1 The Demographic and Epidemiological Context

When is a person's lifespan determined? At conception through genes, *in-utero*, during childhood and adolescence, or at adult ages through environmental factors? Different opinions prevailed at different times in the course of the 20th century and are still hotly debated. Infancy and childhood were seen as the critical phase in the first thirty years of the twentieth century. Since then the emphasis has been more on lifestyle factors and, thus, adult ages. Since the 1970s, however, new evidence has been emerging that chronic disease is rooted in infancy and childhood. An influential theory developed in the course of the last decade traces the causes of heart disease and diabetes back to the womb. The theory claims that the mother's nutrition and any infectious diseases she might have had during pregnancy are responsible for an increased susceptibility of the child to heart disease and diabetes once it reaches adult ages. The interpretation of this recent research has been challenged, however. Deprivation *in-utero* and during childhood may simply be the starting point of deprivation throughout life. The increased susceptibility later in life may thus be the result of the life-long accumulation of detrimental effects.

The month of birth fits into the debate about whether chronic disease at adult ages is determined by "programming" *in-utero* or in childhood on the one hand, or whether early-life factors are mediated through the lifelong accumulation of detrimental effects. To contribute to the debate, an indicator of the environment early in life is needed which does not have any life course interpretation. Starting with the work of Ellsworth Huntington (1934) a large body of epidemiological research (see Chapter 5) proposes that month of birth is just such an indicator. This monograph takes up this idea and explores the month-of-birth pattern in survival and causes of death. An extensive part of this monograph, however, is devoted to the question whether month of birth is indeed free of social confounding and of life-course interpretation.

If month of birth is a measure of the seasonal changes in the environment early in life and is independent of life-course factors, then the differences by month of birth indicate that the very first period of life influences late-life mortality and the susceptibility to chronic disease.

This chapter follows the debate about the critical age at which adult mortality is determined from the first articles that were published at the beginning of the 20th century to the most recent research today. With a better understanding of this research, the reader of this monograph will be able to put the results of the following chapters, which mainly deal with the differences in life span by month of birth, into a broader perspective.

Cohort analysis from the 1920s and 1930s for England, Wales and Scotland (Derrick 1927, Kermack, McKendrick & McKinley 1934) suggested that, up until 1925, year of birth was more important than year of death for predicting mortality. In 1927, Derrick plotted age-specific mortality rates for the period 1716 to 1916 against year of birth – rather than year of death – and found that the curves were strikingly parallel. The parallel curves imply that the relative mortality decline of successive birth cohorts is the same in all age groups. Derrick rightly interpreted the parallel curves as indicating that each succeeding cohort experienced a lower mortality risk at all ages. This is contrary to period effects, which would affect different age groups in different birth cohorts and would thus distort the parallelism of the mortality trajectories.

Derrick excluded child mortality under the age of ten because he was interested in the general law of mortality. He argued that the environmental improvements that had resulted in the reduction of child mortality would disturb this general law. Seven years later Kermack, McKendrick and McKinley postulated that it is the level of child mortality that determines the mortality of the cohorts at older ages. In their 1934 article, which has recently been reprinted (Kermack et al. 2001), they used the same data as Derrick but included child and infant mortality. They took the age-specific mortality in the year 1845 for England and Wales as their base year and calculated the relative mortality of the same age groups in the period 1855 to 1925 relative to that base year. They found the following general pattern: that cohorts carried with them the same relative mortality throughout life. At each age, each succeeding cohort had a lower relative mortality than the previous cohort. However, infant mortality did not follow this general pattern and only started to decline after the turn of the century, well after mortality at later ages. The authors argue:

"It has been observed that the improvement in the infantile death-rate became apparent only after 1901. If we remember that before birth and during its first year of life, the child is dependent of its welfare to a very large degree upon the general health and vitality of the mother, then it would be expected that a substantial improvement in the health of the latter would show itself in a reflected improvement in the infantile death-rate. The mothers of 1901 would on the average be born about 1870 or possibly a

little later, and, (...), the health of females born at that date has so far improved that the death-rate was improved by about 30 per cent in the case of Scottish and by about 40 per cent in the case of English mothers. It is suggested that this may constitute at least one of the factors conducive to the improvement of infantile mortality in the present century." (p. 681, Kermack, McKendrick & McKinley 1934, 2001)

As an explanation for the regularity of the relative mortality-rates at ages other than infancy and childhood they remark that "the figures behave as if the expectation of life was determined by the conditions which existed during the child's earlier years." And they postulate

"..the health of the child is determined by the environmental conditions existing during the years 0–15, and (...) the health of the man is determined by the physical constitution which the child has built up." (p. 680, Kermack, McKendrick & McKinley 1934, 2001)

The latter two statements obviously contradict the first statement about the onset of the decrease in infant mortality. Since the onset of the decrease in infant mortality is delayed in comparison to the onset of the decrease in adult mortality, it can hardly determine the mortality of the survivors of each cohort.

