Journal of Developmental Origins of Health and Disease

www.cambridge.org/doh

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

Alexander Vaiserman

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

Review

Cite this article: Vaiserman A. (2021) Season-of-birth phenomenon in health and longevity: epidemiologic evidence and mechanistic considerations. *Journal of Developmental Origins of Health and Disease* **12**: 849–858. doi: 10.1017/S2040174420001221

Received: 17 August 2020
Revised: 2 October 2020
Accepted: 8 November 2020
First published online: 10 December 2020

Keywords:
DOHaD; developmental programming; seasonality of birth; disease risk; longevity

Address for correspondence:
Alexander Vaiserman, Laboratory of Epigenetics, D.F. Chebotarev Institute of Gerontology, NAMS, 67 Vyshgorodska str., Kyiv 04114, Ukraine.
Email: vaiserman@geront.kiev.ua

Abstract

In many human populations, especially those living in regions with pronounced climatic differences between seasons, the most sensitive (prenatal and neonatal) developmental stages occur in contrasting conditions depending on the season of conception. The difference in 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.

Introduction

Genetic and environmental factors are commonly considered as basic determinants of chronic disease and longevity.[1] 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.[2,3] In the majority of human populations, especially those living in regions with pronounced climatic differences between seasons, the most sensitive (prenatal and neonatal) stages of human development occur in seasonally contrasting conditions. It might likely 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 the season in these countries.[4] Other potentially important factors that change seasonally include outdoor temperature,[5,6] infectious exposures,[7] as well as the duration of sunlight and vitamin D synthesis.[8] Moreover, potentially contributing to maternal lifestyle factors such as physical activity[9] and substance abuse[10] 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.

Search strategy

A literature search was conducted in the PubMed and ScienceDirect databases to find all published studies providing (or not) evidence for the season-of-birth patterns in human anthropometric parameters, adult-life physiological characteristics and health status, and also mortality and longevity. Various combinations of search terms such as “early development”, “season of birth”, “month of birth”, “seasonality”, “seasonal programming”, “birth weight”, “climatic factors”, “health”, “disease”, “incidence”, “prevalence”, “aging”, “mortality”, and “longevity” were used in searching relevant references from journal articles and book chapters. Moreover, since conceptual issues were discussed regarding the potential mechanistic basis for the “seasonal programming” phenomenon, an additional search was carried out with terms “developmental programming”, “DOHaD”, “predictive adaptive response”, “catch-up growth”, and “thrifty phenotype hypothesis”. The time period covered by the search was January 1988–June 2020. Only papers written in English were included. There was no restriction on the type of study design; therefore, all the cohort, cross-sectional, and case–control studies satisfying search criteria were included. In the case if multiple publications exist in the literature concerning a specific topic discussed (e.g. seasonality of birth in schizophrenia), then review articles (including meta-analyses) on this particular topic were used as information sources. During the literature searching process, the exclusion criteria were grey or non-English literature, inappropriate research methodology, and also not statistically significant results due to the small sample size. If the methodological quality of the included study was assessed as dubious (e.g. due to a low statistical power because of small sample size), these methodological deficiencies were indicated in the text.

Season of birth and life course physiology

Birth weight

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.*[11] review of global patterns, individuals born during the winter period tended to have low birth weight and those born during the summer period tended to have high birth weight in the high- and low-latitude regions, while the opposite association was found in the midlatitude regions. In a more recent study by Day *et al.*[12], summer-born infants also had higher birth weights compared to those born in other seasons in the UK population. In comparing the extreme differences between birth months, those individuals who were born in February had 1.23 times higher odds to have low birth weight than those who were born in September ($p < 0.001$). An association between the month of birth and future anthropometric measures has been reported in a recent systematic review by Hemati *et al.*[13] More specifically, those persons who were born in winter months tended to have higher weight and body mass index (BMI) in childhood across countries. Interestingly, this association is opposite to that reported by Chodick *et al.*[11] for the birth weight. The 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[14]) could be one potential explanation for this inconsistency.

Life cycle events

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.[15] 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.[16] In China, more early ages of both menarche and menopause were revealed in women born in spring compared to ones born in other seasons.[17] In Italy, menopause was found to occur earlier in women born in the spring than in the autumn.[18] The earliest menopause has been observed in women born in March and the latest one in women born in October.

Adult physiological characteristics and health status

Since birth weight is, in turn, associated with adult-life health outcomes,[19] it is not surprising 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 lifelong, 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.[20] At any given age, spring- and summer-born persons developed about 3.5% 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 nonsignificant 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% 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).[21,22] 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).[23] More specifically, individuals who were born in July had a higher basal metabolic rate (Fig. 1b) and frequency of having allergy later in life (Fig. 1c) compared to those born in December.[22] Moreover, findings from this study indicated that season of birth may affect growth parameters (Fig. 1a).

Sleep characteristics

Season of birth was also 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 a higher risk of type 2 diabetes, obesity, cardiovascular diseases, psychiatric disorders, and also with increased mortality than the morning-oriented ones.[24] Importantly, the adult chronotype was shown to be differently programmed depending on the season of birth.[21]

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 in the US (total $n = 1{,}749{,}400$), the association with birth month was found for 55 diseases[25] (Fig. 2). Findings from these phenome-wide studies were subsequently partly confirmed in the same US cohort.[26] The results of the latter research, however, indicate that observed outcomes may be context-sensitive, and significantly influenced by

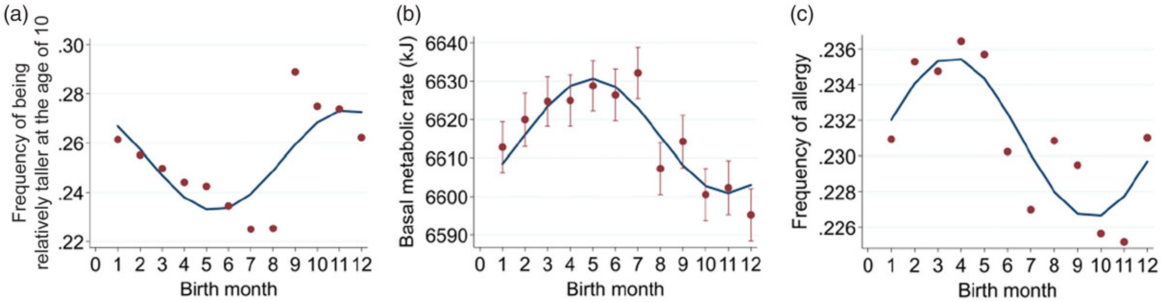

Fig. 1. Month of birth and (a) frequency of being taller at the age of 10, (b) basal metabolic rate, and (c) frequency of having allergy in the UK Biobank cohort. Red scatter plots show prevalence in (a) and (c) and mean ± standard error in (b). Reproduced from the article by Didikoglu *et al.*[22] with permission of the publisher. *© 2020 Wiley Periodicals, Inc*.

