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## Increasing occurrence of multiple sclerosis in women correlates to hygiene level

### Wzrastające występowanie stwardnienia rozsianego u kobiet koreluje z poziomem higieny

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#### Abstract

**Introduction:** The increasing incidence of multiple sclerosis, particularly among women in Europe and North America, has a multifactorial aetiology. **Method:** The aim of the current study was to ascertain the relation between the hygiene level and occurrence of multiple sclerosis in women in Poland. The study was based on a large cohort of 14,200 multiple sclerosis individuals (male – 6,106, female – 8,094) who died in the years 1981–2010 in Poland. The female to male ratio (the F:M ratio) in the multiple sclerosis group was calculated using the number of deaths per year. The rate of late mortality in infants (LMI) per 1,000 live births yearly was used as a marker of the hygiene level. A correlation analysis was carried out between the rate of LMI and the F:M ratio in the multiple sclerosis cohort in the years 1981–2010. Demographic data were obtained from the Central Statistical Office in Warsaw. **Results:** The F:M ratio in the multiple sclerosis group evidently increased (range 1.08–1.79) in the years 1981–2010, showing increasing occurrence of multiple sclerosis in women ( $p < 0.0001$ ). A significant, strong and inverse correlation was found between the marker of the hygiene level (LMI rate) and the F:M ratio in the multiple sclerosis group over three decades: linear correlation coefficient by Pearson:  $r = -0.693$ ,  $p < 0.0001$ . By contrast with this result, no correlation was established between the hygiene level marker and proportion of women to men in the general population on account of extremely low variance of the F:M ratio (0.000025). **Conclusion:** The improvement of the hygiene level showed association with the increasing occurrence of multiple sclerosis in women in the years 1981–2010. The higher the hygiene level was, the greater the occurrence of female multiple sclerosis in Poland.

**Key words:** multiple sclerosis, sex ratio, hygiene level, Poland

#### Streszczenie

**Wprowadzenie:** Wzrastająca zachorowalność na stwardnienie rozsiane, szczególnie u kobiet w Europie i Ameryce Północnej, ma wieloczynnikową etiologię. **Metoda:** Celem bieżącego badania było ustalenie relacji między poziomem higieny i występowaniem stwardnienia rozsianego u kobiet w Polsce. Badanie oparto na dużej kohorcie 14 200 chorych na stwardnienie rozsiane (mężczyźni – 6106, kobiety – 8094), którzy zmarli w latach 1981–2010 w Polsce. Wskaźnik kobiet do mężczyzn (WKM) ze stwardnieniem rozsianym obliczono na podstawie rocznej liczby zgonów. Współczynnik późnej umieralności niemowląt (PUN) na 1000 żywych urodzeń rocznie zastosowano jako miernik poziomu higieny. Wykonano badanie korelacji pomiędzy współczynnikiem PUN i WKM w stwardnieniu rozsianym w latach 1981–2010. Dane demograficzne uzyskano z Głównego Urzędu Statystycznego w Warszawie. **Wyniki:** Wskaźnik kobiet do mężczyzn w zbiorowości osób ze stwardnieniem rozsianym wzrósł znacząco (zasięg 1,08–1,79) w latach 1981–2010, wykazując rosnące występowanie stwardnienia rozsianego u kobiet ( $p < 0,0001$ ). Stwierdzono istotną, mocną, odwrotną korelację między miernikiem poziomu higieny (współczynnikiem PUN) i WKM w stwardnieniu rozsianym w ciągu trzech dekad; współczynnik liniowej korelacji Pearsona:  $r = -0,693$ ,  $p < 0,0001$ . W przeciwieństwie do tego wyniku nie ustalono korelacji między markerem poziomu higieny i proporcją kobiet do mężczyzn w ogólnej populacji ze względu na skrajnie niską wariancję WKM (0,000025). **Wniosek:** Poprawa poziomu higieny wykazała asocjację z wzrastającym występowaniem stwardnienia rozsianego u kobiet w latach 1981–2010. Im wyższy był poziom higieny, tym większe było występowanie stwardnienia rozsianego u kobiet w Polsce.

