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Season-of-birth phenomenon in health and longevity: Epidemiologic evidence and mechanistic considerations

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Alexander Vaiserman

Laboratory of Epigenetics, D.F. Chebotarev Institute of Gerontology, NAMS, 67 Vyshgorodska str., Kyiv, 04114, Ukraine.

Address for correspondence: Alexander Vaiserman, D.F. Chebotarev Institute of Gerontology, NAMS, 67 Vyshgorodska str., Kyiv, 04114, Ukraine. Tel: + 38 (044) 254-15-58; Email: vaiserman@geront.kiev.ua

Abstract

In many human populations, especially those living in regions with pronounced climatic differences between seasons, most sensitive (prenatal and neonatal) developmental stages occur in contrasting conditions depending on the season of conception. Thus, the mismatch between prenatal and postnatal environments may be a factor significantly affecting human development and risk for later-life chronic diseases. Factors potentially contributing to this kind of developmental programming include nutrition, outdoor temperature, infectious exposures, duration of sunlight, vitamin D synthesis, etc. Month of birth is commonly used as a proxy for exposures which vary seasonally around the perinatal period. Season-of-birth patterns have been identified for many chronic health outcomes. In this review, the research evidence for the seasonality of birth in adult-life disorders is provided and potential mechanisms underlying the phenomenon of early-life seasonal programming of chronic disease and longevity are discussed.

Keywords

DOHaD; developmental programming; seasonality of birth; disease risk; longevity.

Introduction

Genetic and environmental factors are commonly considered as basic determinants of chronic disease and longevity (Passarino et al., 2016). Emerging evidence, however, indicates that both health status and longevity potential may be programmed early in life, in particular, during the prenatal and neonatal periods (Vaiserman et al., 2014; Vaiserman et al., 2018). Based on the accumulated findings, a Developmental Origins of Health and Disease (DOHaD) hypothesis was proposed. This concept postulates that, during critical windows of early-life susceptibility, structure and physiology of an organism can be adapted to adverse environmental factors in such a way that may predispose to various pathological conditions in adult life (Hoffman et al., 2017; Safi-Stibler and Gabory, 2020). According to the related predictive adaptive response hypothesis, the developing organism can use the information from environmental cues to express a phenotype maximizing fitness based on expected environmental conditions (Bateson et al., 2014). However, when the actual and predicted environments are mismatched, it can lead to adverse health consequences in later life. One example of such a mismatch is a situation when unfavorable conditions during intrauterine development, such as poor nutrient intake, maternal stress, hypoxia etc., impair fetal growth, thereby causing intrauterine growth restriction (IUGR) mediated by impaired development of fetal pancreatic and adipose tissues. IUGR-induced metabolic adaptation may provide transitional survival benefits in poor postnatal environments owing to enhanced ability to store fat during the periods of limited accessibility of food resources. These adaptive functional changes are often accompanied by corresponding changes in growth trajectory, namely, catch-up growth phenomenon, i.e., a development mode when those individuals who are born with low birth weight subsequently exhibit accelerated weight gain in infancy (Martin et al., 2017a). Such a developmental scenario usually results in long-term adverse health outcomes (Singhal, 2017). In particular, persons with catch-up growth trajectories are often characterized by high risk for metabolic disorders such as obesity and type 2 diabetes (Fernandez-Twinn et al., 2019; Vaiserman and Lushchak, 2019) and also cardiovascular diseases (Eriksson et al., 1999) if they live in conditions of abundant food intake throughout adult life. These disorders are known to be associated with accelerated aging rate (Burton and Faragher, 2018) and, accordingly, with reduced life expectancy.

In majority of human populations, especially those living in regions with pronounced climatic differences between seasons, most sensitive (prenatal and neonatal) stages of human development occur in contrasting conditions. Thus, the mismatch between prenatal and postnatal environments may be a factor significantly affecting human development and risk for adult-life chronic diseases. The seasonal differences, in particular, in the food availability, are particularly expressed in low-income developing countries. More specifically, quantity, variety, and freshness of fruits, vegetables, and cereals vary significantly according to season in these countries (Watson et al., 2007). Other potentially important factors that change seasonally include outdoor temperature (Poeran et al., 2016; Li et al., 2018), infectious exposures (Roy, 2016), as well as duration of sunlight and vitamin D synthesis (Fang et al., 2019). Moreover, potentially contributing maternal lifestyle factors such as physical activity (Smith et al., 2016) and substance abuse (Vaiserman, 2015) also vary seasonally. Therefore, it is not unexpected that season-of-birth patterns exist for many human developmental outcomes. Moreover, and more unexpectedly, such patterns were repeatedly found for late-life health outcomes, including risks for chronic diseases and longevity.

In this review, the research evidence for the seasonality of birth in adult-life disorders is provided and potential mechanisms underlying the phenomenon of seasonal programming of chronic disease and longevity are discussed.

