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DISCUSSION

Variability of Mortality: Additional Information on Mortality and Morbidity Curves under Normal and Pathological Conditions [Commentary on the article by A. G. Malygin "Programmed Risks of Death in Male Patients with Diabetes" published in *Biochemistry (Moscow)*, vol. 86, pp. 1553-1562 (2021)]

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Abstract—Analysis of demographic data indicates uneven distribution of mortality within a year, month, and even week time period. This is of great practical importance for the operation of medical institutions, including intensive care units, and makes it possible to calculate economic and labor requirements of medical institutions. All the above is especially relevant during the era of the COVID-19 pandemic. Malygin showed the presence of one to two fluctuations per week in the mortality of male patients with type 2 diabetes. The height of the peaks of such fluctuations is determined, as expected, by the regular parameter indicating their position on the axis of lifespan and random parameter reflecting adverse effects of external environmental factors on the body, as well as the extent of the periodically occurring sharp decrease in the nonspecific resistance. This article discusses results of recent research in the field of small (semi-weekly, weekly, monthly, and seasonal) fluctuations of mortality. Based on a large array of accumulated data, it can be concluded that the decrease in seasonal variability of mortality accompanies an increase in the life expectancy. Studying characteristics of mortality fluctuations makes it possible to move from investigating the impact of biorhythms (Master Clock) on the development of acute and chronic phenoptotic processes directly to studying the patterns of mortality rhythms themselves (rhythms of phenoptosis).

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INTRODUCTION

Weekly mortality indicators provide possibility for detailed evaluation of the short-term peaks of mortality in time [1]. Much less is known about the origin, functional significance, adaptive importance, synchronization, and potential clinical relevance of weekly and semi-weekly biorhythms than about circadian and annual rhythms. Nevertheless, these biorhythms have been observed at different levels of organization in species from unicellular algae to plants, insects, fish, birds, and mammals, both under natural and artificially created conditions [1]. The objective of these studies is evaluation of uneven distribution of mortality based on statistical data with consideration of the cause of death.

That is why the article "Programmed Risks of Death in Male Patients with Diabetes" by A. G. Malygin [2], in which he investigated the number and positions of local maxima on the mortality curves for aged male patients (53-79 years old) with type 2 diabetes, has generated a heated debate. The presence of peaks on the mortality curves was verified via comparison of results obtained by dividing the patients into subgroups using different approaches. The discussed study [2] is a continuation of a series of publications (see "References" section) on the non-monotonicity of mortality curves. The works by Malygin have been published numerous times in the

Abbreviations: BP, arterial blood pressure; CI, confidence interval; IRR, incidence rate ratio; LE, life expectancy; MCE, medical care expenditure; MINOCA, myocardial infarction with non-obstructive coronary arteries.

Biochemistry (Moscow) journal [2-5], as well as in other journals, and have been presented at different conferences. Their high importance for basic science and potential practical applications causes no doubt. In turn, new studies in this series open new areas and possibilities for the application of the author's theory.

In this commentary, I also described several tools (not mentioned in the manuscript [2]) used for investigating the short-term fluctuations of mortality, as well as presented the results of a number of studies using Big Data (table).

TEMPORAL FLUCTUATIONS OF MORTALITY

Non-monotonicity of mortality trend. An increase in the risk of death with age is important for gerontologists. The Gompertz model does not always describe adequately the behavior of survival curves at their beginning and end [6]. An important drawback of the Gompertz approach is that mortality is studied at the population level. The probability of death is assumed to be the same for all people of the same age. Indeed, all studies of additional demographic indicators, including those described by Baudisch, Vaupel, and Colchero (see review Skulachev et al. [7]), were started with the assumption that there are other methods providing information on the course of the mortality curves.

Another drawback of the Gompertz model is that mortality is averaged over the year interval. There are reasons to believed that the short-term oscillations of mortality could provide additional information on the extent of irregularity of mortality at very different scales (weekly, monthly, quarterly). It is sufficient to mention that unlike smooth trends, the actual dependence of the risk of death is characterized by non-random jumps due probably to the fact that the periods of higher resistance in ontogenesis are followed by the drops in resistance in a regular manner [7].

