9 Summary

9.1 Early-Life Circumstances and Adult Mortality

When mortality started to decline in the second half of the 19th century, the decline followed a cohort pattern, which is direct evidence for the effect of early-life circumstances on adult mortality. Early studies by Kermack et al. in 1934 suggest that, as far as mortality up to the year 1925 is concerned, the year of birth had more predictive power than the year of death. This was reflected in the general view of public-health policy at the beginning of the 20th century. Mortality at adult ages was considered to be largely influenced by conditions that existed during childhood and in the earliest periods of life. After 1925, the year of birth as compared to the year of death lost much of its predictive power. Period factors became more important.

Today there is widespread evidence that, during a mortality regime that is determined by infectious disease, early-life conditions play a detrimental role for adult health and mortality. One major cause of death that declined on a cohort basis rather than on a period basis during the last 100 years is tuberculosis. Tuberculosis in late adulthood is believed to originate in infections experienced during childhood. Other important causes of death that have exhibited a cohort decline since the beginning of the 20th century are stroke, stomach cancer, and bronchitis. In the case of peptic ulcer-morbidity, the cohort-specific decline can be traced back to cohort-specific Heligopacter pylori infections in childhood. It seems that heligobacter pylori infections in childhood caused by poor living circumstances before and during World War II are responsible for the high rates of stomach cancer in Japan today. Adult mortality in Sweden during the 18th and 19th centuries was heavily influenced by the disease load during the first year of life: people born in years with extremely high infant mortality due to smallpox and whooping cough had increased mortality later in life.

Much controversy exists, however, about whether cohort effects, and thus early-life circumstances, are still important in a mortality regime that is largely determined by chronic diseases. With the epidemiological transition from infectious to chronic disease, cohort effects on mortality have largely lost their importance. Mortality is determined by period effects.

Coronary heart disease initially shows period-specific increase; the intro-duction of antibiotics influenced mortality in a period-specific way; and medical therapeutics usually acts in a period-specific manner. One coun-terexample is lung cancer, which increased from cohort to cohort, reflect-ing the increase in the number of smokers among the younger cohorts. For this reason, the main emphasis in research and public policy shifted to life-course factors such as adult socioeconomic status and lifestyle factors such as diet, physical exercise, and smoking behavior.

In the 1970s Forsdahl, a medical doctor in Norway, observed that re-gional differences in adult lung cancer and heart disease were not related to contemporary differences in lifestyle, smoking behaviour, or socioeco-nomic status but rather to differences in regional infant mortality during childhood and youth of the cohorts under study. His study is now consid-ered to be the starting point of a large and productive area of research that tries to link early-life conditions to the manifestation of chronic disease later in life. The discussion about early-life effects on health at adult ages gained momentum with studies conducted by the Southampton group of Barker and colleagues. The group developed the fetal-origins hypothesis of adult disease (also known as the 'Barker hypothesis'), which suggests that coronary heart disease at adult ages results from poor conditions *in-utero* caused by inadequate nutrition on the part of the mother and infectious diseases she suffered during pregnancy. Since inadequate nutrition of the fetus is reflected in low birth weight, the Barker hypothesis claims that growth retardation *in-utero* leads to low birth weight and to an increased risk of chronic disease later in life. It seems that the main connection be-tween birth weight and heart disease later in life is systolic blood pressure – infants with a low birth weight experience increased systolic blood pres-sure at adult ages.

The fetal-origins hypothesis has led to a large amount of research which generally comes to the conclusion that low birth weight is associated with an increased risk of heart disease at adult ages and that low-birth weight infants suffer from increased systolic blood pressure later in life. The in-terpretation of these outcomes has been repeatedly challenged, however. The main idea underlying the fetal-origins hypothesis is that a critical time period exists early in life and that negative effects during this period can-not be reversed later in life. Critics of the hypothesis frequently bring for-ward the argument that birth weight is confounded with socioeconomic status. Negative social factors in the early-life environment may set people onto life trajectories that negatively affect their health over the whole life course. Therefore, the almost universally observed relationship between birth weight and the risk of chronic disease later in life may be an outcome

of the whole life course rather than the result of a critical period early in life.

This criticism leads to the question whether one can find an indicator for the prenatal and early postnatal environment that is not related to the life-course. Birth weight certainly does not fulfil this criterion and, in addition, it is not widely available. Studies that use birth weight or other direct indicators of early-life circumstances are usually based on hospital data, which are invariable subject to selection bias. Moreover, their sample sizes tend to be modest. The fetal-origins hypothesis suggests that nutrition and infectious diseases during the pregnancy of the mother are responsible for growth retardation in the infant, which leads to an increased risk of heart disease at adult ages. Both nutrition and infectious diseases are highly seasonal: Respiratory infections peak in the autumn and winter, and gastrointestinal infections peak during warm periods of the summer months. The availability of fresh fruits and vegetables – and thus of micronutrients – changes with the seasons of the year. An indicator that reflects the seasonally changing environment during the prenatal and early postnatal period is month of birth.