Despite this contradiction (see also Harris 2001) their paper was a landmark in the analysis of birth cohort influences on adult disease risk since it was the first to formulate hypotheses regarding early-life exposures and their influence on later disease (Davey Smith & Kuh 2001).

Kermack et al. (1934, 2001) performed a similar analysis for Sweden in which they calculated mortality rates relative to the base year 1755. The cohort decline is not as clear in the case of Sweden as it was for England and Wales. The authors argue that a rectangular block dating from 1855 onwards and affecting the age groups 10 to 30 years was the primary cause of disturbances in the cohort decline. If the block is omitted, a cohort decline is observed. This result could not be replicated, however, in a study of Swedish mortality between 1778 and 1993 by Vaupel et al. (1997). The authors calculated the probabilities of death relative to age-specific levels from 1778 to 1799 and plotted them in form of a shaded contour map. They come to the conclusion that "the pattern is clearly more complex than a pure cohort-effect model would suggest" (Vaupel et al. 1997, p. 63). Further studies which took death rates relative to a period earlier than 1870 and which found a pattern that suggests a cohort decline in adult mortality were conducted by Preston and van der Walle (1978) and Coale and Kisker (1990).

In their review of the historical debate on the question of when the mortality risk is determined, Kuh and Davey Smith (1993) show how these early studies influenced public health policies in Great Britain. Public interest in early-life determinants of adult mortality soon dissipated, however. One reason for this was that the year of birth lost its predictive power in terms of mortality prediction by 1925 and period factors became more and more important. Davey Smith and Kuh (2001) updated the table of relative mortality-rates for England and Wales from the Kermack paper and showed that there are dramatic differences between observed and predicted mortality rates. At younger ages, mortality rates fell faster than predicted on the basis of birth cohort regularities, whereas at older ages, mortality declined at a much slower rate than predicted.

Elo and Preston (1992) point out that these early studies were probably so successful in demonstrating cohort effects because they were based on mortality data from a time period before the process of mortality decline on a period level had begun. Once both cohorts and periods began to show mortality improvements it became more difficult to separate the two. Period factors of mortality gained importance as the mortality spectrum shifted from infectious disease towards chronic disease. In the middle of the 19th century, over a third of the deaths in the 15–55 year age group and 15 percent of the deaths at ages 45–64 in Great Britain were due to respiratory tuberculosis (Davey Smith & Kuh 2001). In the United States, TB remained the second leading cause of death at the turn of the century, when it accounted for approximately 11 percent of all deaths (Elo & Preston 1992 citing Mason & Smith 1985). Respiratory tuberculosis is the major cause of death in which childhood conditions are implicated in cohort mortality, and it has received extensive treatment in the analysis of cohort effects on mortality. Davey Smith & Kuh (2001) mention John Brownlee (Brownlee 1916) and the report of the British General Registrar in 1921 (Greenwood 1936) as the first studies that dealt with cohort effects in respiratory tuberculosis. The most frequently referenced article is Frost (1939), where it is pointed out that the changes in mortality from tuberculosis were more consistent on a cohort than on a period basis. Mason and Smith (1985) came to the same conclusion when analyzing the trend in respirator tuberculosis in Massachusetts from 1880 to 1970. Each following cohort had a lower mortality than the previous one, while period coefficients showed little trend with the exception of the advent of successful chemotherapy after 1950 (Elo & Preston 1992). Tuberculosis in late adulthood is believed to originate in infections during childhood. Thus, im-

provements in earlier life conditions should be reflected in a lower incidence of tuberculosis later in life.

Davey Smith and Kuh (2001) mention stroke, stomach cancer and bronchitis as other important contributors to adult mortality that declined between the mid-19th century and today. For all three of these ailments, there exists evidence of important early-life influences or of a declining birth cohort pattern.

