Circannual Rhythmicity of Death Distribution

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Objectives. Circannual rhythmicity is central to chronobiology. The aim of the present study was to compare the expression and significance of the circannual distribution of cardiovascular and non-cardiovascular deaths in Israel and Lithuania. Gender and age differences were also examined. **Methods**. The Cosinor analysis was used to determine the significance of the measure of the rhythm parameters: mesor, amplitude and acrophase. We analyzed 344,165 deaths in Lithuania – 169,671 cardiovascular-related (IHD, MI, CVA, CHF) over a 96-month period, and 26,627 in Israel – 10,727 cardiovascular-related over a 228-month period in addition to 11,704 fatal suicides in Lithuania and 2,964 fatal suicides and 16,911 suicide attempts in Israel. **Results and Conclusions**. Both in Lithuania and Israel, the general annual death distribution is significantly rhythmic; the acrophase of cardiovascular deaths occurs in February–March ($P < 0.0001$), for suicide – around June ($P < 0.0001$). By contrast, for non-cardiovascular deaths, the circannual distribution does not achieve statistical significance in general or for men separately, though it does for women. Cardiovascular- and suicide-related deaths show different annual acrophases. They are temporally inversely correlated to each other and to many environmental physical activity factors.

Key words: circannual rhythmicity, death, ischemic heart disease (IHD), stroke, suicide

Mors certa, hora incerta (Latin proverb)

INTRODUCTION

In the last few decades, many studies have been carried out to determine the connection between time and different biologic processes, including death. A special scientific discipline known as chronobiology emerged (1). In addition to the studies concentrating on circadian (24 hours) distribution of events and mechanisms related to such rhythmicity, annual and more extensive (solar cycle – 11 years and more) investigations were provided.

The additional background of well-known mechanisms involved in the chronobiologic effects has given new results on the effects, especially the cold-related influence on the serotonin–melatonin metabolism system (light/darkness effects, etc.) which plays an important role in the function of the CNS, antioxidant processes, behavior and other aspects of human homeostasis.

Studies on environmental physical factors such as the solar flux, radiowave propagation, geomagnetic activity, space proton flux links to death distribution in time have been published in the last few years (2–4).

OBJECTIVES

The purpose of this study was to determine the monthly death distribution from such "big killers" as ischemic heart disease (IHD), stroke (CVA), suicide, accidents, road accidents and hospital mortality for a long period of time. We used modern therapeutic measures plus total mortality (data) in two countries – Israel (hospital) and Lithuania (national data). The differences in geographic, climatic and many other parameters were compared. We checked the monthly death distribution from these causes *vs*. rhythmic, in general and in both genders, and tried to determine the reason for the differences in the annual time distribution of deaths.

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METHODS

In Lithuania, for the period of 1990–1997 (96 months), we analyzed: total deaths – 344,165; ischemic heart disease – 129,835 deaths; stroke – 39,836; suicide-related deaths – 11,704; accidents – 281,880; deaths from road accidents – 8,750.

In Israel, for the period of 1974–1992 (228 months), Rabin Medical Center, Beilinson Campus, a 1000-bed multi-complex medical center, total hospital mortality – 26,627 deaths. Cardiovascular deaths in hospital during 1974–1998 (236 months) – 7437; deaths as a results of congestive heart failure in the hospital in 1975–1986 (132 months) – 747;

