

Indications for Synergetic and Antagonistic Effects between Trace Elements in The Environment to Human Health

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ABSTRACT

The objective of this work was to investigate the interactions between the level of concentrations of Ca, V, Cr, Mn, Fe, Ni, Cu, Zn, As and Pb in potable water, soil, vegetation and school children hair and disease incidences of neoplasms, diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism, endocrine, nutritional and metabolic diseases, mental and behavioral disorders and diseases of the circulatory system on the population groups which are homogeneously exposed to the environmental conditions. It was found that potable water among the other investigated aspects of the physical environment has the greatest impact on the public health. The environment-disease incidence interactions have been found for all investigated diseases groups. The results reported here emphasize the importance of the observation of the mutual effects of the environmental variables on the human health for the identification of their synergetic as well as antagonistic effects.

Key words: disease incidence, public health, trace elements, environment

Introduction

The interaction of humans with their environment proceeds in two ways. As much as humans have an impact on the viability of ecosystem conditions, these conditions have an impact on the well-being of humans. The well-being of humans has many dimensions, but one of the most important is the state of the public health. Many studies have been done with the aim to correlate incidence of disease, and/or mortality, with the characteristics of the environment¹⁻³. Most of them deal with very specific interactions (one environmental variable in relation to a specific disease). It has been shown that there are many such interactions, some increasing, some decreasing the effect under the investigation⁴. Anyhow, the problem of mutual interactions is very complex due to synergistic and antagonistic effects of numerous variables involved and their changes over time and space. Such studies require a complex data-basis over a long period of time.

Due to our inability, either because of technical, economical or other reasons, to comprehend and measure all

the variables within the exploring ecosystem and to completely isolate the subject under the investigation from side influences, there is always a dose of uncertainty when considering the environment-human health interactions. With regards to the limitations mentioned, the aim of the present study was to identify the mutual impact of the measured environmental characteristics on human health, based on the case study of the Island of Krk in the Northern Adriatic Sea (Figure 1). For this purpose we have investigated the geochemical characteristics of the environment by determining 10 chemical elements in potable water, soil, vegetation and human hair. The elements of interest were those influencing biochemical processes⁵: Ca, V, Mn, Fe, Ni, Cu, Zn, As, Cr and Pb. It is well known that insufficient intakes of vital elements as well as an overexposure to vital or toxic elements can result in diseases. The influences of these elements on health have been intensively investigated and abundantly reported in literature⁶⁻⁸.

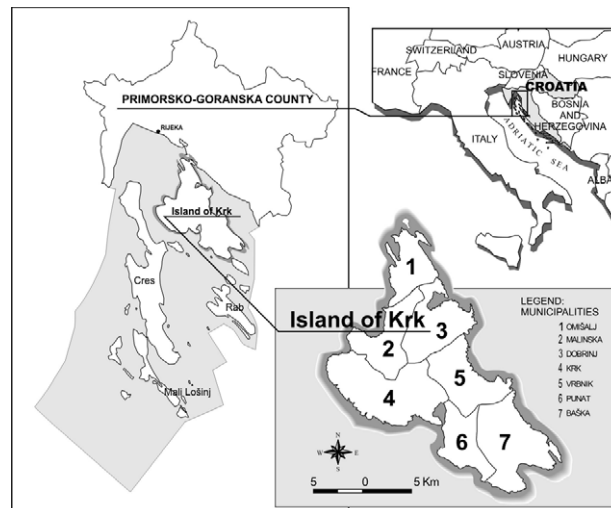


Fig. 1. Geographical location of the Island of Krk. There are seven municipalities on the Island of Krk.

In this report the average elemental concentrations have been correlated with disease incidence rates of five groups of diseases. The investigation was conducted on the Island of Krk for two reasons. First, the incidence of endemic diseases (i.e. goiter, Figure 2) has been reported on the Island of Krk more than 50 years ago^{9,10}. It was assumed in these reports that one of the possible etiological disease factors could be the geochemistry of the environment. Also, the life on an island is more isolated in terms of mobility compared to inland urban centers. Therefore, one could assume that groups within the population of the Island of Krk are homogenous in their environmental exposures.

Methods and Materials

The analyses were performed on the comprehensive database obtained from the study of the environmental

quality of the Island of Krk conducted during the period 1998–2000. Data on the concentrations of chemical elements in potable water, soil, vegetation and school children hair as well as data on disease incidences were incorporated.

Within the environmental quality study, soil and vegetation samples were collected from the 112 georeferenced locations. Detailed sampling and analysis procedures are presented elsewhere^{11–13} together with the descriptive statistics of the elemental concentration data.

Potable water was taken from 83 households. Potable water on the island is supplied as tap water from the municipal drinking water distribution system, cistern drinking water, rain water and water drawn from private wells. The data on the elemental concentrations in drinking water samples collected on the island are presented elsewhere¹¹.