With the shift from infectious to chronic disease in the course of the 20th century, coronary heart disease and lung cancer dominated adult mortality. Coronary heart disease initially shows period-specific rather than cohort-specific increases, and lung cancer shows cohort-specific increases, which reflects the fact that successive groups of young adults take up smoking (Davey Smith & Kuh 2001). Additionally, the introduction of antibiotics for the treatment of infectious disease, which became increasingly effective from the end of the 1930s, influenced mortality in a period-specific rather than a cohort-specific way. Taking all these factors together,

"...the change in the cause-of-death profile (and thus of particular aetiological agents) and the development of medical therapeutics led to change in the relative importance of birth cohort and period effects on all-cause mortality. This change coincided with a shift in focus of public health and epidemiological thinking, from the importance of childhood environment (in particular childhood nutrition) to the importance of adult lifestyles, as major determinants of population health." (p. 696, Davey Smith & Kuh 2001).

It wasn't until the end of the 1970s that the idea of early-life influences on mortality was taken up again. In 1973, Forsdahl published his first paper in a series of five about the effect of very poor living conditions in childhood and adolescence on adult mortality (Forsdahl 1973). This paper, which was originally written in Norwegian, has recently been reprinted in English (Forsdahl 2001). Forsdahl observed that, ever since the start of registration of county mortality in Norway, the mortality of the county of Finnmark has been higher than for the rest of the country. Current socioeconomic differences or current differences in life-style behavior like smoking or diet could not explain the difference in mortality. He concluded that the mortality rates, which are 25 percent higher than in other parts of Norway, must be the result of events during childhood and adolescence. To test this hypothesis, he gathered data on infant mortality and adult mortality for the municipality of Sør-Varanger in Finnmark, which is

situated between the northern parts of Russia and Norway and is the most remote municipality in the country.

Forsdahl writes in his commentary to the reprint of his paper (Fohrsdahl 2001a) that he was particularly qualified to do the investigation of this region since he grew up in this municipality, where his father was a district doctor and where later, from 1963 to 1974, he became the district doctor. He found that infant mortality in Sør-Varanger was consistent with the infant mortality pattern in Finnmark and that in the past, both had been more than twice as high as in Norway as a whole. Only in the most recent years of his analysis did the infant mortality rates in Norway as a whole and those of Finnmark and Sør-Varanger converge. When he divided the population of Sør-Varanger into people of Finnish and non-Finnish origin he found that both infant mortality and adult mortality are higher for the Finnish than for the non-Finnish population. He observes that, in the past, the Finnish part of the population was generally employed in the more vulnerable branches of the economy such as farming and fishing. At the beginning of the 20th century, Sør-Varanger suffered twice from famine, particularly in regions where the Finnish population is in the majority. In addition, the fertility of the Finnish population was higher and people lived in more crowded environments than the rest of the population. Since the 1950s these differences have disappeared and at the time when he wrote his paper he did not find any difference in current socio-economic and current lifestyle behaviors between the two groups. He concluded his article by observing that

"This study may suggest an association between very poor living conditions in childhood and adolescence and high mortality in adulthood so that the worse the living standards, the higher the later mortality. Thus, one should not expect that the difference in mortality between Finnmark and the rest of the country will disappear until the generation that grew up under these adverse conditions are gone." (p. 307, Forsdahl 2001).

Already in his first paper he mentions that the difference in mortality between the Finnish and the non-Finnish population is mainly due to arteriosclerotic heart disease. Four years later (Forsdahl 1977), he confirmed in an article the hypothesis that poor living conditions in childhood are positively correlated with the risk of dying from arteriosclerotic heart disease. He compares the twenty county rates of all-cause mortality among adults aged 40 to 69 in the period 1964 to 1967 with county infant mortality during the period of their childhood and youth (1896 to 1925). He finds a positive correlation of 0.93 for men and a somewhat weaker correlation

of 0.75 for females. This implies that, in counties where infant mortality was high, the same generation had high mortality later in life. The correlation was particularly high and highly significant for arteriosclerotic heart disease and for lung cancer. When he compared adult death rates at county level to current levels of infant mortality, the correlations disappeared. In his next paper he reports a positive correlation between infant mortality and serum cholesterol levels of the same generation at ages 34 to 49 (Forsdahl 1978). In this paper he further develops the explanation given above and suggests "poverty in childhood and adolescence, followed by later prosperity, results in high cholesterol levels."

Forsdahl's analyses have been subject to criticism because he did not control for current socio-economic circumstances, current lifestyle factors or any other current or historical characteristics. He thus cannot exclude the possibility that what he observed was the indirect effects of childhood environment mediated through current life-course conditions. Despite this valid criticism, his studies stand out insofar as they re-introduced the idea that the critical period determining adult mortality is childhood and adolescence. His analyses are the first in a long series of ecological studies that investigated the relationship between infant and childhood mortality and adult mortality of the same generation by geographical area.

