olds, in 1994–1996 it no longer had such a protective effect, with little differentiation between low and high income strata (Zizza *et al*. 2001). A similar pattern was found in a recent child cohort in the UK where less healthy food choices—convenience, snack and finger foods—were found in children with less educated mothers, but also in children from socially advantaged backgrounds (North *et al*. 2000).

Finally, cohort and gender differences are demonstrated, for example, in the impact of educational level on smoking in Switzerland. Among older cohorts of women, higher levels of education were associated with a higher risk of starting smoking early, whereas among men higher education had no effect. In contrast, among younger cohorts, higher education in men had come to be protective of starting smoking early, whereas among women it no longer had an effect (Curtin *et al*. 1997). A similar switch in the effect of higher socio-economic or educational level has been observed in Spain around 1988/92 (Borras *et al*. 2000).

These variations indicate the crucial importance of the prevailing historical, social, economic and cultural context in shaping the effect that lifecourse SEP, race/ethnicity, or gender (or ethnic group) may have on risk behaviours.

b. Patterns in developing countries

The social gradient of unhealthy lifestyles in developing countries, just as that of the biological risk factors, is generally assumed to be opposite to that in developed countries, i.e. unhealthy diet, physical inactivity and smoking are assumed to be higher in the more affluent, 'westernised' urban populations.

The available evidence suggests that this urban-rural and SEP gradient often holds. In China, for example, tobacco use, fat and meat intake, as well as reduced vegetable intake and physical inactivity has been found to be associated with higher income level and urban residence (Popkin *et al*. 1995; Peto, 1996; Paeratakul *et al*. 1998; Gao *et al*. 1999; Yu *et al*. 2000).

Evidence from Latin America, similarly, suggests that physical activity and energy expenditure is much higher in rural than in urban areas (Torun, 2000). However, the evidence also clearly indicates that in many cases the patterns of risk behaviours do not follow this classical pattern. In Brazil, for example, the intake of a high-fat, high-sugar diet is particularly high

among the poor population, who simply can not afford a healthier diet, especially in cities (Pena and Bacallao, 2000).

Similarly, smoking in urban China has been found to be highest in the lower socio-economic groups, in particular the lowest educational groups (Yu *et al*. 2000). Finally in India, contrary to assumptions, smoking rates among most age groups have been found to be much higher in rural than in urban areas (Shah, *personal communication*).

These variations indicate that in the developing world, too, the impact of SEP on health behaviours is shaped by the prevailing socio-economic or cultural context, and that 'urbanisation' or 'westernisation' cannot simply be assumed to have uniform impacts on disease risk patterns.

1.7.4 ***Importance of the macro-structural context***

The significant population, gender, and cohort variations in the relationship between early and later SEP and unhealthy lifestyles in developed and developing countries have highlighted the crucial importance of the ***prevailing macro-structural context***—i.e. the main social, economic, cultural and political forces—in shaping the social determinants and trends in risk behaviour.

It is the macro-context that determines the resources available to different groups; the resources necessary for opting for healthy (or unhealthy) lifestyles; the exposure to risk factors, and the social meaning that risk behaviours (for example smoking) have for different population groups.

However in many cases the patterns of risk behaviours do not follow this classical pattern.

Specific forces that are of particular importance in this regard include:

i. The macroeconomic and political factors that determine level of income, poverty and income inequality

ii. Legislation, such as anti-smoking laws or fiscal policies, which have been shown to successfully curb smoking in several developed, but also in some developing countries, e.g. in South Africa (Corrao et al. 2000)

iii. The extent of advertising, for example of unhealthy as opposed to healthy foods

iv. The level of influence, market control and expansion of the fast food industry (Schlosser, 2001).

1.8 Potential mechansims underpinning the association of intrauterine growth retardation to later disease risk

1.8.1 ***Introduction***

The previous sections have illustrated the evidently important associations that exist, in many populations, between intrauterine growth retardation (small size at birth or exposure to famine *in utero*) and risk of adult disease or risk factor prevalence.

This section aims to explore in some detail what is known about the mechanisms underpinning these associations.

A first point to emphasize at the outset is that these mechanisms are still extremely poorly understood, with research only at the beginning.

A second point is that the development of a better understanding of the mechanisms has, to some degree, been hampered by the limitations in the currently used measures of fetal growth retardation. Low birth weight, as the previous sections have indicated, is too crude a marker to capture the range of possible uterine exposures and experiences that may relate to disease risk.

At the same time, the somewhat haphazard use of several other measures of size at birth, e.g. head circumference or length at birth, has limited the comparability and interpretation of findings (see Kramer and Joseph, 1996).

Efforts to develop and systematically use more specific measures of important exposures *in utero* are thus a key requisite for developing a better understanding of the mechanisms that link fetal growth to later disease.

The remainder of this section considers the main unresolved issues and questions regarding these mechansims.

1.8.2 ***Main unresolved issues***

a. Underlying determinants—genetic or environmental?

A fundamental unresolved question pertains to the relative role of genetic versus environmen-

tal factors in underpinning the association between IUGR and later disease risk. In other words, is the association due to an environmental exposure in utero, or due to a genetic trait which causes changes that lead to disease risk and at the same time to retarded fetal growth?

Evidence from existing studies, including twin studies—which are generally though to be the best equipped to answer questions relating to the relative importance of genetic versus environmental factors—provides inconclusive evidence, pointing at times to a dominant role of environmental, at other times to genetic traits as the determinants. Evidence from twin studies, moreover, is partly limited by difficulties in assigning birth weights. Furthermore, there are more fundamental questions as to the extent to which conclusions can be drawn from differences in disease concordance between mono- and dizygotic twin pairs (e.g. Phillips, 1993).

Efforts to develop and systematically use more specific measures of important exposures *in utero* are thus a key requisite for developing a better understanding of the mechanisms that link fetal growth to later disease.