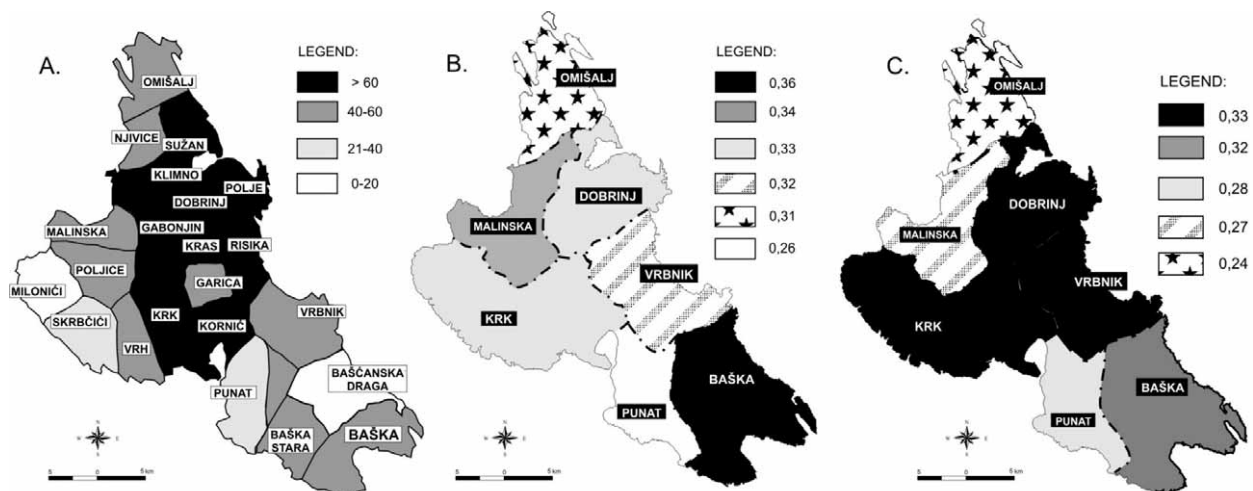


Fig. 2. a) Goiter incidence in 1961, b) Goiter prevalence in 1989/90, c) Goiter prevalence in 1993/94⁹.

TABLE 1
THE STRUCTURE OF THE POPULATION OF THE ISLAND OF KRK BY MUNICIPALITIES (CENSUS 2001)

Municipality	Total	Age 0–6	Age 7–19	Age 20–65	Age >65	Average age	Age index	Age coefficient
Krk	5,491	382	914	3,321	874	39.8	90.4	21.4
Baška	1,554	77	184	932	361	45.3	184.3	31.1
Dobrinj	1,970	110	275	1,092	493	45.1	167.0	32.7
Malinska	2,726	182	439	1,633	472	41.0	104.0	23.9
Omišalj	2,998	188	676	1,856	278	35.8	44.0	12.8
Punat	1,876	142	258	1,099	377	41.8	124.8	26.8
Vrbnik	1,245	75	173	693	304	44.4	159.3	31.9
Island of Krk in whole	17,860	1,156	2,919	10,626	3,159	41.9	124.8	25.8

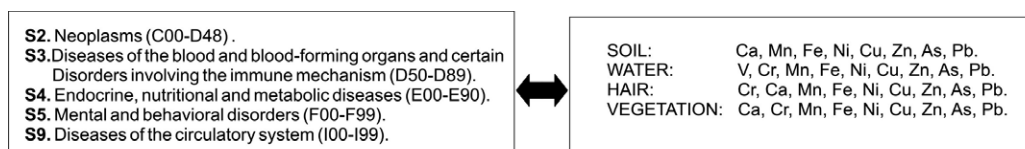


Fig. 3. Diseases and environmental variables submitted to calculation.

School children hair samples (age 6–19) were collected in eight elementary and one secondary school. The study included 1,940 of 2,200 children attending the school in the year 1999 at the time of the sampling campaign. The details on the sampling, analysis and results are presented elsewhere¹¹. It is assumed that hair concentration values reflect the environmental exposure either by deposition and/or through the food intake¹⁴.

Data on diseases, grouped by the World Health Organization¹⁵, were obtained from the Regional Public Health Office in Rijeka¹⁶ as the incidence rates for the period 1997–2001. Disease incidences were calculated as a number of new disease cases per 1,000 persons observed in the municipalities within one year. The groups of diseases were: group of neoplasms (C00-D48), group of diseases of the blood and blood-forming organs and certain disorders involving the immune system (D50-D89), group of endocrine, nutritional and metabolic diseases (E00-E90), group of mental and behavioral disorders (F00-F99) and group of diseases of the circulatory system (I00-I99).

For the sake of simplification, disease groups were marked as S2 (C00-D48), S3 (D50-D89), S4 (E00-E90), S5 (F00-F99) and S9 (I00-I99). Population, all age groups included, was analyzed and significant statistical difference was found for disease groups S2, S3, S4 and S5¹⁷. Table 1 presents the structure of the population of the Island of Krk for individual municipalities.

All measurements on the collected geochemical environmental samples were performed by using the Energy Dispersive X-Ray Fluorescence (EDXRF) as an analytical tool. The qualitative and quantitative analyses were carried out using the International Atomic Energy Agency (IAEA) software for the X-ray fluorescence spectrometry (QXAS). The Quality Assurance/ Quality Control (QA/QC) procedures were done in all the cases by measurements of appropriate reference materials.

