Month of birth influences life span of Mediterranean fruit flies, rats and mice.

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Recent research shows that the month of birth influences life span and disease in humans (Doblhammer 2004). Nutrition of the mother during pregnancy and/or virus infections in-utero or in the first few months of life have been proposed as underlying causal mechanisms. In this study we ask the question whether the month-of-birth effect in life span also exists in other species than humans and in particular, whether it exists in laboratory animals that are used as control groups in experiments. These animals live under strictly controlled environmental conditions and should not be subject to seasonal changing dietary conditions and exposure to virus infections. We use data from large experiments on Mediterranean fruit flies with thousands of animals, as well as smaller experiments on rats and mice. In all three species we find a significant month-of-birth pattern in life span that is not only consistent among the species but also shares similar characteristics with the pattern observed among humans.

Data

Mediterranean fruit flies (Ceratitis capitata)

We used data of the control groups of five different experiments which were conducted in order to investigate the influence of different types of caloric restriction on survival of Mediterranean fruit flies (medflies) *Ceratitis capitata*. Studies were conducted at the Moscamed medfly mass rearing facility in Metapa, Chiapas, Mexico. Adult medflies of both sexes were maintained in mesh-covered, $15\times60\times90$ cm aluminum cages under the following environmental conditions: 12:12 light-dark cycle, $24.0^{\circ}\mathrm{C}$ (±2) and 65% relative humidity ($\pm9\%$). For every experimental cohort a control cohort emerged at the same date was observed. Control cohorts were given full diet of protein, sugar and water, ad libitum. Because each experiment was repeated several times, every experimental data set comprises observation on mortality in medfly cohorts which emerged at different time. This allows us to

combine data by month of eclosion. Table 1 presents the months and the years when the experiments were conducted. Since the general level of mortality and survival varies in the control groups of the five experiments we only included those months of eclosion in our analysis with at least two independent experiments. In other words we excluded the months April, June and October from our analysis because in these months only one experiment was conducted. Altogether we analysed 783.649 med flies by month of eclosion.

Rats

We analysed the life span of all 294 male and 292 female outbred Wistar-derived LIO rats that were bred at the Animal Department of the N.N. Petrov Research Institute of Oncology. Rats were kept in polypropylene cages (38,5 x 28,5 x 14,5 cm), 6 rats a cage at a temperature of 22±2 °C. A regimen of 12 h of light and 12 h of dark was followed. The animals received standard laboratory chow and tap water ad libidum. The mice rats were observed until their natural death. Only 16 female rats were killed at the age of 859 days. In our analysis we treated them as right censored.

Mice

We used information about the life span of 82 female CBA mice that were purchased from the "Rappolovo" Animal Farm of the Russian Academy of Medical Sciences. Mice were kept 5 per polypropylene cages (30 x 21 x 10 cm) under standard light/dark regimen (12 hrs light, 12 hrs dark) at a temperature of 22±2 °C and received standard laboratory chow and tap water ad lib. All mice died from a natural death.

Table 2 contains the seasonal distribution of eclosion/birth dates of flies, rats and mice.

Results

Figures 1a and 1b present mean life span and 95% confidence intervals of medflies by month of eclosion. Med flies with eclosion dates in late spring and early summer have the lowest life span (July: males 12.89 days, females: 13.91 days), those with eclosion in fall and winter, the highest (January: males 17.35 days, females: 19.43 days). The

pattern is similar for males and females with the exception of November where males experience a peak in life span (19.43 days) and females a trough (13.21 days).

Figures 2a and 2b show mean life span and 95% confidence intervals of control groups of rats by month of birth. Highest lifespan is observed for the fall and winter-born (November – April), lowest life span for those born in September and October. The differences in survival between these two groups are highly significant (Log-rank test both males and females: p=0.00). There are no sex-specific differences.

Since we only have data about the lifespan of 82 female mice we group them into quarters of birth (Jan-Mar; Apr-Jun; Jul-Sep; Oct-Dec). Mean life span of those born in the third quarter is lowest (279,14 days), of those born in the first quarter is highest (319,89 days) (Figure 4). The difference in survival is significant (Log-rank test: p=0.04).