What seems clear is that the interaction of both genetic and environmental factors is involved and that the relative importance of one or the other may also vary depending on the particular disease risk concerned. For example, a specific hypothesis has been advanced (though only very weak supporting evidence exists) to indicate a possible genetic determinant of the association between retarded fetal growth and impaired glucose tolerance.

b. The nature of intergenerational transmission

Related to the issue regarding the relative role of genetic versus environmental determinants, is the question of the nature and basis of the apparent intergenerational effects on risk transmission associated with fetal growth. Particular questions in this respect relate to the possible role of maternal gestational diabetes or of parental height, weight, and nutritional history, sub-clinical pathology, and the specific mechanisms by which parental obesity leads to obesity in offspring.

c. The fixedness of early programming

A further question relates to the extent to which early 'programming' of disease risk is fixed or is modifiable by later interventions. The marked success of several high risk life style interventions in reducing risk of diabetes and CVD in middle aged individuals, combined with the large secular changes in major risk factors for CVD (smoking, unhealthy diet, hypertension) suggests that, perhaps, programming of risk is more flexible than previously assumed. For example, a recent randomized controlled trial in Finland showed that weight reduction and improvement of diet led to a 58% reduction in diabetes over 3.2 years of follow up (Tuomilehto *et al*. 2001).

d. Which possible exposures lead to detrimental fetal growth? What is the role of maternal nutrition in this?

A fourth area that remains poorly understood concerns the possible environmental exposures *in utero* that may cause retarded fetal growth or adaptations that lead to later risk of disease.

It is commonly assumed that such adaptations and retarded fetal growth occur in situations in which the fetus' nutrient demand is higher than the placental supply. The resulting undernutrition leads to hypoxaemia which in turn leads to changes in blood distribution, placentation, metabolic and endocrine changes.

However, it is not yet known which exposures or factors cause such detrimental fetal growth or development. Particular questions regard the role that maternal nutrition plays in this. It is becoming increasingly clear that maternal nutrition is not necessarily the same as fetal nutrition (Harding, 2001). For example, maternal nutritional supplementation interventions have been shown to have very little effect on offspring's birth weight (e.g. Kramer, 1987). It is thus assumed that other, non-nutritional factors relating to fetal nutrition or placental functioning may be of importance.

e. What is the importance of timing of insults during pregnancy?

A further unresolved question relates to the possible importance of the timing of insults *in utero* for subsequent risk of disease. That timing may be important has been indicated by the findings of the Dutch Famine Study which has shown that exposures in early and later gestation can have very different effects. These difference may, moreover, depend on the particular disease concerned.

f. Which adaptations may occur in utero in response to stress?

It is assumed, for example by the fetal origins of disease hypothesis, that exposure to stress or undernutrition in utero leads to endocrine and metabolic adaptations or processes that then lead to development of later disease risk.

Although the particular metabolic and endocrine processes are not yet understood, several possible processes that may be involved have been suggested.

i. Elastin

The laying down of elastin, a vital component for the elasticity of arterial walls, occurs only once, early in life. Its half life of 30 to 40 years means that by midlife, half of the elastin in blood vessels has disappeared, thus rendering them less elastic. Processes *in utero* which restrict the laying down of elastin could potentially increase the risk of cardiovascular disease later in life (e.g.Martyn and Greenwald 1997).

The risk of developing CHD, stroke or diabetes is influenced by biological or social factors acting at *all* stages of the life course—in fetal life, childhood, adolescence, and adulthood.

ii. Programmable hormonal systems

There is some evidence to show that several hormonal systems may be programmable *in utero* and could thus potentially be involved in the mechanisms leading to enhanced risk of later disease. These include:

- Adrenocortical Steroids (e.g. Cortisol)
- The Sympathoadrenal System
- GH/IGF-1 Axis
- Pituitary-Thyroid Axis
- Gonadal Steroids
- Insulin Secretion

Programming of the HPA axis (i.e. the system of adrenocortical steroids (cortisol)), in particular, is indicated to possibly play an important role. Evidence from human and animal studies shows that low birth weight is associated with higher cortisol levels, and that stressful experiences such as deprivation *in utero* can act to *prime* the HPA system in such a way as to increase the magnitude of subsequent responses to stress and adverse circumstances later in life. In other words, the degree of adult responsiveness (cortisol levels secreted) to stresses in adult life (e.g low socioeconomic position, job control, self-esteem, or social support) may be determined by events *in utero*. At the same time, evidence from physiological studies shows increased stress response to be associated with atherosclerosis and increased left ventricular mass, and in follow up to predict hypertension. Cross-sectional and case-control study data furthermore shows higher levels of cortisol, especially in conjunction with obesity, to be associated to higher blood pressure, IGT and IR, and dyslipidaemia. However, no link of elevated stress response to CVD or diabetes has yet been demonstrated (e.g. Sapolsky, 1996; Brunner, 1997; Phillips, 1999; Reynolds *et al*.2000, Bjorntorp, 1997), though some prospective evidence exists for a link between CVD and psychosocial factors such as anxiety or depression (which may involve heightened stress responses) (e.g. Hemingway and Marmot, 1999). The particularly adverse effect of stress in conjunction with obesity may be of importance in terms of the apparent mediating effect of obesity on the risk of disease associated to retarded fetal growth.

A role of a raised stress response in lifting the risk of CVD may be of particular significance for developing countries where people from poor origins (i.e. likely to have been exposed to undernutrition *in utero*) increasingly move to stressful urban environments.

g. Which mechanisms underlie the observed mediating effect of enhanced growth in weight?

The mechanisms underlying the apparent interaction between retarded fetal growth and increased post-natal growth in weight or fatness in increasing disease risk, are just as little understood as the association between IUGR and later disease risk in general.