2. Season of birth and life-course physiology

Seasonal factors were repeatedly shown to influence prenatal human development and affect birth characteristics. The seasonality of birth weight has been reported across countries. For example, in the Chodick et al. (2009) review of global patterns, individuals born during the winter period tended to have low birth weigh and those born during the summer period tended to have high birth weigh in the high- and low-latitude regions, while the opposite association was found in the mid-latitude regions. In a more recent study by Day et al. (2015), summer-born infants also had higher birth weights compared to those born in other seasons. An association between month of birth and both birth weight and body weight in childhood has been confirmed in a recent systematic review by Hemati et al. (2020). More specifically, those persons who were born in winter months had higher weight and body mass index (BMI) in childhood. The occurrence of low birth weight was more frequent among those infants who were born in summer than among those born in other seasons.

Since birth weigh is, in turn, associated with adult-life health outcomes (Vaiserman, 2018), it is not surprisingly that seasonality of birth is seen for many human chronic disorders, including the later-life-onset ones. Association between season of birth and human health status has been reported repeatedly. An important point in the context reviewed is that seasonality of birth has been found not only for childhood diseases, but also for age-related late-onset disorders, indicating that season-of-birth effects can persist life-long, thereby contributing to aging-associated processes. In a recent research where a health deficit indices have been calculated for 21 European countries included in the Survey of Health, Aging, and Retirement in Europe (SHARE) dataset, elderly European men were shown to age faster if they were born in spring and summer compared to those born in autumn (Abeliansky and Strulik, 2020). At any given age, spring- and summer-born persons developed about 3.5 percent more health deficits than autumn-born individuals. These differences were not mediated by potentially confounding factors such as body size or education level. Interestingly, the birth season played a non-significant role for old-age health in a subsample of Southern-Europe countries. The authors assumed that this might be due to the smaller seasonal variation in sunlight in these regions. In a subsample of Northern-Europe countries, in contrast, the season of birth was shown to significantly affect most of the indices calculated. At any age, spring-born elderly Northern European men had developed about 8.7 percent more health deficits than those born in autumn. The estimated aging rates were also associated with birth season in this research. Findings suggesting that season of birth can affect later-life characteristics have been also obtained in other recent population-based large (N = 502,536) study conducted using the UK Biobank cohort (Didikoglu et al., 2019, 2020). In this research, evidence was obtained that season of birth can affect the basal metabolic rate, which is regarded as one of the important determinants of the aging rate (Frisard and Ravussin, 2006). More specifically, individuals who were born in July had higher basal metabolic rate compared to those born in December (Didikoglu et al., 2020). Moreover, findings from this study indicated that season of birth may affect growth parameters (Fig. 1). In addition, season of birth was shown to program adult-life sleep characteristics. In particular, spring and summer birth seasons were found to be associated with a higher insomnia rate compared to autumn and winter birth seasons. It seems important because sleep pattern can significantly influence the health status and ultimately affect longevity. In particular, evening-oriented sleep timing preferences (chronotype) have been shown to be associated with higher risk of type 2 diabetes, obesity, cardiovascular diseases, psychiatric disorders, and also with increased mortality than the morning-oriented ones (Knutson and von Schantz, 2018). Importantly, the adult chronotype was shown to be differently programmed depending on the season of birth (Didikoglu et al., 2019).

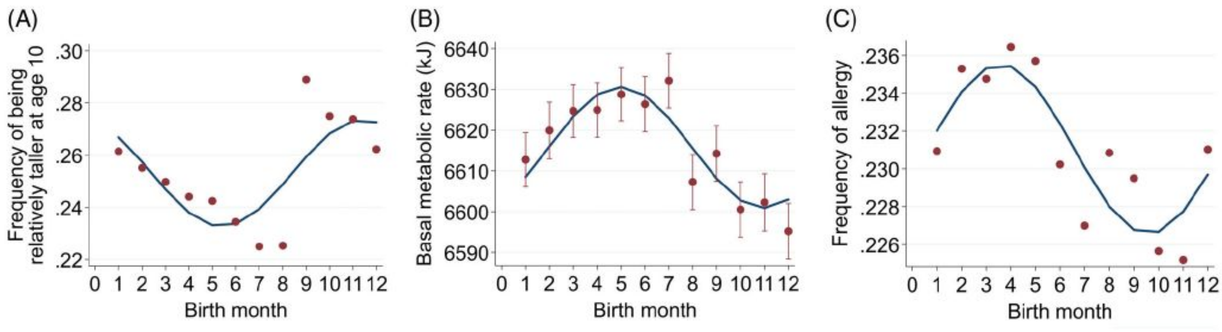

Fig. 1. Month of birth and (A) frequency of being taller at age 10, (B) basal metabolic rate, and (C) frequency of having allergy in the UK Biobank cohort. Red scatter plots show prevalence in A and C and mean ± standard error in B. Reproduced from the article by Didikoglu et al. (2020) with permission of publisher. © *2020 Wiley Periodicals, Inc.*

Associations between season of birth and age at female life-cycle events such as menarche and menopause have been also demonstrated. In determining whether month of birth can affect the maturation rate of Polish females, girls born in summer were found to have the first menstruation at younger ages than girls born in other seasons (Kliś et al., 2016). Remarkably, no association between birth season and age at menarche in Central India, where differences between seasons in temperature and photoperiod are very small, has been observed (Liczbińska et al., 2020). In China, more early ages of both menarche and menopause were revealed in women born in spring compared to ones born in other seasons (Si et al., 2017a). In Italy, menopause was found to occur earlier in women born in the spring than in the autumn (Cagnacci et al., 2005). The earliest menopause has been observed in women born in March and the latest one in women born in October.

