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December insolation and ultraviolet B radiation are associated with multiple sclerosis mortality in Poland

Grudniowe usłonecznienie i nadfioletowe promieniowanie B wykazują asocjację z umieralnością na stwardnienie rozsiane w Polsce

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Summary

Background: The role of environmental factors (EF) determining the occurrence of multiple sclerosis (SM) is the subject of current investigations. **Objective:** To establish association between duration of insolation along with intensity of ultraviolet B (UVB) radiation and mortality rates for SM in Poland. **Method:** The study was based on assemblage of 2172 SM persons (M – 878, F – 1294) who died in Poland in the years 2004–2008. Regional previous duration of insolation was measured in hours, intensity of UVB radiation was monitored in minimal erythema dose units (MED), ozone concentration in the ground layer of atmosphere was recorded in $\mu\text{g}/\text{m}^3$. Measurements of insolation, UVB radiation and ozone concentration were performed at provincial stations and territorial sites of the State Environmental Monitoring. EF were correlated to provincial crude mortality rates (CMR) for MS. Correlational test by Pearson was used in the study. Demographic data were obtained from the Central Statistical Office, information on EF was received from the Institute of Meteorology and the Institute of Environmental Protection. **Results:** Annual, average, crude MR for MS per 100,000 inhabitants in Poland was 1.12 (*SD* 0.14). In northern part it amounted to 1.20 (*SD* 0.18) and in southern part reached 1.03 (*SD* 0.11). Significant inverse correlation was found between previous minimal duration of insolation in December and CMR for SM in the country: $r = -0.518, p = 0.044$. Borderline significance of inverse correlation was established between minimal intensity of UVB radiation in December and crude death rates for SM in Poland: $r = -0.478, p = 0.060$. CMR for SM in northern Poland was accompanied not only by lower UVB radiation level, but also by slower spring increase and autumn faster decrease of radiation. No significant correlation was ascertained between the ground atmospheric ozone concentration or the annual number of days with ozone concentration above $120 \mu\text{g}/\text{m}^3$ and MS mortality rates. **Conclusion:** Inverse association was found between previous December insolation, UVB radiation level and mortality for SM in Poland. No correlation was ascertained between mortality and the part ozone concentration in the ground layer of the atmosphere.

Key words: sclerosis multiplex, mortality, insolation, ultraviolet B radiation, prevention, Poland

Streszczenie

Wstęp: Rola czynników środowiskowych (CS) determinujących występowanie stwardnienia rozsianego (SM) jest przedmiotem bieżących badań. **Cel:** Ustalenie asocjacji pomiędzy przeszłą długością usłonecznienia oraz intensywnością promieniowania nadfioletowego B (UVB) i współczynnikami umieralności (WU) na SM w Polsce. **Metoda:** Badanie prowadzono na grupie 2172 osób z SM (M – 878, K – 1294), które zmarły w Polsce w latach 2004–2008. Regionalną przeszłą długość usłonecznienia zmierzono w godzinach (h), intensywność promieniowania UVB monitorowano w jednostkach odpowiadających minimalnej dawce wywołującej rumień (*minimal erythema dose*, MED), stężenie ozonu w przyziemnej warstwie atmosfery rejestrowano w $\mu\text{g}/\text{m}^3$. Pomiar promieniowania słonecznego i UVB wykonano w prowincjonalnych stacjach, zaś stężenia ozonu w terenowych stanowiskach Państwowego Monitoringu Środowiska. Zbadano korelacje pomiędzy CS i regionalnymi surowymi WU (SWU) na SM. Posłużono się do tego celu testem Pearsona. Demograficzne dane otrzymano z Głównego Urzędu Statystycznego, zaś informację o CS uzyskano z Instytutu Meteorologii i Gospodarki Wodnej oraz Instytutu Ochrony Środowiska. **Wyniki:** Roczny przeciętny, surowy WU na SM wśród 100 000 mieszkańców wyniósł 1,12 (*SD* 0,14). W północnej części kraju SWU sięgnął 1,20 (*SD* 0,18), zaś w części południowej 1,03 (*SD* 0,11). Ustalono istotną, odwróconą korelację pomiędzy przeszłą minimalną długością usłonecznienia w grudniu i SWU na SM w kraju: $r = -0,518, p = 0,044$. Znalaziono graniczną istotność odwróconej korelacji pomiędzy minimalną intensywnością promieniowania UVB w grudniu i SWU w Polsce: $r = -0,478, p = 0,060$. SWU w północnej części kraju kojarzył się nie tylko z niższym poziomem promieniowania UVB, lecz także z jego wiosennym, wolniejszym wzrostem i szybszym jesiennym spadkiem. Nie stwierdzono istotnej zależności pomiędzy stężeniem ozonu w przyziemnej warstwie atmosfery lub roczną liczbą dni ze stężeniem ozonu powyżej $120 \mu\text{g}/\text{m}^3$ i SWU na SM. **Wniosek:** Umieralność na SM wykazała odwróconą asocjację z przeszłą grudniową długością usłonecznienia i intensywnością promieniowania nadfioletowego B w Polsce. Nie wykazano zależności między umieralnością i przeszłym stężeniem ozonu w przyziemnej warstwie atmosfery.