A first question pertains to the timing of enhanced growth in weight. Is such growth only detrimental if it occurs in a certain period or stage of childhood? Existing evidence is not yet able to give solid insights to this.

A second questions concerns the physiological mechanisms that may underpin the increased risk of disease associated with retarded fetal growth followed by rapid growth in weight. These mechanisms, which are likely to differ depending on the particular outcome concerned, again are not understood. However, a potential process, at least relating to increased risk of insulin resistance, has been proposed.

This builds on the increasing evidence that babies who are small or thin at birth have relatively less muscle compared to those of normal or high birth weight (Kahn *et al*.2000; Hediger *et al*.1998)—a phenotype shown to be particularly marked in Indian IUGR babies (Fall *et al*. 1999; Kinare *et al*. 2000)—and evidence that this deficiency persists after birth. The critical period for muscle growth is around 30 weeks *in utero*; there is little cell replication thereafter and later muscle cell hypertrophy may be insufficient to compensate for this deficiency (Widdowson *et al*. 1972; Bassey *et al*. forthcoming).

The idea is that if IUGR babies develop a high body mass index in childhood they may have a disproportionately high fat mass, as low muscle means less energy expenditure, more likelihood of achieving a positive energy balance, and thus increased rate of adipose tissue gain. High fat mass (and low muscle mass), in turn, will lead to an increased risk of development of insulin resistance, as lower muscle mass may also result in lower overall muscle responsiveness to a given insulin signal (Kahn *et al*. 2000). In Indian IUGR babies, the marked thin-fat phenotype has been shown to persist through the post-natal period and to be associated in particular with high central adiposity (Yajnik, 2001).

h. Which mechansims underpin the observed mediating effect of enhanced growth in height?

As is the case for growth in weight, the mechansims underpinning the apparent effect of enhanced growth in height in childhood or adolescence on risk of disease are poorly understood.

A potential mechanism that has been proposed is that slow growth *in utero* resulting in short length at birth may involve a permanently reduced number of cells for example in the kidney, with no further cell replication after birth. Post-natal catch-up could be deleterious either because overgrowth disrupts cell function, or because large body size imposes excessive metabolic demand which in case of the kidney may lead to cycles of nephron death and thus increased blood pressure (e.g Eriksson *et al*. 2000; Forsén *et al*.1999; Lever and Harrap,1992).

Life course impacts on disease cannot simply be generalised from one population to the next.

1.9 Key themes and key gaps in knowledge

1.9.1 ***Introduction***

The previous sections in this part of the report have sought to set out the evidence on the influence of life course impacts on risk of CHD, stroke and diabetes. The discussions have shown the complexity in trying to disentangle the various life course influences that shape the risk of CVD and diabetes later on. They have highlighted, in particular, the limitations imposed by the serious lack of evidence from developing countries.

However, the discussions have also shown that much knowledge has already accumulated, and we are some way (though still at the beginning) towards understanding how factors throughout the life course impact on later disease risk.

The aim of this final section of Part I is first to draw together the major strands—the main themes and issues—emerging from the previous individual domain discussions and, in doing so, to pinpoint the important gaps in knowledge that remain and that need to be addressed by research.

1.9.2 ***Key general points***

Three general, but extremely important issues regarding the use of the life course perspective for policy, warrant re-emphasis at the outset.

a. Risk of disease is influenced by factors at all stages of the life course

The risk of developing CHD, stroke or diabetes is influenced by biological or social factors acting at ***all*** stages of the life course—in fetal life, childhood, adolescence, and adulthood.

Life time risk, however, cannot simply be understood as an additive model: Earlier and later factors are likely to interact, and the consequences of some influences may depend on events at earlier (or later) critical stages of development. For example, negative consequences of fetal growth retardation appear especially in conjunction with high post-natal weight gains. The relative importance of early and later factors in causing later disease, however, is not yet fully understood.

b. Life course influences are disease specific

CHD, stroke and diabetes are likely not the results of the same processes and exposures acting over the life course. The life course influences on risk are specific for each disease, or even subtype of disease—as, for example, for haemorrhagic and ischaemic stroke—thus posing important challenges for research and for integrated policy development.

c. Life course impacts on disease are population (and cohort) specific

Life course impacts on disease cannot simply be generalized from one population to the next, or from one cohort to the next. Important differences appear to exist, reflecting either genetic differences and/or differing social, economic, cultural and nutritional contexts, and differences in the manner of gene expression across a variety of environmental conditions. What determines population or cohort differences, particularly what the relative role is of different social contexts, is not well understood, but is a key area for future research.

The risk behaviours of unhealthy diet, lack of exercise, and tobacco use, and the associated biological risk factors of high blood pressure, obesity and dyslipidaemia, remain the most firmly established risk factors for CHD, stroke and diabetes.

1.9.3 Disease and 'established' risk factors over the life course

a. 'Known' risk factors remain the most firmly established link to disease

The risk behaviours of unhealthy diet, lack of exercise, and tobacco use, and the associated biological risk factors of high blood pressure, obesity and dyslipidaemia, remain the most firmly established risk factors for CHD, stroke and diabetes.

Efforts to disentangle the life course impacts on- and effects of these risk factors, especially in developing countries, are seriously hampered by the dearth of, and methodological limitations in the existing studies on their prevalence and social patterning and trends. The latter include the inability of body mass index (BMI), as the most commonly used index of obesity, to adequately distinguish between lean and fat tissue; the methodological difficulties of accurately identifying hypertension; and the lack of appropriate population norms for both blood pressure and adiposity.

Nevertheless, several key issues can be identified.

b. Rising risk factor trends: obesity and tobacco use

The little evidence that exists shows that in the developing world, the prevalence of the major risk factors obesity and tobacco use is rising.