In this report interrelationships between diseases and geochemical environment were examined by the calculation of correlation coefficients matrix and the linear regression analysis. For this purpose STATISTICA 6.0⁰ program package was used. Variables submitted to calculation are presented in Figure 3. Correlations have been investigated between the groups of diseases (the first box) and the measured major and trace elements in physical environment (the second box). Since the public health data were collected according to municipalities, we have determined their average concentrations for the analyzed chemical elements in different components of the environment (potable water, soil and vegetation, including human hair used as an indicator of exposure).

Results and Discussion

The results on municipal average values of geochemical variables measured in soil (s), potable water (w), hair (h), vegetation (v) and municipal average incidence rates of diseases groups S2, S3, S4, and S5 for the five years period are presented in Table 2. Table 3 presents correlation matrix for all variables considered. Since the number of cases was 8 (7 municipalities and the whole of the Island of Krk), for the 0.95 confidence level and the N-2 degrees of freedom, the statistically significant correlation correspond to the correlation coefficient $r > 0.707$ ¹⁸. The coefficients greater than 0.707 are marked in order to be distinguished from the significantly non-correlated coefficients. Diseases groups themselves appear to be correlated. The statistically significant correlations were found for diseases S4-S2, S9-S4, and for S9-S5. Regarding the environment-health relations, twenty correlations or 11.4% of all correlations examined between diseases incidences and environmental variables were found to be significant. This is above the limit of 5% sig-

TABLE 2
 AVERAGE CONCENTRATION VALUES OF CHEMICAL ELEMENTS AND AVERAGE INCIDENCE RATES OF DISEASE GROUPS FOR THE MUNICIPALITIES OF THE ISLAND OF KRK.

Variables ^{a b}	Cases							
	Omišalj	Malinska	Krk	Dobrinj	Vrbnik	Baška	Punat	I. of Krk
Mn-s (mg/g)	1,513.1	1,761.9	1,707.1	1,622.5	1,528.3	1,472.7	1,670.9	1,605.5
Mn-w (mg/L)	134.3	193	109.1	72.8	121	118	106.5	129.8
Mn-h (mg/g)	3	2.6	2.7	2.5	2.5	2.6	2.8	2.8
Mn-v (mg/g)	236.1	325.3	247.2	262	218.7	135.4	325.5	236.9
Fe-s (%?)	5.71	6.8	6.6	6.2	5.8	5.6	6	6.1
Fe-w (mg/L)	29.7	148.7	117.3	46.9	118.8	78	57.5	102.7
Fe-h (mg/g)	42.3	35.9	37.6	39	38.9	38.1	38	39.8
Fe-v (mg/g)	365.8	553.9	562.7	469.4	439.3	988	1,029.2	666.5
pnumNi-s (mg/g)	39.3	40.1	34.6	36.1	28.9	32.7	31.1	33.9
Ni-w (mg/L)	73.7	138.7	24.5	14.9	11.3	84.8	75	66
Ni-h (mg/g)	1.9	1.5	1.7	1.6	1.8	2	1.7	1.8
Ni-v (mg/g)	0.87	0.83	0.84	0.79	0.86	0.92	0.92	0.87
Cu-s (mg/g)	22.2	25.9	27.1	22.5	43.1	27.6	27.2	28.4
Cu-w (mg/L)	9.7	14.9	8.4	19.2	21	7.8	10	14.1
Cu-h (mg/g)	15.5	13.7	13.6	12.5	12.2	12.5	15.5	14.3
pnumCu-v (mg/g)	12.8	12.8	14.2	9.3	11.4	11.5	15.7	12.4
Zn-s (mg/g)	145	156.8	166.2	142.9	144.2	142.2	162.7	151.7
Zn-w (mg/L)	279	1,466.4	749	195.9	623.3	566.7	311.8	802
Zn-h (mg/g)	185.2	180	179.9	178.8	183.5	192.6	189.8	183.4
Zn-v (mg/g)	72.2	71.9	97.4	61.4	74.8	66	79.1	75.7
As-s (mg/g)	21.1	27.2	30.6	27.2	25.3	24.8	24.1	26.4
As-w (mg/L)	1.6	1.1	1	1	0.3	0.8	1.7	1
As-h (mg/g)	0.42	0.47	0.44	0.4	0.42	0.47	0.45	0.43
As-v (mg/g)	0.24	0.04	1.18	0.81	1.99	0.54	1.49	1
Pb-s (mg/g)	58.9	72.3	71.7	66.1	59.7	61.4	68.9	65.8
Pb-w (mg/L)	2.3	5.6	2.3	2.2	2.7	0.25	0	3.2
Pb-h (mg/g)	7.5	8.3	7.7	8	8	9.2	7.3	7.7
Pb-v (mg/g)	1.2	1.3	1.3	1.7	1.3	1.5	1.3	1.4
Ca-s (%?)	12.9	12.3	13.4	11.7	12	13.6	11.8	12.6
Ca-h (mg/g)	1,944.5	2,065.3	2,439.6	2,369.1	1,868	3,766.7	1,981.3	2,142.5
Ca-v (mg/g)	13.3	15.4	24.1	20.4	17.1	17.9	19.9	19.3
V-w (mg/L)	31.3	51	30.3	27.4	21.1	41.3	36.5	36.3
Cr-w (mg/L)	101.3	147.9	77.2	69.3	92.9	81.8	104	101.5
Cr-h (mg/g)	5.5	5.5	5.9	5.6	5.6	5	6.2	5.7
Cr-v (mg/g)	1.3	1.5	1.4	1.3	1.3	1.7	1.9	1.5
S2	12.6	9.4	14.6	16	23.6	10	16.2	14.6
S3	19.4	39.6	22.6	15.6	16.8	6.4	12.6	19
S4	18.2	25.8	29	32.6	46.2	20.6	32.6	29.3
S5	30.6	50.8	39.2	59.4	40.4	34.2	32	40.9
S9	60.4	131	106.8	146	143.8	97.2	107.2	113.2