**Słowa kluczowe:** stwardnienie rozsiane, wskaźnik płci, poziom higieny, Polska

## INTRODUCTION

The hygiene hypothesis claims that lower exposure to childhood infections, as a consequence of higher standards of sanitation, predisposes native residents of Europe to multiple sclerosis (MS) (Poskanzer *et al.*, 1963). Late, more frequent instances of exposure to Epstein–Barr virus (EBV) or other viruses in adolescence, low level of serum 25-hydroxyvitamin D, smoking, obesity and carrying of HLA-DRB1\*15 allele increase the risk of MS (Alter and Cendrowski, 1976; Ascherio, 2013; Chao *et al.*, 2011, Correale *et al.*, 2010). In addition, a higher level of hygiene (HLH) favours higher incidence of MS particularly in women, but higher sanitation and personal hygiene prevent infections, lengthen survival, improve the quality of life and reduce mortality (Cendrowski, 1989). HLH, jointly with other risk factors, is thought to cause a considerable increase in MS incidence (Alonso and Hernán, 2008; Beebe *et al.*, 1967; Freedman *et al.*, 2000; Kotzamani *et al.*, 2012). A temporary change in the hygiene of the environment, occupation or personal and social life may influence MS occurrence (Alonso and Hernán, 2008; Koch-Henriksen and Sørensen, 2010; Kotzamani *et al.*, 2012).

In the present study, the relation between a marker of the hygiene level and the ratio of females to males with MS was investigated over three decades in the Polish population. The aim of this study was to ascertain whether the long-term and nationwide hygiene marker correlates to the occurrence of MS based on a large group of deceased women.

## MATERIAL AND METHOD

The study of the relation between the level of hygiene and the female to male ratio (the F:M ratio) in MS individuals was based on demographic data in Poland. A large cohort included 14,200 MS patients (6,106 men, 8,094 women) who died in the years 1981–2010. The diagnosis of MS was established according to the codes from the International Classification of the Diseases: 6/7–10, 340, 345, G35. The average F:M ratio in the MS group in the individual years was calculated considering the annual number of deaths over three decades (1981–2010). The rate of late mortality in infants (LMI) was used as a marker of the hygiene level. A group of 56,780 infants, who died during 30 years (1981–2010), was included in the study. The average annual rate of LMI was calculated per 1,000 live births yearly taking into account those who died between the 28<sup>th</sup> day and the 1<sup>st</sup> year of life. The data concerning the number of deceased MS individuals, gender, the year and province of death as well as data pertaining to infant mortality were obtained from the Central Statistical Office in Warsaw. A temporal change of the F:M ratio in the MS group and long-term LMI rate was examined by correlating them with consecutive calendar years. A linear correlation test by Pearson was used in order to measure the

relation of long-term LMI rate as a marker of the hygiene level to the F:M ratio in the MS group (1981–2010). An attempt was also made to correlate the LMI rate to the control sex ratio in the general Polish population.

## RESULTS

The total cohort of MS individuals included 6,106 men and 8,094 women who died in the years 1981–2010 in Poland. The average female to male ratio calculated on the basis of the annual number of deceased MS patients was 1.35 (SD 0.18). The distribution of the F:M ratio in particular provinces of the country is shown in Fig. 1.

The F:M ratio in the MS group increased gradually from 1.08 to 1.53 in the years 1981–2010. The long-term increase of the F:M ratio over the three decades was highly significant. If on a *y* axis the F:M ratio was plotted against calendar years on an *x* axis by a linear correlation test, a significant relationship emerged:  $r = 0.7366$ ,  $p < 0.0001$ . The increase of the sex ratio was even throughout 30 years. The main part of this study concerned the relation between the hygiene level and the F:M ratio in the MS group in the whole country (1981–2010). The rate of late mortality of infants (LMI) per 1,000 live births was used as a marker of the hygiene level in the general population. The total number of deceased infants was 56,780. The mean of the LMI rate was 3.51 (SD 1.57). The rate of LMI continually decreased from  $6.4/10^3$  to  $1.5/10^3$  in the general population. The statistical analysis showed a strong