3. Seasonality-of-birth in disease phenotype

An association between month of birth and risk for chronic diseases that develop during the individual's lifetime has been reported repeatedly in the literature. In a retrospective population study of relationships between month of birth and lifetime risks for 1688 pathological conditions (total N = 1,749,400), the association with birth month was found for 55 diseases (Boland et al., 2015) (Fig. 2). Findings from these phenome-wide studies were subsequently partly confirmed by Borsi et al. (2016). The results of the latter research, however, indicate that observed outcomes may be context-sensitive, and significantly influenced by differences in the cohort composition and location. The epidemiological and clinical findings indicative for the link between season of birth and the risk for pathological conditions in later life are reviewed below.

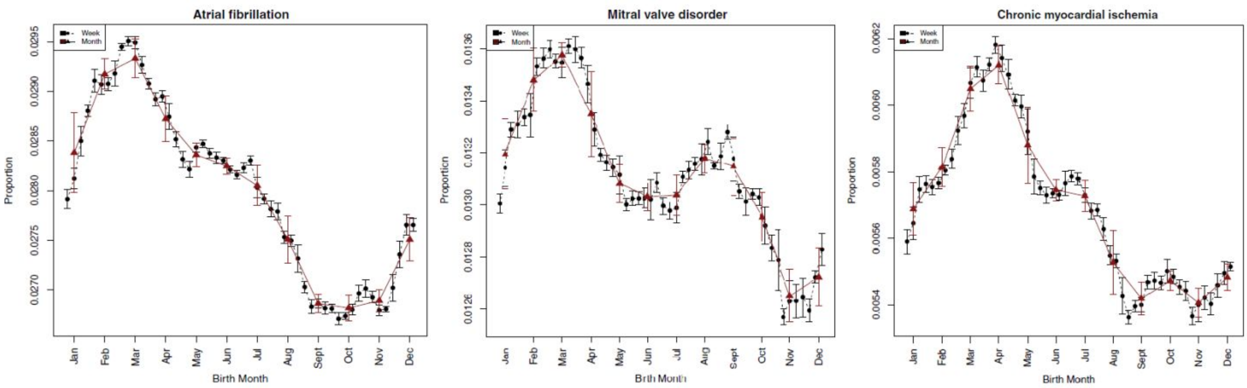

Fig. 2. Association between month of birth and risks for cardiac pathological conditions such as atrial fibrillation (left panel), mitral valve disorder (central panel) and chronic myocardial ischemia (right panel) in adulthood. Prevalences are shown as percentages (mean ± standard error) of corresponding general populations. Reproduced from the article by Boland et al. (2015) available under the Creative Commons CC-BY-NC license. *Copyright © 2015, Oxford University Press*.

Neurological disorders

In the context reviewed here, the seasonality of birth has been most thoroughly studied for its role in developing schizophrenia. Schizophrenia is obviously not an age-related disease (its symptoms usually begin between ages 16 and 30), although it shortens life expectancy by up to 15 to 20 years, primarily owing to the high risk of cardiovascular disease and obesity likely related to the lack of physical activity, unbalanced diet, smoking and substance abuse (Ringen et al., 2014). A significant excess of winter-spring births and a decrease of summer births has been observed consistently among schizophrenia patients. Such a pattern was described in more than 200 papers to date (Demler, 2011). Recently, in studying whether effects of season of birth can be confounded by gene-environment interactions, it has been demonstrated in the UK Biobank cohort (N=136,538) that season-of-birth effect in schizophrenia does not depend on genetic factors and reflects a true pathogenic effect of early-life environmental exposures (Escott-Price et al., 2019). Among the factors most likely contributing to this season-of-birth pattern, there are nutrition, ambient temperature, sperm quality, and also exposures to infections, maternal hormones and external toxins (Tochigi et al., 2004).

Birth seasonality was also found for some other neuropsychiatric disorders. Seasonal variation in autism spectrum disorder births with modestly increased risk for children born in the fall and decreased risk for children born in the spring was observed in Finland and Sweden (Lee et al., 2019). In the U.S., a significant association between month of birth and subsequent depression risk, with spring and summer month births corresponding to significantly more depression, has been reported (Schnittker, 2018). Remarkably, this association was strong in earlier cohorts born at the beginning of the 20th century, but it has largely disappeared in the 1940 birth cohort when living conditions have improved and seasonal variation in food supply has decreased. The consistent seasonal pattern was also observed in epilepsy, with an excess of patients born in December and January and a deficit of those born in September, compared to the general population (Procopio et al., 1997). Seasonal pattern of birth was found for multiple sclerosis, an autoimmune disease of the central nervous system characterized by chronic inflammation, demyelination, gliosis, and neuronal loss (Ghasemi et al., 2017). In a recent meta-analysis, an excessive risk for development of multiple sclerosis was observed in those individuals born in spring months and a reduced risk in those born in October and November (Pantavou and Bagos, 2019). The maternal vitamin D levels and exposure to ultraviolet light were regarded to be potential mechanistic candidates (Dobson et al., 2013).