In developed and developing populations the prevalence of obesity among both adults and children has shown sharp increases, somewhat off-setting the progress made with some of the other biological risk factors in many countries. The rise in obesity particularly, is a reflection of the increased marketing and availability of a westernised diet rich in refined foods, saturated fats, sugar and salt ('nutritional transition'), as well as changes in lifestyles towards decreased physical activity.

Tobacco use, though declining in some, mainly developed country populations, is showing alarming rates or increases in others. A particularly worrying trend is the marked rise in smoking amongst women and teenagers in many developing and developed countries.

c. Major biological risk factors emerge and act in early life

Contrary to what was long assumed, high blood pressure, dyslipidaemia, impaired glucose tolerance (IGT), and obesity already emerge in childhood and adolescence, and are often clustered together. Obesity, especially abdominal adiposity, seems to play a central role in the development of the other factors, although some race and gender differences in the clustering of risk factors do appear to exist.

Three critical periods or exposures in early life appear to increase the risk of developing obesity that persists into adulthood: 1) exposure to gestational maternal diabetes and high birth weight; 2) an early adiposity rebound (the age at which BMI increases after its nadir in early childhood), and 3) development of obesity in adolescence. The mechanisms underpinning these apparent associations are not yet understood.

The presence of risk factors ***early*** in life already influences risk of later disease, either

through the social and biological tracking of these behaviours over time, and /or through their direct biological effects. Obesity, high blood pressure and dyslipidaemia track from childhood through to adolescence and young adulthood, where they lead to atherosclerosis and, in many cases, diabetes. The presence of risk factors in adolescence or young adulthood (e.g. high blood pressure) has additionally been shown to independently predict an increased risk of CVD later on.

The relative predictive power of risk factors present in childhood, compared to risk factors in mid-life will depend on the disease concerned. In many cases, however, it is indicated to be equal, if not stronger, than that of risk factor presence in mid-adulthood.

What is not yet understood, for example in the case of blood pressure, is the relative importance of long-term exposures to raised levels as opposed to acute high transient levels. In the case of obesity and insulin resistance syndrome it appears that long-term exposure to obesity has an aggravating effect.

Risk factors in early life, particularly tobacco use and obesity, moreover, not only affect one's own later health but also the health of the ***next generation***.

Obesity, especially in mothers, for example, clearly increases the risk of obesity and, consequently, disease risk in their offspring.

Similarly, tobacco use during pregnancy is strongly linked to low birth weight and associated disease or mortality risk in the offspring. Parental smoking, moreover, exposes children to environmental tobacco smoke (ETS), and thus an increased risk of asthma, certain infections and reduced lung functioning.

Risk factors in early life, particularly tobacco use and obesity, moreover, not only affect one's own later health but also the health of the next generation.

1.9.4 ***Disease and unhealthy lifestyles over the life course***

a. Unhealthy lifestyles drive the emergence of disease risk in early life

Unhealthy lifestyles—tobacco use, physical inactivity and unhealthy diet (a diet high in sugar, saturated fat, salt and calorie content)—are already taken up by children, leading to the early development of obesity, high blood pressure, dyslipidaemia, IGT and the associated disease risk. In addition, unhealthy lifestyles in early life, for example physical inactivity, are shown to independently predict later CVD—regardless of their presence in mid or late adulthood.

Unhealthy lifestyles are taken up by children or adolescents largely as a result of massive marketing and media pressures, as well as parents' own health behaviours. Parents' lifestyles, for example, have an important impact on children's dietary habits, level of physical activity, and uptake of tobacco use.

b. Socioeconomic position over the life course influences risk factor development

The prevalence of behavioural or biological risk factors is clearly influenced by socio-economic position (SEP) ***over the life course***. In adults, for example, the prevalence of risk factors is not just determined by adult SEP, but also by their socioeconomic position in childhood and the different social trajectories that individuals traverse as they become educated, enter the labour market, generate income, change jobs, and gather assets.

In developed countries, prevalence of risk behaviours and factors among adults, just as prevalence of disease, is generally higher among those from lower socio-economic strata. Similarly, it is typically poorer childhood SEP that is associated with more risk behaviour, suggesting that early socio-economic disadvantage may increase later disease risk through developmental processes whereby children adopt particular detrimental behaviours and attitudes.

Poor early SEP can also have intergenerational effects on disease risk. Among young females in Japan, for example, raising SEP through education has been shown to not only decrease their own risk of disease, but also that of their offspring in the next generation. (Hasegawa, *personal communication*).

The general developed country pattern of low SEP = high risk, however, clearly does not hold in all cases. The effect, detrimental or protective, of SEP on risk behaviours can differ considerably between populations, ethnic groups, cohorts and genders. For example, among older women cohorts, low early SEP was shown to protect against smoking, whereas among younger cohorts at present it is associated with an increased risk.

In developing countries the social gradient of disease risk is commonly assumed, and

often found to be opposite to that in developed countries. Risk factors are often highest in those population groups that are the most westernised or modern—i.e. the affluent, urban population. However, the patterns of risk are at times more complex and do not follow this uniform pattern. Obesity, for example, is emerging as a serious problem among the poor in Latin America. In India, smoking rates are found to be higher in rural than in urban areas.

c. Importance of the macro-structural context

The specific socio-economic and rural-urban risk factor patterns that prevail in different populations are shaped, to a large degree, by the underlying macro-structural context—the prevailing social, economic, political and cultural forces. These forces determine the exposure to risk inducing environments, the resources necessary and available to opt for healthy lifestyles, and the social meaning that risk behaviours have for different population groups.

The processes by which 'urbanisation' and 'development' lead to increased risk cannot simply be assumed to be the same across different societies.