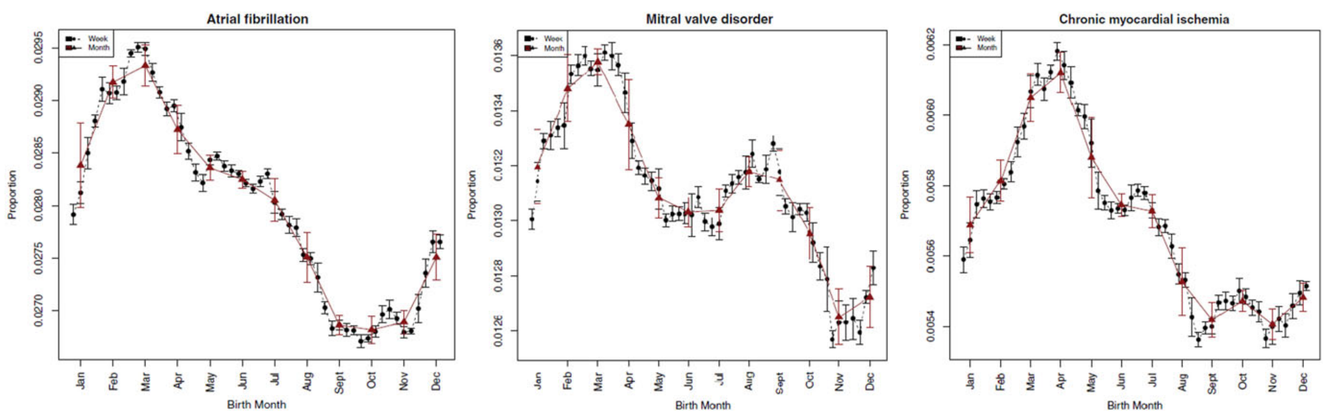

Fig. 2. Association between month of birth and risks for cardiac pathological conditions such as atrial fibrillation (left panel), mitral valve disorder (central panel), and chronic myocardial ischemia (right panel) in adulthood. Prevalences are shown as percentages (mean ± standard error) of corresponding general populations. Reproduced from the article by Boland *et al.*[25] available under the Creative Commons CC-BY-NC license. *Copyright © 2015, Oxford University Press*.

differences in the cohort composition and location. The epidemiological and clinical findings indicative of the link between season of birth and the risk for pathological conditions in later life are reviewed below.

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 15–20 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.[27] A significant excess of winter–spring births and a decrease of summer births have been observed consistently among schizophrenia patients. Such a pattern was described in more than 200 papers to date.[28] 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.[29] 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.[30] 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.[31]

The effects of month of birth on adult depression were also demonstrated. In the US, 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.[32] 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 the 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.[33]

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).[34] In a recent meta-analysis, an excessive risk for development of multiple sclerosis was observed in those individuals born in the spring months and a reduced risk in those born in October and November.[35] The maternal vitamin D levels and exposure to ultraviolet light were regarded to be potential mechanistic candidates (Dobson *et al.*, 2013).[36]

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

https://doi.org/10.1017/S2040174420001221 Published online by Cambridge University Press

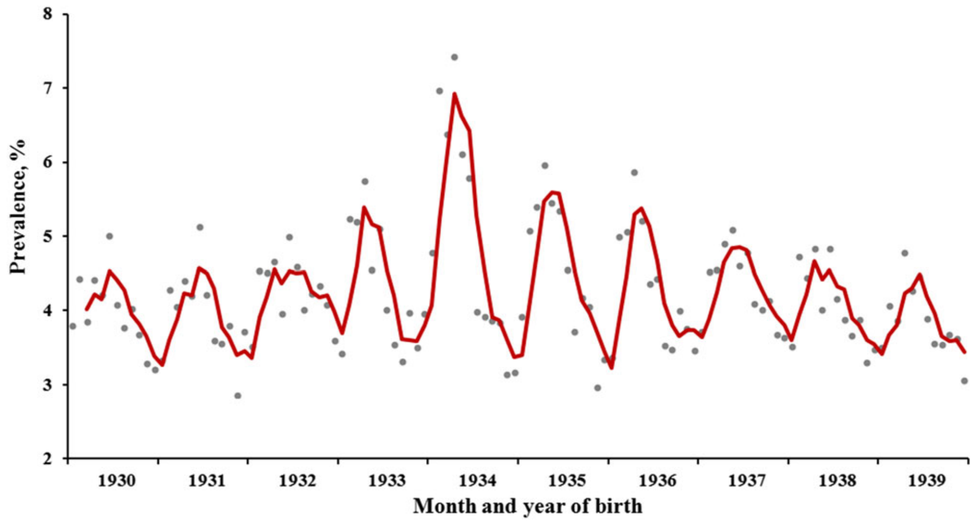

Fig. 3. Prevalence of type 2 diabetes in Ukraine cohort born during 1930–1939 years, according to month and year of birth. Points indicate monthly prevalence estimates.

to the expected general population birth rates in the UK.[37] Similar season-of-birth pattern in AD was subsequently found in California.[38] In Québec, a significant deficit of AD births was observed in May.[39] 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.[40] 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.[41–44] No seasonal pattern was also observed in the Southern Hemisphere (Australia) (Henderson *et al.*, 1991).[45]