Neurodegenerative diseases

An association between the season of birth and the risk for Alzheimer's disease (AD), a neurodegenerative disorder which is the most common cause of aging-related dementia worldwide, was investigated in several studies. A substantial excess of first-quarter births among AD patients has been revealed compared to the expected general population birth rates in the UK (Philpot et al., 1989). Similar season-of-birth pattern in AD was subsequently found in California (Frazee et al., 2004). In Québec, significant deficit of AD births was observed in May (Vézina et al., 1996). In Chinese elderly aged 60 and above, the risk for dementia was shown to be substantially lower among those born in winter than that for the summer-born (Ding et al., 2020). These findings, however, have not been confirmed in studies conducted in other Northern Hemisphere countries, where no evidence for seasonality of birth in AD patients was found

(Dysken et al.,1991; Vitiello et al., 1991; Ptok et al., 2001; Tolppanen et al., 2016). No seasonal pattern was also observed the Southern Hemisphere (Australia) (Henderson et al., 1991).

The association between season of birth and the risk of developing Parkinson's disease (PD), a second most common neurodegenerative disease affecting 1–2% of people over 60 years of age (de Lau and Breteler, 2006), was also evaluated in several studies. The reported findings are, however, modest and inconsistent. For example, 30% higher risk of PD associated with spring versus winter birth was observed in the U.S. study (Gardener et al., 2010). This association was, however, modest and non-significant only. No evidence for the systematic season-of-birth variations for PD incidence was found in the Postuma et al. (2007) and Palladino et al. (2015) studies. The sample sizes in most studies aimed at investigating seasonality of birth in AD and PD were, however, small, so findings from these studies are rather inconclusive.

Evidence for seasonality of birth was also obtained for the amyotrophic lateral sclerosis (ALS), a neurodegenerative disease predominantly affecting upper and lower motor neurons, resulting in progressive paralysis and death from respiratory failure. The peak age of onset of this disease is 55 to 70 years (Martin et al., 2017b). Among the Swiss ALS patients, an excess of births was found in the spring months (March to May) (Ajdacic-Gross et al., 1998). In Sweden, individuals born from October through December were at 11% increased risk of ALS compared to those born from April through June (Fang et al., 2009). In Australia, ALS birth rates were shown to increase between late summer and early winter, and to decrease between mid-winter and early summer (Pamphlett and Fang, 2012).

Cardio-metabolic disorders

Skewed season-of-birth patterns have been found for various cardio-metabolic pathological conditions. Prevalence of obesity was found to be greater among those men who were born in Hertfordshire (UK) in January–June than among those born in July–December (Phillips and Young, 2000). In Canada, the proportion of class III obese persons was higher among adult individuals who were born throughout winter/spring (Wattie et al., 2008). Seasonality of birth for patients with type 1 diabetes has been reported repeatedly around the world (Laron et al., 2005). In contrast to the well-established seasonality of birth in childhood diabetes persons, the birth seasonality in adult type 2 diabetic patients has been detected in few studies only. Most of these studies were small-sample sized and findings were inconsistent. For example, seasonal birth patterns were found for 155 type 2 diabetic adolescent African-Americans (Grover et al., 2004) and for 282 adult patients in the Netherlands (Jongbloet et al., 1988). By now, most convincing evidence for seasonality of birth in type 2 diabetes patients was obtained in Ukrainian population (Vaiserman et al., 2009). The peak prevalence of type 2 diabetes has been revealed in both men and women which were born in April and the lowest one was observed in women born in December and in men born in November. Remarkably, in cohort born during 1930-1939 years, the highest monthly prevalence of type 2 diabetes was observed among individuals born in April 1934, i.e., about 9 months after mortality caused by the Ukraine famine of 1932–1933 peaked (Lumey et al., 2015; see also Fig. 3 based on our unpublished data). This suggests that the long-term effects of early-life seasonal factors may be more pronounced if early human development occurs in severe conditions such as natural or man-made disasters. In another large prospective study conducted in China, both male and female participants born in summer had a lower risk of type 2 diabetes in comparison with those born during other seasons (Si et al., 2017b). No evidence for seasonality of birth, however, was obtained in adult patients with type 2 diabetes in Denmark (Jensen et al., 2015).