Discussion

Among the three species flies, rats and mice we find a significant pattern in mean life span by month of birth or month of eclosion. This pattern is unexpected insofar, as that all observed animals belong to control groups of experiments that try to control for confounding environmental factors. The observed seasonal patterns share the characteristic that mean life span of mice, rats and flies born at the end and the beginning of the year is higher than of those born in the second or third quarter. This similarity exists despite the fact that environmental conditions and seasons differ largely between the laboratories in St. Petersburg where the experiment on mice and rats were conducted and Chiapas, where the flies were reared.

The pattern observed among flies, rats and mice in this study reflects the pattern in life span by month of birth found in earlier studies on human populations. As an example we show the birth pattern in the remaining life expectancy at age 50 of the Danish population (Figure 4). This pattern is based on Danish register data with a mortality follow-up of all Danes who were at least 50 years old on 1 April 1968. This is a total of 1,371,003 people, who were followed up to week 32 of 1998.

Previous research (Doblhammer 2004, Doblhammer & Vaupel 2001) has shown that the month-of-birth pattern among the adult Danish population today is positively correlated with the month-of-birth pattern in survival during the first year of life of the respective cohorts born at the beginning of the 20th century. This finding suggests that debilitating factors at the beginning of life are responsible for the month-

of-birth pattern in survival at adult ages: Infants born in spring had a higher risk to die during their first year of life than those born in other seasons. Those who survived were debilitated and had higher mortality risks later in life. Seasonal differences in the diet of the pregnant mother and the seasonal incidence in infectious disease have been suggested as the underlying factors.

It is not very likely, however, that above factors are responsible for the month-of-birth patterns in the life spans of laboratory flies, rats and mice because diet and environmental conditions are strictly controlled. Other mechanisms have to be found. For example, it has been shown that the seasonal changes in the hours of daylight influence the human neuroendocrine functions, in particular melatonin production (Wehr 1998). Several researchers have postulated that the widely observed winter-spring birth excess in schizophrenia and bi-polar disorders might be caused by variations in internal chemistry or neural development brought about by seasonal variations in light.

The finding that the life span of laboratory animals used in experiments systematically differs by uncontrolled factors such as the month of birth opens not only new question about the underlying mechanisms that link the environment early in life to health and survival later in life. It also opens questions about the interpretation of experimental results.

References

Doblhammer, G.(2004): The Late Life Legacy of Very Early Life; Springer Verlag, Heidelberg.

Doblhammer, G., Vaupel, J.W. (2001): Lifespan Depends on Month of Birth. Proceedings of the National Academy of Sciences of the United States of America. 98(5), 2934–2939

Wehr, T. (1998): Effect of Seasonal Changes in Daylength on Human Neuroendocrine Function. Hormone Research 49, 118–124

Table 1. Months and years of experiments with Mediterranean fruit flies

		Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
Exp.#1	1993							+	+	+	*	+	
Exp.#2	1994	+		+		+	*	+					
Exp.#3	1994											+	
Exp.#3	1995	+	+	+	*	+							
Exp.#4	1995							+	+	+			
Exp.#5	1996	+	+	+		+		+	+	+			

*: excluded from the study

Table 2. Number of Mediterranean fruit flies, rats and mice by month of eclosion/birth

Number	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
Female flies	25360	16632	61124	*7627*	31685	*11053*	110545	65718	21549	*5606*	18336	
Male flies	27774	17663	68318	*8279*	33240	*12834*	120818	72811	22847	*6204*	17626	
Female rats	49	18		3	*1*	58	*1*	23	72	33	9	25
Male rats	43	13				67	*2*	20	79	32	8	30
Female mice	7	8	6		7	22	8	6			18	

italic figures: excluded from the study

Figure 1a: Lifespan and 95% confidence intervals of male flies by month of eclosion