The association between season of birth and the risk of developing Parkinson's disease (PD), the second most common neurodegenerative disease affecting 1%–2% of people over 60 years of age,[46] was also evaluated in several studies. The reported findings are, however, modest and inconsistent. For example, a 30% higher risk of PD associated with spring versus winter birth was observed in the US study.[47] This association was, however, modest and nonsignificant only. No evidence for the systematic season-of-birth variations for PD incidence was found in the Postuma *et al.*[48] and Palladino *et al.*[49] 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 55–70 years.[50] Among the Swiss ALS patients, an excess of births was found in the spring months (March–May).[51] In Sweden, individuals born from October through December were at 11% increased risk of ALS compared to those born from April to June.[52] In Australia, ALS birth rates were shown to increase between late summer and early winter, and to decrease between midwinter and early summer.[53]

Cardiometabolic disorders

Skewed season-of-birth patterns have been found for various cardiometabolic 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.[54] In Canada, the proportion of class III obese persons was higher among adult individuals who were born throughout winter/spring.[55]

Seasonality of birth for patients with type 1 diabetes has been reported repeatedly around the world.[56] 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 a 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[57] and for 282 adult patients in the Netherlands.[58] By now, the most convincing evidence for seasonality of birth in type 2 diabetes patients was obtained in the Ukrainian population.[59] The peak prevalence of type 2 diabetes has been revealed in both men and women born in April and the lowest one was observed in women born in December and in men born in November. Remarkably, in the 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[60] (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.[61] No evidence for seasonality of birth, however, was obtained in adult patients with type 2 diabetes in Denmark.[62]

Seasonal variations in mean systolic blood pressure, with a 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.[63] In China, those persons who were born in winter were shown to have an increased risk of coronary artery disease in adult life compared to those born in spring.[64] In a large US sample ($n = 1{,}169{,}599$), strong season-of-birth patterns were found for lifelong risks of the cardiovascular condition such as essential hypertension, coronary arteriosclerosis, cardiomyopathy, atrial fibrillation, chronic myocardial ischemia, and pre-infarction syndrome.[65] 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

https://doi.org/10.1017/S2040174420001221 Published online by Cambridge University Press

and April.[66] In the UK, women born during the winter had a significantly higher prevalence of coronary heart disease, dyslipidemia, insulin resistance, and poor lung function than those born during other seasons.[67]

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 leukemia (peak in March), acute non-lymphocytic leukemia (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's lymphoma (peak in January) in girls.[68] In a subsequent UK study, birth peaks for patients with gliomas (except for astrocytoma and ependymoma) were observed in May and November.[69] A significant February month-of-birth peak was also shown for childhood leukemia in another UK study.[70] In Sweden, an increased risk of non-Hodgkin (but not Hodgkin) lymphoma was revealed in children and young adults born in spring or summer.[71]

In a meta-analysis by Georgakis *et al.*,[72] the risk for occurrence of central nervous system tumors or tumor subtypes was significantly associated with birth season in 8 of the 10 included studies in children and in 4 of the 8 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,[73] colorectal cancer,[74] lung cancer,[75] and breast cancer.[76] 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.

Early life seasonal programming of longevity

Among all identified season-of-birth effects, the impacts on mortality are of great interest because they represent lifelong 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.[77] 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 US death certificates for the years 1989–1997, Doblhammer[78] 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 the seasonal programming of longevity. In another prospective cohort study performed in the US, those women who were born in the spring and summer demonstrated a slight but significant increase in cardiovascular

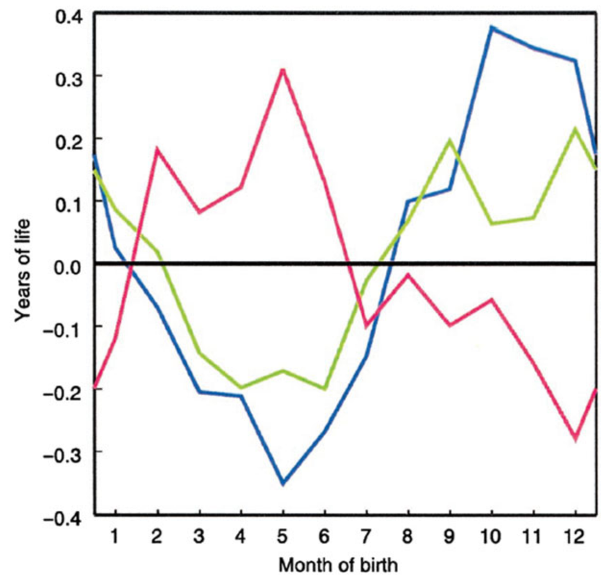

Fig. 4. Deviation in the remaining lifespan of people born in specific months from the average remaining lifespan at the age of 50. In the Northern Hemisphere countries of Denmark (green line) and Austria (blue line), the people born in the fourth quarter of the year live longer than those born in the second quarter. For Australia (red line), the pattern is shifted by half a year. Reproduced from the article by Doblhammer and Vaupel[77] with permission from Proc Natl Acad Sci USA. *Copyright (2001) National Academy of Sciences, U.S.A.*

mortality; no birth-of-month effect was found, however, for overall mortality.[79] In analyzing 17,082 male and 19,075 female individuals who were followed from 1986 to 2006 in the US, males born in the fourth quarter were 11% less likely to die and females born in the third quarter were 14% less likely to die than those born in the first quarter.[80]

In studying genealogical longevity records for women from European aristocratic families, Gavrilov and Gavrilova[81] 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.[82] 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).[83] 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.[84] These effects were mediated, at least in part, by outdoor temperature at the time of birth. Longevity was shown to be significantly associated with season of birth of both male and female individuals in Kiev (Ukraine).[85] 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 fourth quarter. In a large ($n = 6{,}194{,}745$) nationwide population-based cohort study conducted in Sweden, month of birth was found to be a significant predictor of mortality.[86] 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

https://doi.org/10.1017/S2040174420001221 Published online by Cambridge University Press

from infectious and cardiovascular diseases, but not from cancers or external causes.[87] 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.[88] 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.[89]

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–December) were up to 10 times more likely to die prematurely during their young adulthood.[90] 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.[91] 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.[92,93]

In several studies, evidence was obtained that season of birth can affect the chance of becoming a centenarian. In the US population, siblings born in September–November was shown to have significantly higher odds to live to be 100 years old than their siblings born in March.[94] More recently, it has been demonstrated that most centenarians were born in the US in the second half of the year.[95] 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.[96]

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[97] or oocytes at ovulation or at fertilization.[98] More recent findings, however, indicate that such effects may be rather explained by processes related to developmental programming. The mechanisms potentially contributing to these effects are described in subsections below.