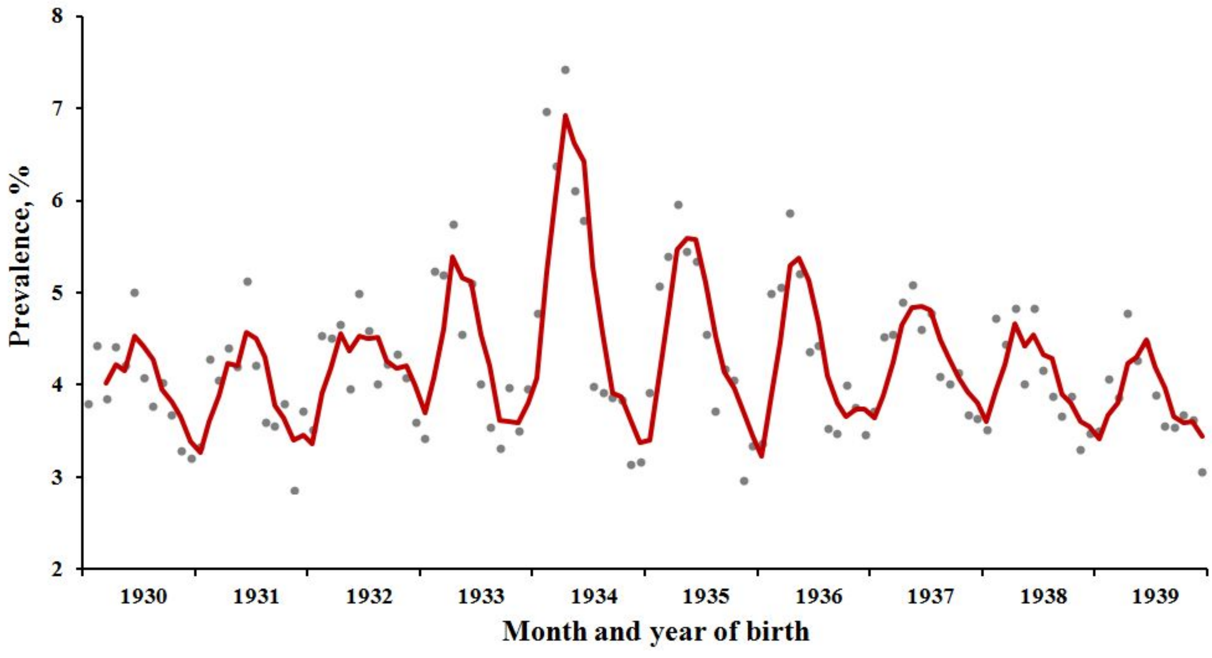

Fig. 3. Prevalence of type 2 diabetes in Ukraine cohort born during 1930-1939 years, according to month and year of birth. Points indicate monthly prevalence estimates.

Birth month was also shown to be associated with metabolic syndrome-associated cardio-vascular complications. Seasonal variations in mean systolic blood pressure, with minimum level in adults born in spring and summer and maximum level in those born in autumn and winter, have been observed in Spanish men aged 45–64 years (Banegas et al., 2000). In China, those persons who were born in winter were shown to have increased risk of coronary artery disease in adult life compared to those born in spring (Zhang et al., 2019a). In a large U.S. sample (N = 1,169,599), strong season-of-birth patterns were found for life-long risks of cardiovascular condition such as essential hypertension, coronary arteriosclerosis, cardiomyopathy, atrial fibrillation, chronic myocardial ischemia and pre-infarction syndrome (Li et al., 2016). The risks for these cardiovascular adverse events were shown to be highest in those individuals who are born during the late winter/early spring. In a Canadian province, Ontario, higher risks of hypertension and coronary heart disease were found in those persons who were born in January and April (Poltavskiy et al., 2016). In the UK, women born during the winter had significantly higher prevalence of coronary heart disease, dyslipidaemia, insulin resistance and poor lung function than those born during other seasons (Lawlor et al., 2004).

Cancer

Seasonality of birth has been repeatedly reported for different types of tumors. In Northern England, significant sinusoidal variation in month of birth was observed for childhood acute lymphoblastic leukaemia (peak in March), acute non-lymphocytic leukaemia (peak in September) and also astrocytoma and osteosarcoma (for both, peaks in October). Such sinusoidal month-of-birth patterns were found for all lymphomas (peak in March) and Hodgkin lymphoma (peak in January) in girls (Basta et al., 2010). In a subsequent UK study, birth peaks for patients with gliomas (except for astrocytoma and ependymoma) were observed in May and November (van Laar et al., 2013). A significant February month-of-birth peak was also shown for childhood leukaemia in another UK study (Higgins et al., 2001). In Sweden, an increased risk of non-Hodgkin (but not Hodgkin) lymphoma was revealed in children and young adults born in spring or summer (Crump et al., 2014). In a meta-analysis by Georgakis et al. (2017), risk for occurrence of central nervous system tumors or tumor subtypes was significantly associated with birth season in eight of ten included studies in children and in four of eight studies in adults, with a clustering of births mainly in autumn and winter months. Seasonality of birth was also observed for other cancer types such as skin cancer (La Rosa et al., 2014), colorectal cancer

(Francis et al., 2017), lung cancer (Hao et al., 2017) and breast cancer (Yuen et al., 1994). Most of these studies, however, were conducted with small-size samples, so, these findings are rather inconclusive and show only correlation but no causal relationships.