The 1980s saw a resurgence of interest in the effects of early-life conditions on late-life mortality which continues up to the present today. Researchers have mainly applied three approaches to demonstrate the importance of early-life conditions. Following the approach of Derrick and Kermack, they tried to separate period and cohort effects; they undertook ecological analysis following Forsdahl's ideas; and they studied the relationship between anthropometric measures, particularly height, and adult mortality. Elo and Preston (1992) reviewed these studies extensively.

1.1 Cohort Studies

Since the 1930s both cohort and period effects have simultaneously influenced old-age mortality. Thus, more sophisticated models were needed to separate the two. Again, Elo and Preston (1992) extensively reviewed those cohort studies that were published until the beginning of the 1990s and this part draws on their results. Caselli and Capocaccia (1989) studied trends in Italian mortality during the 20th century and tried to shed light on the effects of mortality decline in infancy and childhood on a cohort's mortality at older ages. They used age-specific probabilities of dying between the ages of 29 and 79 for the time period 1907 to 1978. These co-

horts were born between 1882 and 1953. The cohorts had experienced very different patterns of early mortality – for example, the probability of men surviving to age 15 had increased from 68 percent in 1918 to 82 percent by 1935 (Caselli 1990). The authors estimated logistic regression models of age-specific probabilities of dying which included age, period and a cohort's infant mortality or a cohort's probability of dying during the first 15 years of life as independent variables. Introducing an interaction effect between the latter two variables and age allowed them to study which ages were most affected later in life by changes in early-life mortality. They found that for both sexes higher mortality between the ages of 0 and 15 was associated with higher mortality between the ages of 25 and 45. At older ages, they found the opposite effect, although slightly weaker.

A number of studies (Horiuchi 1983, Wilmoth 1986, Caselli et al. 1987, Vaupel et al. 1987, Wilmoth et al. 1989) took advantage of abrupt changes to identify cohort effects. During the 20th century, the two major wars constituted abrupt changes which affected different cohorts at different ages. A number of these studies found elevated mortality for cohorts who were either born during the two world wars or were in their adolescence at the time. Both male and female children born during World War I in Italy, France, and the former Soviet Union have subsequently experienced higher mortality. Cohort mortality was elevated for German male cohorts whose members were adolescents during World War I. Elevated cohort mortality after World War II has been found for Japanese male cohorts and cohorts of both sexes from the former Soviet Union whose members were adolescents during the war. Both wars affected the subsequent mortality of adolescent cohorts in France and in Italy. Generally, the effect was somewhat stronger for males than females, which suggests that the effects on male cohorts may be due to their participation in the wars at very young ages rather than to nutritional deprivation or poor health conditions.

One example from epidemiological research in which a cohort effect was originally attributed to World War I but is now believed to be rooted in poor living conditions during childhood is peptic ulcer morbidity. Susser and Stein (1962) observed:

"the timing of the first world war, and the unemployment of the 1930s, roughly fit the fluctuations, and the cohorts with the highest peptic-ulcer death-rates were also the chief victims of the first world war. The immediate effects of war are evident in the rise in perforations and deaths from peptic ulcer which followed air-raids and the stress of war. Perhaps in a chronic condition such as this acute events might precipitate prolonged effects". (Susser & Stein 1962, cited by Davey Smith & Kuh 2001)

In 1985 Sonnenberg and colleagues demonstrated that birth cohort dependency of peptic ulcer morbidity could be seen in many countries and that the causative factors became effective before age 15 (Sonnenberg, Mueller & Pace 1985 Sonnenberg 1987). The probable explanation of the cohort effects today is H pylori infection, which occurrs during childhood and is associated with peptic ulcer many years later (Susser 2001). The most recent study analyzes peptic ulcer morbidity and mortality in Iceland (Thors et al. 2002) and cites twelve studies that had demonstrated a cohort pattern previously. The authors find that in Iceland, for all manifestations of peptic ulcer, the disease risk was particularly high in individuals born just after the turn of the century and that it was lower in previous and subsequent cohorts. This time period saw the advent of the fishing industry, which led to overcrowded and poor living conditions. The same cohorts that experienced the highest risk of peptic ulcer disease were also the cohorts with the highest prevalence of H pylori antibodies.