Słowa kluczowe: stwardnienie rozsiane, umieralność, usłonecznienie, promieniowanie nadfioletowe B, zapobieganie, Polska

INTRODUCTION

Sclerotic multiplex (SM) is unevenly distributed throughout the world^(1,2). The disease shows consistent association with latitude, solar radiation, viral infections and prevalence of HLA-DRB1*15 allele⁽¹⁻³⁾. Sunshine effect is related to geography, climate, season, daytime, ethnic origin, skin pigmentation and outdoor activity⁽⁴⁻⁶⁾. Early age at exposure to solar radiation reduces likelihood of developing SM^(4,7). Place and month of birth of SM patients is also related to ultraviolet B (UVB) radiation level^(2,8). UVB is sunlight fraction (280–315 nm) which inhibits T_H17 , T_H1 cell activity, restrains maturation of dendritic cells, induces function of T_{REG} cells and down-regulates the expression of HLA-DRB alleles⁽⁹⁻¹¹⁾. Nevertheless, the effect of UVB radiation is blocked in majority by total concentration of ozone (O_3) in the atmosphere, by aerosols and air pollutants⁽¹²⁾. Lower monthly total ozone concentration correlated to the smaller number of autumn born offspring destined to develop SM⁽⁸⁾. Previous study showed that SM mortality rates in Poland were inversely correlated to minimal monthly insolation and mean annual air temperature⁽¹³⁾. Regional difference in exposure to solar radiation, lower dietary vitamin D intake, lower air temperature and more frequent infections of the upper respiratory tract (URT) might contribute to the distribution of SM^(1,2,14-16). Sclerotic multiplex mortality in Poland depended on several factors,

but there is no information whether death rates were associated with previous intensity of UVB radiation and the past ozone concentration in the ground layer of the atmosphere. The objective of present study was to ascertain if particular physical factor was associated with SM. Current investigation may provide evidence concerning the role of environmental factors in aetiology of the disease.

MATERIAL AND METHOD

Data concerning gender, diagnosis, the year and place of death of 2172 SM people (878 men, 1294 women) were derived from the Central Statistical Office in Warsaw. All SM individuals died in the years 2004–2008 in Poland. Diagnosis of SM was taken into account using the ICD code G35. Average, annual, crude mortality rates (CMR) per 100,000 inhabitants of 16 provinces in the country was calculated. Two large assemblages of SM people, who died either in northern Poland ($n = 523$) or southern part of the country ($n = 717$), were separated in order to carry out additional environmental study. Northern Poland included following provinces: zachodniopomorskie, pomorskie, kujawsko-pomorskie, warmińsko-mazurskie, podlaskie and southern Poland comprised dolnośląskie, opolskie, śląskie, małopolskie, podkarpackie. Provincial CMR for SM was compared using t test by Student. Three environmental factors were considered with respect to mortality rates. The factors included previous,