4. Early-life seasonal programming of longevity

Among all identified season-of-birth effects, the impacts on mortality are of great interest because they represent life-long health outcomes. Evidence for the impacts of season of birth on human longevity has been repeatedly demonstrated across countries. To date, the dependency of human longevity on month of birth has been most firmly established in the study by Doblhammer and Vaupel (2001). In this research, it has been shown that those individuals who are born in autumn tend to live longer than those who are born in spring in the Northern Hemisphere countries such as Denmark and Austria. Remarkably, in the Southern Hemisphere country, such as Australia, the season-of-birth pattern was shifted by half a year, with a minimum of the mean age at death in the autumn-born persons and maximum in the spring-born ones (Fig. 4). In the subsequent study conducted on the basis of 15 million U.S. death certificates for the years 1989 to 1997, Doblhammer (2002) found that those people who were born in autumn lived almost half a year longer than those born in spring. These differences were largest for those who were less educated, were never married and for African Americans, and they were more pronounced in the South than in the North. Significant month-of-birth patterns were also observed for all major causes of death including infectious diseases, cardiovascular disorders and malignant neoplasms. The author concluded that findings from her study are consistent with a role of nutrition and infectious exposures (but not temperature or daylight) in seasonal programming of longevity. In other prospective cohort study performed in the U.S., those women who were born in the spring and summer demonstrated a slight but significant increase in cardiovascular mortality; no birth-of-month effect was found, however, for overall mortality (Zhang et al., 2019b). In analyzing 17,082 male and 19,075 female individuals who were followed from 1986 to 2006 in the U.S., males born in the 4th quarter were 11% less likely to die and females born in the 3rd quarter were 14% less likely to die than those born in the 1st quarter (Sohn, 2016).

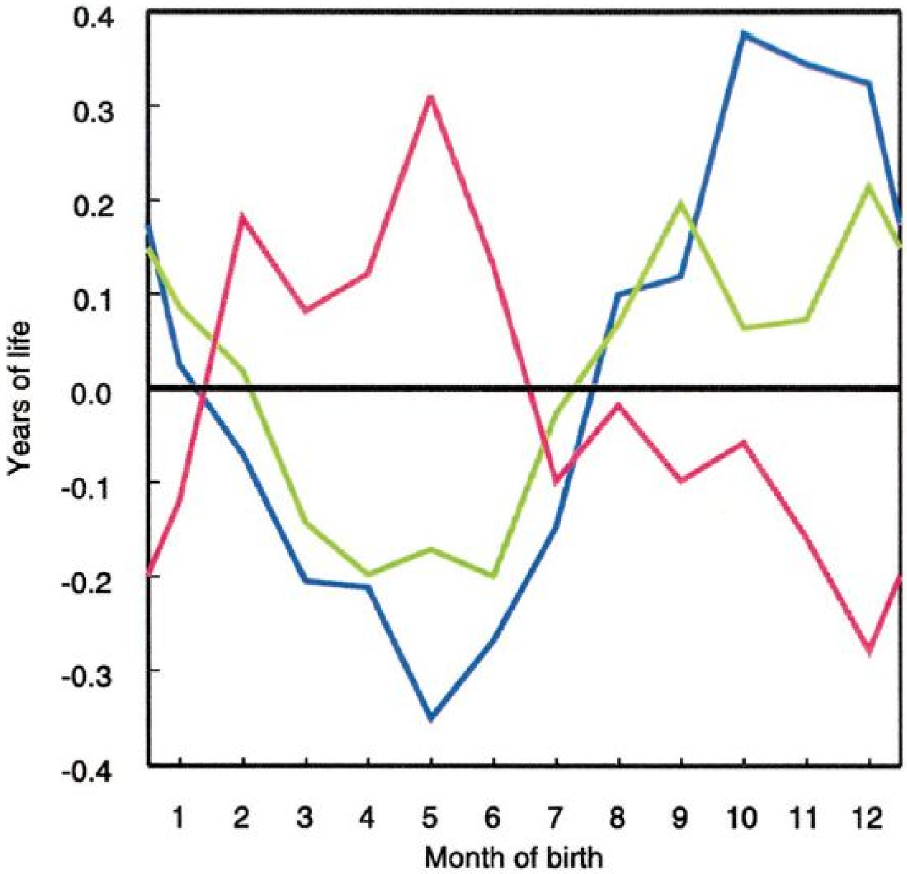

Fig. 4. Deviation in remaining lifespan of people born in specific months from the average remaining lifespan at age 50. In the Northern Hemisphere countries of Denmark (green line) and Austria (blue line), the people born in the fourth quarter of the year live longer than those born in the second quarter. For Australia (red line), the pattern is shifted by half a year. Reproduced from the article by Doblhammer and Vaupel (2001) with permission from Proc Natl Acad Sci U S A. *Copyright (2001) National Academy of Sciences, U.S.A.*