For the developing world in particular, this means that the processes by which 'urbanisation' and 'development' lead to increased risk cannot simply be assumed to be the same across different societies.

d. Additional influence of poor childhood SEP

The relationship of poor early SEP to risk factors or behaviours only partly explains its association to later disease. The clear link of lower early SEP to CHD and stroke, which is reflected in the consistent association shown between short stature (i.e. impaired linear growth) and these diseases, is possibly mediated by two other factors.

Infectious factors

A first factor thought to possibly underpin the association of poor childhood SEP to CVD is early exposure to infectious agents. The specific bacterial pathogens that appear linked to poor conditions and have so far been implicated include Helicobacter pylori and Chlamidia pneumoniae, though evidence is far from conclusive.

A further, possibly infectious but yet unidentified factor is assumed to underpin the particularly consistent association that is seen between poor childhood SEP and haemorrhagic stroke.

The possible role of other infectious agents in the development of chronic disease risk, especially in developing countries where infectious disease is still pervasive, has not yet been explored.

Nutritional factors

A further indirect way in which childhood deprivation, especially nutritional deprivation, may be associated to a raised disease risk, is through the apparent association between stunting (especially severe stunting) and an increased risk of (abdominal) adiposity. This association is possibly due to impaired fat oxidation in stunted children and a consequent increased susceptibility (in terms of weight gain) to high fat 'urban' diets.

A link between stunting and risk of central adiposity would be of particular importance in those developing countries who have recently or are currently undergoing the 'nutrition transition.

1.9.5 ***Disease risk and protective factors in childhood***

a. Breastfeeding

In contrast to the detrimental effects of unhealthy diet and lack of exercise in childhood, breastfeeding is indicated to have a protective effect on the development of disease risk.

Apart from its well-established short term benefits for child health and development, breastfeeding is increasingly indicated to confer a lower risk of high blood pressure, as well as of dyslipidaemia and obesity. However, this protective effect is not yet unequivocally established, as some weak evidence of a long-term negative impact of breastfeeding on CVD risk exists.

1.9.6 ***Disease, risk factors and fetal growth***

In addition to factors in childhood and adolescence, factors relating to fetal growth are clearly involved in shaping risk of disease.

a. Fetal growth and later disease

In many populations intrauterine growth retardation (IUGR) (as indexed by small size at birth or exposure to famine in gestation) is shown to be associated with a higher risk of CHD, stroke and diabetes. This association forms the basis of the 'Barker' or the 'Fetal Origins of Adult Disease'(FOAD) hypothesis. Some evidence suggests moreover that this risk may be transmitted intergenerationally.

At the same time, however, large size at birth, too, is found to be linked to an increased risk of diabetes or CVD. Thus, the relationship of fetal growth to later disease is, in fact, U-shaped. This effect of fetal overnutrition is important to bear in mind, particularly in view of the current prominence of the FOAD hypothesis.

b. Fetal growth, blood pressure, dyslipidaemias and impaired glucose tolerance (IGT)

In addition to its link to adult disease, IUGR is clearly found, in both adults and children, to be associated to a higher risk of high blood pressure and impaired glucose tolerance. Its association to the most important dyslipidaemias (i.e. high triglyceride and low HDL-c levels) is less clear cut.

At least in a statistical sense, the association of IUGR to these biological risk factors does not appear to mediate its link to CVD, though this may reflect the limitations of available data. In the case of diabetes, a mediating effect of the association to IGT seems more indicated.

c. Population and cohort differences: importance of the post-natal context

Though associations between IUGR and disease risk are found in most populations studied, some evidence shows conflicting results, indicating the existence of important population and cohort differences in the relationship of fetal growth to later disease. Examples include the apparent lack of an association between small size at birth and diabetes in Indians; the absence of a relationship between IUGR and blood pressure in some black populations; and the divergent relationship between IUGR and impaired glucose tolerance in children and adults in India.

These population and cohort differences may reflect underlying genetic differences, expression of genes, and/or the impact of divergent post-natal contexts and environments. The latter may reflect differences in a particular populations' stage of the epidemiological or nutritional transition or, between cohorts of the same population, the result of rapid social and economic change.

d. Interaction between IUGR and later weight or height gained: importance of post-natal nutrition

Increasing evidence indicates the association between IUGR and later disease risk is somehow mediated or enhanced by the rate of growth in weight or height in childhood or adolescence.

The apparent role of growth in weight or height is indicated by three factors:

- in most cases significant associations between low size at birth and later disease risk factor are only found *after* adjustment for current weight
- in many cases the association between low birth weight and disease risk is strongest in those with highest BMI or fatness
- in some studies the association between IUGR and disease risk is shown to be highest in individuals who have had accelerated growth in height to become tall.

It is not yet clear how this apparent effect of post-natally gained weight or height is to be interpreted, but four (not mutually exclusive) interpretations are possible:

i. It represents a negative effect of enhanced growth in childhood or adolescence *per se*. In other words, accelerated growth in weight (or height) itself could have negative consequences.

ii. It is the *difference* in size between birth and the later stage that better defines detrimental impaired early growth: the higher the difference, the higher the risk (see e.g. Lucas *et al*. 1999).

iii. Obesity reveals/activates an underlying susceptibility induced by impaired early growth and, vice versa, low birth weight enhances the risk associated to obesity, i.e. obesity is particularly harmful in those with early growth retardation.

iv. The effect of enhanced growth in height in IUGR babies may reflect a failure of the fetus to realise its genetic growth potential *in utero*, possibly due to placental failure. It may be this insult on fetal growth that underlies the

increased risk of disease (e.g. Leon et al. 1996).

Whilst the particular interpretation may depend on the specific disease or risk factor concerned, they all indicate the importance of an adequate post-natal nutritional environment in bringing to the fore a risk associated with fetal growth retardation.