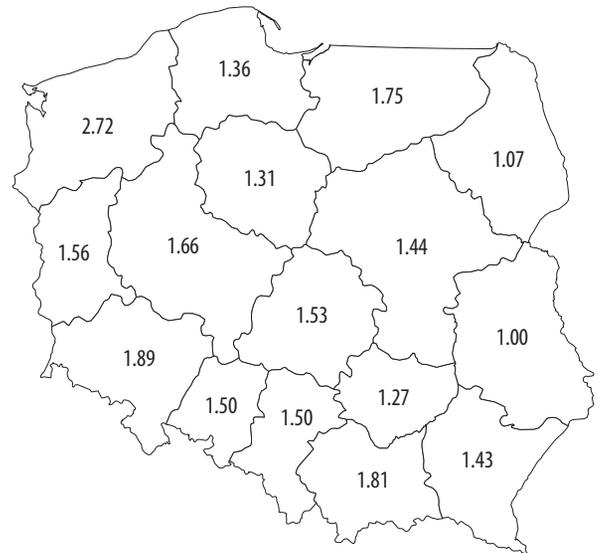


Fig. 1. The average, annual female to male ratio in the MS group within 16 provinces of Poland (2004–2008). The ratio was higher in three western and lower in three eastern provinces. When looking at the distribution of the F:M ratio, note higher proportion of women with MS in Zachodniopomorskie (2.72) and lower proportion in Lubelskie (1.00) provinces. The cause of such a disproportional distribution is unknown

Year	The annual number of deceased MS individuals		The F:M ratio in the MS group	The F:M ratio in the general population	The average annual late mortality rate in infants per 1,000 live births
	Men	Women			
1981	267	290	1.08	1.05	6.4
1982	243	273	1.12	1.05	6.2
1983	284	319	1.12	1.05	6.0
1984	229	308	1.35	1.05	5.9
1985	251	291	1.15	1.05	5.4
1986	238	304	1.27	1.05	5.2
1987	201	283	1.40	1.05	5.0
1988	232	293	1.26	1.05	4.6
1989	231	275	1.12	1.05	4.4
1990	261	312	1.19	1.05	4.4
1991	235	309	1.31	1.05	4.2
1992	206	277	1.34	1.05	4.3
1993	216	276	1.27	1.05	3.8
1994	294	191	1.50	1.05	3.8
1995	200	275	1.37	1.05	3.5
1996	223	273	1.22	1.05	3.3
1997	168	190	1.13	1.05	2.8
1998	144	184	1.27	1.06	2.6
1999	204	256	1.25	1.06	2.5
2000	171	264	1.54	1.06	2.5
2001	186	271	1.45	1.06	2.3
2002	183	264	1.44	1.06	2.2
2003	156	270	1.73	1.06	2.0
2004	158	218	1.37	1.06	1.9
2005	184	267	1.45	1.06	1.9
2006	169	272	1.60	1.06	1.6
2007	171	265	1.55	1.06	1.7
2008	174	268	1.37	1.06	1.7
2009	162	290	1.79	1.06	1.6
2010	165	253	1.53	1.06	1.5
1981–2010	6106	8094			
Mean			1.35	1.05	3.51
SD			0.18	0.005	1.57

Tab. 1. Long-term annual female to male ratio in the MS group and in the general population related to the average, annual late mortality rate in infants in Poland (1981–2010)

decrease in the LMI rate that points to a progressive improvement of a hygiene level;  $p < 0.0001$  (Tab. 1).

An inverse correlation of long-term, overall LMI rate and the F:M ratio in the MS group was found throughout the three decades; a linear correlation coefficient by Pearson was  $r = -0.6936$ ,  $p < 0.0001$ . The outcome implies that the higher the hygiene level (or the lower the rate of LMI) is the greater the occurrence of MS in Polish women. The relationship between the decreasing rate of LMI and increasing ratio of F:M in the MS group is presented in Fig. 2.