Influenced by the fetal origin hypothesis – which suggests that nourishment before birth and during the individual's infancy programs the development of risk factors for several important diseases of middle and old age – several studies have investigated the effect of famine on cohort mortality. The results, however, are not conclusive. Between 1866 and 1868 a severe famine hit Finland. Kannisto et al. (1997) studied the cohort mortality of more than 600,000 individuals born 5 years before and after the famine and of about 160,000 individuals born during the famine. They found that survival in childhood and adolescence was significantly lower for cohorts born before and during the famine. At subsequent ages, however, including old age, mortality for those born during the famine did not differ from the mortality of those born before or after it.

The effect of the Dutch famine in 1944-1945 on later life disease and mortality is explored in a series of study (Rosenboom et al. 2001, Rosenboom et al. 2000a, Rosenboom et al. 2000b). The authors find that mortality up to age 18 was higher for those born before the famine and those exposed to the famine in the third trimester. Between the ages of 18 and 50, however, no effect of prenatal exposure to the famine could be demonstrated. Results differed for atherogenic lipid profile and heart disease later in life because those who were exposed during early gestation had an increased risk.

Two studies about the long term effects of severe starvation during the siege of Leningrad come to contrary results. (Stanner et al. 1997, Sparén et al. 2003). Stanner et al. did not find a long term effect in 549 children who were born in or near Leningrad during the siege: neither blood pressure, nor glucose intolerance nor lipid concentrations were increased in adult

life. In the latter study Sparén et al. find increased blood pressure levels, an increased risk of ischemic heart disease including haemorrhagic stroke among men who experienced the siege at the onset or during puberty They conclude that starvation, or accompanying stress, during adolescence may increase vulnerability to later cardiovascular disease.

Bengtsson et al. (2001) analyzed the effect of environmental stress on old-age mortality in Sweden for the period 1760–1894. They used infant mortality of an individual's cohort to measure the disease load early in life and rye prices to account for nutritional changes. They did not find a significant effect of rye prices during the first years of life on late life mortality, and they also rejected the hypothesis that the disease load on the mother during pregnancy affects the adult mortality of her child. They did, however, find a significant effect of the crude death rate in the first year of life on later-life mortality. The authors concluded that the disease environment in the first year of life rather than nutrition *in-utero* is the critical factor that influences late-life mortality

1.2 Ecological Studies and Place of Birth

Barker and colleagues (Barker & Osmond 1986a, 1986b, 1987, Barker et al. 1989a, Barker et al. 1990, Osmond et al. 1990) performed the most extensive series of ecological analysis to date. Basically, all these studies follow one general research design. They compare adult death rates for specific age groups with infant mortality rates for the same generation on the basis of local administrative regions in England and Wales. In their initial paper (Barker & Osmond 1986a), they found high positive correlations between infant mortality in 1921–1925 and standardized mortality ratios for chronic bronchitis, ischemic heart disease, stomach cancer, and rheumatic heart disease among adults in 1968–1978. For lung cancer and stroke the associations were weaker. They did not correct for any other current or historical conditions. In their next paper – using the same data – they studied the relationship between geographical distributions of infant mortality from bronchitis and pneumonia and current distributions of mortality at ages 35–74 from chronic bronchitis. They found that infant mortality from bronchitis and pneumonia were more closely related with adult mortality from chronic bronchitis in the periods 1959–1967 and 1968–1978 than with any other major cause of death. They controlled for smoking behavior by including lung cancer death rates in their regression model, since smoking is one of the established risk factors for lung cancer. The authors concluded that pulmonary infections in infancy may have per-

sistent effects and raise the risk of death from chronic bronchitis in adulthood. In their next study (Barker & Osmond 1987), they use maternal mortality as an indicator of intrauterine environment and demonstrate a positive correlation between maternal mortality rates in 1911–1915 and mortality from stroke among people aged 55–74 in 1968–1978.

Their next article further develops the idea that the increased susceptibility to cardiovascular disease and chronic bronchitis originates in the intrauterine and early postnatal environment (Barker & Osmond 1989). Barker refers to this study as the first one to show that coronary heart disease results primarily from poor conditions *in-utero* (Barker 2002). Using 212 local authority areas by age at death, the authors found that the geographical distribution of the death rates of stroke at ages 35–74 between 1968 and 1978 are more closely related to neonatal mortality (mortality in the first month) of the same generation than to post-neonatal mortality (mortality between the ages of two months and one year). The reverse is true for ischemic heart disease and bronchitis. This study may thus be seen as the founding study for the fetal origins hypothesis, which states that chronic disease later in life is caused by programming of the infant *in-utero*. It suggests to Barker, that

"...research should be directed towards the intrauterine environment rather than the environment of late childhood-housing, family income, diet, and other influences." (p. 1111, Barker 1990)

The above statement explains why he writes in his commentary to the reprint of Forsdahl's 1993 article:

"Forsdahl's best known paper is entitled: Are poor living conditions in childhood and adolescence an important risk factor for ateriosclerotic disease? The short answer is that they are not." (p. 309, Barker 2002)

However, the ecological studies by Barker and Osmond have been heavily criticized (e.g. Elo & Preston 1992) because the authors failed to control for current socioeconomic conditions, the statistical details presented were insufficient to judge the significance of the reported results, the units and dates of the analyses changed haphazardly from study to study, and statistical controls were inadequate.