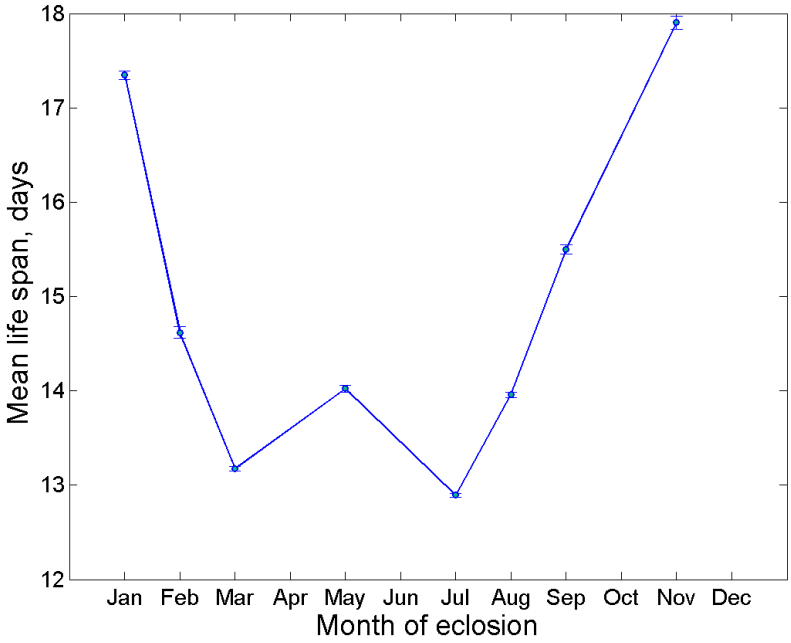

Figure 1b: Lifespan and 95% confidence intervals of female flies by month of eclosion

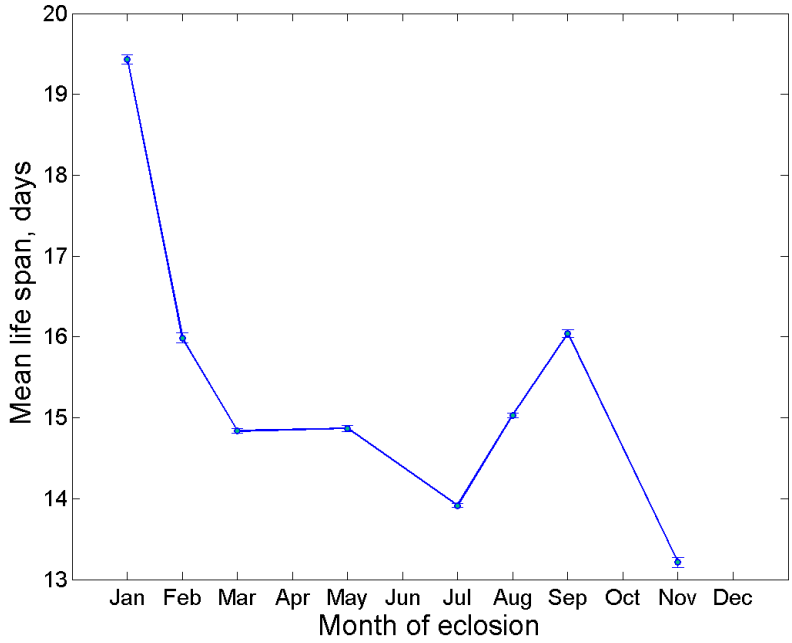

Figure 2a: Lifespan and 95% confidence intervals of male rats by month of birth

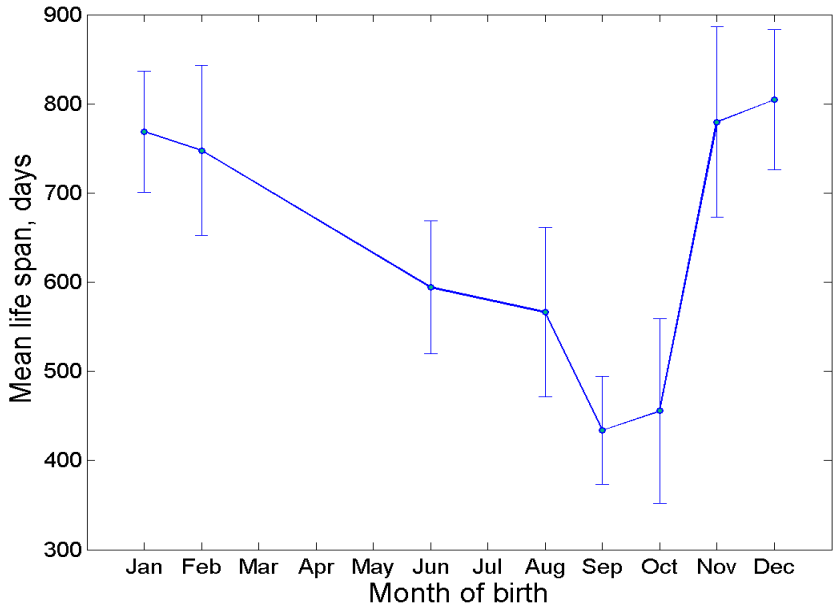

Figure 2b: Lifespan and 95% confidence intervals of female rats by month of birth