Table 1. **Circannual death distribution**

	Death sources	No. of months	No. of deaths	Mean	Amplitude	Acrophase	Probability (P)	% of rhythm
1	**Total Lithuania**	96	344,165	3,585,1	339.66	1.16 1st week of February	< 0.0001	38.67
2	**Total Rabin Medical Center, Beilinson Campus**	288	26,627	92.5	10.3	1.1 1st week of February	< 0.0001	16.9
3	**Ischemic heart disease Lithuania**	96	129,835	1.352.4	221.97	1.22 1–2 week of February	< 0.0001	63.1
4	**Stroke Lithuania**	96	39,836	415.0	57.1	1.28 2nd week of February	< 0.0001	55.4
5	**Suicide Lithuania**	96	11,704	121.9	28.8	6.3 2nd week of July	< 0.0001	36.5
6	**Road accidents – victims Lithuania**	96	8,750	91.1	27.9	9.1 1st week of September	< 0.0001	39.7
7	**Accidents – victims Lithuania**	96	28,188	293.6	28.33	10.1 1st week of September	0.008	9.8
8	**Suicide Israel**	108	2,359	21.8	1.02	5.1 1st week of June	0.49 (N.S.)	1.35
9	**Non-cardiovascular Rabin Medical Center, Beilinson Campus**	236	13,448	57.0	2.89	0.5 Middle of January	0.057 (Strong trend)	2.4
10	**Cardiovascular Rabin Medical Center, Beilinson Campus**	236	7,437	31.5	6.8	1.3 2nd week of February	< 0.0001	2.7
11	**Myocardial infarction Rabin Medical Center, Beilinson Campus**	236	1,973	8.4	2.11	1.28 2nd week of February	< 0.0001	14.4
12	**Stroke Rabin Medical Center, Beilinson Campus**	236	1,317	5.6	0.86	1.389 2nd week of February	0.0015	5.4
13	**Suicide – fatal Israel**	120	2,964	24.7	0.86	15.59 2nd half of June	0.22 (N.S.)	1.28
14	**Suicide – attempts Israel**	120	16,911	140.9	9.7	5.01 1st week of June	0.0004	6.4
15	**Suicide (fatal + attempts) Israel**	120	19,875	165.6	10.5	5.06 1st week of June	0.00066	6
16	**Non-cardiovascular Lithuania**	96	174,494	1,817.6	63.73	0.43 1st half of January	0.155 (N.S.)	3.93

two groups of hospital deaths from acute myocardial infarction (1) in 1975–1986 (132 months) – 1,456; (2) 1,973 in 1974–1992 (236 months). Non-cardiovascular deaths in hospital in 1974–1988 (168 months) – total of 5,836; (1) stroke-related hospital deaths in 1975–1986 (132 months) – 903; (2) stroke-related hospital deaths in 1974–1998 (236 months) – 1317; two groups of (1) suicide in 1983–1990 – 2.359 deaths; (2) 1972–1992 (excluding 1989) – 2,964 deaths; suicide attempts – 16,911 – in 1972–1992 (excluding 1989) – 19,875 total (fatalities and attempts).

The Cosinor analysis was used to determine the significance of rhythmicity of annual death distribution, measures of the rhythm parameters: mesor, amplitude and acrophase. The Cosinor involves fitting a cosine curve to the data and thus assumes that the time series are approximated by a cosine curve (5). Statistics: probability (p) 95% and higher was accepted as significant; 89–94% values were interpreted as a strong trend.

RESULTS

Table 1 shows the cirannual rhythmicity parameters – number of months studied, number of deaths, mean monthly number of deaths, the amplitude, the acrophase percent of variability accounted for (by the filtered curve of data) (R) and the probability of rhythmicity (P).

Figures 1 and 2 show the annual distribution of acrophases for different causes of death in Lithuania and Israel – the analogy was used with the clock, but 1–12 represent months of the year and not hours.