The month of birth can be used as an indicator for the seasonally changing environment around the time of birth provided that it is not confounded by social factors and that it does not have any life-course interpretation. This monograph tests a series of alternative hypotheses which all assume the existence of life-course factors or social factors that are related to the month of birth. Only after having rejected all these hypotheses is a thorough analysis of the possible causal mechanisms performed.

Epidemiological research on the underlying factors of schizophrenia has long used month of birth as an indicator for early-life circumstances that affect the risk of schizophrenia later in life. This line of research dates back to Ellsworth Huntington, who in 1938 published his book *Seasonality*, in which he describes the relationship between the seasons of the year and social, psychological, and demographic phenomena. By 1997 more than 250 studies about the month-of-birth effect in Schizophrenia had appeared and many more are still being published. The most recent research links the relationship between the month of birth and the risk of schizophrenia to influenza infections experienced by the mother during pregnancy, although results are not always conclusive. A month-of-birth effect has also been shown for other mental disorders such as manic depression and bipolar disorder, autistic disorder, Alzheimer's disease or anorexia nervosa. Little research, however, has been done on the month-of-birth effect in chronic diseases, which are what determine life expectancy in contemporary populations.

9.2 How to Study the Effect of the Month of Birth on the Life Span?

This monograph establishes the month-of-birth effect in the life span on the basis of large and complete population data for over 17 million people. It is based mainly on the analysis of three populations in the Northern Hemisphere – Austria, Denmark and the United States – and one population in the Southern Hemisphere, namely Australia. The rationale underlying this selection of populations is that those in the Northern Hemisphere should reveal a similar month-of-birth pattern, while the pattern should be shifted by half a year in the Southern Hemisphere population.

For Austria, Australia, and the United States death records form the basis of the analysis. These death records contain the date of birth and the date of death. Since only deaths are known while the population at risk is unknown, mean age at death is used as a substitute for life expectancy. An advantage of using US data is that the US territory ranges over more than 20 degrees latitude and consists of six major climatic zones. Since the death records contain the state of birth of the decedents, the data allow for regional analysis. The Danish data come from the Danish population register. The register allows us to follow each person alive in March 1968 until the present and records date of birth, date of death for those who have died, and date at the end of the follow-up for those who survived. From these data both exposures (number of person months of people born in a specific month) and occurrences (number of deaths for people born in a specific month) are known. We thus estimate death rates and life expectancies based on life-table techniques.

The advantage of studying Austria and Denmark is that they are geographically close and should therefore reveal similar month-of-birth patterns. And although they are geographically close they belong to different climatic zones and have different histories of adult and infant mortality. At the beginning of the 20th century infant mortality in Denmark was about half the mortality in Austria, where short periods of breastfeeding – or the complete absence thereof – took its toll. Thus, despite their geographical proximity, early-life circumstances, in terms of disease environment for example, differed widely.

The data of all four populations are used to study the mean age at death for ages 50+ (Austria, Australia, and United States) and remaining life expectancy at age 50 (Denmark). Although age 50 is certainly an arbitrary cut-off point, there are several reasons why this age has been chosen. First, infant mortality is deliberately excluded in order to guarantee that differences in mean age at death are caused not by differences in survival during

the first year of life but rather by differential survival later in life. Second, in contemporary populations mortality during childhood and young adulthood is so low that dividing populations according to their month of birth would result in even higher mortality fluctuations that may have distorted the general month-of-birth pattern. Third, mortality starts to accelerate around age 50, with the increasing incidence of chronic diseases. Thus, the month-of-birth pattern in longevity is statistically primarily a function of the number of deaths at middle and old ages.

The cut-point at age 50 is disadvantageous, however, in terms of information about the month-of-birth pattern at younger ages. To overcome this limitation three additional data sources are studied. Aggregate data on infant mortality in the years 1911-1915 in Denmark by age and month of death are used to estimate infant mortality in the first year of life by month of birth. The Danish twin registry allows for the study of all twins born between 1870 and 1930 who survived at least up to the age of six. The twins are followed up to the present, and for the deceased the date of death is recorded. Finally, the US census samples for the years 1960, 1970, and 1980 contain information about the quarter of birth. The comparison of the age-specific percentages of cohorts born in a specific quarter between two succeeding census rounds provides an indication of differential survival by quarter of birth. For example, one can compare the percentage of people born in the second quarter at ages 10 in the 1960 census with the respective percentage of the 20 year-olds in the 1970 census and the 30 year-olds in the 1980 census. If the percentage changes from one census to the next, then the quarter of birth influences survival. The direction of the change indicates whether those born in the second quarter experience higher or lower mortality as compared to the total population.

There is an additional advantage of the US census data and the Danish twin data. Both datasets constitute a second, independent source for the two populations that can be used to verify the month-of-birth patterns. Since the US results (together with the Austrian and Australian results) are based on death counts only, it could be argued that the result is at worst an artefact and at best confounded because of the approximation of life expectancy by mean age at death. The use of repeated census rounds avoids the calculation of life expectancy and is therefore not subject to this criticism. Both the Danish register data and the Danish twin data are longitudinal data and thus provide all the necessary information to calculate life expectancy. The advantage of the Danish twin register is that the month-of-birth pattern of the general population can be replicated in a very specific sub-population. Furthermore, one would expect that the peak-to-trough difference in life expectancy is larger among twins than among the

general population because they experience harsher conditions early in life than singletons.