In studying genealogical longevity records for women from European aristocratic families, Gavrilov and Gavrilova (1999) found that women born in May lived 3.61 years longer and those born in December lived 3.21 years longer on average than those born in August. Effect of the birth's season on longevity was revealed in historical cohorts of French Canadian women who were born before 1750 (Gagnon, 2012). A significant impact of the season of birth on long-term survival has been also found in birth cohort 1800-1870 born in Minorca Island (Spain) (Muñoz-Tudurí and García-Moro, 2008). In this cohort, summer births had a decreased death risk after 15 years of age. In-utero nutrition was proposed to be a leading causal factor. In Greece, birth during the autumn and winter seasons was associated with significantly increased longevity (Flouris et al., 2009). These effects were mediated, at least in part, by outdoor temperature at time of birth. Longevity was shown to be significantly associated with season of birth of both male and female individuals in Kiev (Ukraine) (Vaiserman et al., 2002). Mean age at death was lowest in those who were born in April-July, and highest in those born at the beginning and end of the year. Minimum and maximum monthly values differed by 2.6 years in males and 2.3 years in females. For all major death causes, longevity was highest in individuals born during the 4th quarter. In a large (N = 6,194,745) nation-wide population-based cohort study conducted in Sweden, month of birth was found to be a significant predictor of mortality (Ueda et al., 2013). After adjusting for sex and education level, the lowest level of mortality in ages above 50 years was found for persons born in November and the highest level in those born during the spring/summer. In the same cohort, month of birth has been also shown to be associated with mortality from infectious and cardiovascular diseases, but not from cancers or external causes (Ueda et al., 2014). The cardiovascular mortality rate was highest in those born in March/April, and the mortality from infections was lowest in the September-born, compared to persons born in November. Among residents of North Rhine Westphalia who died in the years 1984 (N = 188,515) and 1999 (N = 188,850), those who were born in May through July had the lowest age at death, and those born between October and December had the highest (Lerchl et al., 2004). In Japan, healthy male elderly individuals who were born in December were found to be more likely to die earlier whereas those who were born in January had lower mortality (Inoue et al., 2016).

Evidence for the impact of season of birth on the later-life mortality was also obtained in some low-income developing countries. In rural Gambia, people born during the annual wet "hungry" season (July to December) were up to 10 times more likely to die prematurely during their young adulthood (Moore et al., 1997). Since the majority of these premature deaths were caused by infections or infection-associated disorders, a permanent effect of malnutrition throughout prenatal growth on development of the immune system was proposed as a likely explanation (Moore et al., 1999). These findings, however, have not been consequently confirmed in other populations residing in regions with distinct differences between seasons, such as rural Senegal and Bangladeshi populations (Simondon et al., 2004; Moore et al., 2004).

In several studies, evidence was obtained that season of birth can affect the chance of becoming a centenarian. In the U.S. population, siblings born in September-November were shown to have significantly higher odds to live to be 100 years old than their siblings born in March (Gavrilov and Gavrilova, 2011). More recently, it has been demonstrated that most centenarians were born in the U.S. in the second half of the year (Gavrilov and Gavrilova, 2014). In studying German semi-supercentenarians aged 105+, it has been shown that odds to survive to age 105+ was 16% higher in December-born persons than average, while among the June-born, these odds were 23% lower (Doblhammer et al., 2005).

4. Mechanistic insights

In discussing mechanisms underlying season-of-birth effects, it has been initially assumed that this phenomenon may be explained by seasonal differences in the quality of semen (Rojansky et al., 1992) or oocytes at ovulation or at fertilization (Jongbloet et al., 2007). More recent findings, however, indicate that these effects may be rather explained by processes related to developmental programming. One of the most important factors that influence these processes is nutrition (Vaiserman et al., 2014). Currently, the impact of this factor is rather low in developed countries depending only slightly on seasonal factors owing to the year-round availability of fresh produce from a global market, but it is certainly high in low-income and primarily agricultural societies. In these populations, babies born during periods of seasonal malnutrition can develop adaptive metabolic responses aimed at maximizing the metabolic efficiency in order to optimize use and storage of nutrients (Zhu et al., 2019). Such developmental adaptation can lead to a reallocation of resources aimed at better protection of brain at the expense of other fetal organs, such as adipose tissue, liver, muscles and pancreas (Kim, 2016). These processes may be mediated by impaired development of hypothalamic appetite-regulating circuits and feeding behavior (Zeltser, 2018). As a consequence, long-lasting alterations can arise in glucose–insulin metabolism. Such metabolic changes, including lowered insulin secretion and insulin resistance, may result in an improved capacity to store fat throughout adult life. If the prenatal development occurs under poor climatic conditions and seasonal malnutrition, while postnatal development occurs during the abundant seasonal supply of nutrition, such a developmental scenario can lead to catch-up postnatal growth and, consequently, to long-term adverse health outcomes.

Infection exposure can be one more factor potentially influencing processes involved in developmental programming. It is firmly established that adult immune responses can be programmed by neonatal exposure to certain immune-modulating stimuli throughout the process of priming of the antibody-forming system (Spencer et al., 2011). The process of neonatal maturation of the immune system seems to be very important in determining life-long health status since chronic inflammation is well known to contribute to most chronic pathologies such as cardio-metabolic disorders, neurodegeneration and cancer (Rajendran et al., 2018*).* It seems to be important in the context discussed because patterns of infectious exposures are definitely different in various seasons. Indeed, in the Northern Hemisphere, late-summer or early-autumn seasonality exists in enteroviral infections and predominantly winter-time seasonality exists in viral respiratory infections (Fisman, 2012). So, neonatal exposure to differing seasonal infectious patterns may likely result in differing disease profiles in adult life.