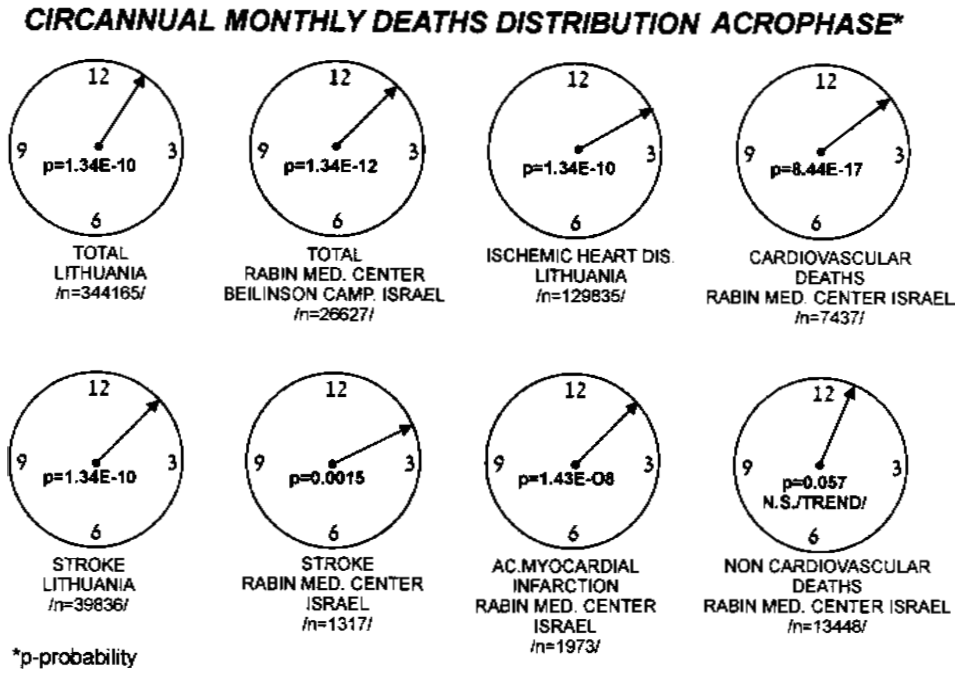

Fig. 1. Circannual death acrophase distribution in Lithuania and Israel and their probabilities (P) (n = death number) for total, major cardiovascular and non-cardiovascular deaths

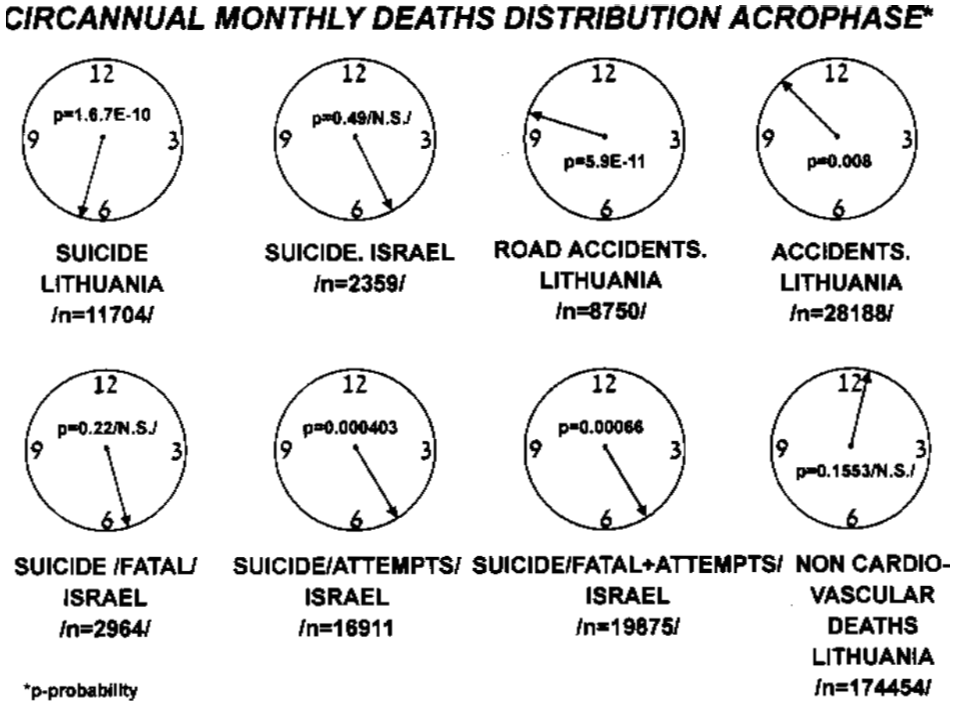

Fig. 2. Circannual death acrophase distribution in Lithuania and Israel and their probabilities (P), (n = death number) for suicide, accidents and non-cardiovascular deaths

Table 2. **Circannual rhythmicity of deaths in male and female, Lithuania 1990–1997**

	Total		IHD		Stroke		Suicide		Accident		Road Accident		Noncardio-vascular	
	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Acrophase (month 1–12)	1.09	1.2	1.21	1.23	1.1	1.41	6.28	6.52	9.365	11.38	9.06	9.37	0.059	0.575
Rhythmicity (%)	20.34	55.31	50.93	65.44	54.01	44.37	34.03	29.7	8.92	21.69	36.66	31.91	0.776	12.63
P value	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.013	< 0.0001	< 0.0001	< 0.0001	0,696	< 0.0019
Mean	1,909	1,675	624	728	159	255	100	22	229	65	70	21	1,125	692
Amplitude	126.89	213.14	88.36	133.61	24.13	33.53	23.37	5.54	22.05	10.01	22.22	6.84	17.46	47.55
No. of deaths	183,349	160,816	60,001	69,912	15,354	24,565	9,564	2,140	21,947	6,241	6,709	2,041	107,994	66,339

Table 2 demonstrates the circannual parameters for six groups (categories) of causes of death in Lithuania in 1990–1997, separating them for male and female.