For the United States and Australia neither register data nor information about the seasonal distribution of birth dates at the beginning of the 20th century is available. Mean age at death is therefore used as an approximation of lifespan. This monograph shows that in two populations, the Danish twins and the Austrian general population, using mean age at death from death records of not extinct cohorts results into a minor bias concerning the month-of-birth pattern. For populations without information about the seasonal distribution of births and without population registries mean age at death gives therefore a reasonable approximation of the month-of-birth pattern.

9.3 The Month-of-Birth Effect Depends on the Season

A significant effect of the season of birth on survival at adult ages exists in all populations studied. In the Northern Hemisphere mortality at ages 50+ peaks for the spring-born (April–June) and reaches a trough for the autumn-born (October–December). In the Southern Hemisphere the pattern is shifted by half a year: mean age at death peaks for the spring-born and reaches a minimum for the autumn-born. The difference in life span between the spring- and the autumn-born is 0.6 years in Austria – twice that of Denmark (0.3 years). For the total US population the peak-to-trough difference is 0.4 years. There is, however, a large amount of variability by region of birth. With 0.31 years, the difference is lowest for people born in New England, followed by the Middle Atlantic region (0.36 years). It reaches a maximum for those born in the East South Central (0.86 years) and West South Central regions (0.69 years), while all other regions show differences of around 0.44 years. The regional variability in the peak-to-trough differences persists when the results are corrected for the effects of race, education, and marital status. The maximum difference in Australia, which is 0.6 years, compares to that of Austria, although the pattern is shifted by half a year, as noted above.

Similarly to the US death records, the Australian death data contain state and territory of birth. In general, the pattern is similar in all states and territories – with high mortality for decedents born in the fourth quarter and low mortality for those born in the second quarter. Within Australia the peak in mortality of those born in the fourth quarter is highest for decedents born in Victoria (0.89 years), followed by those born in South Aus-

tralia (0.61 years), Western Australia (0.49 years) and in New South Wales (0.39 years).

There are two exceptions: the first is Tasmania, where the peak-to-trough difference is not significant due to the small number of decedents. The second exception is Queensland, which exhibits a pattern that differs from those of all the other states. Here the trough in mean age at death occurs for people born in the first four months, while the peak is for those born in April and May. Queensland belongs to tropical northern Australia and the trough in life expectancy coincides with the hot and wet summer season, the peak with the beginning of the more moderate and dry winter season. Since the US death records also contain information about decedents born in Hawaii, it is possible to compare the pattern of Queensland with that of Hawaii. The two regions belong to similar climatic zones. It turns out that the trough in life expectancy is linked to the hot summer period and the peak to the more moderate winter period also in Hawaii.

The results for the United States and Denmark are supported by the analysis of the US census rounds and the Danish twin register. The three US census rounds show a significant disadvantage in survival for people born in the second quarter and an advantage for those born in the autumn. Up to the age of 40, the conditional survival probability of males surviving the next 20 years is about one per cent higher for the autumn-born than for the general population; between the ages 40 and 60, it is about 2.4 percent; and it increases to 7.8 percent at ages 60–69.

In general, the Danish twins experience a month-of-birth pattern that is similar to that of the general Danish population. There are differences, however. The most important one is that the peak-to-trough difference in life expectancy is much larger among for twins than for the general population. On the basis of the Danish register data, the difference in remaining life expectancy at age 50 between the autumn- and the spring-born is 0.3 years; for the Danish twins it ranges from 0.58 years in the youngest cohort (1910–1930) to 0.88 years in the cohort 1890–1909. In other words, the difference is at least twice to three times as high for twins than for the general population. This result is in agreement with the initially formulated hypothesis that the harsher environmental circumstances *in-utero* and in the first year of life will result in larger differences in life span by month of birth. It must be noted, however, that the mortality advantage of the autumn-born is not as consistent for the male Danish twins as it is for the general Danish male population.

The results from Austria, Denmark, the United States, Australia, and Hawaii suggest that the month-of-birth pattern in lifespan is linked to the

seasons of the year. It appears that those born during periods of moderate weather, which coincides with autumn for populations living at higher latitudes and winter in populations close to the equator, experience higher life expectancy. Those born during spring and early summer exhibit lower life expectancies; at lower latitudes, periods with high temperatures seem to be detrimental. At first glance it seems surprising that the month-of-birth pattern exists at all in regions close to the equator. Although it is commonly thought that there are no seasonal changes at lower latitudes, this is not true. Differences in temperatures, humidity, and precipitation define the seasons of the year in these areas. The total effect of these factors combined, however, may vary depending on the climate zone.