Environmental factors acting during early-life development also contribute to establishment of the gut microbiota profile (the totality of microorganisms inhabiting the intestine) (Vandenplas et al. 2020). It is certainly an important point to consider with respect to the early-life seasonal programming, since microbiota composition is known to establish early in life [a "microbial programming" phenomenon (Koleva et al., 2015)] and then remains fairly unchanged and determines health status throughout the whole life course (Codagnone et al., 2019; Stinson, 2020). Remarkably, the establishment of the adult-like profile of the gut microbiota is known to continue from the periconception period up to two years of age (Butel et al., 2018) and thus, it largely coincides with a critical period of human developmental plasticity. Nutritional factors certainly play a crucial role in these processes (Dahl et al., 2020), although other environmental exposures (day length, infections, environmental toxicants and pollutants, etc.) (Karl et al., 2018), perinatal vitamin D levels (McGrath, 2001) and lifestyle factors (alcohol and drug intake, smoking, physical activity, etc.) (Flandroy et al., 2018) can be also of great importance. All these factors significantly fluctuate with the season changes, especially in regions with strong climatic seasonality. Substantial seasonal differences in the human microbiota composition have been observed in some studies. Most evidence for such differences was obtained in autochthonous hunter-gatherer communities like the Hadza hunter-gatherers of Tanzania (Smits et al., 2017) or in isolated ethno-religious groups such as Hutterites (Davenport et al., 2014). Evidence for seasonal microbiome shifts was also found on the population level in the U.S. (Korownyk et al., 2018), and also in samples from general populations in Mongolia (Zhang et al., 2014) and Ukraine (Koliada et al., 2020).

The effects of all above factors can be mediated by epigenetic processes (including DNA methylation, histone modifications, chromatin remodeling and non-coding regulatory RNAs) known to play a central role in the DOHaD phenomenon (Safi-Stibler and Gabory, 2020). The persistent epigenetic alterations triggered by certain seasonal cues during early development may, due to predictive adaptive response, have adaptive significance in postnatal development, but they might predispose to chronic disorders later in life. The evidence for an association among season of birth and profiles of DNA methylation in adult life has been obtained in the study by Lockett et al. (2016a). In this epigenome-wide association study *(*EWAS) conducted in 367 participants aged 18 from the UK, methylation at 92 CpG dinucleotides has been found to be associated with the season of birth. Four of the associations observed have been replicated in an independent series of 207 children aged 8 from the Netherlands. Season-of-birth-associated methylation patterns were enriched in gene pathways involved in cell cycle, development, and apoptosis. Remarkably, these season-related methylation profiles were nearly absent in newborns, but they were evident in 18-year-old participants. These findings, however, have not been confirmed in subsequent study by Dugué et al. (2016) attempted to replicate 92 associations revealed by Lockett et al. (2016a) using 2774 adults aged 40–70 residing in Southern Hemisphere (Australia). The difference between analytical approaches applied was proposed as potential explanation for inconsistency between these studies (Lockett et al., 2016b). The authors agreed that more in-depth research is required to determine the role of epigenetic mechanisms in season-of-birth programming of adult-life disease.

5. Discussion

People who are born in different seasons experience different environmental exposures during their prenatal and early postnatal development. Therefore, studying effects of the season of birth on long-term health status may be an effective research approach in clarifying mechanistic pathways underlying developmental programming phenomenon. In these studies, month of birth can serve as a useful proxy for seasonally varying environmental conditions including diet, outdoor temperature, day length, infections, etc. around the perinatal period. This is especially the case in low-income countries, predominantly rural, where populations are more dependent on climatic factors, and for those individuals who were born several decades ago, when living conditions were more seasonally contrasting than they are now. For example, in temperate Northern Hemisphere countries, including most regions of Europe and the U.S., the development of subjects born in April-May took place in conditions of the nutritionally marginal period from late autumn to early spring. Moreover, these persons were at high risk to be prenatally exposed to unfavorable factors (maternal respiratory infections, low vitamin D levels, etc.). Postnatal months of these individuals, on the contrary, took place during prosperous and plentiful months of the year. Such a developmental scenario conforms to the thrifty phenotype hypothesis, assuming that if developing fetus is undernourished due to suboptimal nutrient supply caused by maternal malnutrition, stress, infection, etc., adaptive response can occur aimed at reallocation of resources in order to maximizing the metabolic efficiency (Hales and Barker, 2001). As a consequence of this ontogenetic adaptive strategy, long-lasting adaptive alterations occur in glucose–insulin metabolism, including reduced ability for insulin secretion and insulin resistance, which ultimately result in an enhanced capacity to store fat and in development various metabolic disorders, including obesity and type 2 diabetes later in life. Remarkably, just this period of the year (April-May) were found to be the highest-risk birth period for subsequent developing type 2 diabetes in a temperate-climate country such as Ukraine (Vaiserman et al., 2009). In contrast, the prenatal development of subjects born in November–December, which demonstrated lowest risk of type 2 diabetes, occurred during the nutritionally plentiful season, followed by scarce seasons (winter - spring) throughout their early postnatal development.

These findings indicate that seasonal developmental programming phenomenon can likely have important implications for health status in human populations. This is especially true, given the central role of epigenetic mechanisms in developmental programming processes. Due to involvement of these mechanisms, developmentally programmed epigenetic changes may be transgenerationally transmitted to subsequent generations, determining their health status (Xavier et al., 2019; King and Skinner, 2020) and even longevity (Vaiserman et al., 2017). Given this, it seems important to take into account season of birth as an additional risk factor for developing various diseases, especially in populations living in seasonally contrast conditions. The mechanistic basis for the seasonal developmental programming phenomenon should be addressed in future studies.

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