In 1991 Ben Shlomo and Davey Smith (1991) addressed the idea that the relationship between past infant mortality rates and present adult mortality simply reflects an unchanging distribution of impoverished socioeconomic circumstances over time. They used infant mortality rates for the period 1895–1903 from 43 administrative county units in England and

Wales and calculated the correlation with current mortality rates with and without correction for current socioeconomic circumstances. They found that the correlations between infant mortality and adult death rates only remained significant for bronchitis, emphysema and asthma when current socioeconomic conditions were corrected for.

Ecological studies of similar research designs have been continued for different countries up to the present (e.g. Elford et al. 1992, Pringle 1998, Maheshwaran et al. 2002, Leon & Davey Smith 2000). Other studies have looked at migrants within a country and whether region of birth contributes to adult mortality independently of the region of residence (Strachan et al. 1995, Schneider et al. 1997a,b, Regidor 2002). Most recently, a survey which was undertaken by Charles Booth at the end of the 19th century in London was digitized using GIS (geographical information systems). The survey portrayed the social and economic conditions and displayed the social classes of inner London on a street-by-street basis. These maps have been digitized, geo-referenced and linked to contemporary ward boundaries. This linkage allowed one to match Booth's measurements of social class with measurements of social class in the 1991 census population and with standardized mortality rates for cause-specific death (Dorling et al. 2000, Orford et al. 2002). An index of relative poverty was calculated for the end of the 19th and 20th centuries respectively. Using partial correlation coefficients, they found that the index of poverty derived from Booth's 19th century observations contributed more to predicting deaths from stroke and stomach cancer in the late 20th century than the index derived from the 1991 census. For other causes of death the modern index contributed more. The authors of the study point out that almost everyone surveyed by Booth's enquiry will have died or moved by 1991. The 19th century index therefore is a truly ecological index and describes area type rather than aggregate characteristics of the resident population. They conclude that the

"ecological associations with past and present deprivation levels of areas do reflect individual level associations of deprivation at different stages of the life course and health outcomes. In short, the longer people spend both in poverty and in poor places, the earlier they tend to die." (p. 1547, Dorling et al. 2000)

The above statement is the antipode of the theory proposed by Barker. To answer the question which of the two hypotheses is true, study designs other than ecological ones were needed. Thus, in the 1990s the emphasis shifted to longitudinal studies on the individual level which included both

information about early-life circumstances and life-course information for adult ages.

1.3 The Fetal Origins Hypothesis of Adult Diseases

Since it takes decades for a cohort to age, Barker and his colleagues decided to take a retrospective approach. They traced subjects for whom data are available from their first year of life. They followed up on a historical cohort of 5,654 men born between 1911 and 1930 in Hertfordshire, England (Barker et al. 1989). Information about early-life circumstances was obtained from records kept by attending midwives and local health visitors who made periodic visits during the first year of life. The authors' analysis showed that men with the lowest birth weights and weights at age one had the highest death rates from coronary heart disease and chronic obstructive lung disease. For other causes of death no such trend was seen. Joseph and Kramer (1996) cite 30 studies that followed the same retrospective study design. They investigated the link between measurements of placental weight, birth weight, abdominal and head circumference, ponderal index at birth, weight at age one, infant feeding practices, maternal skinfold thickness and maternal weight gain in pregnancy. The outcomes that were associated with these measurements were clinical phenomena such as blood pressure, serum cholesterol, plasma glucose, plasma fibrinogen, serum concentrations of factor VII and immunoglobulin E, abdominal obesity, and lung function. Direct associations have also been observed between fetal and/or infant growth indices and the prevalence of coronary heart disease, renal complications, and autoimmune thyroiditis. Birth weight, weight at age one and type of infant feeding were correlated with mortality from coronary heart disease, cardiovascular disease, chronic obstructive lung disease, ovarian cancer, and suicide.