regional duration of solar radiation: mean daily insolation in hours in the years 1960–1969; mean monthly maximal (June) and minimal (December) solar radiation in the years 1960–1969, 1965–1970. Intensity of ultraviolet B (UVB) radiation was recorded as mean monthly minimal (December) or maximal (June) emission of rays in the years 1996–2000. Average maximal 8-hour ozone concentration in the ground layer of the atmosphere was determined during 24 hours and monitored in the years 1998, 2000–2008. Mean annual number of days with ozone concentration above $120 \mu\text{g}/\text{m}^3$ was also taken into consideration.

Intensity of UVB radiation was measured Poland by stations of the State Environmental Monitoring. Measurements were performed in northern pomorskie province (Łeba station), in central mazowieckie province (Legionowo), southern małopolskie province (Zakopane). Values of radiation in some adjacent provinces were estimated on results observed in lying near regions. Energy of UVB radiation was determined in minimal erythema dose units (MED; $1 \text{ MED} = 200 \text{ J}/\text{m}^2$). Skin erythema was recorded by biometer after 1 h exposure to sunlight. Data on duration of solar radiation in h and UVB intensity in MED units were obtained from the Institute of Meteorology in Warsaw. Ozone concentration in the ground layer of the atmosphere was determined in $\mu\text{g}/\text{m}^3$ by the State Environmental Monitoring in particular provinces. Information concerning ozone concentration was received from the Institute of Environmental Protection in Warsaw. All correlations between previous, regional environmental factors and provincial mortality rates in SM were performed by Pearson's test. Linear regression analysis was also used in the study.

RESULTS

Average, annual crude mortality rates (CMR) for 2172 SM persons were ascertained in Poland in the years 2004–2008. Mean CMR all over the country was 1.12 (SD 0.14; range 0.95–1.45). Distribution of CMR in 16 provinces is shown in fig. 1.

Variation of CMR was unexpectedly very small. Mortality rates in the country showed insignificant variation; $\chi^2 = 0.99$, $df = 15$, $p = \text{ns}$. Slightly higher CMR was identified in north-eastern province podlaskie amounting to 1.45/100,000 individuals and marginally lower rate was found in south-western province dolnośląskie reaching 0.95/100,000. Average CMR in northern ($n = 523$ SM persons) and southern part ($n = 717$) of the country were 1.20 (SD 0.18; range 1.11–1.45) and 1.03 (SD 0.14; range 0.95–1.22). The difference between mortality rates in northern and southern provinces was equivocal. A comparison of CMR based on 50 rates/5 years by Student's t -test showed significant difference ($p = 0.016$), whereas calculation based on accumulated 10 rates/5 years demonstrated insignificant difference ($p = 0.122$).

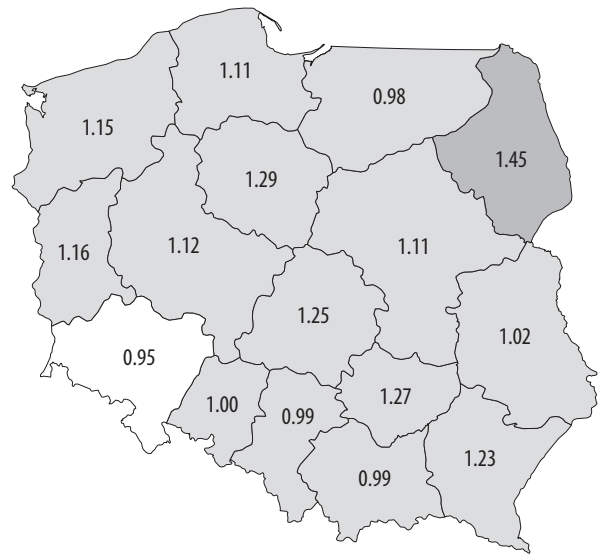


Fig. 1. SM crude mortality rates in Poland (2004–2008). Slightly higher mortality (1.45/100,000 individuals) in podlaskie province is shown by area with crossing lines, intermediate mortality (0.98–1.29) in 14 provinces is presented by area with longitudinal lines and marginally lower mortality area (0.95) in dolnośląskie province is marked with blank surface