In his work, Malygin [2] had studied the smoothness of the trend, whether it followed the Gompertz model or not, and not the correlation with the general trend. Instead of force of mortality, which is a relative mortality value, the author investigated changes in the absolute death rate of male patients with diabetes [2]. The studied groups were random cohorts with all pros and cons arising from this fact. As any periodic oscillation, observed rhythmic oscillations were characterized not only by the peaks (maxima), but also by the period and amplitude, which are other essential characteristics of oscillations. Prior to studying such function, it is important to verify it (similarly to how it was done in [2]), in particular, by removing odd maxima and verifying that even maxima were retained or by removing the left part of the values and verifying that peaks in the right part are retained. However, if the study is limited to the calculation of the peak number, one can encounter a situation when (e.g., as a result of a certain therapeutic procedure) the power of the peak number will remain the same (each peak on the initial graph will correspond to exactly one peak on the new graph), but due to the fact that the interval of observations was limited (age range of 53-79 years in the discussed study), the conclusion on the decrease in the number of peaks (i.e., intervals of vulnerability, frailty of an organism) could be incorrect. Due to the temporal scaling (graph extension), the number of peaks will decrease (because of the deceleration of mortality, but not because of reduction in the number of intervals with increased vulnerability in ontogenesis). Similarly, the lack of verification of the oscillation amplitude (if only the number of maxima is accounted for) creates a risk of either "losing" some of the peaks (i.e., by presuming the absence of existing peaks) in the case of a very high threshold, or (in the case of very low threshold) defining certain peaks as a "white noise". Another important characteristic is the presence of slope in the existing trend. Indeed, when comparing, for example, the levels of mortality in spring and autumn, one should take into account that even in the absence of seasonal oscillations, in the latter case individuals have become older by half a year (and, hence, the probability of their death increased). Due to the relatively small datasets, overlapping stochastic noise, and discrete nature of death event, the absolute mortality rate in the discussed study [2] displays significant fluctuations due to the specifics of numerical differentiation of such type of dependencies. The most significant drawback of the method is likely that it ignores the fact that the fraction of individuals reaching a certain age decreases with the age increase. This leads to the increased contribution of the "shot noise", when even small changes in a small sample result in a significant jump of the derivative. Hence, from a general point of view (not considering phenoptosis), one could expect an increase in the number of peaks with the increase in age. We suggest that calculations could be conducted by determining the number of peaks of the mortality (i.e., local maxima of the derivative) while taking into account the decrease in the fraction of individuals reaching certain age, whereas the author used absolute mortality values [2], which, for example, do not allow to compare the data reported in different studies. It is also important to take into account the scale of mortality fluctuations (first, as death of several individuals in one thousand or in 10 million would have different significance (e.g., in the evaluation of epidemics scale). Second, the data from a relatively small dataset (less than 3000) should be averaged (smoothed) starting from a relatively large interval, but not from the minimal one (as was done by the author [2]). The size of this interval could be determined experimentally by gradually increasing its width and monitoring stability of the obtained results until this stability is reached. If no stability is achieved, the obtained