Further evidence for this comes from the discrepant findings of the two existing famine studies. Whereas an associations between exposure to famine and later disease risk were found in the Dutch famine, which was followed by a period of adequate nutritional supply, no association was found in the Russian famine, which was followed by a long period of inadequate nutritional supply. Another indication of the importance of the post-natal nutritional context are the marked rural-urban differences in CVD and diabetes risk, for example in India. While low birth weight is more common in rural areas, disease risk is much higher in the nutritionally more adequate urban areas (e.g. Yajnik, 2000).

e. IUGR and increased risk of obesity—a paradox?

The crucial question of whether IUGR also enhances the risk of obesity in a nutritionally rich post-natal environment (i.e. the thrifty phenotype hypothesis) is still unresolved.

The available evidence is inconclusive and presents a paradox by consistently showing a positive, often linear, relationship between birth weight and obesity (BMI) which is difficult to reconcile with the association between low birth weight and higher risk of disease.

A possible explanation of this paradox may lie in the inadequacy of BMI to adequately measure fatness, thus disguising a possibly important relationship between low birth weight and greater risk especially of central body fat.

f. Mechanisms underpinning the association of fetal growth to disease risk

The mechanisms and processes underpinning the association between retarded fetal growth and later disease risk remain poorly understood.

The mechanisms and processes underpinning the association between retarded fetal growth and later disease risk remain poorly understood.

The generation of a greater understanding has, amongst others, been hampered by the somewhat haphazard use of multiple measures of birth size, and by the limitations of low birth weight (the currently most commonly used index of fetal growth retardation) as an adequate marker to capture the range of possibly important exposures or birth outcomes.

The main unresolved issues include the following:

- the relative role of environmental versus genetic exposures
- the nature and role of intergenerational transmission of risk, including the role of maternal gestational diabetes, and parental body size and nutritional history
- the nature of the exposures that may lead to detrimental fetal growth retardation in particular the role of maternal nutrition in this
- the potential importance of the timing of insults *in utero*
- the potential endocrine, metabolic and haemodynamic adaptations that may occur in the fetus in response to insults, in particular the population relevance of the apparently important adaptations in the cortisol stress response system.
- the nature and significance of the apparent mediating effect of rapid post-natal weight and height gain, including the questions as to why catch-up growth is detrimental? and whether it has to occur in a specific period to be detrimental?

1.9.7 Importance of fetal vs. post-natal factors for population trends in disease

a. A greater importance of post-natal factors

The clear association of both fetal and of post-natal factors (incl. the classical established risk factors) to risk of CHD, stroke and diabetes raises the crucial question as to the relative importance of fetal vs. later factors in determining population patterns and trends in disease.

The evidence so far points to a limited role of fetal factors. Serious doubts exist concerning the causality of their association to disease, and indications are that their population attributable risk is small.

The rapid increases as well as the social patterns of risk factors, CVD, and diabetes in developing countries are clearly not explained by changes in fetal growth. Impaired fetal growth (low birth weight) has been pervasive for a long time whereas the epidemic in CVD and diabetes are a recent occurrence. In most countries, moreover, disease rates are much higher in urban areas although birth weights are much lower in rural areas.

The temporal trends and patterns of risk factors and disease in populations thus seem largely related to changes in post-natal lifestyle and environment. The period in which the trends, for example of CVD in developing countries, have evolved is too short for any changes in the gene pool to account for them.

b. Interaction (potentiating effect) between fetal and post-natal effects

Despite questions over the limited direct role of fetal factors in determining trends and patterns of disease, they may nevertheless have a potentially important influence if their effects depend in part on interactions with exposures in later life. The association of IUGR to risk factor development as well as its apparent interaction with obesity to enhance risk of disease suggests that, in many populations, fetal undernutrition may ***increase susceptibility*** to the adverse effects of life style or environmental change. In addition, it may have a ***potentiating*** effect on the risk of disease associated with obesity. These effects, given the apparent intergenerational transmission of risk associated to fetal growth, may last not just for one, but for several generations.

In many populations, fetal undernutrition may increase susceptibility to the adverse effects of life style or environmental change. In addition, it may have a potentiating effect on the risk of disease associated with obesity.

A potentiating effect of fetal growth retardation (which in statistical analyses would manifest in steeper slopes in the link between obesity and disease found in developing compared to developed countries) would have grave implications for the expected future rates of disease in the developing world.

PART II

Emerging implications for policy and research

2.1 Introduction

In light of the evidence on the influences of life course factors on the risk of CHD, stroke, and diabetes, several implications for policy and for research have been identified by the experts, and a set of firm recommendations have been made.

This second part of the report presents first the emerging recommendations for policy, and then the recommended research agenda.

2.2 Emerging implications and recommendations for policy

Whilst carrying a great potential for disease prevention, the move from research to policy based on the life course impacts on disease presents a great challenge. The disease specific nature of life course impacts on disease risk means that integration of policies may be difficult. There are no simple models such as, for example, in the case of tobacco.

Policies specifically geared to reducing the risk of one disease, may have no, or even adverse effects on the risk of another. Policies may, moreover, have different effects in different settings and cohorts, and could have possible unintended detrimental outcomes in the short term.

Much more, therefore, needs to be known about the life course influences on various diseases, in particular what aspects may be common to them, what trade-offs exist between short and possible long-term outcomes, and what effects prevail in different environmental contexts and in different cohorts. This notwithstanding, however, some clear implications and recommendations for policy already emerge.

Given that the scientific knowledge on life course and disease is still evolving, these recommendations are placed in a hierarchy according to the firmness of currently available evidence.

1. Firm positive recommendations for policy

- *Continue focus on major known risk factors*

The major known risk behaviours—unhealthy diet, physical inactivity and tobacco use—and the associated biological risk factors of obesity, high blood pressure, dyslipidaemias, remain the most firmly established causal factors for CHD, stroke and diabetes. These factors should therefore remain the focus of prevention policy.