a – soil (s), potable water (w), hair (h), vegetation (v), b – S2, S3, S4, S5 and S9: disease groups.

TABLE 3
(CONTINUED)

	Mn-s	Mn-w	Mn-h	Mn-v	Fe-s	Fe-w	Fe-h	Fe-v	Ni-s	Ni-w	Ni-h	Ni-v	Cu-s	Cu-w	Cu-h	Cu-v	Zn-s	Zn-w	Zn-h	Zn-v
Pb-s	956*	212	-132	674	903*	478	-739*	189	257	274	-778*	-297	-308	-138	140	428	821*	521	-426	462
Pb-w	490	697	-153	382	664	638	-236	-637	575	313	-583	-640	034	448	-102	-193	077	767*	-739*	006
Pb-h	-338	164	-566	-622	-157	255	-374	263	-020	255	279	109	093	-040	-693	-502	-477	288	291	-456
Pb-v	-120	-573	-589	-253	-046	-238	-121	127	-073	-305	-113	-359	-230	325	-591	-719*	-440	-290	-116	-572
Ca-s	-286	152	270	-644	-121	099	065	152	141	164	590	327	-174	-731*	-029	140	043	158	296	335
Ca-h	-394	-192	-272	-717*	-285	-072	-208	527	-118	108	492	330	-173	-454	-446	-260	-283	-057	500	-229
Ca-v	376	-586	-270	037	350	139	-364	274	-393	-523	-221	-144	-003	-121	-210	169	526	-126	-206	548
V-w	402	693	107	252	385	320	-517	433	489	942*	-225	214	-430	-404	237	275	273	647	191	-130
Cr-w	461	918*	179	566	411	471	-335	-022	436	822*	-408	054	-019	038	374	349	275	730*	-077	-037
Cr-h	582	-226	269	720*	351	-022	-080	069	-220	-245	-464	-033	020	013	520	638	738*	-150	-229	590
Cr-v	133	038	148	152	-112	-056	-394	961*	-323	47	103	753*	-108	-520	339	588	392	010	719*	055
S2	-187	-453	-287	010	-250	014	194	-263	-704*	-771*	002	-104	747*	621	-256	-115	-108	-359	-155	147
S3	720*	757*	-017	613	815*	621	-395	-478	650	465	-710*	-534	-120	199	128	137	391	793*	-671	206
S4	094	-282	-559	177	040	322	-201	-156	-681	-601	-286	-209	788*	738*	-417	-128	027	-045	-268	122
S5	431	-063	-666	293	563	253	-370	-396	305	-140	-723*	-860*	-132	678	-532	-633	-152	248	-741*	-364
S9	352	-119	-869*	244	394	487	-559	-128	-298	-304	-611	-529	445	805*	-670	-435	-044	266	-486	-183

a - Since the matrix is triangular, for the sake of presentation the variables As-s to Cr-v. are folded over and compared to disease groups variables. * - statistical significant correlation