9.4 The Month-of-Birth Pattern of Migrants

A further test of whether the month-of-birth pattern depends on the seasonal environment early in life is to investigate the pattern of migrants. The Australian death records contain information on about 43,000 British-born immigrants to Australia who died at ages 50+. One would expect that these immigrants reveal the month-of-birth pattern of the Northern Hemisphere rather than that of the Southern Hemisphere. Since the peak in life expectancy for the November-to-January-born is 0.36 years higher among the immigrants than among the Australian-born while it is 0.26 years lower for the March-to-May-born, this seems indeed to be the case. Contrary to the unimodal patterns of the populations of Northern Hemisphere, however, the month-of-birth pattern of the migrants is bimodal. One possible explanation for this bimodal pattern is that the month-of-birth pattern of the total British population is bimodal. Another explanation is that migrants are not representative of the total British population. At present, no published information exists that would enable one to test the first explanation. An exploratory analysis of the month-of-birth effect on the basis of the genealogy of the British peerage did not yield any conclusive results.

This monograph provides two examples based on US death records that migrants are selected – both socially and as concerns health – and therefore not representative of the total population. The first example shows that social status and race influence the month-of-birth pattern in life span. The peak-to-trough difference in mean age at death among US decedents with a low level of education is, with 0.62 years, almost twice as large as among those with a high level of education (0.38 years), while the basic pattern remains unchanged. This is different in the case of race. Among African-American decedents the peak-to-trough difference is only slightly

larger (0.57 years) than among white decedents (0.49 years). The shape of the pattern differs widely, however. Both for whites and African Americans, those born in June and July show the lowest mean ages at death, while the peak in life expectancy is shifted from autumn to winter among African-Americans. Those born in the autumn do not experience the same mortality advantage as the white population, although a secondary peak in mean age at death does exist.

An indication that health status affects the month-of-birth pattern is the larger peak-to-trough difference for never-married decedents (0.62 years) as compared to those who married (0.40 years). It is now generally agreed upon that the beneficial effect of marriage on health and mortality results from two forces. On the one hand, marriage has a protective effect. On the other hand, individuals are selected into marriage according to their health status, and frail individuals tend to remain unmarried. Thus, health status precedes marriage, and to a certain extent marital status can be regarded as an indicator of health.

The US death certificates thus provide evidence that social and health factors modulate the month-of-birth pattern in life span and that migrants, who are selected both socially and as regards health, may therefore reveal a pattern that is somewhat different from that of their population of origin.

The second example applies to internal US migration. It shows that the month-of-birth pattern of migrants differs from that of their population of origin. In the US, large disparities by region of birth exist in the peak-to-trough difference in mean age at death. The lowest difference exists for decedents born in New England, and the largest for those born in the South East, which is generally referred to as the South of the US. Due to the sizeable migration flows within the US, it is possible to study migrants who were born in the North and who died in the South and vice versa. The two migration flows differ remarkably in their social composition as well as in their timing of migration. North-to-South migration is primarily retirement migration of healthy, married, and comparably well-off Americans who moved to the "sunbelt". This migration flow has become increasingly popular during the last few decades. In contrast, South-to-North migration was primarily labour migration caused by the economic upheavals of the first part of the 20th century. This migration peaked in the 1960s. These migrants had usually been born in rural areas and had lost their land or their status as sharecroppers because of the increasing industrialization of the southern agricultural system.

It appears that the North-to-South migration of the retirees is consistent with the expectation that migrants reveal the month-of-birth pattern of their birth region rather than that of their residence region. The peak-to-trough difference of the migrants born in the North is smaller than it is for

those who were born and who died in the South. This is not generally true for labour migrants from the South to the North. Although most of the southern migrants stem from rural areas, they are by no means a homogenous group. The social-class relations in the South were structured along the lines of land ownership, and those who did not own their land were particularly badly off. The analysis of the month-of-birth pattern of farmers and farm workers shows that, in the South, the peak-to-trough difference of the farm workers is significantly larger than that of farmers. In other words, the labour migrants from the South to the North probably are less representative of the general southern population than the retirement migrants from the North to the South.

   Three conclusions can be drawn from the analysis of the month-of-birth patterns of the Northern and Southern Hemisphere and of the migrants between the hemispheres: First, the differences in life span by season of birth are linked to seasonal factors existing at the time of birth. Since the seasons in the Northern and the Southern Hemisphere are shifted by half a year the month-of-birth pattern is also shifted by half a year. Second, at higher latitudes with four distinct seasons, those born in the spring have a lower life expectancy than those born in the autumn. At lower latitudes close to the equator, those born during the hottest season of the year experience a lower life expectancy than those born during the moderate winter season. Third, the peak-to-trough difference in the month-of-birth pattern varies for different social groups: the higher the social status, the lower the difference in life span. There are two alternative implications of this result. Since the education level of the deceased is closely linked to the social status at the time of birth, the educational gradient in the peak-to-trough difference may reveal the impact of social status. Alternatively, educational status later in life may modify the effect of the early-life environment. This explanation implies that early life is a critical period in terms of adult health and mortality, although its effect may be partly reversed by life-course factors.