Small mortality rhythms in chronic age-related diseases

Object of the study	Mortality and morbidity rhythms	References
Dutch individuals 65 years of age and older (2007-2010) (*n* = 61,495)	mortality rates for the elderly differed significantly depending on the season and were 21% higher in winter than in summer; MCE increased by 13% from summer to winter; this seasonal difference was higher for living than for the dead (14 vs. 6%, respectively); seasonal mortality oscillations were more pronounced for the individuals living in long-term care facilities and in men vs. women; seasonal variability of MCE was more pronounced in women; hospitalization rate was much higher in winter with no significant jumps during other seasons	[10]
Swedes (born 1800-1901, 59 years old and older)	seasonal oscillations in the mortality rate had decreased significantly from 1860 to 1995; for the cohort of individual born in 1800, the risk of death in winter was almost 2 times higher than in summer; relative increase in the winter mortality was only 10% for the cohort born in 1900; LE for the 60-year-old cohort increased by 4.3 years during the 20th century; the decrease in the seasonal fluctuations of mortality accounted for approximately 40% of this average LE increase	[11]
Swedes (2003-2013) (9,092 patients with MINOCA from 199,163 patients hospitalized with MI); average age, 65.5 years	average age, 65.5; 62.0% women; risk of MINOCA was the highest in mornings (IRR, 1.70; 95% CI, 1.63-1.84) with peak at 08:00 am (IRR, 2.25; 95% CI, 1.96-2.59) and on Mondays (IRR, 1.28; 95% CI, 1.18-1.38); no changes in the level of the risk of dying in different seasons, during Christmas and New Year celebrations, and during celebration of Swedish summer solstice were observed; no association was found between the time of MINOCA onset and short-term and long-term prognosis	[13]
Japanese (50,000) (1988-2003); 169 recorded cases of SAB	mortality of SAB during 28 days was higher on weekdays (51.7%) than on weekends (32.6%); (ratio of chances of death, 2.19; 95% CI, 1.10-4.49); differences in the mortality were retained after corrections for age, sex, severity, family stroke anamnesis and anamnesis of patients with hypertension, diabetes, dyslipidemia, and alcohol consumption and smoking were introduced; daily oscillation of SAB mortality were observed with higher mortality levels on weekdays for the studied population	[15]
Japanese (2001-2003) 217 individuals; average age, 56.8 ± 11.3 years	depression scores were obtained for 192 from 217 individuals participating in the study; depression score was above 5 for 72 tested individuals; average systolic blood pressure (SBP) and average diastolic blood pressure (DBP) were significantly higher in patients with depression (SBP: 129.2 vs. 124.5 mm Hg ; p = 0.034; DBP: 79.0 vs. 76.5 mm Hg; p = 0.041); average HR over 7 days did not differ between the groups with depression score 5 (no depression) and 5 (depression); variability of HR in the group with depression (evaluated from SD of HR) was higher during holidays and lower on Mondays; daily measurements of BP demonstrated effect of novelty and increase on Mondays; the group with depression demonstrated pronounced circaseptan rhythm of BP	[12]
Patients with chronic kidney failure (review)	unlike in the case of physiological variability characterized with constant structure, increase in the random variability of such parameters as BP was also associated with higher mortality risk; availability of continuous trajectories of risk factors had a prognostic value, which was higher in comparison with the prognostic value of regular single measurements; this could improve calculation of the risk profile and identify the window of opportunity for effective intervention	[14]
Metanalysis of data of medical centers in USA, UK, and Canada	higher mortality (“weekend effect”) could be explained by a higher disease severity in patients hospitalized on weekends and/or by understaffing and lower experience of available medical personnel and limited access to therapeutic and diagnostic procedures	[19]

Note. BP, blood pressure; CI, confidence interval; MI, myocardial infarction; HR, heart rate; SAB, subarachnoid bleeding; IRR, incidence rate ratio); MCE, medical care expenditure; SD, standard deviation.

results should be considered unreliable, and the size of dataset should be increased. Third, the author's results can be verified by modeling with random data. It is likely that if this random dataset is processed by the methods used by the author (without suggested improvements), the observed results will be approximately the same as in the figures presented in the paper [2].

In general, modeling can be used for simulation of future behavior of demographic processes based on the available data in order to reveal main and additional rhythms. In particular, construction of wavelet spectrograms provides a possibility to calculate the matrix for synchronization value and synchronicity (simultaneous occurrence), synphase behavior (phase coincidence), and coherence (interconnection) of the investigated parameters of studied biorhythms. Statistical significance of the rhythms is evaluated through multiple random permutations of levels of the initial temporal series [8]. Decomposition into seasons and trends using the Loess approach (seasonal and trend decomposition using Loess, STL) is used for analysis of seasonal fluctuations of mortality risk, medical care expenditure (MCE), and even hospitalization levels. The STL method expands longitudinal data into the long-term trend, seasonal variations, and remaining variations not associated with the long-term trend or seasonal variations [9]. The long-term trend in the STL method reflects a number of possible external factors that change gradually with time, such as increase in the population average age, increase in the risk of widowhood, changes in healthcare polices, and inflation [10].

Results of studies of morbidity and mortality. It is known that the mortality rate in aged populations changes with seasons [10]. In moderate climates, it peaks in winter (21% higher than in summer) [11]. Seasonal fluctuations of mortality are more pronounced in males and in individuals living in long-term care facilities [10]. Even MCEs demonstrate seasonal fluctuations [10]. The range of seasonal mortality fluctuations had decreased in many countries during the XX century. Nevertheless, the decrease in the mortality "entropy", which facilitates an increase in life expectancy (LE), differs significantly in different countries and populations (table). For example, the seasonality of mortality from all causes among the individuals of 60 years of age and older in Sweden had changed from 1860 to 1995. The risk of dying during winter for Swedes 59 years of age and older born in 1800 was 2-fold higher than the risk of dying in summer. The relative increase in the winter mortality for the cohort born in 1900s was only 10% [11].