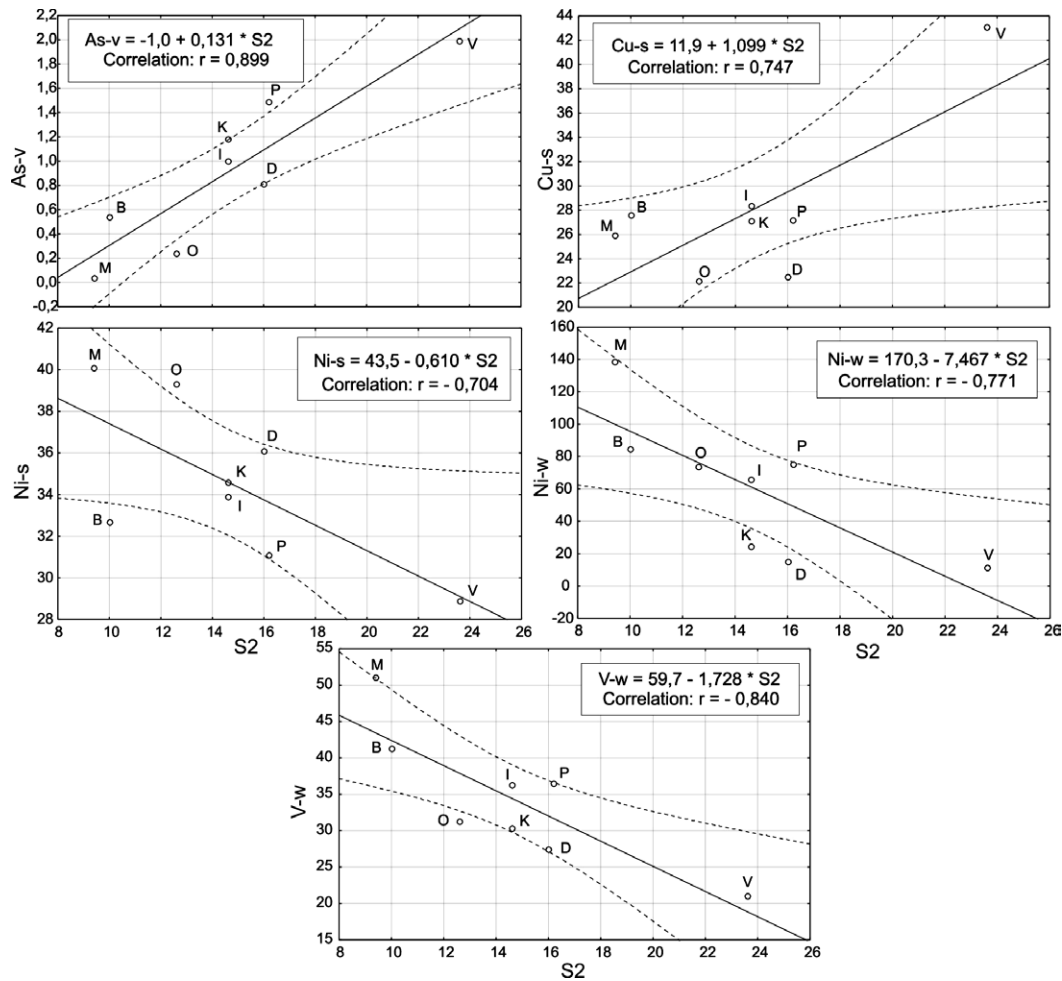


Fig. 4. Linear regression with 0.95 confidence interval obtained for environmental variables found to be significantly correlated with disease group (S2), group of neoplasms (C00-D48). Cases (municipalities) are marked as O – Omišalj, M – Malinska, K – Krka, D – Dobrinj, V – Vrbnik, B – Baška, P – Punat, I – Island of Krka.

nificant correlations expected to be found for independent variables. All environmental variables that were found to be significantly correlated with disease groups S2, S3, S4, S5 and S9 are presented as linear regression graphs in Figures 4, 5, 6, 7 and 8, respectively.

By examining the significant correlations between the diseases' incidences and the environmental variables it can be seen that the water is the most frequently correlated variable (8 correlations), follows soil (5 correlations), hair (4 correlations) and vegetation (3 correlations). Among the diseases, the S3 group is most highly impacted by the environment (7 correlations), then S2 (5 correlations), follow groups S4 and S5 (3 correlations) and S9 (2 correlations).

It could be also seen that all the elements analyzed, except Ca, participated in the correlations. Unfortunately, Ca and Mg were not analyzed in water samples due to the technical limits of the methods used¹⁹. This was unfortunate because the negative correlation between the Ca and Mg enrichment and the cardiovascular diseases has been hypothesized in many studies^{20,21}.

However, we did analyze the influence of these two ions indirectly by correlating the type of water supply (TWS) used by households with disease incidences. Namely, the collected water samples were grouped as the water from the distribution system (DSW), known to be abundant in Ca^{2+} and Mg^{2+} ions (high water hardness), rain-water (RW) known to be poor in Ca^{2+} and Mg^{2+} ions (low water hardness), and the mixed water (MW) which is a combination of DSW and RW since some households use both types. The values given to TWS are descriptive. In this way, numbers 3, 2 and 1 were assigned to DSW, MW and RW, respectively. Decimal numbers describe the average municipalities' water supply systems for the analyzed samples that are a combination of three sources. Therefore, municipalities Omišalj and Baška which are 100% supplied by DSW are described by number 3, Malinska which is 56% supplied by DSW is described by number 2.22, Punat (50% by DSW) 2, Vrbnik (44% by DSW) 1.86, Krka (32% by DSW) 1.68, Dobrinj (18% by DSW) 1.67 and the whole Island of Krka (44% by DSW) by number 1.99. The correlation matrix for the groups of diseases and the