Nutrition

Nutrition is one of the most important factors that influence these processes.[2] 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 the use and storage of nutrients.[99] 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.[100] These processes may be mediated by impaired development of hypothalamic appetite-regulating circuits and feeding behavior.[101] 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

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.[102] The process of neonatal maturation of the immune system seems to be very important in determining lifelong health status since chronic inflammation is well known to contribute to most chronic pathologies such as cardiometabolic disorders, neurodegeneration, and cancer.[103] 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 wintertime seasonality exists in viral respiratory infections.[104] So, neonatal exposure to differing seasonal infectious patterns may likely result in differing disease profiles in adult life.

Gut microbiota profile

Environmental factors acting during early life development also contribute to establishment of the gut microbiota profile (the totality of microorganisms inhabiting the intestine).[105] 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[106]) and then remains fairly unchanged and determines health status throughout the whole life course.[107,108] Remarkably, the establishment of the adult-like profile of the gut microbiota is known to continue from the periconception period up to 2 years of age[109] and thus, it largely coincides with a critical period of human developmental plasticity. Nutritional factors certainly play a crucial role in these processes,[110] although other environmental exposures (day length, infections, environmental toxicants and pollutants, etc.),[111] perinatal vitamin D levels[112] and lifestyle factors (alcohol and drug intake, smoking, physical activity, etc.)[113] 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[114] or in isolated ethnoreligious groups such as Hutterites.[115] Evidence for seasonal microbiome shifts was also found on the population level in the US,[116] and also in samples from general populations in Mongolia[117] and Ukraine.[118]

Epigenetic processes

The effects of all the above factors can be mediated by epigenetic processes (including DNA methylation, histone modifications, chromatin remodeling, and noncoding regulatory RNAs) known to play a central role in the Developmental Origins of Health

https://doi.org/10.1017/S2040174420001221 Published online by Cambridge University Press

and Disease (DOHaD) phenomenon.[119] 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.*[120] 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 a subsequent study by Dugué *et al.*[121] attempted to replicate 92 associations revealed by Lockett *et al.*[120] using 2774 adults aged 40–70 residing in Southern Hemisphere (Australia). The difference between analytical approaches applied was proposed as a potential explanation for the inconsistency between these studies.[122] 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.

Discussion

People who are born in different seasons experience different environmental exposures during their prenatal and early postnatal development. Therefore, studying the effects of the season of birth on long-term health status may be an effective research approach in clarifying mechanistic pathways underlying the 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 US, the prenatal 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 the developing fetus is undernourished due to suboptimal nutrient supply caused by maternal malnutrition, stress, infection, etc., an adaptive response can occur aimed at reallocation of resources in order to maximize the metabolic efficiency.[123] As a consequence of this ontogenetic adaptive strategy, long-lasting adaptive alterations occur in glucose–insulin metabolism, including the reduced ability for insulin secretion and insulin resistance, which ultimately result in an enhanced capacity to store fat and in the development of various metabolic disorders, including obesity and type 2 diabetes later in life. Remarkably, just this period of the year (April–May) was found to be the highest risk birth period for subsequent developing type 2 diabetes in a temperate-climate country such as Ukraine.[59] In contrast, the prenatal development of subjects born in November–December, which demonstrated the lowest risk of type 2 diabetes, occurred during the nutritionally plentiful season, followed by scarce seasons (winter–spring) throughout their early postnatal development.

In discussing mechanisms underlying the season-of-birth effects, it must be taken into account that most associations between season of birth and long-term health outcomes were found in observational (mostly cross-sectional) studies. The cross-sectional design is an important limitation of these studies because it precludes causal inference. In particular, nonbiological mechanisms might also contribute to these effects. For instance, findings from many studies indicate that season of birth can affect the children's educational attainment. Indeed, it has been reported in many studies across Europe and the US that those children who are born later in the academic year have, on average, lower educational attainment than those who are born earlier in the year.[124] This is attributed to the fact that schoolchildren born shortly before the cut-off date for the start of the school year are usually almost a year younger than their classmates. These children are in earlier stages of their physical, intellectual, and emotional development and they may be thereby relatively disadvantaged.[125] These early life effects can likely influence the professional success and income, as well as, indirectly, the health status in adulthood.[126] Such effects are, however, usually more pronounced in the first 2 years of primary school and largely disappear during the next school years.[127] Therefore, they are unlikely to significantly affect the season-of-birth-related long-term health outcomes.

In conclusion, research findings summarized in this review 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 the involvement of these mechanisms, developmentally programmed epigenetic changes may be transgenerationally transmitted to subsequent generations, determining their health status[128,129] and even longevity.[130] 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.

Acknowledgments. The author would like to thank Ms. Tatyana Papurina for the technical assistance.

Financial support. This research received no specific grant from any funding agency, commercial, or not-for-profit sectors.

Conflict of interest. None.

References

1. Passarino G, De Rango F, Montesanto A. Human longevity: genetics or lifestyle? It takes two to tango. *Immun Ageing.* 2016; 13(1), 1–6.
2. Vaiserman AM. Early-life nutritional programming of longevity. *J Dev Orig Health Dis.* 2014; 5(5), 325–338.
3. Vaiserman A, Koliada A, Lushchak O. Developmental programming of aging trajectory. *Ageing Res Rev.* 2018; 47, 105–122.
4. Watson PE, McDonald BW. Seasonal variation of nutrient intake in pregnancy: effects on infant measures and possible influence on diseases related to season of birth. *Eur J Clin Nutr.* 2007; 61, 1271–1280.