Cardiovascular system. Changes in the arterial blood pressure (BP) and heart rate (HR), as well as many acute cardiovascular disorders, such as myocardial infarction (MI), could be described by weekly (circaseptan) and semi-weekly (circasemiseptan) rhythms, including the jump of BP on Mondays [12, 13]. Ambulatory monitoring of systolic (SBP) and diastolic (DBP) BP is an important tool for diagnostics and treatment of hypertension [12]. In particular, average BP values were higher for the patients with depression (SBP, 129.2 vs. 124.5 mm Hg; $p = 0.034$; DBP, 79.0 vs. 76.5 mm Hg; $p = 0.041$), while average HR over 7 days did not differ between the patients with depression and control subjects. Daily measurements of BP also demonstrated the jump of BP on Mondays. In the group of patients with depression, BP exhibited pronounced weekly rhythm [12]. Furthermore, in patients with the terminal stage of kidney failure, seasonal fluctuations of BP were observed in addition to a significant increase in mortality during winter months. Moreover, it was shown that weekly fluctuations of other clinical parameters, such as body temperature and serum albumin level, have prognostic value [14].

Myocardial infarction. The development of MI with non-obstructive coronary arteries (MINOCA) demonstrates weekly and semi-weekly rhythms with an increased risk early in the morning and on Mondays, which suggests that its triggering mechanisms are associated with stress [13]. The average age of 9092 patients participating in the study was 65.5 years (62.0% women, 16.6% of which were diagnosed with MINOCA). No association was observed between the time of MINOCA onset and prognosis of clinical outcome, which indicated that the main pathological mechanisms of MINOCA and results of treatment are similar even when the time of onset is different, but the triggering mechanism could be more active early in the morning or on Mondays [13]. The risk of MINOCA development was found to be the highest in the morning [incidence rate ratio (IRR), 1.70; 95% confidence interval (CI), 1.63-1.84] with the peak at 08:00 am (IRR, 2.25; 95% CI, 1.96-2.59) and on Mondays (IRR, 1.28; 95% CI, 1.18-1.38). No seasonal changes in the risk were observed, as well as for the Christmas and New Year celebrations or during celebration of summer solstice in Sweden. No association has been revealed between the onset of MINOCA and short-term and long-term prognosis of clinical outcome [13]. However, the number of MI cases (but not MINOCA) traditional increased during the holidays.

Stroke. Weekly fluctuations of lethal outcomes were examined in the patients with subarachnoid bleeding (SAB) on different days of the week within 4 weeks (28 days) (based on the data of Takashima stroke registry) [15]. One hundred sixty-nine cases of the first-time registered per ~50,000 Japanese were divided into two groups depending on the day of SAB onset (weekdays or weekends) [15]. The mortality of SAB over the period of 28 days was higher on weekdays (51.7%) than on weekends (32.6%) (ratio, 2.19 to 1; 95% CI, 1.10-4.49). The differences in the mortality were retained after adjustments for age, sex, severity, family anamnesis of stroke, and anamnesis of patients with hypertension, diabetes, dyslipidemia, consumption of alcohol, and smoking [15].

The rhythms of mortality revealed by Malygin in male patients with type 2 diabetes exhibit the periodicity of 1-2 per week [2], i.e., they belong to either circaseptan or circasemiseptan fluctuations. Further studies are required for more detailed differentiation.

COVID-19. Lingering COVID-19 pandemic has stimulated the interest of scientists, decision makers, and general public to the short-term oscillations of mortality caused by the epidemics and other natural or technogenic disasters. Weekly data and mortality coefficients for different age and sex groups for 38 countries and regions have been made available [16]. The most reliable approach for qualitative evaluation of the dependence of time of death on the short-term risks is based on weekly estimates of excess deaths. This approach is more reliable than death monitoring using COVID-19 diagnostics or calculation of morbidity or mortality coefficients, which have numerous methodological problems such as the size of tested population and comparability of diagnostic approaches [17]. Moreover, this new approach allows to analyze weekly estimates of excess deaths for each year and country. At present, the first international database has been created for the development of strategies for fast and timely measures that provides an open access to the unified and fully documented data on weekly mortality from all causes. The Short-Term Mortality Fluctuations Data series (STMF) is accessible at www.mortality.org and contains weekly calculations and mortality coefficients for different age and sex groups for 38 countries and regions [16, 17].