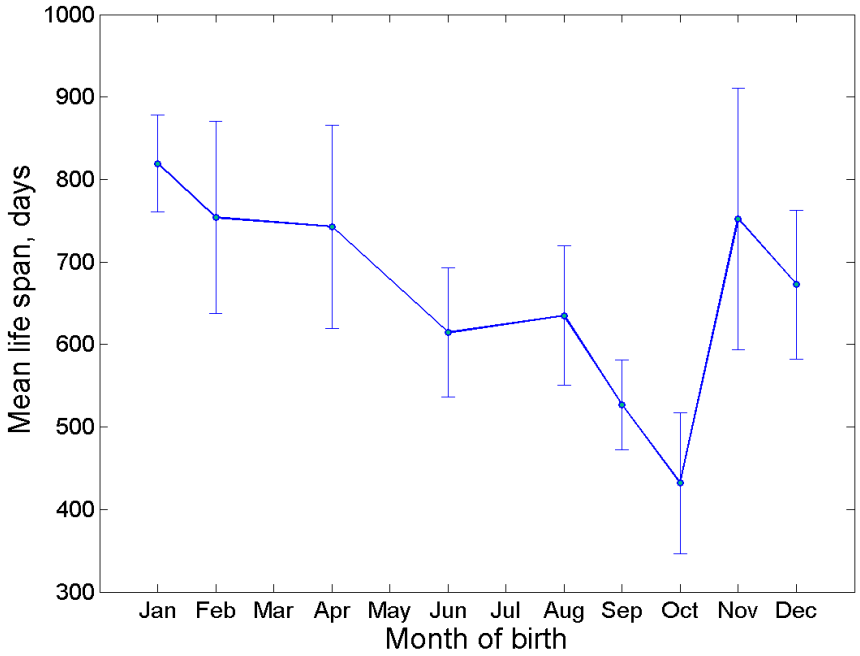

Figure 3: Lifespan and 95% confidence intervals of female mice by quarter of birth

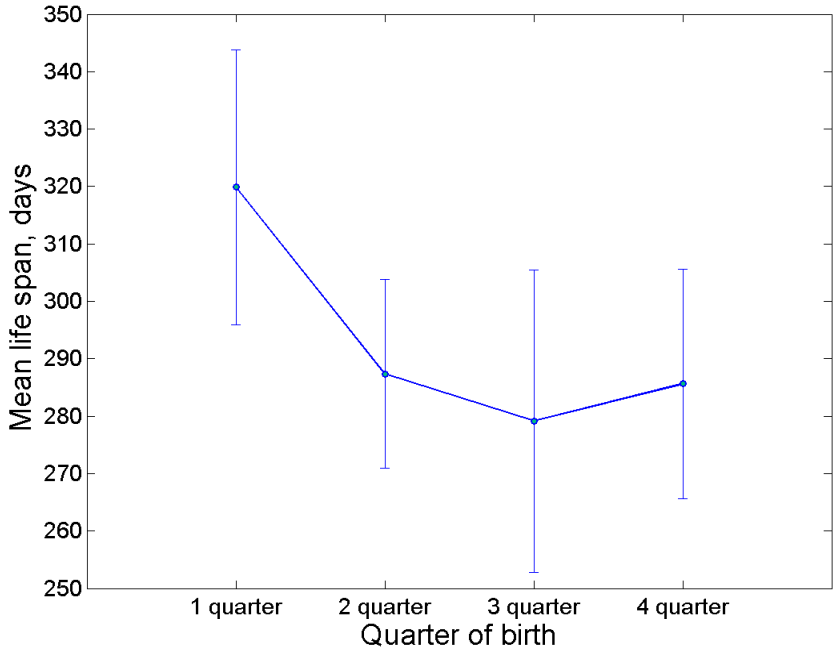

Figure 4: Deviation of remaining life expectancy at age 50 for people born in a specific month from average remaining life expectancy for Denmark 1968 -1998.