5. Poeran J, Birnie E, Steegers EA, Bonsel GJ. The impact of extremes in outdoor temperature and sunshine exposure on birth weight. *J Environ Health.* 2016; 78(6), 92–100.
6. Li S, Wang J, Xu Z, *et al.* Exploring associations of maternal exposure to ambient temperature with duration of gestation and birth weight: a prospective study. *BMC Pregnancy Childbirth.* 2018; 18(1), 513.
7. Roy MP. Maternal infection, malnutrition, and low birth weight. *J Postgrad Med.* 2016; 62(4), 270–271.
8. Ideraabdullah FY, Belenchia AM, Rosenfeld CS, *et al.* Maternal vitamin D deficiency and developmental origins of health and disease (DOHaD). *J Endocrinol.* 2019; JOE–18–0541.R2.
9. Smith AD, Crippa A, Woodcock J, Brage S. Physical activity and incident type 2 diabetes mellitus: a systematic review and dose–response meta–analysis of prospective cohort studies. *Diabetologia.* 2016; 59(12), 2527–2545.
10. Vaiserman AM. Early–life exposure to substance abuse and risk of type 2 diabetes in adulthood. *Curr Diabetes Rep.* 2015; 15(8), 48.
11. Chodick G, Flash S, Deoitch Y, Shalev V. Seasonality in birth weight: review of global patterns and potential causes. *Hum Biol.* 2009; 81(4), 463–477.
12. Day FR, Forouhi NG, Ong KK, Perry JR. Season of birth is associated with birth weight, pubertal timing, adult body size and educational attainment: a UK Biobank study. *Heliyon.* 2015; 1(2), e00031.
13. Hemati Z, Keikha M, Riahi R, *et al.* A systematic review on the association of month and season of birth with future anthropometric measures. *Pediatr Res.* 2020 [Epub ahead of print].
14. Martin A, Connelly A, Bland RM, Reilly JJ. Health impact of catch–up growth in low–birth weight infants: systematic review, evidence appraisal, and meta–analysis. *Matern Child Nutr.* 2017a; 13(1). doi: 10.1111/mcn.12297.
15. Kliś K, Jarzebak K, Borowska-Strugińska B, *et al.* Season of birth influences the timing of first menstruation. *Am J Hum Biol.* 2016; 28(2), 226–232.
16. Liczbińska G, Gautam RK, Dubey P, Ahirwar AK, Chaurasia A, Kosińska M. Season of birth is not associated with age at menarche in young adults from Central India. *Am J Hum Biol.* 2020; 32(3), e23373.
17. Si JH, Meng RR, Lyu J, *et al.* Associations between season of birth and age both at menarche and at menopause. *Zhonghua Liu Xing Bing Xue Za Zhi.* 2017a; 38(7), 877–882.
18. Cagnacci A, Pansini FS, Bacchi-Modena A, *et al.* Season of birth influences the timing of menopause. *Hum Reprod.* 2005; 20(8), 2190–2193.
19. Vaiserman AM. Birth weight predicts aging trajectory: a hypothesis. *Mech Ageing Dev.* 2018; 173, 61–70.
20. Abeliansky AL, Strulik H. Season of birth, health and aging. *Econ Hum Biol.* 2020; 36, 100812.
21. Didikoglu A, Maharani A, Payton A, Pendleton N, Canal MM. Longitudinal change of sleep timing: association between chronotype and longevity in older adults. *Chronobiol Int.* 2019; 36(9), 1285–1300.
22. Didikoglu A, Canal MM, Pendleton N, Payton A. Seasonality and season of birth effect in the UK Biobank cohort. *Am J Hum Biol.* 2020; 32(6), e23417.
23. Frisard M, Ravussin E. Energy metabolism and oxidative stress: impact on the metabolic syndrome and the aging process. *Endocrine.* 2006; 29(1), 27–32.
24. Knutson KL, von Schantz M. Associations between chronotype, morbidity and mortality in the UK Biobank cohort. *Chronobiol Int.* 2018; 35(8), 1045–1053.
25. Boland MR, Shahn Z, Madigan D, Hripcsak G, Tatonetti NP. Birth month affects lifetime disease risk: a phenome–wide method. *J Am Med Inf Assoc.* 2015; 22(5) 1042–1053.
26. Borsi JP. Hypothesis–free search for connections between birth month and disease prevalence in large, geographically varied cohorts. *AMIA Annu Symp Proc.* 2017; 2016, 319–325.
27. Ringen PA, Engh JA, Birkenaes AB, Dieset I, Andreassen OA. Increased mortality in schizophrenia due to cardiovascular disease – a non–systematic review of epidemiology, possible causes, and interventions. *Front Psychiatry.* 2014; 5, 137.
28. Demler TL. Challenging the hypothesized link to season of birth in patients with schizophrenia. *Innov Clin Neurosci.* 2011; 8(9), 14–19.
29. Escott-Price V, Smith DJ, Kendall K, *et al.* Polygenic risk for schizophrenia and season of birth within the UK Biobank cohort. *Psychol Med.* 2019; 49(15), 2499–2504.