Weekly (~7 days), monthly (~30 days), and seasonal (~3 months) rhythms are considered as genetically determined features that provide functional advantages to individual organisms in the course of evolution and are important for survival of entire species [1]. It has been assumed that the structure of biorhythms in humans has an endogenous origin and is synchronized with the sociocultural factors associated with Saturdays or Sundays as days of rest. It was also suggested that these rhythms reflect, at least partially, biological requirements for rest and restoration for an entire day over a 7-day period, similarly to circadian rhythms partially reflecting the need for rest and restoration every 24 h [1]. Moreover, the studies in humans or even insects conducted under controlled conditions without the impact of ecological, social, and other temporal factors revealed the preservation of the 7-day rhythms, but with slightly different (free) period (τ), which also indicated their endogenous origin.

CONCLUSIONS

Investigation of mortality fluctuation allows to solve the following problems: evaluation of quality and comparability of statistical data on mortality (in general and based on the cause of death); comparison of changes in the LE at the national level with the changes in individual regions; identification of regions, where with changes in LE are significantly higher or lower than the national ones; analysis of dynamics of changes in the regional "lifespan inequality" and its association with LE dynamics at the country level; estimation of the contribution of individual age groups and causes of death to the regional differences in LE and changes of this contribution in time; determination of characteristics of mortality and causes of death for individual groups, and estimation of the degree of "lifespan inequality" in different regions [7, 17]. COVID-19 pandemic has revealed significant gaps in the coverage and quality of existing international and national statistical monitoring systems. Ensuring prompt availability of accurate and comparable data in each country for an adequate response to unexpected epidemiological threats is a very challenging task. The interest in studying associations between mortality oscillations and fluctuation of economic conditions has been rekindled recently. The traditional view according to which economic decline negatively affects health and increases mortality has been replaced with the notion that mortality is characterized with periodic oscillations [18]. The development of infarctions and strokes is uneven over a week. The peak observed on Mondays is likely associated with stress caused by the start of working days. Furthermore, patients hospitalized on weekend with exacerbation of cardiovascular and other diseases demonstrated increased mortality levels on Mondays. This phenomenon, known as the "weekend effect" could be explained by more severe conditions of patients hospitalized on weekends and/or by inadequate quality of medical help caused by understaffing or unexperienced medical staff and limited access to therapeutic and diagnostic procedures [19]. The study by Otsuka et al. [12] indicated a clinical importance of monitoring patients with depression, especially monitoring changes in BP and HR (i.e., abnormal time-courses of BP and HR). Disruptions of physiological variability, such as heart rate, characterized by the loss of fractal (repeated in time) structures are also associated with increased mortality [14]. Analysis of changes in various indicators of cardiovascular and digestive systems, as well as inflammation, prior to hospitalization or lethal outcome showed that such changes could take place several months and even 1-2 years before the event, which suggests the possibility of early intervention [12].

In summary, it can be stated that during the last 150 years, the decrease in the seasonal fluctuation of mortality has facilitated increase in the LE [11]. New methods based on the analysis of time-dependent variability, trends and interactions of numerous physiological and laboratory parameters, for which machine learning and artificial intelligence could be applied, will help clinicians in future. It is also necessary to establish whether the dynamic regularities observed in large epidemiological studies have significance for the risk profile of an individual patient [14]. From the gerontological point of view, studying mortality fluctuation allows to switch from investigating the effects of biorhythms (Master Clock) on the development of acute and chronic phenoptosis [7] to the elucidating the patterns of programmed death rhythms (rhythms of phenoptosis).

Ethics declarations. The author declares no conflicts of interest. This article does not contain studies with human participants or animals performed by the author.