Based on these findings it has been hypothesized that physiological or metabolic "programming" occurs at critical periods of early development and substantially determines the occurrence of pathological phenomena later in life. Barker and his colleagues originally proposed this theory in their 1989 paper and have since then further developed it. Most recent studies (Eriksson et al. 1999, Forsen et al. 1999, Eriksson et al. 2001, Forsen et al. 2000, Eriksson et al. 2000) suggest that low birth weight, shortness or thinness at birth, followed by poor infant growth and thereafter rapid growth are associated with coronary heart disease, hypertension and type 2 diabetes. Barker writes:

"People who are small at birth remain biologically different through life because of the persisting constraints and adaptations that accompany slow early growth. Their different morphology and physiology leads them to respond differently to the biological and social environments in later life. Thus the discontinuity in nutritional experience that leads to later disease does not seem to be primarily poor nutrition in childhood and adolescence followed by excess nutrition in adult life (...). Rather it is poor nutrition in-utero and during infancy, the so-called 'fetal' phase of endocrine control of growth, followed by improved nutrition in the second phase of growth, which begins in early childhood " (p. 310, Barker 2002)

One of the strongest and most consistent lines of support for the fetal origins hypothesis of adult disease has been a large series of studies about the relationship between low birth weight, indicating restricted fetal growth, and increased blood pressure later in life. It has been estimated that 1 kg higher birth weight is typically associated with a 2–4 mm Hg lower systolic blood pressure (for a review see Huxley et al. 2002). A recent paper by Leon et al. (2000) demonstrates that among 165,136 Swedish men aged 18 years a 1 kg increase in gestational age-adjusted birth weight was associated with a fall of 1.6 mm HG in systolic blood pressure. However, it has been pointed out (Kramer 2000) that a 1-kg difference in birth weight is enormous (about five or six times the difference in mean birth weight between infants of smoking and non-smoking mothers) and reasonable differences in birth weight are more in the range of a 100g. This makes the effect of birth weight on adult systolic blood pressure levels rather small. In addition, frequent concerns are voiced about confounding by socioeconomic status (e.g. Joseph & Kramer 1996, Kramer 2000).

A recent study by Huxley et al. (2002) casts further doubt on the causal pathway between low birth weight and increased blood pressure. The authors review 55 studies that reported regression coefficients of systolic blood pressure on birth weight. When they weighted each study with the inverse of the variance of the regression coefficient to correct for "statistical size" they found a clear trend: the association between birth weight and blood pressure was weaker in larger studies. It ranged from -1.9 mm HG/kg in those with less than 1,000 participants to -0.6 mm Hg/kg with more than 3,000 participants. Furthermore, in 49 studies which only reported the direction of the association but not the correlation coefficient, only 25 studies found an inverse association. The authors come to the conclusion that the

"strong association between birthweight and subsequent blood pressure may chiefly reflect the impact of random error, selective emphasis of particular results, and inappropriate adjustment (...) for confounding factors. These findings suggest that birthweight is of little relevance to blood pressure levels later in life." (p. 659, Huxley et al. 2002)

1.4 Life-Course Factors

The main idea underlying the fetal origins hypothesis of adult diseases is that a critical time period exists early in life. Exposure to deleterious factors during this critical period affects adult health, independently of intervening experience later in life. In an extension of this theory, effect modifiers later in life, e.g. the catch-up growth of low birth weight babies, are recognized. The pathway is predominantly biological.

A life-course approach takes into account that there are mediating factors between the exposure early in life and the manifestation of the disease later in life. A second pathway may be that negative social factors in the early-life environment set individuals onto life trajectories that negatively affect their later health. This pathway is predominantly social. A third pathway is that the cumulative effects of repeated exposure to negative factors adversely affect one's health status either through a biological process (e.g. repeated infections per se) or through a social process (e.g. repeated infections resulting in lower educational attainment).

The life-course approach to chronic disease epidemiology challenges the idea of a critical period and tries instead to disentangle the effect of a critical period from mediating factors of biological or social origin. Ben-Shlomo and Kuh (2002) define the life-course approach as

"the study of long-term effects on chronic disease risk of physical and social exposures during gestation, childhood, adolescence, young adulthood and later adult life. It includes studies of the biological, behavioral and psychosocial pathways that operate across an individual's life course, as well as across generations, to influence the development of chronic diseases". (p. 285, Ben-Shlomo & Kuh 2002)

This definition encopasses the life courses of entire generations and, as the authors mention, is "empirically complex". A large series of studies have been published that fall under this life-course definition (for a review and definition see, e.g., Ben Shlomo & Kuh 2002) many of them dealing with socioeconomic differences early and later in life.