Relation of three environmental factors to SM mortality in the country was main question of the study (table 1). Previous mean daily duration of solar radiation measured in hours (4.1, SD 0.1 h) and mean monthly maximal duration of insolation (236.7, SD 15.1 h) did not show significant correlation to mortality rates. However, significant inverse correlation was found between monthly minimal duration of solar radiation in December and all over the country MS mortality rates; $r = -0.518$, $p = 0.044$.

Mean minimal duration of insolation in December was significantly shorter in northern than in southern provinces of Poland (19.2, SD 3.5 h vs. 27.8, SD 3.8 h), $p = 0.006$. Former correlation suggested that deficient December solar light is one of the factors inducing development of SM. Difference of solar light duration between north-eastern province podlaskie and south-western province of dolnośląskie reached in December on average -3 h (-44%) and difference in CMR for SM amounted +0.50 (+34%). Evident difference was calculated for minimal duration of solar radiation in northern and southern provinces (-5.6 h) and difference of CMR (+0.17/10⁵).

Next point of investigation was relation between previous regional level of ultraviolet B radiation and provincial SM mortality rates. Mean monthly maximal UVB radiation level (376.2, SD 44.6 MED units) did not demonstrate significant correlation to mortality rate. Nevertheless, borderline significance of inverse correlation was ascertained between minimal intensity of UVB radiation

Province	Regional, average, annual mortality rated for sclerosis multiplex (2004–2008)	Duration of solar radiation measured in hours			Intensity of ultraviolet B radiation measured in MED units (200 J/m ²)	
		Mean daily insolation per year (1960–1969)	Mean monthly maximal insolation (1960–1969)	Mean monthly minimal insolation (1960–1969)	Mean monthly maximal radiation (1996–2000)	Mean monthly minimal radiation (1996–2000)
Zachodniopomorskie	1.15	4.0	226	23	346.2	8.0
Pomorskie	1.11	4.4	285	18	323.3	8.8
Kujawsko-pomorskie	1.29	4.3	254	16	445.8	7.4
Warmińsko-mazurskie	0.98	4.6	286	23	386.1	7.4
Podlaskie	1.45	4.3	261	16	361.6	7.1
Wielkopolskie	1.12	4.1	239	26	280.3	11.8
Łódzkie	1.25	4.3	248	20	309.7	12.7
Mazowieckie	1.11	4.5	263	25	390.3	12.5
Lubelskie	1.02	4.4	229	17	407.5	13.6
Lubuskie	1.16	4.2	226	26	365.4	11.4
Świętokrzyskie	1.27	4.0	210	22	420.0	14.3
Dolnośląskie	0.95	4.0	206	29	339.8	27.0
Opolskie	1.00	4.1	219	26	374.4	27.6
Śląskie	0.99	3.8	207	32	391.7	28.6
Małopolskie	0.99	4.0	210	22	455.7	31.2
Podkarpackie	1.23	4.3	218	30	408.0	30.4

Table 1. Average, annual, crude mortality rates for multiple sclerosis and duration of solar radiation along with intensity of ultraviolet B radiation values in Poland. Mortality rates per 100,000 individuals

in December and CMR for SM throughout the country; $r = -0.478, p = 0.060$. Noteworthy is highly significant difference between UVB radiation levels in the north and in the south of Poland: 7.7 ($SD 0.6$) vs. 29.0 ($SD 1.7$) MED units, $p = 0.007$ ⁶. Graphic presentation of regression between regional UVB radiation intensity and provincial CMR is shown in fig. 2.