30. Tochigi M, Okazaki Y, Kato N, Sasaki T. What causes seasonality of birth in schizophrenia? *Neurosci Res.* 2004; 48(1), 1–11.
31. Lee BK, Gross R, Francis RW, *et al.* Birth seasonality and risk of autism spectrum disorder. *Eur J Epidemiol.* 2019; 34(8), 785–792.
32. Schnittker J. Season of birth and depression in adulthood: revisiting historical forerunner evidence for in–utero effects. *SSM Popul Health.* 2018; 4, 307–316.
33. Procopio M, Marriott PK, Williams P. Season of birth: aetiological implications for epilepsy. *Seizure.* 1997; 6(2), 99–105.
34. Ghasemi N, Razavi S, Nikzad E. Multiple sclerosis: pathogenesis, symptoms, diagnoses and cell–based therapy. *Cell J.* 2017; 19(1), 1–10.
35. Pantavou KG, Bagos PG. Season of birth and multiple sclerosis: a systematic review and multivariate meta–analysis. *J Neurol.* 2020; 267(10), 2815–2822.
36. Dobson R, Giovannoni G, Ramagopalan S. The month of birth effect in multiple sclerosis: systematic review, meta–analysis and effect of latitude. *J Neurol Neurosurg Psychiatry.* 2013; 84(4), 427–432.
37. Philpot M, Rottenstein M, Burns A, Der G. Season of birth in Alzheimer's disease. *Br J Psychiatry.* 1989; 155, 662–666.
38. Frazee J, Russell M, Chicota C, *et al.* Seasonality of birth in Alzheimer's disease. *J Orthomol Med.* 2004; 19(3), 162–166.
39. Vézina H, Houde L, Charbonneau H, *et al.* Season of birth and Alzheimer's disease: a population–based study in Saguenay–Lac–St–Jean/Québec (IMAGE Project). *Psychol Med.* 1996; 26(1), 143–149.
40. Ding R, He P, Song X, Zheng X. Season of birth and dementia: findings from Chinese elderly based on a nationwide data. *Am J Hum Biol.* 2020; 32(2), e23319.
41. Dysken MW, Kuskowski M, Skare SS, *et al.* Seasonal distribution of births in Alzheimer's disease. *Int Psychogeriatr.* 1991; 3(1), 53–58.
42. Vitiello B, Hill JL, Molchan SE, *et al.* Lack of seasonal variation in the births of patients with dementia of the Alzheimer type. *Psychiatry Res.* 1991; 39(1), 21–24.
43. Ptok U, Papassotiropoulos A, Maier W, Heun R. Seasonal distribution of births in patients with Alzheimer's disease and elderly depressive patients. *Eur Psychiatry.* 2001; 16(3), 157–161.
44. Tolppanen AM, Ahonen R, Koponen M, *et al.* Month and season of birth as a risk factor for Alzheimer's disease: a nationwide nested case–control study. *J Prev Med Public Health.* 2016; 49(2), 134–138.
45. Henderson AS, Korten AE, Jorm AF, *et al.* Season of birth for Alzheimer's disease in the southern hemisphere. *Psychol Med.* 1991; 21(2), 371–374.
46. de Lau LM, Breteler MM. Epidemiology of Parkinson's disease. *Lancet Neurol.* 2006; 5, 525–535.
47. Gardener H, Gao X, Chen H, *et al.* Prenatal and early life factors and risk of Parkinson's disease. *Mov Disord.* 2010; 25(11), 1560–1567.
48. Postuma RB, Wolfson C, Rajput A, *et al.* Is there seasonal variation in risk of Parkinson's disease? *Mov Disord.* 2007; 22(8), 1097–1101.
49. Palladino R, Moccia M, De Pascale T, *et al.* Season of birth and Parkinson's disease: possible relationship? *Neurol Sci.* 2015; 36(8), 1457–1462.
50. Martin S, Al Khleifat A, Al-Chalabi A. What causes amyotrophic lateral sclerosis? *F1000Res.* 2017b; 6, 371.
51. Ajdacic-Gross V, Wang J, Gutzwiller F. Season of birth in amyotrophic lateral sclerosis. *Eur J Epidemiol.* 1998; 14(4), 359–361.
52. Fang F, Valdimarsdóttir U, Bellocco R, *et al.* Amyotrophic lateral sclerosis in Sweden, 1991–2005. *Arch Neurol.* 2009; 66(4), 515–519.
53. Pamphlett R, Fang F. Season and weather patterns at time of birth in amyotrophic lateral sclerosis. *Amyotroph Lateral Scler.* 2012; 13(5), 459–464.
54. Phillips DI, Young JB. Birth weight, climate at birth and the risk of obesity in adult life. *Int J Obes Relat Metab Disord.* 2000; 24, 281–287.
55. Wattie N, Ardern CI, Baker J. Season of birth and prevalence of overweight and obesity in Canada. *Early Hum Dev.* 2008; 84, 539–547.
56. Laron Z, Lewy H, Wilderman I, *et al.* Seasonality of month of birth of children and adolescents with type 1 diabetes mellitus in homogenous and heterogeneous populations. *Isr Med Assoc J.* 2005; 7, 381–384.