REFERENCES

1. Reinberg, A. E., Dejardin, L., Smolensky, M. H., and Touitou, Y. (2017) Seven-day human biological rhythms: An expedition in search of their origin, synchronization, functional advantage, adaptive value and clinical relevance, *Chronobiol. Int.*, **34**, 162-191, doi: 10.1080/07420528.2016.1236807.
2. Malygin, A. G. (2021) The programmed risks of dying at men of patients with the diabetes, *Biochemistry (Moscow)*, **86**, 1798-1807, doi: 10.31857/s0320972521120046.
3. Malygin, A. G. (2013) Age fluctuations in mortality of mice with mutation causing growth retardation, *Biochemistry (Moscow)*, **78**, 1033-1042, doi: 10.1134/S0006297913090095.
4. Malygin, A. G. (2017) New data on programmed risks of death in normal mice and mutants with growth delay, *Biochemistry (Moscow)*, **82**, 834-843, doi: 10.1134/S0006297917070094.
5. Malygin, A. G. (2018) Reproducible peak clusters on differential mouse mortality curves and their relation to the Gompertz model, *Biochemistry (Moscow)*, **83**, 836-845.
6. Vaupel, J. W., Carey, J. R., Christensen, K., Johnson, T. E., Yashin, A. I., et al. (1998) Biodemographic trajectories of longevity, *Science*, **280**, 855-860, doi: 10.1126/science.280.5365.855.
7. Skulachev, V. P., Shilovsky, G. A., Putyatina, T. S., Popov, N. A., Markov, A. V., et al. (2020) Perspectives of *Homo sapiens* lifespan extension: Focus on external or internal resources? *Aging (Albany NY)*, **12**, 55665584, doi: 10.18632/aging.102981.
8. Hainaut, D., and Denuit, M. (2020) Wavelet-based feature extraction for mortality projection, *ASTIN Bull.*, **50**, 675-707, doi: 10.1017/asb.2020.18.
9. Ebmeier, S., Thayabaran, D., Braithwaite, I., Bénamara, C., Weatherall, M., et al. (2017) Trends in international asthma mortality: Analysis of data from the WHO Mortality Database from 46 countries (1993-2012), *Lancet*, **390**, 935-945, doi: 10.1016/S0140-6736(17)31448-4.
10. Rolden, H. J., Rohling, J. H., van Bodegom, D., and Westendorp, R. G. (2015) Seasonal variation in mortality, medical care expenditure and institutionalization in older people: evidence from a Dutch cohort of older health insurance clients, *PLoS One*, **10**, e0143154, doi: 10.1371/journal.pone.0143154.
11. Ledberg, A. (2020) A large decrease in the magnitude of seasonal fluctuations in mortality among elderly explains part of the increase in longevity in Sweden during 20th century, *BMC Public Health*, **20**, 1674, doi: 10.1186/s12889-020-09749-4.
12. Otsuka, K., Yamanaka, G., Shinagawa, M., Murakami, S., Yamanaka, T., et al. (2004) Chronomic community screening reveals about 31% depression, elevated blood pressure and infradian vascular rhythm alteration, *Biomed. Pharmacother.*, **58 Suppl. 1**, 48-55, doi: 10.1016/s0753-3322(04)80010-6.
13. Nordenskjöld, A. M., Eggers, K. M., Jernberg, T., Mohammad, M. A., Erlinge, D., et al. (2019) Circadian onset and prognosis of myocardial infarction with non-obstructive coronary arteries (MINOCA), *PLoS One*, **14**, e0216073, doi: 10.1371/journal.pone.0216073.
14. Kooman, J. P., Usvyat, L. A., Dekker, M. J. E., Maddux, D. W., et al. (2019) Cycles, arrows and turbulence: Time patterns in renal disease, a path from epidemiology to personalized medicine? *Blood Purif.*, **47**, 171-184, doi: 10.1159/000494827.
15. Turin, T. C., Kita, Y., Rumana, N., Takashima, N., Ichikawa, M., et al. (2010) Circaseptan variation in case-fatality rate for patients with acute subarachnoid hemorrhage (Takashima Stroke Registry 1988-2003), *J. Clin. Neurosci.*, **17**, 869-873, doi: 10.1016/j.jocn.2009.11.004.
16. Németh, L., Jdanov, D. A., and Shkolnikov, V. M. (2021) An open-sourced, web-based application to analyze weekly excess mortality based on the Short-term Mortality Fluctuations data series, *PLoS One*, **16**, e0246663, doi: 10.1371/journal.pone.0246663.
17. Jdanov, D. A., Galarza, A. A., Shkolnikov, V. M., Jasilionis, D., Németh, L., et al. (2021) The short-term mortality fluctuation data series, monitoring mortality shocks across time and space, *Sci. Data*, **8**, 235, doi: 10.1038/s41597-021-01019-1.
18. Edwards, R. (2008) Who is hurt by procyclical mortality? *Soc. Sci. Med.*, **67**, 2051-2058, doi: 10.1016/j.socscimed.2008.09.032.
19. Gallerani, M., Pala, M., and Fedeli, U. (2017) Circaseptan periodicity of cardiovascular diseases, *Heart Fail. Clin.*, **13**, 703-717, doi: 10.1016/j.hfc.2017.05.007.