A simple comparison of UVB level indicated nearly four-fold lower radiation intensity in pomorskie province than in małopolskie province: 8.8 vs. 31.2 MED units (table 1). Furthermore, latitude-related slower increase of UVB radiation occurred in pomorskie province in the first half of the years 1996–2009 and faster decrease in the second half as compared to that of małopolskie province. Evidence supports the role of residential and December deficient UVB radiation in inducing the disease process.

Ambient UVB radiation is in majority absorbed by total ozone concentration in the atmosphere. Mean maximal 8-hour ozone concentration in the ground layer of the atmosphere (158.2, $SD 15.3 \mu\text{g}/\text{m}^3$) did not significantly correlate to CMR in the country. Mean annual number of days (20.8, $SD 10.8$) with the ground ozone concentration above $120 \mu\text{g}/\text{m}^3$ also did not correlate significantly to SM mortality rates.

DISCUSSION

Present study proved that CM rates for SM have shown insignificant variation in 16 provinces of Poland

(2004–2008). That finding is in contrast to varied SM mortality rates in 46 counties of Sweden (1997–2007)⁽¹⁷⁾. Sex-adjusted SM MR in Poland were much higher than relevant rates in south-eastern Europe or the Middle East. The rates in Poland reached 1.19 for men and 1.47 for women (1982–1995)⁽¹⁸⁾. The rates in Greece were scarcely 0.3 and 0.4 as well as the rates 0.5 and 0.7

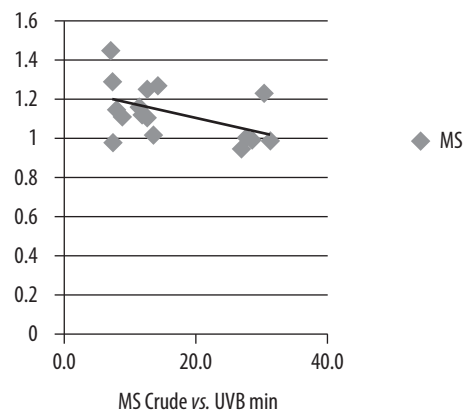


Fig. 2. Graphic presentation of regression between mean, monthly, minimal UVB radiation values (1996–2000) and average, annual, crude mortality rates for SM (2004–2008) in Poland. On ordinate axis CMR for SM are presented and on abscissa coordinate mean values of UVB radiation are shown. Inverse correlation coefficient demonstrated borderline significance: $r = -0.478, p = 0.060$

in Israel (1967–1977)⁽¹⁹⁾. Difference in regional SM death rates can depend on demographic, socioeconomic or medical factors. However, it is unknown whether differences in provincial age structure, migration, socioeconomic rates or standard of treatment caused moderately higher SM mortality rate in northern Poland. Inverse association was found between minimal solar radiation or minimal UVB radiation in December and higher mortality for SM in Poland; $p = 0.044$, $p = 0.060$. Results agree with data from other countries showing inverse UVB radiation and higher SM prevalence or mortality^(15,16). Observations indicated that lower level of UVB radiation was critical for deficient generation of 25-hydroxyvitamin D and immune dysregulation^(4,20,21). The past shorter solar radiation during maternal gestation was inversely correlated to the greater number of offspring with subsequent SM; $r = -0.579$, $p = 0.048$ ⁽⁸⁾. The peak of effective exposure to sunshine occurred at age 0–5 yr. in Italians and at age 16–18 yr. in Norwegians^(7,22).