9.5 Alternative Hypotheses for the Month-of-Birth Effect

Before proceeding further with the analysis of the month-of-birth effect on the life span it is worthwhile to consider whether explanations exist other than those that are related to the beginning of life. One frequently raised concern is that the month-of-birth effect reflects the seasonal distribution of deaths rather than the seasonal changes in the early-life environment. More specifically, the concern is that the interaction between the seasonal

distribution of deaths and the monthly increase in adult mortality causes a month-of-birth pattern. This hypothesis has been already widely discussed in the research about the month-of-birth effect in schizophrenia, whose incidence is seasonal and whose risk increases with age.

The Danish register data used in this study allow us to test this hypothesis explicitly due to the longitudinal nature of the dataset. The result is that, although month of birth, age, and month of death influence mortality simultaneously, they are independent of each other. This is consistent with the outcomes of the tests that were developed in the area of schizophrenia.

A second, frequently raised concern is that the month-of-birth effect is caused by socioeconomic differences in the seasonal distribution of births. The number of births is distributed seasonally over the year with the exception of only a few populations. If the seasonality in births is partly driven by the preference of couples for giving birth in certain seasons of the year, then this preference may differ between social groups. In schizophrenia research, this explanation is generally known as the procreational habits theory. Individuals with schizophrenia may have a procreational pattern that differs from those of the non-schizophrenic population. Since schizophrenia is heritable to a large degree, this would result in a seasonal distribution of births of individuals at increased risk of developing schizophrenia that differs from the seasonal distribution in the general population. Two predictions of this theory have already been falsified: First, it is not the case that individuals with schizophrenia who have a family history of schizophrenia reveal a larger peak-to-trough difference in their seasonality of births than those who do not have a family history. Second, schizophrenic individuals and their siblings have different seasonal birth distributions.

In this study education is used as an indicator for social groups and the seasonal birth distribution at age 50+ is analysed on the basis of the 1981 census for Austria. It turns out that proportionally more people with a high level of education are born in spring than in the autumn, while proportionally more people with basic education have their birthday in the autumn. Among the cohorts analysed, one's own education is closely linked with the education of one's parents, so this result indicates that social differences in the seasonal distribution of births cannot explain the month-of-birth pattern in the life span. On the contrary, it appears that they even tend to reduce the differences in life span by month of birth.

Another prominent hypothesis in social and psychological research is the deadline hypothesis. Starting school is usually tied to reaching a certain age before a certain deadline. Children who are born shortly after the deadline have to wait an additional year before the can start school and will therefore be among the oldest of their classmates. This may pose a

special advantage compared to those who are born shortly before the deadline, who will thus always be among the youngest. There is, however, also a second interpretation of the deadline hypothesis. Children born shortly after the school attendance deadline will be older when they start school and will attain the legal drop-out rate earlier in the educational year than those born shortly before the deadline. This may result in fewer years of school enrolment. Being born after the deadline is therefore considered to be disadvantageous in terms of one's educational career and research suggests that this is reflected in income later in life. The seasonal distribution of the month of birth of Austrians aged 50+ seems to provide support the second interpretation of the deadline hypothesis. In Austria, school started on 1 October, and children who had not turned six by that date had to wait another year before they could start school. Since the autumn-born belong to a larger percentage to the group with basic education only, the deadline effect would be detrimental rather than beneficial for those born shortly after the deadline of 1 October. However, since the mean age at death of the autumn-born is higher than that of the spring-born, the deadline hypothesis cannot explain the month-of-birth effect on the life span.

9.6 The Causal Mechanisms

What are the mechanisms that cause the month of birth pattern in the life span? One can rule out the possibility that the month of birth has any major life-course interpretation in terms of longevity. This means that any month-of-birth pattern must necessarily relate back to the very first period of life. One can also rule out the possibility that the month of birth is confounded by socioeconomic status and that the differences in life span by month of birth are simply differences in socioeconomic status.

The study of the month of birth pattern in infant mortality at the beginning of the 20th century allows us to rule out a third alternative as well. If autumn-born infants suffer higher mortality in their first year of life than spring-born infants, then the increased life expectancy of the autumn-born may simply be the result of selective survival. Among the autumn-born only the more robust individuals would survive the first year of life, who would then have lower mortality later in life. Danish data on historical infant mortality between the years 1911 and 1915 show, however, that it is the spring-born rather than the autumn-born who experience higher mortality in their first year of life. The standardized death rate of the June-born infants is 30 per cent higher than the death rate of the December-born. It

thus appears that selective survival cannot explain the month-of-birth pattern in the life span.

The month-of-birth pattern in infant mortality points to another explanation. For Denmark the correlation between infant mortality in the first year of life and adult mortality after age 50 is 0.87 and highly significant. This result indicates that the causal mechanism of the month-of-birth pattern is related to debilitating factors *in-utero* or in the first year of life. In other words those factors that contributed to the high infant mortality of the past are also the factors that cause the differences in life span by month of birth. Public health experts at the beginning of the 20th century felt that mothers' health status and whether mothers breastfed their babies were the two most important factors, followed by housing, sanitation and general poverty, all of which were closely linked with the survival of infants. The health status of pregnant women depends largely on their diet and on the general disease load. Breastfeeding the infant is related primarily to a lower incidence of infectious diseases of the gastrointestinal tract, which historically is the major cause of infant mortality.