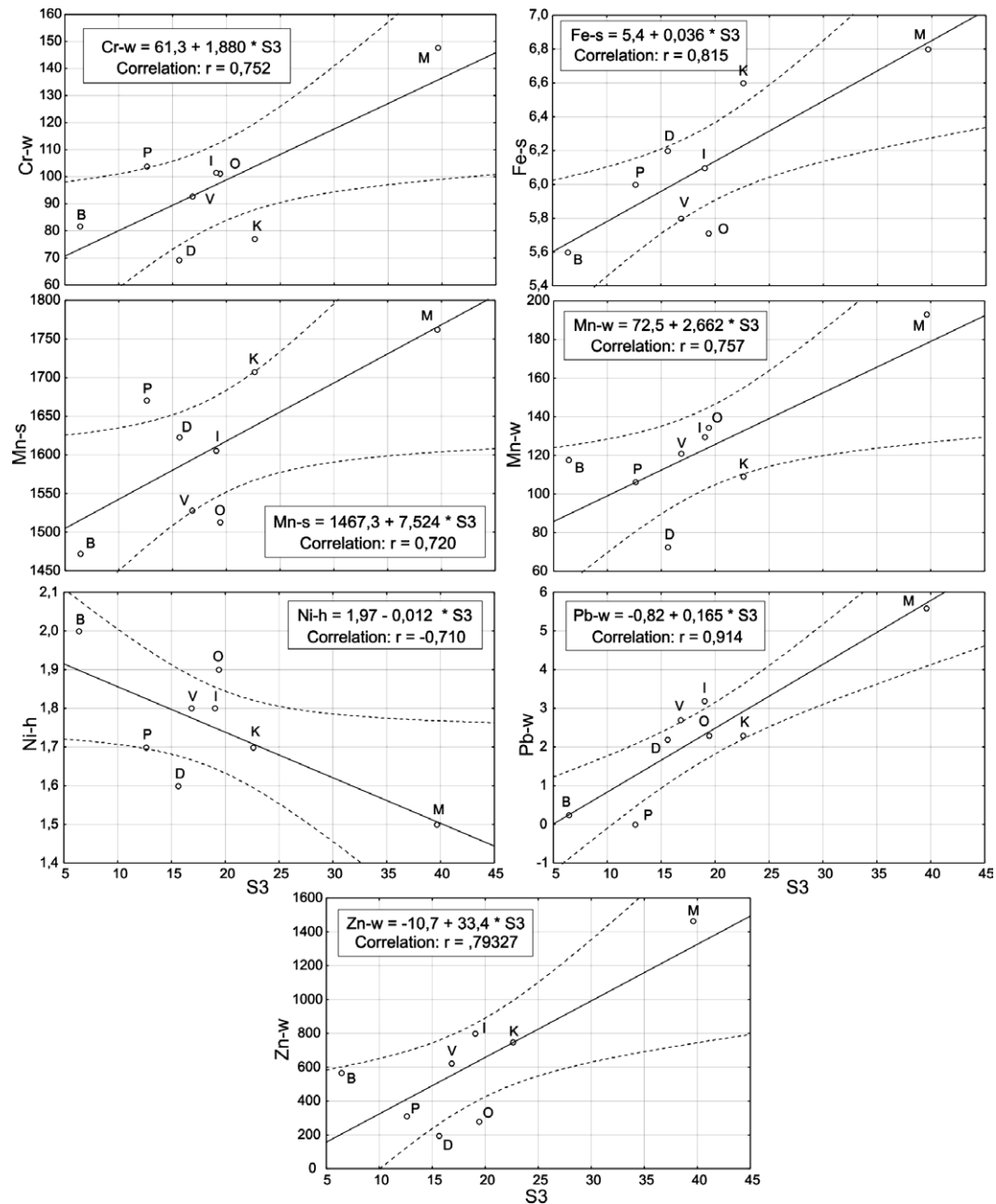


Fig. 5. Linear regression with 0.95 confidence interval obtained for environmental variables found to be significantly correlated with disease group (S3), diseases of the blood and blood-forming organs and certain disorders involving the immune system (D50-D89). Cases (municipalities) are marked as in Figure 4.

type of water are presented in Table 4. Figure 9 shows graphs with linear regression analysis results for statistically significant correlations of variable TWS with the variables S9 and S4, respectively.

Referring to the significant correlations observed between the diseases and the concentrations of the chemical elements in the environment presented in Table 2, it is evident that the correlations with Ni have been the most frequent ones. In all five cases, the Ni concentrations were found to be negatively correlated with the disease groups S2, S3 and S5. On the contrary, in all the

cases Cu (4 correlations) and As (2 correlations) were found to be positively correlated with disease groups S2, S4, S9 and S2, S4, respectively. Mn with three and Zn with two significant correlations are in the group of elements found to be positively and negatively correlated with some of the examined disease groups. They both are positively correlated with S3, Mn is negatively correlated with S9 and Zn is negatively correlated with S5. Only one correlation has been found for V (negatively correlated with S2), Fe, Pb and Cr (positively correlated with S3).