57. Grover V, Lipton RB, Sclove SL. Seasonality of month of birth among African American children with diabetes mellitus in the city of Chicago. *J Pediatr Endocrinol Metab.* 2004; 17, 289–296.
58. Jongbloet PH, van Soestbergen M, van der Veen EA. Month–of–birth distribution of diabetics and ovopathy: a new aetiological view. *Diabetes Res.* 1988; 9, 51–58.
59. Vaiserman AM, Khalangot MD, Carstensen B, *et al.* Seasonality of birth in adult type 2 diabetic patients in three Ukrainian regions. *Diabetologia.* 2009; 52, 2665–2667.
60. Lumey LH, Khalangot MD, Vaiserman AM. Association between type 2 diabetes and prenatal exposure to the Ukraine famine of 1932–33: a retrospective cohort study. *Lancet Diabetes Endocrinol.* 2015; 3(10), 787–794.
61. Si J, Yu C, Guo Y, *et al.* Season of birth and the risk of type 2 diabetes in adulthood: a prospective cohort study of 0.5 million Chinese adults. *Diabetologia.* 2017b; 60(5), 836–842.
62. Jensen CB, Zimmermann E, Gamborg M, *et al.* No evidence of seasonality of birth in adult type 2 diabetes in Denmark. *Diabetologia.* 2015; 58(9), 2045–2050.
63. Banegas JB, Rodríguez-Artalejo F, de la Cruz JJ, *et al.* Adult men born in spring have lower blood pressure. *J Hypertens.* 2000; 18, 1763–1766.
64. Zhang BB, Zhao GA, Yang M, *et al.* Birth month associates with risk of coronary artery disease and its complications: a propensity score matched analysis. *Med Clin (Barc).* 2019a; 153(12), 454–459.
65. Li L, Boland MR, Miotto R, Tatonetti NP, Dudley JT. Replicating cardiovascular condition–birth month associations. *Sci Rep.* 2016; 6, 33166.
66. Poltavskiy E, Spence JD, Kim J, Bang H. Birth month and cardiovascular disease risk association: is meaningfulness in the eye of the beholder? *Online J Public Health Inform.* 2016; 8(2), e186.
67. Lawlor DA, Davey Smith G, Mitchell R, Ebrahim S. Temperature at birth, coronary heart disease, and insulin resistance: cross sectional analyses of the British women's heart and health study. *Heart.* 2004; 90, 381–388.
68. Basta NO, James PW, Craft AW, McNally RJ. Season of birth and diagnosis for childhood cancer in Northern England, 1968–2005. *Paediatr Perinat Epidemiol.* 2010; 24(3), 309–318.
69. van Laar M, Kinsey SE, Picton SV, Feltbower RG. First description of seasonality of birth and diagnosis amongst teenagers and young adults with cancer aged 15–24 years in England, 1996–2005. *BMC Cancer.* 2013; 13, 365.
70. Higgins CD, dos-Santos-Silva I, Stiller CA, Swerdlow AJ. Season of birth and diagnosis of children with leukaemia: an analysis of over 15 000 UK cases occurring from 1953–1995. *Br J Cancer.* 2001; 84(3), 406–412.
71. Crump C, Sundquist J, Sieh W, Winkleby MA, Sundquist K. Season of birth and risk of Hodgkin and non–Hodgkin lymphoma. *Int J Cancer.* 2014; 135(11), 2735–2739.
72. Georgakis MK, Ntinopoulou E, Chatzopoulou D, Petridou ET. Season of birth and primary central nervous system tumors: a systematic review of the literature with critical appraisal of underlying mechanisms. *Ann Epidemiol.* 2017; 27(9), 593–602.
73. La Rosa F, Liso A, Bianconi F, Duca E, Stracci F. Seasonal variation in the month of birth in patients with skin cancer. *Br J Cancer.* 2014; 111(9), 1810–1813.
74. Francis NK, Curtis NJ, Noble E, Cortina-Borja M, Salib E. Is month of birth a risk factor for colorectal cancer? *Gastroenterol Res Pract.* 2017; 2017, 1–5.
75. Hao Y, Yan L, Ke E, Wang H, He J. Birth in winter can reduce the risk of lung cancer: a retrospective study of the birth season of patients with lung cancer in Beijing area, China. *Chronobiol Int.* 2017; 34(4), 511–518.
76. Yuen J, Ekbom A, Trichopoulos D, Hsieh CC, Adami HO. Season of birth and breast cancer risk in Sweden. *Br J Cancer.* 1994; 70(3), 564–568.
77. Doblhammer G, Vaupel JW. Lifespan depends on month of birth. *Proc Natl Acad Sci U S A.* 2001; 98(5), 2934–2939.
78. Doblhammer G. Differences in lifespan by month of birth for the United States: the impact of early life events and conditions on late life mortality. MPIDR Working Paper 2002–19. 2002.
79. Zhang Y, Devore EE, Strohmaier S, Grodstein F, Schernhammer ES. Birth month, birth season, and overall and cardiovascular disease mortality in US women: prospective cohort study. *BMJ.* 2019b; 367, l6058.
80. Sohn K. The influence of birth season on mortality in the United States. *Am J Hum Biol.* 2016; 28(5), 662–670.
81. Gavrilov LA, Gavrilova NS. Season of birth and human longevity. *J Anti–Aging Med.* 1999; 2(4), 365–366.
82. Gagnon A. Effect of birth season on longevity: thrifty and hopeful phenotypes in historical Quebec. *Am J Hum Biol.* 2012; 24(5), 654–660.
83. Muñoz-Tudurí M, García-Moro C. Season of birth affects short– and long–term survival. *Am J Phys Anthropol.* 2008; 135(4), 462–468.
84. Flouris AD, Spiropoulos Y, Sakellariou GJ, Koutedakis Y. Effect of seasonal programming on fetal development and longevity: links with environmental temperature. *Am J Hum Biol.* 2009; 21(2), 214–216.
85. Vaiserman AM, Collinson AC, Koshel NM, Belaja II, Voitenko VP. Seasonal programming of adult longevity in Ukraine. *Int J Biometeorol.* 2002; 47(1), 49–52.
86. Ueda P, Edstedt Bonamy AK, Granath F, Cnattingius S. Month of birth and mortality in Sweden: a nation–wide population–based cohort study. *PLoS One.* 2013; 8(2), e56425.
87. Ueda P, Edstedt Bonamy AK, Granath F, Cnattingius S. Month of birth and cause–specific mortality between 50 and 80 years: a population–based longitudinal cohort study in Sweden. *Eur J Epidemiol.* 2014; 29(2), 89–94.
88. Lerchl A. Month of birth and life expectancy: role of gender and age in a comparative approach. *Naturwissenschaften.* 2004; 91(9), 422–425.
89. Inoue Y, Stickley A, Yazawa A, *et al.* Month of birth is associated with mortality among older people in Japan: findings from the JAGES cohort. *Chronobiol Int.* 2016; 33(4), 441–447.
90. Moore S, Cole T, Poskitt E, *et al.* Season of birth predicts mortality in rural Gambia. *Nature.* 1997; 388, 434.
91. Moore SE, Cole TJ, Collinson AC, *et al.* Prenatal or early postnatal events predict infectious deaths in young adulthood in rural Africa. *Int J Epidemiol.* 1999; 28, 1088–1095.
92. Moore SE, Fulford AJ, Streatfield PK, Persson LA, Prentice AM. Comparative analysis of patterns of survival by season of birth in rural Bangladeshi and Gambian populations. *Int J Epidemiol.* 2004; 33, 137–143.
93. Simondon KB, Elguero E, Marra A, *et al.* Season of birth is not associated with risk of early adult death in rural Senegal. *Int J Epidemiol.* 2004; 33(1), 130–136.
94. Gavrilov LA, Gavrilova NS. Season of birth and exceptional longevity: comparative study of American centenarians, their siblings, and spouses. *J Aging Res.* 2011; 2011(2), 1–11.
95. Gavrilov LA, Gavrilova NS. Predictors of exceptional longevity: effects of early–life childhood conditions, midlife environment and parental characteristics. *Living 100 Monogr.* 2014; 2014, 1–18.
96. Doblhammer G, Scholz R, Maier H. Month of birth and survival to age 105+: evidence from the age validation study of German semi–supercentenarians. *Exp Gerontol.* 2005; 40(10), 829–835.
97. Rojansky N, Brzezinski A, Schenker JG. Seasonality in human reproduction: an update. *Hum Reprod.* 1992; 7(6), 735–745.
98. Jongbloet PH, Groenewoud HM, Huber S, Fieder M, Roeleveld N. Month of birth related to fecundity and childlessness among contemporary women. *Hum Biol.* 2007; 79(5), 479–490.
99. Zhu Z, Cao F, Li X. Epigenetic programming and fetal metabolic programming. *Front Endocrinol (Lausanne).* 2019; 10, 764.
100. Kim JB. Dynamic cross talk between metabolic organs in obesity and metabolic diseases. *Exp Mol Med.* 2016; 48(3), e214.
101. Zeltser LM. Feeding circuit development and early–life influences on future feeding behaviour. *Nat Rev Neurosci.* 2018; 19(5), 302–316.
102. Spencer SJ, Galic MA, Pittman QJ. Neonatal programming of innate immune function. *Am J Physiol Endocrinol Metab.* 2011; 300(1), E11–E18.
103. Rajendran P, Chen YF, Chen YF, *et al.* The multifaceted link between inflammation and human diseases. *J Cell Physiol.* 2018; 233(9), 6458–6471.
104. Fisman D. Seasonality of viral infections: mechanisms and unknowns. *Clin Microbiol Infect.* 2012; 18(10), 946–954.
105. Vandenplas Y, Carnielli VP, Ksiazyk J, *et al.* Factors affecting early–life intestinal microbiota development. *Nutrition.* 2020; 78, 110812.