Both nutrition and infectious diseases are highly seasonal. Diet at the beginning of the 20th century did not much resemble contemporary dietary patterns. People ate less meat, fruits, and vegetables and more starchy staple food. The first vitamins were not discovered until 1911, and in the early 1900s nutritionists were even opposed to greens, which were considered to require more bodily energy for digestion that they provided. Although severe malnourishment was not widespread, people had inadequate nutrition – particularly during the winter and early spring. Peak growth of the fetus *in-utero* occurs during the third trimester. For infants born in spring, the third trimester coincides with a period of largely inadequate nutrition; for those born in the autumn it coincides with a period of plenty.

The incidence of infectious diseases depends on the climate and on the seasons of the year. The incidence of waterborne infectious diseases, which affect mainly the gastrointestinal tract, is correlated with warmer temperatures and flooding. Peak climatological temperatures coincide with the incidence of foodborne diseases. Many childhood diseases are highly seasonal; airborne diseases affecting the respiratory tract usually peak in autumn and winter.

The effect of the mother's nutrition during pregnancy on the health of the child at adult ages is highly contested. Nutrition is considered to be the central causal mechanism in the fetal-origins hypothesis, which claims that inadequate nutrition of the mother during pregnancy leads to growth retardation *in-utero* and to an increased risk of heart disease later in life. Studies that looked at the old-age mortality of cohorts born shortly after periods of famine, which were thus presumably marked by severe malnutrition of

the mother during the gestational period of their unborn, did not find any differences. In other words, those born shortly before, during, or after a famine had similar mortality rates at older ages. On the other hand, the study of the social composition of births during and shortly after the Dutch Famine in 1945 has shown that this composition has changed. Primarily, women of higher social background continued to give birth while women of lower background stopped having babies. Unobserved differences in the social composition might therefore be the reason that cohorts born during and shortly after a famine do not have higher mortality later in life than those unaffected by the famine. Still, the evidence is weak concerning the effect of nutrition during gestational age on mortality later in life.

The situation is different concerning the effect of infectious diseases. There exists ample evidence that infectious diseases early in life affect later-life health and mortality. Historically, people born in years with extremely high infant mortality caused primarily by whooping cough and smallpox tend to have higher mortality later in life. Tuberculosis in late adulthood is believed to originate in infections during childhood. H pylori infections in childhood are responsible for peptic ulcer morbidity later in life. Increased H pylori infections in childhood caused by poor living circumstances before and during World Ware II seem to be responsible for the high rates of stomach cancer in Japan today. Chronic respiratory disease later in life seems to be related to lower respiratory tract infections in childhood.

The indicator "month of birth" does not allow us to distinguish between the period *in-utero* and the first year of life. It therefore does not tell us whether it is the nutrition of the mother during pregnancy or infectious diseases in the first year of life that are of crucial importance. The investigation of causes of death reveals that the month-of-birth effect exists for all major groups of causes of death. The pattern is particularly strong and consistent for heart disease. It is less strong but nevertheless consistent for many types of cancer. Significant month-of-birth patterns exist for causes of death such as stroke, stomach cancer, and bronchitis, which declined between the mid 19th century and today, following a birth cohort pattern. There are two possible explanations: First, since the etiology of all the different causes of death differs, there may be more than one causal mechanism and some of them may be related to the period *in-utero*, others to the first year of life. Research conducted by Barker and colleagues, who formulated the fetal-origins hypothesis, links the increased risk of heart disease later in life to nutrition *in-utero*. A large body of literature investigates the month-of-birth effect in the prevalence of schizophrenia and discusses the effect of influenza infection of the mother during pregnancy on the child's risk of developing schizophrenia. Historically, children born

in years with extremely high infant mortality caused by smallpox experience higher mortality later in life. A second explanation is that the spring-born are generally weaker than the autumn-born and that their rate of aging is higher.

Explanations other than nutrition and infectious disease have also been brought forward to explain the month-of-birth effect. One of the first to study the influence of the month of birth on the life span is Elsworth Huntington, who formulated the hypothesis in 1936 that high temperatures at the time of conception weaken the "germ plasma" of the parents, with negative effects on the development of the foetus. Recent research has shown that the sperm quality of men who work outdoors does indeed decrease during periods of high temperatures. A related hypothesis is that hot summers are the cause of protein deficiencies at the time of conception. This hypothesis is clearly ruled out on the basis of the US death data. The United States consists of six major climatic zones with very different climatic conditions. Since the US death data contain the state of birth, it is possible to correlate the peak-to-trough difference in life span by month of birth for people born in a specific state with maximum and minimum temperature and with the maximum difference in temperature. It appears that no correlation exists between the peak-to-trough difference and the temperature variables, neither for total mortality nor for major causes of death.