By contrast with the significant association between the hygiene level and occurrence of MS in women, there was no measurable relation of the LMI rate to the F:M ratio in the general population. As previously presented, the LMI rate became lower whereas the F:M ratio in the general population was stable (range 1.05–1.06) in the years 1981–2010. The F:M ratio in the general population showed very low standard deviation (0.005) and extremely low

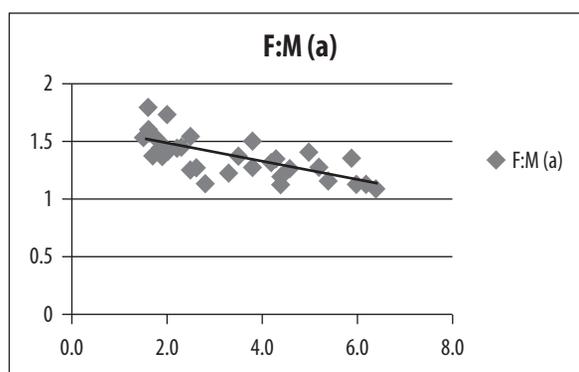


Fig. 2. Inverse correlation was found between the long-term LMI rate used as a marker of the hygiene level and the F:M ratio in the MS group (1981–2010). The horizontal x-axis presents the LMI rate (variable b) whereas the vertical y-axis measures the F:M ratio (variable a) in the MS group. A linear correlation between the variables is strong:  $r = -0.69396$ ,  $p < 0.0001$

variance (0.000025). On account of that fact, a correlation between the LMI rate and the control F:M ratio in the general population was not established.

## DISCUSSION

Several studies have documented the increasing F:M ratio in MS patients over a half of the century in most countries of the world (Alonso and Hernán, 2008; Koch-Henriksen and Sørensen, 2010; Wasay *et al.*, 2006). One meta-analysis has proven that the F:M ratio increases with MS incidence, but decreases with latitude (Koch-Henriksen and Sørensen, 2010). A plausible hypothesis relates the growing F:M ratio to environmental, biological, socioeconomic and genetic factors (Alonso and Hernán, 2008; Cendrowski, 2013b; Hensiek *et al.*, 2002; Koch-Henriksen and Sørensen, 2010; Kotzamani *et al.*, 2012; Wasay *et al.*, 2006). The present study has confirmed that the hygiene level is correlated to the increasing occurrence of MS in women. In the data from the literature, infectious mononucleosis is considered as a marker of the hygiene level (Ascherio and Munger, 2010; Ascherio *et al.*, 2012). This infectious disease is of particular interest because EBV is recognised as the strongest known risk factor of MS (Ascherio and Munger, 2010). In countries with HLH, 60% of children at the age of 4–6 are seronegative for EBV antibodies and the seroconversion at the age of 16–21 is associated with a sharp, 15–30-fold increase in MS risk (Ascherio *et al.*, 2012). Another marker of the hygiene level is helminthiasis. An inverse correlation between global prevalence of parasite infections (*Trichuris trichiura*) and prevalence of MS has been shown (Fleming and Cook, 2006). The correlation coefficient between MS prevalence and parasite infections was  $r = 0.53$  ( $p = 0.00001$ ) (Fleming and Cook, 2006). It indicates that the more common parasite infections are, the lower the prevalence of MS. Parasite-driven infections induce the activity of regulatory T cells secreting anti-inflammatory cytokines IL-10 and TGF beta that exhibit suppressive effects (Correale and Farez, 2011). HLH has been correlated to low LMI rate in Europe and the Middle East (Lauer, 1993; Leibowitz *et al.*, 1967). The analysis has shown a striking inverse correlation of lower LMI rate to higher MS prevalence ( $p = 0.001$ ) (Lauer, 1993). The relation of HLH to MS is characterised by evident dichotomy. On the one hand, HLH is associated with increased risk of MS and autoimmune diseases and on the other hand, hygiene protects against concomitant infections which have deleterious effects on the clinical course of the disease (Cendrowski, 1993). A frequent use of antibiotics, smoking or improper diet lead to the extinction of the natural microbiome (microorganisms) in the gut (Kasper *et al.*, 2014). Physiological intestinal microorganisms are important in the maintenance of the adaptive immune system homeostasis (Ehlers and Kaufmann, 2010). The microbiome produces, among others, polysaccharide A that protects a host against autoimmunity