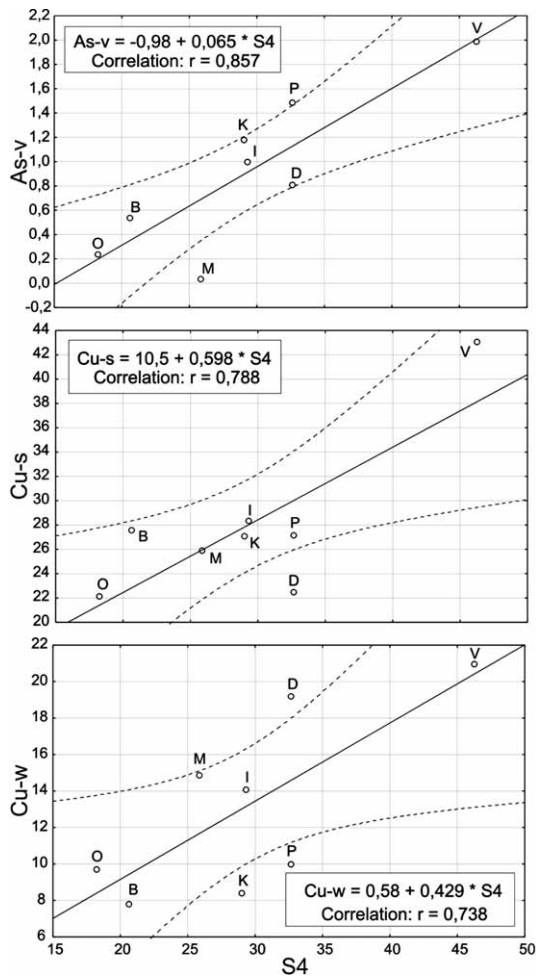


Fig. 6. Linear regression with 0.95 confidence interval obtained for environmental variables found to be significantly correlated with disease group (S4), endocrine, nutritional and metabolic diseases (E00-E90). Cases (municipalities) are marked as in Figure 4.

The results presented in Table 4 and Figure 9 show that water hardness is negatively correlated with the incidence of disease groups S9 and S4. This confirms the hypothesis stated in the other reports²² that cardiovascular diseases and the water hardness are negatively correlated.

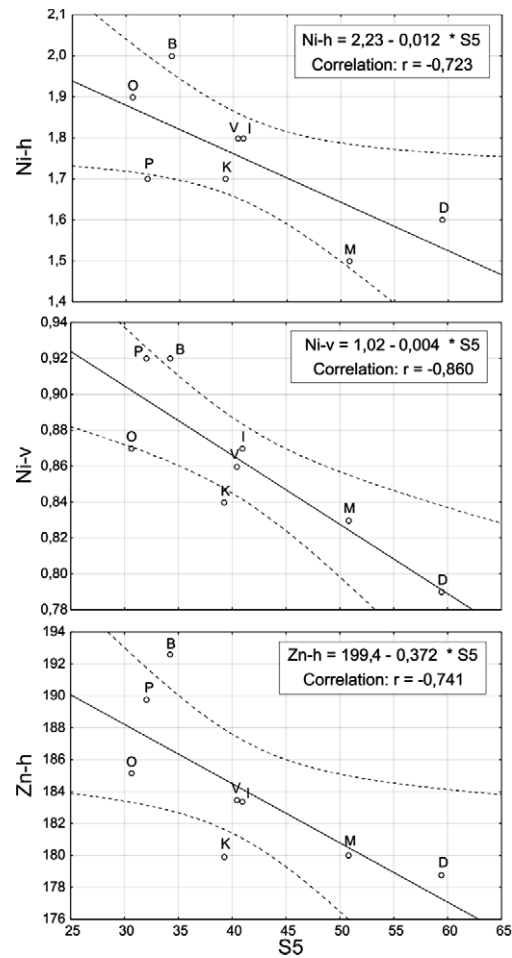


Fig. 7. Linear regression with 0.95 confidence interval obtained for environmental variables found to be significantly correlated with disease group (S5), mental and behavioral disorders (F00-F99). Cases (municipalities) are marked as in Figure 4.

The results presented here are in an agreement with the results of our previous investigations of synergetic and antagonistic effects of different environmental variables on the public health which were obtained by using a multivariate statistical approach. We have already reported¹⁷ that higher concentrations of Mn, Fe and Zn in the environment, with low Cu concentrations, can de-

TABLE 4
CORRELATION MATRIX OBTAINED FOR DISEASE GROUPS AND VARIABLE THAT DESCRIBE TYPE OF WATER SUPPLY (TWS)

	S2	S3	S4	S5	S9	TWS
S2	1.00					
S3	-0.28	1.00				
S4	0.91*	-0.06	1.00			
S5	0.02	0.41	0.27	1.00		
S9	0.46	0.20	0.76*	0.77*	1.00	
TWS	-0.57	-0.20	-0.74*	-0.55	-0.74*	1.00

* Statistically significant correlations.

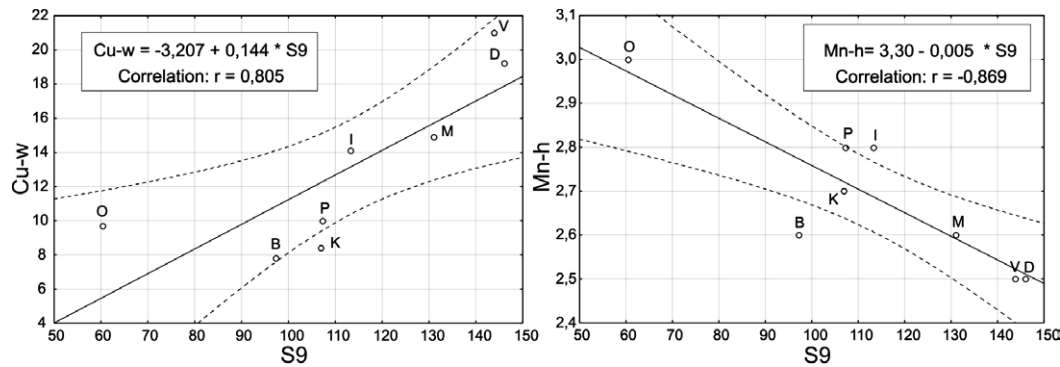


Fig. 8. Linear regression with 0.95 confidence interval obtained for environmental variables found to be significantly correlated with disease group (S9), diseases of the circulatory system (I00-I99). Cases (municipalities) are marked as in Figure 4.