DISCUSSION

Time is related to the sun, light, temperature, sleep (waking state, etc.) Circadian phenomena include the physiobiology and pathology which are discussed in detail. Early morning peak in blood pressure, heart attacks, and certain types of arrhythmia are described. W. R. Keatinga (6) in his convincing paper entitled "Mortality in Winter" (1998) showed that as a result of cold weather as an independent risk factor, the rate of deaths significantly increased in London and Athens.

Environmental influences related to the maximum number of cardiovascular deaths may be connected with the closest sun–earth position on January 3rd (considering some solar–terrestrial differences in the annual cardiovascular mortality) (4). Further support of the increase in cardiovascular deaths in winter is provided by many publications that connect atherosclerotic plaque, vascular and myocardial damage by infections (*Chlamydia pneumonia, Carinobacter, Herpes virus*), changes in food intake usually documented in winter months, such as reducing vegetables and fruits in the diet, which may be an additional factor for plaque instability and rupture resulting in acute cardiac ischemia and myocardial infarction, viral myocarditis with severe clinical consequences (7–9). Cold weather can provoke coronary spasm, rise in blood pressure, changes in endothelial function and in cerebral circulation (7, 10, 11).

The serotonin–melatonin metabolism is involved in the pathogenesis of seasonal psychiatric disorders, depression, appetite, sleep regulation, adaptation to time changes (12).

The possibly insufficient melatonin synthesis at the time of the shortest night (darkness) (around June) may be one of the causes involved in the mechanism of the suicide acrophase at this time of the year. In addition, the suicide timing and relationship to many environmental physical changes (13, 14) requires further studies to determine the interaction of environmental physical activity with the human organism (proton flux, radiowave propagation, geomagnetic field level, etc.) (3, 13, 15).

It is important to note that the monthly distribution of deaths from myocardial infarction, ischemic heart disease in general is adversely related to the number of deaths from suicide (13–15). High temperatures are accompanied by a drop in arterial pressure, vasodilatation, in extremes – dehydration, increase in hematocrit, hemoconcentration, loss of nat-

rium by perspiration and other ways of excretion. Perhaps some changes are seasonally-genetically fixed and related to the "biological clock" system (1, 16, 17). The seasonal changes effect not only the cardiovascular system, but also the endocrine and central nervous systems and human behavior.

In the last few decades, there has been a special emphasis on the role of serotonin–melatonin metabolism and their receptors in these dynamic changes (12, 18, 19). Melatonin, one of the serotonin metabolites in the CNS, is closely related to the optic system and light/darkness and the pineal gland preparing the production of melatonin during the dark time of the 24-hour period (12). For example, the light/darkness affecting the melatonin mechanism and changing the behavior can be accompanied by influences of the geomagnetic, solar activity and thus even change the level of blood coagulation (also involving serotonin). Changes in coagulation related to environmental factors play a major role in vascular thrombosis, myocardial ischemia, ischemic stroke, myocardial and cerebral infarction timing (13), resulting in the maximum occurrence of mortality in the middle of winter (January–February) when cold, darkness, shortest sun–earth distance (January 3rd) can influence the annual rhythmicity of the events. It is interesting to note that cardiovascular and suicide-related deaths rather than other causes of death are affected by these environmental influences. When road accidents occur, these factors, along with the number of vehicles on the road, road surface (snow or rain), nighttime, directly influence the driving security level. Also, daily stress affects cardiovascular events, especially sudden arrhythmia death (11).

Besides the "biologic clock", social tension may affect the annual rhythmicity of cardiovascular deaths, especially in the working population. It is, however, quite surprising that only 17% of sudden deaths in this group occur at work, mostly in the early hours (00–06:00). The elderly are not affected by the yearly peak which affects the working population at the beginning of the business year – in April in Japan, according to Kawamura et al. (11).