Another explanation is that seasonal changes in the hours of daylight influence the human endocrine functions and that the month-of-birth effect might be caused by variations in the internal chemistry or neural development brought about by the seasonal variations in light. This hypothesis implies that the peak-to-trough differences should be larger at higher than at lower latitudes. Again, the hypothesis can be refuted on the basis of the US death data, since there is no correlation between latitude and the peak-to-trough difference in life span by month of birth.

9.7 Does the Month-of-Birth Effect Exist in Cohorts Born Today?

All the observed differences in life span by month of birth pertain to individuals who are born during the first part of the 20th century. The Danish results are based on the birth cohorts 1868 to 1918, the Austrian results on births between 1888 and 1946, the Australian results on births between 1893 and 1947, and the US results on births between 1889 and 1947. The question whether the differences in life span by month of birth still exist in infants born today cannot be answered on the basis of mortality data, since

one does not know anything about the future mortality of contemporary cohorts. Other measures have to be applied.

The fetal-origins hypothesis of adult disease states that growth retardation *in-utero* leads to low birth weight and causes an increased susceptibility to chronic diseases at adult ages. According to Barker and colleagues, the main reason for growth retardation *in-utero* is deficient nutrition. Since nutrition is seasonal, one would expect that growth retardation is seasonal and that this is reflected in a seasonal pattern in birth weight. Evidence for seasonal growth retardation *in-utero* exists from less developed countries. A positive correlation between the seasonal pattern in birth weight and the month-of-birth pattern in the life span after age 50 of cohorts born earlier in time would suggest that the differences in life span still exist in contemporary cohorts.

This hypothesis is tested on twin data from the Minnesota twin registry. The seasonal pattern in the birth weight of twins born in the 1970s and 1990s is compared with the month-of-birth pattern in the mean age at death of decedents aged 50+ who were born in Minnesota. Twin data are used because twins belong to the most vulnerable group early in life in contemporary populations. They have higher spontaneous abortion rates and higher infant and child mortality up to the age of six. At adult ages, however, their mortality does not differ from the mortality of singletons. This is also true for the month-of-birth pattern in the life span, as has been shown in this monograph by the Danish twins and the Danish general population. There is, however, one difference between the Danish twin population and the general population. The peak-to-trough difference in the month-of-birth pattern is two to three times as large among the twins.

Since twins face much tougher conditions early in life than singletons, a seasonal pattern in birth weight due to growth retardation may be more readily detectable among twins. Results suggest that the seasonal pattern in birth weight is bimodal, with birth weight reaching its maximum in spring and autumn and its minimum in winter and summer. This result is consistent with earlier findings that the risk of pre-term births in Minnesota is bimodal, with peaks in summer and in winter.

A positive correlation of borderline significance exists between the life span pattern and the birth weight pattern for male twins. For female twins the results are not conclusive. This result may be a first indication that the differences in life span by month of birth still exist in cohorts born today.

Although the evidence presented is weak, one has to keep in mind that birth weight is only an imperfect measure of growth retardation since it does not take gestational age into account. For example, preterm infants may have just the right birth weight for their gestational age. Even if their birth weight is lower than that of term babies, they may not have suffered

from growth retardation. A better measure would be birth weight corrected for gestational age, but information about gestational time is not available for the Minnesota twins. An earlier study of seasonal differences in the risk of preterm births in Minnesota shows that the risk is elevated during winter and summer. Thus, the seasonal pattern in birth weight of the Minnesota twins reflects not only seasonal growth retardation but also seasonal differences in gestational age. Further studies should therefore examine the correlation between the seasonal pattern in birth weight corrected for gestational age and the month-of-birth pattern after age 50.

The second "cornerstone" of the fetal-origins hypothesis is the claimed negative correlation between low birth weight and increased systolic blood pressure later in life. Growth retardation caused by deficient nutrition *in-utero* is reflected in low birth weight, and it leads to increased systolic blood pressure later in life and therefore to an increased risk of chronic diseases. The negative relationship between birth weight and systolic blood pressure has been found in a large series of studies, but has it also been challenged repeatedly. In terms of seasonal differences in nutrition, this hypothesis implies a) that a month-of-birth pattern exists in systolic blood pressure, and b) that the pattern is correlated with the seasonal pattern in birth weight. The Minnesota twin data also allow us to test this hypothesis.

In adolescence and young adulthood significant month-of-birth patterns exist for height, weight and systolic blood pressure, particularly among males. In adolescence about half of the week-of-birth pattern in systolic blood pressure is explained by the week-of-birth pattern in height and weight and the other half by the week-of-birth pattern in birth weight. This implies that, in adolescence, about half of the seasonal early-life effects on systolic blood pressure are related to factors *in-utero* that simultaneously affect birth weight and later systolic blood pressure. The other half affect systolic blood pressure through weight and height. The effect of birth weight is larger for males than for females.