The major known risk behaviours—unhealthy diet, physical inactivity and tobacco use—and the associated biological risk factors of obesity, high blood pressure, dyslipidaemias should remain the focus of prevention policy.

Fetal factors, given their potential importance in shaping risk of disease, also need to be considered. Above all, efforts are needed to develop a fuller understanding of the nature and basis of their effect.

Prevention policies should specifically ***focus on tobacco use*** and ***obesity***.

Prevention of tobacco use and, perhaps more importantly, reductions in total exposure to smoking over the life course by encouraging young adults to stop, must be a priority given its clear and reversible link to CVD and certain cancers; its alarming and rising prevalence among women and youth in many countries; and its detrimental effect not only on the health of those who use tobacco but also of the next generation.

A focus on obesity prevention is needed in view of the alarming global rises in its prevalence; its central role in the development of other risk factors; its potential interaction with retarded early growth to enhance disease risk; and finally its adverse effect also on the health of the subsequent generation.

In developing countries, obesity prevention policies must go hand in hand with strategies to prevent undernutrition.

- *Need for strategies of primary and primordial prevention*

Given that risk behaviours and factors are more commonly established in childhood and adolescence and 'track' through to adulthood, and given the difficulty of reversing especially obesity in adulthood, strategies of primary and primordial prevention are of utmost importance—though high risk lifestyle intervention strategies can clearly also be effective.

Primary prevention strategies should be aimed particularly at children, and preferably involve school-based health education and promotion programmes, focusing on behavioural and psychosocial components and aimed at promoting healthy diets, exercise and reduced tobacco use. Such strategies must be appropriate and responsive to the particular setting and to the prevailing cultural perceptions, for example regarding body weight.

Targeting primary prevention policies at the following groups may be beneficial:

- Young girls or women. Preventing tobacco use will not just reduce their own risk of disease but also the risk of low birth weight and later disease risk in their offspring. In the same vein, preventing obesity in girls or young women will not just benefit their own health, but also the risk of obesity and associated disease in their children. Given the critical effect of obesity development in adolescence, policies may perhaps focus particularly on pre-puberty girls
- Those socially or biologically disadvantaged from early life, for example, those with low birth weight, stunting, or exposed to gestational maternal diabetes, or with parents who are obese
- Youth at those ages where particular 'lifestyles' are adopted, i.e. where 'programming of lifestyle' occurs
- Adolescents and young adults who already smoke should be specifically targeted by efforts to help them quit smoking—the earlier one quits the greater the benefit

Strategies of primary and primordial prevention are of utmost importance.

Primary prevention strategies must be underpinned and complemented by ***policies of primordial prevention***. Such policies must address the various macro-structural social, economic, and cultural forces that influence and determine (or protect from) the uptake of risk behaviours among different populations in different settings, in particular in the developing world. Specifically, such policies should aim at:

- Reduction of advertising or positive cultural representations of known risk factors—e.g. tobacco or unhealthy foods
- Wide use of smoke-free environments
- Fiscal policies to reduce smoking
- Promotion of public healthy food policies
- Reduction of the influence of big food corporations, especially on the young
- Encouragement of public and private partnerships. This is the most realistic and promising way to move forward on creating healthy developmental environments, in particular with regard to adoption of risk behaviours such as tobacco use, poor diet and lack of physical activity.

- *Reduction of poverty*

Reducing poverty and increasing education will improve children's health trajectories both in relation to infectious and non-communicable diseases. Among girls, such strategies will not just improve their own health trajectories, but also that of their offspring in the next generation.

Policies, specifically to prevent severe undernutrition and stunting—as have already been successfully pursued in some populations—are likely to increase work capacity, intellectual functioning and educational achievement, and reduce risk of developing central adiposity. By additionally lowering the risk of low birth weight in offspring, such interventions may also reduce disease risk in the next generation. Concrete interventions, thus, could thus take the form of public support for nutrition programmes from infancy through school.

2. Unspecified recommendations

- *No clear direction regarding fetal growth*

Despite the high profile of evidence linking early life factors such as impaired fetal or childhood growth to risk of later disease, no firm policy recommendations can yet be made.

First, there are potentially important short and long-term negative effects and trade-offs of strategies to increase fetal growth. For increased fetal growth these include, in the short term, a raised risk for obstetric complications through growing larger babies in many developing populations. In the long term, they may cause a possibly increased risk of other chronic diseases: higher birth weight and stature, for example, are associated with a higher risk of some neoplasms.

Second, the U-shaped relationship between size at birth and risk of later diabetes or CVD, as well as the existence of apparent population and cohort differences in the association between fetal growth and later disease, indicate that no clear direction can yet be given in terms of what is the 'optimum' birth size to target for.

Third, current evidence casts serious doubt on the feasibility and effectiveness of currently

available interventions to modify fetal growth, in particular through maternal nutrition. Some strategies such as protein supplementation of maternal diet have, moreover, been shown to have negative effects including increased fetal mortality and reduced birth weight.

- *No direction on initiation, duration and exclusivity of breastfeeding*

Though breastfeeding seems promising as a protective factors against CVD and diabetes risk, the existence of evidence suggesting also potentially adverse long term consequences means that no specific recommendations can yet be made regarding initiation, duration and exclusivity. However, given its indisputable benefits to overall childhood mortality, unqualified support is given to breastfeeding *per se*.

- *Reducing stress*

There is some, though weak, evidence to suggest that general strategies to reduce stress in the adult environment (e.g. in the workplace) may be beneficial in reducing CVD risk—perhaps especially in poor populations, exposed to undernutrition *in utero*.