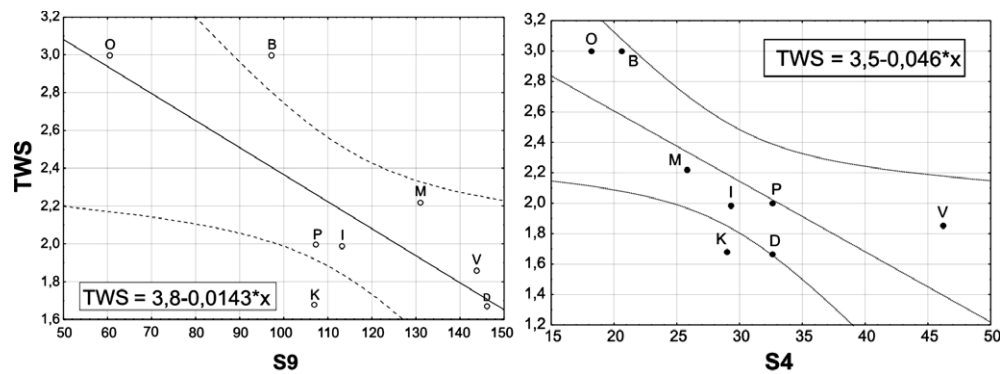


Fig. 9. Linear regression with 0.95 confidence interval obtained for type of water supply (TWS) found to be significantly correlated with disease groups (S9), diseases of the circulatory system (I00-I99) and (S4), endocrine, nutritional and metabolic diseases (E00-E90). Cases (municipalities) are marked as in Figure 4.

crease the incidence of S2, S4 and S9. At the same time, an increase in Mn, Fe and Zn can increase the incidence rate of S3.

Conclusion

As a result of this study, it can be concluded that potable water among the other investigated aspects of the physical environment has the greatest impact on the public health.

The environment-disease incidence interactions have been found for all investigated diseases groups. Diseases of the blood and blood-forming organs and certain disorders involving the immune system (D50-D89) are in the group of diseases which is most highly impacted by the environment. The disease group of neoplasms (C00-D48) is the second on this list.

There is a possibility that the environment poor in Ni can increase incidences of diseases of the blood and blood-forming organs and certain disorders involving the immune system (D50-D89), neoplasms (C00-D48) and mental and behavioral disorders group of diseases (F00-F99). An environment abundant in Cu and As can increase incidences of neoplasms disease group (C00-D48) and endocrine, nutritional and metabolic disease group

(E00-E90). In addition, the higher concentrations of Cu in the environment can increase the incidence of the circulatory system disease group (I00-I99). Further, the incidence of diseases of the blood and blood-forming organs and certain disorders involving the immune system (D50-D89) is positively correlated with Mn, Fe, Zn, Cr and Pb. Vanadium, Mn and Zn are negatively correlated with disease groups of neoplasms (C00-D48), circulatory system (I00-I99) and mental and behavioral disorders (F00-F99), respectively. To summarize, in all the cases V and Ni have been negatively correlated while Cr, Fe, Cu, As and Pb in all the cases have been positively correlated. Manganese and Zn have been found to be positively and negatively correlated with different groups of diseases.

In addition, it has been found that the water hardness is negatively correlated with the incidence of the circulatory system disease group (I00-I99) and endocrine, nutritional and metabolic disease group (E00-E90).

Even though there are some uncertainties in the interdependence of the health events and the characteristics of the environment, the observed interactions are worthy of further studies. The results reported here emphasize the importance of the observation of the mutual effects of the environmental variables on the human health for the identification of their synergetic as well as antagonistic effects.

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INDIKACIJE O SINERGIJSKOM I ANTAGONISTIČKOM DJELOVANJU ELEMENATA U TRAGOVIMA U OKOLIŠU NA LJUDSKO ZDRAVLJE

S A Ž E T A K

Cilj ovog rada bio je istražiti povezanost između koncentracija Ca, V, Cr, Mn, Fe, Ni, Cu, Zn, As i Pb u pitkoj vodi, tlu, vegetaciji i kosi školske djece i učestalosti grupa bolesti novotvorina, bolesti krvi, krvotvornog sustava, bolesti imunološkog sustava, endokrinih bolesti, bolesti prehrane i bolesti metabolizma, duševnih poremećaja i poremećaja ponašanja te bolesti cirkulacijskog sustava na grupe unutar populacije koje su homogeno izložene uvjetima iz okoliša. Otkriveno je da voda za piće između svih istraživanih parametara okoliša ima najveći utjecaj na zdravlje populacije. Korelacije između okoliša i učestalosti bolesti nađene su za sve istraživane grupe bolesti. Ovdje prikazani rezultati naglašavaju potrebu istovremenog praćenja djelovanja više parametara okoliša u svrhu identificiranja njihovih sinergijskih kao i antagonističkih djelovanja na ljudsko zdravlje.