106. Koleva PT, Kim JS, Scott JA, Kozyrskyj AL. Microbial programming of health and disease starts during fetal life. *Birth Defects Res C Embryo Today*. 2015; 105, 265−277.
107. Codagnone MG, Spichak S, O'Mahony SM, *et al.* Programming bugs: microbiota and the developmental origins of brain health and disease. *Biol Psychiatry.* 2019; 85(2), 150–163.
108. Stinson LF. Establishment of the early–life microbiome: a DOHaD perspective. *J Dev Orig Health Dis.* 2020; 11(3), 201–210.
109. Butel MJ, Waligora-Dupriet AJ, Wydau-Dematteis S. The developing gut microbiota and its consequences for health. *J Dev Orig Health Dis.* 2018; 22, 1–8.
110. Dahl WJ, Rivero Mendoza D, Lambert JM. Diet, nutrients and the microbiome. *Prog Mol Biol Transl Sci*. 2020; 171, 237–263.
111. Karl JP, Hatch AM, Arcidiacono SM, *et al.* Effects of psychological, environmental and physical stressors on the gut microbiota. *Front Microbiol.* 2018; 9, 2013.
112. McGrath J. Does 'imprinting' with low prenatal vitamin D contribute to the risk of various adult disorders? *Med Hypotheses.* 2001; 56(3), 367–371.
113. Flandroy L, Poutahidis T, Berg G, *et al.* The impact of human activities and lifestyles on the interlinked microbiota and health of humans and of ecosystems. *Sci Total Environ.* 2018; 627, 1018–1038.
114. Smits SA, Leach J, Sonnenburg ED, *et al.* Seasonal cycling in the gut microbiome of the Hadza hunter–gatherers of Tanzania. *Science.* 2017; 357(6353), 802–806.
115. Davenport ER, Mizrahi-Man O, Michelini K, *et al.* Seasonal variation in human gut microbiome composition. *PLoS One.* 2014; 9(3), e90731.
116. Korownyk C, Liu F, Garrison S. Population level evidence for seasonality of the human microbiome. *Chronobiol Int.* 2018; 35(4), 573–577.
117. Zhang J, Guo Z, Lim AA, *et al.* Mongolians core gut microbiota and its correlation with seasonal dietary changes. *Sci Rep.* 2014; 4, 5001.
118. Koliada A, Moseiko V, Romanenko M, *et al.* Seasonal variation in gut microbiota composition: cross–sectional evidence from Ukrainian population. *BMC Microbiol.* 2020; 20(1), 100.
119. Safi-Stibler S, Gabory A. Epigenetics and the developmental origins of health and disease: parental environment signalling to the epigenome, critical time windows and sculpting the adult phenotype. *Semin Cell Dev Biol.* 2020; 97, 172–180.
120. Lockett GA, Soto-Ramírez N, Ray MA, *et al.* Association of season of birth with DNA methylation and allergic disease. *Allergy*. 2016a; 71(9), 1314–1324.
121. Dugué PA, Geurts YM, Milne RL. Is there an association between season of birth and blood DNA methylation in adulthood? *Allergy*. 2016; 71, 1501–1502.
122. Lockett GA, Zhang H, Karmaus W, Holloway JW. Epigenetic association with season of birth: a complex relationship. *Allergy*. 2016b; 71, 1503–1504.
123. Hales CN, Barker DJ. The thrifty phenotype hypothesis. *Br Med Bull.* 2001; 60:5–20.
124. Crawford C, Dearden L, Greaves E. The drivers of month-of-birth differences in children's cognitive and non-cognitive skills. *J R Stat Soc Ser A Stat Soc.* 2014;177(4), 829–860.
125. Doebler, S., Shuttleworth, I., Gould, M. Does the month of birth affect educational and health outcomes? A population-based analysis using the Northern Ireland longitudinal study. *Econ Soc Rev.* 2017; 48, 281–304.
126. Solli IF. Left behind by birth month. *Educ Econ.* 2017; 25(4), 323–346.
127. Verachtert P, De Fraine B, Onghena P, Ghesquière P. Season of birth and school success in the early years of primary education. *Oxford Rev Educ.* 2010; 36 (3), 285–306.
128. Xavier MJ, Roman SD, Aitken RJ, Nixon B. Transgenerational inheritance: how impacts to the epigenetic and genetic information of parents affect offspring health. *Hum Reprod Update.* 2019; 25(5), 518–540.
129. King SE, Skinner MK. Epigenetic transgenerational inheritance of obesity susceptibility. *Trends Endocrinol Metab.* 2020; 31(7), 478–494.
130. Vaiserman AM, Koliada AK, Jirtle RL. Non–genomic transmission of longevity between generations: potential mechanisms and evidence across species. *Epigenetics Chromatin.* 2017; 10(1), 38.