Analyzing the female and male circannual death rhythmicity, we can see that there is a clearly rhythmic annual process for both genders. The acrophase is in the same month (total, IHD, stroke – February, suicide – July).

In our previous study (1996) (4), we found an increase in environmental influences on mortality from ischemic heart disease and stroke at 70 years of age and over and at the beginning of the year. In recent publications of Sheth et al. (10), the authors stressed an increase of deaths in winter from myocardial infarction in Canada and a rise in the influence of winter on the myocardial infarction rate in old age (5.8% in the age group <65 achieving 15.8% for >85 compared to the summer). The authors point out a similar trend for stroke-related deaths (7) analyzing the Monica Study results in Lille (France) in the 35–64-year-old male population. This study showed that the rate of events decreased linearly with increasing the atmospheric temperature (a 10 °C drop was associated with a 13% increase in the rate of events). The atmospheric pressure of 1016 millibar (mbar) was optimal with an 11–12% increase in events in every 10 mbar fluctuations above or below the optimum. It is necessary to bear in mind that climate changes are associated with changes in solar, GMA and other physical influences of the space environment on our planet.

For women, general accidents occur only in December, whereas in men they occur in October. Also, road accidents have the acrophase in October. However, in all six death groups, the annual acrophase in women occurs slightly (3–7–8 days) later than in men. Perhaps a further analysis for women before and after menopause would show additional differences. The natural history of diseases and certain differences in the medical services for men and women described in many countries (20–23) may have an influence on these differences. As in the main group, both gender victims show antagonistic annual distribution for the total, IHD and stroke death acrophase with this parameter for suicide.

The opposite monthly annual time distribution for cardiovascular diseases and suicide may be a consequence of different environmental influences on the pathogenetic mechanisms for atherosclerotic and hypertensive patients' complications (plaque rupture, thrombosis, blood pressure elevation) and development of depression, one of the major precursors of suicidal behavior.

CONCLUSION

Both in Lithuania and Israel, the circannual death distribution is clearly rhythmic, especially from cardiovascular diseases. The acrophase of circannual death distribution is highly significant and in both countries occurs in February and March.

For suicide, the acrophase occurs in the midsummer months (June–July). It is highly significant in Lithuania and achieves significance in Israel only if fatal cases and suicide attempts are analyzed together.

Non-cardiovascular deaths do not show a statistically significant rhythmicity in men, whereas in women they also show rhythmicity. Deaths from accidents show their acrophase in Lithuania in Octo-

ber–November, in the middle between the annual peak for cardiovascular and suicide-related deaths.

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METINIS MIRTINGUMO RITMINGUMAS

S a n t r a u k a

Šio darbo tikslas – palyginti mirtingumo nuo širdies ir kraujagyslių ligų bei mirtingumo nuo kitų priežasčių metinį ritmingumą Izraelyje ir Lietuvoje, atsižvelgiant į lytį ir amžių.

Metodai. Ritmingumo parametrai buvo įvertinti atliekant Cosinor analizę. Nagrinėti 344 165 mirčių atvejai Lietuvoje per 96 mėnesius (iš jų 169 671 nuo širdies ir kraujagyslių ligų, kiti nuo savižudybių) ir 26 627 mirčių atvejai Izraelyje per 228 mėnesius (iš jų 10 727 nuo širdies ir kraujagyslių ligų, kiti nuo savižudybių).

Rezultatai ir išvados. Ir Lietuvoje, ir Izraelyje bendras metinis mirčių pasiskirstymas buvo patikimai ritmingas: mirčių nuo širdies ir kraujagyslių ligų akrofazė nustatyta vasario–kovo mėnesiais ($p < 0{,}0001$), savižudybių – birželio mėnesį ($p < 0{,}0001$). Vyrų mirtingumas nuo savižudybių, skirtingai negu moterų, nebuvo patikimai ritmingas. Mirtingumo nuo širdies ir kraujagyslių ligų bei savižudybių akrofazės skyrėsi: jos priešingai koreliavo tarpusavyje ir su daugeliu aplinkos fizinio aktyvumo veiksnių.

Raktažodžiai: metinis ritmingumas, mirtingumas, ischeminė širdies liga, insultas, savižudybės