1.5 Month of Birth

How does the indicator month of birth fit into this research? Month of birth is used as an indicator for a critical period early in life. Negative factors during this period affect the metabolism of the body and influence later susceptibility to disease. There is no or little modification of this effect by later-life circumstances and the pathway is purely biological.

Month of birth is not simply another indicator of birth weight. First, birth weight studies usually are based on small samples, obtained from hospital populations. Month of birth is widely available for complete populations, which means that studies based on the month of birth are free of selection biases. Second, birth weight restricts the critical period to the pregnancy of the mother. Month of birth measures seasonal influences during pregnancy and during the first year(s) of life. Third, birth weight is influenced by socioeconomic factors. Thus, the relationship between birth weight and mortality and clinical outcome measures later in life may be confounded by unobserved socioeconomic differences. Birth weight studies definitely require a life-course approach to adjust for possible confounding factors. The month of birth is also not free of socioeconomic confounding. Chapter 3 demonstrates, however, that the social differences, which affect the month of birth, tend to reduce the month-of-birth effect on the life span rather than to strengthen it.

Month of birth has been used extensively in epidemiological research (see Chapter 5), particularly in the area of schizophrenia and other diseases of the mental and nervous system. However, since these epidemiological studies are mainly interested in finding the biological trigger of a particular disease, they have failed to demonstrate the general importance of the month of birth, and thus the early-life environment, on the human life span. If the life expectancy of today's elderly is significantly influenced by their month of birth, then the month of birth must be related to heart disease and cancer, as these are the major causes of death among the elderly. So far, there have been no studies investigating this relationship for heart disease and only very few for cancer.

Differences in life span by month of birth thus demonstrate the importance of the first period of life and the health of the mother during pregnancy, independently of other life-course factors. This monograph shows that the variance in adult life span by month of birth is small compared to the total variance and to the differences among social groups or between men and women. The finding, however, that these differences by month of birth are most probably linked to prenatal or early postnatal conditions re-

lated to nutrition or disease is of broad significance and with profound implications for clinical practice and public health policy.

Including this chapter about the epidemiological and demographic context of the month of birth this monograph consists of eight chapters. In the second chapter the differences in life span by month of birth are explored for different populations of the Northern and Southern Hemisphere. The optimal data to test whether a month-of-birth effect exists are longitudinal data where birth cohorts born in a specific season are followed from birth to death. Such data, however, is rare and in most cases only death records are available without information about the population at risk. Therefore, different statistical approaches are used and special attention is given to the question whether the analysis of death data alone introduces a bias into the observed pattern in life span by month of birth. The third chapter is devoted to testing several hypotheses that could explain the month-of-birth effect. A very prominent possible explanation is that the interaction between age and the seasonality in mortality causes the month-of-birth effect. Three different approaches are used to explore this hypothesis. Another explanation is that social differences in the seasonal distribution of births are responsible for the differences in life span. The third hypothesis explores the possibility that children who are born after a certain deadline have to wait another year before they can enroll at school, which makes them approximately a year older than their youngest classmates. This age difference may turn into a lifelong advantage. Finally, selective survival in the first years of life or debilitation in-utero or in infancy may be responsible for the differences observed in life span by month of birth.

The fourth chapter is based on approximately 16 million death records for the United States and explores differences in the month-of-birth pattern in mean age at death by region of birth as well as by education, marital status and ethnicity. The same data is used in chapter five to investigate the month-of-birth pattern for different causes of death. The chapter also contains an extensive review of earlier research that explores the effect of month of birth on diseases and causes of death.

The sixth chapter is devoted to the question whether the month-of-birth effect exists at all ages and whether it is similar for all age groups. Three different data sets – the Danish register data, the Danish twin registry and three consecutive US censuses – are analyzed to answer this question. The choice of the different data sets is motivated by the need to overcome two problems. First, one needs longitudinal data over a long time-period to identify age-specific effects; and second, one needs large data sets to allow for the estimation of age-specific month-of-birth patterns at ages where death rates are low. Since there is no one single data set that combines all

these virtues, this chapter resorts to the analysis of several sources that together give a more complete picture.

The seventh chapter explores the month-of-birth pattern of migrants and shows that migrants are subject to the pattern of their region of birth rather than that of their region of residence. It also provides evidence that unobserved socioeconomic characteristics of the migrants may bias their month-of-birth pattern.

The eighth chapter, finally, provides evidence that the month-of-birth pattern in life span is not merely of historical interest but that it may still exist in contemporary cohorts. The monograph closes with a summary and discussion of the evidence presented in the different chapters.