Relation between insolation and nutritional, infectious or other environmental factors is not yet fully clarified. The ground layer of ozone in the atmosphere did not decrease the effect of UVB radiation on SM mortality in Poland. However, immunosuppressive effect of UVB rays was in majority absorbed by total atmospheric ozone concentration⁽¹²⁾. Linear regression analysis proved positive correlation between lower total ozone concentration in the atmosphere during month of birth and the smaller number of SM monthly birth; $r = 0.631$, $p = 0.028$ ⁽⁸⁾. Sunlight effect may be inversely correlated to better sanitation level, higher socioeconomic status, shorter breast feeding (<7 months), positively correlated to diet richer in juice and vitamin C^(1,4,5,20,23,24). The outcome of longer solar radiation may be synergistic with protective effect of maternal greater consumption of fortified milk or sufficient vitamin D intake during pregnancy⁽²⁵⁾. Shorter duration of insolation and lower UVB radiation level in the North accompany increased incidence of mononucleosis and the URT infections^(16,20,21). No interaction was found between UVB radiation level or circulating vitamin D level and presence of HLA-DRB1*15 allele in Sweden⁽²⁶⁾. On the other hand, the role of genetic factor in relation to the past sun exposure was proved by finding in Australia⁽²⁷⁾. There was evidence of interaction between the vitamin D receptor gene polymorphism (*Cdx-2* variant) and low sun exposure⁽²⁷⁾. It is also known that vitamin D receptor element (VDRE) is associated with HLA-DRB1* alleles⁽²⁸⁾. The less frequent is “unresponsive” VDRE in HLA-DRB1* 04/07/09 alleles, the more reduced is risk of SM⁽²⁸⁾.

Immunosuppressive effect of UVB radiation depends on conversion of 7-dehydrocholesterol in skin to cholecalciferol (vitamin D₃), on chemical change of trans-urocanic acid into cis-urocanic acid, stimulation of skin keratinocytes to produce IL-10 and TNF- α cytokines and reduction of expression of MHC class II molecules^(5,9,10,21).

Vitamin D₃ is major immunomediator of protective effect exerted by UVB^(5,21).

UVB radiation level in southern provinces was higher from that in northern provinces of Poland or in Scandinavia⁽²⁹⁾. Nevertheless, average annual intensity of UVB radiation remained relatively stable in both parts of Poland (1996–2000). That observation of stable UVB level is not consistent with temporal changes of SM mortality rates. Unpublished data showed that through 5 years (2004–2008) CMR for SM either decreased by -0.08 (from 1.18 to 1.10/10⁵) in the north, or increased by +0.16 (from 0.87 to 1.03/10⁵) in the south. That relation implicates no influence of UVB radiation level on temporal changes of SM death rate.

The question arises by which means environmental factors in Poland can either contribute to the process of autoimmunity or, on the contrary, enhance protective mechanism against the initiation of SM. It is unlikely that SM occurrence in Poland can be explained only by an increased frequency of anti-EBV seropositivity, prevalence of smoking and lower dietary intake of vitamin D. Multifactorial aetiology of the disease implicates that higher latitude, shorter December solar light, less intensive minimal UVB radiation, low winter air temperature and frequent the URT infections more likely induced in genetically susceptible individuals in Poland immune dysregulation^(13,18). On the other hand, lower latitude, longer December solar light, higher minimal level of UVB radiation, early through infections and rare EBV infection may more often in some Afro-Asian residents to develop protective immunity^(2,21,30–32). Topical result of the study gives incomplete clue to possible prevention of the disease. Longer gestational exposure to UVB radiation, regular winter holidays in sunny mountains, diet supplementation with 1000 IU of vitamin D daily, early exposure in childhood to human herpesviruses (EBV, HHV-6, HSV-1) and avoiding of smoking may in part protect residents of Europe and USA from SM^(4,8,9,33).

Results of present study require short comment. Firstly, data on insolation before the year 1960 and on UVB radiation level before the year 1996 were not available. Secondly, the effect of insolation and UVB was analysed at population level and not at individual level. Mortality for SM obviously does not depend only on insufficient insolation and UVB radiation experienced by residents in Poland. Thirdly, factors influencing SM mortality are complex and diversified. SM death rates are linked with comorbidity (concomitant diseases), nutrition (excessive consumption of animal fats), life style (overworking, smoking), with less accessible medical care and paradoxically with higher socioeconomic status in developed societies^(1,4,6,20,30). Nevertheless, the study describes relation between previous, regional environmental factors and mortality from SM in Poland. The result supports significant role of selected physical factors in aetiology of the disease.

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