(Ehlers and Kaufmann, 2010). The bacterial microflora stimulates CD4+ regulatory T cells to produce anti-inflammatory cytokines in animals (Wang *et al.*, 2014). The composition of the intestinal microbiome in MS women differed from that of age- and gender-matched controls (Baranzini *et al.*, 2014).

A birth by a caesarean section, nursing of infants in quasi-sterile conditions, low exposure of children to siblings or peers at preschool age, excessive daily personal hygiene, higher consumption of pasteurised or manufactured food, and the fact that meals are not consumed together or that children do not live in a single room prior to early adulthood may predispose susceptible individuals to MS (Ascherio and Munger, 2010; Kotzamani *et al.*, 2012; Lauer, 2010; Ponsonby *et al.*, 2005; Wang *et al.*, 2014). According to a recent view, excessive personal hygiene makes the physiological microflora of the skin and gut extinct (Wang *et al.*, 2014). This extinction causes a decrease in the activity of dendritic cells that stimulate regulatory T cells ( $T_{R1}$ ,  $nT_{REG}$ ,  $iT_{REG}$ ) (Correale and Farez, 2007; Lauer, 2010). “Immoderate” hygiene may also cause lower activity of T helper cells ( $T_{H2}$ ) that produce anti-inflammatory cytokines (Moro *et al.*, 2010). HLH is mainly connected with lower exposure to viral antigens in early childhood. Late exposure of adolescents to infection brings about important immunological dysregulation. One may speculate that late primary infection with EBV and other viruses sets back the differentiation of thymic cells and delays the maturation of dendritic cells (Rook *et al.*, 2004). Therefore, the influence of infections as well as immunological and other factors, explains why HLH, particularly in women, increases the risk of MS (Ehlers and Kaufmann, 2010; Rook *et al.*, 2004; Sellner *et al.*, 2011).

The increasing occurrence of the disease in females depends on numerous factors that have been analysed in recent studies (Alonso and Hernán, 2008; Correale and Farez, 2007; Dunn and Steinman, 2013; Kotzamani *et al.*, 2012; Ponsonby *et al.*, 2012; Sellner *et al.*, 2011; Wasay *et al.*, 2006). It may be added that the major histocompatibility complex (MHC) is a site of interaction between environmental and genetic factors (Chao *et al.*, 2011). The transmission of HLA-DRB\*15 allele was much more probable in female-female pairs affected by MS than in female-male pairs (Chao *et al.*, 2011). Nonetheless, MS is a virtually exogenous disease. Partial prevention of MS is possible by modifying behavioural and environmental factors. A natural delivery of two or more children and breast-feeding longer than 7 months protects mothers or offspring against the development of MS (Lauer, 2010; Ponsonby *et al.*, 2005). Nursing of infants in ordinary hygienic milieu, higher exposure at preschool age to siblings or peers, longer exposure in childhood to UVB radiation, non-smoking of tobacco and marihuana, “coming back” to rural settings at weekends and rejection of oral contraceptives may contribute to the prevention of the disease (Brosseau *et al.*, 1993; Cendrowski, 2013a; Langer-Gould *et al.*, 2014; Ponsonby *et al.*, 2012).

## CONCLUSION

A long-term improvement of the hygiene level is associated with the increasing occurrence of MS in Polish women over the years 1981–2010. The outcome of the analysis has shown that the higher the hygiene level is, the greater the occurrence of female MS.

### Conflict of interest

The author does not report any financial or personal affiliations to persons or organisations that could negatively affect the content of this publication or claim to have rights to this publication.

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