3. Firm negative recommendations for policy

- *Do not discourage post-natal growth*

Despite the existence of evidence showing that under certain conditions, enhanced growth (in weight or height) in childhood may be linked to a higher risk of insulin resistance or cardiovascular disease, this long term effect is outweighed by a far greater and more certain and scientifically established benefit in the short term for child health, through its links for instance with greater resilience to infectious diseases. Moreover, it is not yet clear in what particular period in childhood rapid growth has a detrimental effect. Strategies to reduce such growth are therefore, at this point, clearly not recommended.

2.3 Key priority areas for future research

The many gaps remaining in our knowledge of how early and later factors impact on risk of CHD, stroke and diabetes, highlight the vital need for more research. Only further research will be able to provide the information base necessary for effective and appropriate policy development in different populations.

The following four key areas have been identified by the experts as priority topics for future research:

1. **Research on causes and interactions**
2. **Trends analysis and surveillance**
3. **Intervention research**
4. **Refinement of methodology**

1. Research on causes and interactions

The core focus of, and challenge for future research must be efforts to investigate the early and later causes and interactions of life course links to later disease. Such research must address the following questions:

a. *The nature of the effects of fetal and post-natal growth on later disease risk*. This includes the interaction between intrauterine growth retardation and rapid post-natal catch-up growth, and obesity.

b. *The influence of maternal factors on fetal growth and offspring's risk of disease.* This includes maternal nutrition, GDM, maternal cardiovascular function and maternal psychosocial factors.

c. *The biological mechanisms underlying the association of fetal growth to later disease risk.* This includes the role of stress and hormonal response systems, and inter-generational processes of risk transmission.

d. *The association of infectious disease to chronic disease risk.* This includes the possibly infectious factor underpinning the particularly strong link of poor child SEP to haemorrhagic stroke.

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.

g. *The major risk factors for CVD and diabetes in developing country populations*.

Ideally, such research would involve:

- Well designed *prospective maternal and birth (or child) cohort studies*, to generate integrated life time measures of growth, risk factors, socio-economic, and psychosocial

parameters. One opportunity in this respect would be extension of the WHO road to health studies of child health and growth studies, beyond the age of five.

- **Historical cohort studies** with available data sets on early growth parameters. Possible examples include the Bambui or Pelotas longitudinal study cohorts in Brazil, or possibly a cohort from the 1956 famine in India. Potentially valuable cohorts may also be identified from past monitoring studies on maternal and/or child growth and development, especially in developing countries. Efforts are necessary, in this respect, to preserve and make such existing data sets accessible.
- **Multi-generational studies**, especially of migrants (and those remaining in the country of origin). The by now three generations of Asian migrants in the U.K., as well as Japanese migrants in Brazil may provide important opportunities for this.

2. Trends analysis and surveillance

Investigations of causes and interactions of life course links to later disease must be complemented by research to establish and analyse trends in risk factors and disease This would specifically involve:

a. *Surveillance of trends and socioeconomic patterns in major risk factors*

b. *Surveillance of trends and patterns in maternal and child health, nutrition and growth*

3. Intervention research

Investigations of causes and interactions and surveillance and analysis of trends must be complemented by research to assess the potential effectiveness and impact of interventions. This specifically includes:

a. *Comprehensive policy reviews on actions targeting under- and over-nutrition in developing countries*

b. *Investigation of the efficacy, long and short term effects (on both mother and child) of interventions to increase birth weight*

c. *Investigation of the short and long-term outcomes of enhanced early growth for infants born small*

d. *Establishment of the long term effects of breastfeeding with regard to non communicable diseases*

e. *Research to identify ways of applying current knowledge to prevention programmes*

4. Methodological issues

Finally, for life course research to be as effective as possible, efforts are necessary to improve on existing, or foster certain methodologies. This involves:

a. *Improvement of measures of intra-uterine growth retardation (alternatives to low birth weight).* These must reflect new born body composition and fetal exposures that may not necessarily be expressed in birth size.

b. *Improvement of measures of early socioeconomic disadvantage and psychosocial experiences*

c. *Improvement of measures for adiposity, and establishment of appropriate population norms across the life course*

d. *Improvement of reliability and accuracy of measures for blood pressure and establishment of appropriate population norms*

e. *Development of specific measures for underlying pathophysiological factors, e.g. endothelial dysfunction*

f. *Conduct of comparative research between populations at different stages of the epidemiological/nutritional transition, as well as between cohorts.*

Comparative analyses can powerfully illuminate the role of the postnatal environment in shaping disease risk in interaction with early growth experiences.

3.4 Conclusion: Taking policy and research agendas forward

The experts' recommendations on policy and research in light of current evidence on the life course links to CHD, stroke and diabetes present a vital starting point for harnessing the potential of the life course perspective to identify the most appropriate and effective prevention policies in different populations.

WHO, together with the group of experts who are committed to guiding and supporting its efforts, is taking steps to foster this life course initiative, through collaborative work and con-

sultation across departments within WHO and with partner institutions.

A specific focus of this work will be the development, in consultation with the experts, of a protocol for a multi-centre comparative study to address some of the key gaps in knowledge on life course and NCD risk in different populations—especially in developing countries.

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Glossary of terms and abbreviations

AR	Adiposity Rebound
BMI	Body Mass Index
BP	Blood Pressure
CAH	Child and Adolescent Health
CHD	Coronary Heart Disease
GDM	Gestational Maternal Diabetes Mellitus
HDL-c	High Density Lipoprotein Cholesterol
IGT	Impaired Glucose Tolerance
IR	Insulin Resistance
ID	Insulin Deficiency
IUGR	Intrauterine Growth Retardation
LBW	Low Birth Weight
LDL-c	Low Density Lipoprotein Cholesterol
NCD	Noncommunicable Diseases
NPH	Department of Noncommunicable Diseases Prevention & Health Promotion
SEP	Socioeconomic Position
TG	Triglycerides
WHR	Waist to Hip Ratio

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