With increasing age, the month-of-birth patterns in systolic blood pressure, weight, and height become less distinct, and birth weight contributes only marginally to the explanation of the season-of-birth pattern in systolic blood pressure. At that age, most of the explanatory power comes from the season-of-birth patterns in weight and height. This suggests that, at young adult ages, the season-of-birth differences in systolic blood pressure are related primarily to early-life factors that affect height and weight rather than birth weight.

9.8 Summary of Accomplishments and Outlook

This monograph has achieved six major accomplishments:

- First, it demonstrates the widespread existence of differences in life span by month of birth in the elderly populations of contemporary societies.
- Second, it provides evidence that the pattern is linked to the seasons of the year, by comparing the Northern and the Southern Hemisphere.
- Third, it formulates and tests a series of explanations for the month-of-birth effect and rejects many of the most frequently offered explanations. In particular, it rejects those that attribute the month-of-birth effect to social or statistical confounding.
- Fourth, in the case of Denmark it establishes a link between the month-of-birth pattern in the life span and the month-of-birth pattern in survival during the first year of life. The major determinants of infant mortality at the beginning of the 20th century are the health status of the mother and whether or not the child was breastfed. The first is related to the nutritional and disease environment of the mother during pregnancy, the latter to the risk to the infant of suffering from infectious diseases in the first year of life. The positive correlation between the month-of-birth pattern in the life span after the age of 50 and infant survival during the first year of life is therefore direct evidence that nutrition and infectious disease early in life play an important role in adult health and survival later in life.
- Fifth, it provides preliminary evidence that the differences in life span by month of birth still exist in cohorts born today.
- Finally, it contributes to the ongoing debate about the pathway that links growth retardation *in-utero* and the increased risk of chronic disease later in life by presenting evidence that this pathway need not necessarily be systolic blood pressure.

Although the month of birth has been used for a long time in research on mental disorders, the question as to whether a month-of-birth pattern exists in different populations and for different causes of death was never tested systematically. Research was mainly confined to specific diseases, historically this were mental diseases, more recently diseases such as diabetes, multiple sclerosis, or lung and breast cancer. Since the interest in the month-of-birth effect arouse primarily from an epidemiological point of view, more emphasis was given to the specific disease rather than to the

phenomenon of the month-of-birth effect itself. Usually, the datasets are rather small and the results subject to random fluctuations. With some notable exceptions in the research on schizophrenia, anorexia nervosa, etc, the intention of most of the studies was to show that a month-of-birth effect exists rather than to test hypotheses regarding the underlying factors of the month-of-birth effect.

Some first steps to uncover the causal mechanisms behind the month-of birth effect in the life span are presented in this monograph. The next steps will have to consider the following topics: The indicator "month of birth" does not allow us to establish whether the critical period early in life is *in-utero* or the first year of life. It also does not provide an answer to the question whether it is infectious diseases or nutrition that cause the differences. One way to address this question is to study the effect of food shortage – and in its severest form, the effect of famine – on the differences in life span by month of birth. Peak growth *in-utero* takes place during the third trimester. Infants born in the spring experience worse nutritional conditions during the last trimester than infants born in the autumn. This is consistent with the finding that the spring-born have a lower life expectancy than the autumn-born. So the hypothesis is that foetuses affected by famine during their last trimester of gestation should experience higher mortality risks later in life.

Based on current research findings this line of research does not seem to be very promising, however. Studies of cohorts born during or shortly after a famine do not experience increased old-age mortality and the old-age mortality of twins is similar to that of singletons, although they usually have much lower birth weights.

The study of infectious diseases, on the other hand, shows more potential. There is ample evidence that infectious diseases during infancy and childhood affect late-life mortality. In Sweden, historical cohorts with exceptionally high infant mortality also have higher old-age mortality. In Denmark, the month-of-birth pattern in infant mortality at the beginning of the 20th century is positively correlated with the month-of-birth pattern in the life span at ages 50+ at the end of the 20th century.

To test whether infectious disease plays an important role, one can make use of the seasonal pattern of major outbreaks of infectious diseases. One example is the Spanish flu pandemic in 1918. Another possibility is the use of seasonal indices for the incidence of respiratory disease, gastrointestinal disease, and common childhood diseases such as smallpox, whooping cough, or rubella. One could test whether there is a positive correlation between these indices and the month-of-birth patterns for specific causes of death. Unfortunately, these indices are not readily available for the beginning of the 20th century. This means that contemporary indices would

have to suffice, under the assumption that the seasonality has not changed over time. Another problem is that these indices are not available on an individual basis for the elderly population, so one would therefore have to use an ecological study design. A third possibility is to use seasonal infant mortality as an indicator of the infectious disease environment in the first three months, the second three months, and the second half-year. The three time periods should reflect the developmental stages of the infants regarding the immune system and the likelihood of weaning. A similar approach could be applied using seasonal adult mortality during childbearing ages to account for the disease environment of the mother during the three trimesters of pregnancy.

Future research into the month-of-birth effect on the life span and into the causes of death will have to proceed from the description of the phenomenon to finding the underlying causal mechanisms. They will probably differ for different causes of death. Some first steps to unravelling the mechanisms have been taken in this monograph, but much remains to be done.