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Chronic Respiratory Symptoms in Croatian Adriatic Island Metapopulations

Eugenija Žuškin¹, Nina Smolej Narančić², Tatjana Škarić-Jurić², Maja Barbalić², Pavao Rudan², Mirjana Kujundžić-Tiljak³, Jasna Pucarín-Cvetković¹, E. Neil Schachter⁴

¹Department of Environmental and Occupational Health, Andrija Štampar School of Public Health, Zagreb University School of Medicine, Zagreb, Croatia

²Institute for Anthropological Research, Zagreb, Croatia

³Department of Medical Statistics, Epidemiology, and Medical Informatics, Andrija Štampar School of Public Health, Zagreb University School of Medicine, Zagreb, Croatia

⁴The Mount Sinai School of Medicine, New York, NY, USA

> **Correspondence to:**

Eugenija Žuškin
Andrija Štampar School of
Public Health
Zagreb University School of
Medicine
Rockefellerova 4
10000 Zagreb, Croatia
ezuskin@snz.hr

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Aim To investigate the prevalence of chronic respiratory symptoms in 9 metapopulations on Adriatic islands in Croatia, and the relationship between respiratory symptoms and individual genetic background.

Methods We obtained random sample of 1001 adult inhabitants of 9 Adriatic island villages in Croatia, that also included immigrants to these villages. European Union respiratory health questionnaire and World Health Organization non-communicable diseases questionnaire were used. Personal genetic histories were reconstructed, based on the two-generation ancestral pedigrees. Bivariate and multivariate methods were used in the analysis.

Results Women reported the occurrence of acute dyspnea ($P=0.017$), cough ($P=0.002$), and asthma ($P=0.002$) more often than men. Gender was the strongest predictor for acute and/or chronic cough (odds ratio [OR], 1.69; 95% confidence interval [CI], 1.23-2.33) and asthma (OR, 2.00; 95% CI, 1.00-4.01), whereas smoking was the strongest risk factor for acute and chronic dyspnea (OR, 1.90; 95% CI, 1.21-2.99) and airway narrowing (OR, 1.84; 95% CI, 1.18-2.87). Residence on the northern islands increased the odds of allergy, whereas the highest odds ratio of 3.20 was associated with the interaction of northern residence and immigrant background. Genetic background was a significant predictor only for the occurrence of allergy symptoms.

Conclusion Differences in respiratory findings among the island inhabitants were often associated with smoking prevalence. Interaction of residence on northern Adriatic islands and immigrant background proved to be the strongest predictor for the occurrence of allergy symptoms. This study indicated that environmental factors played a very important role in the occurrence of respiratory symptoms.

Nonspecific respiratory symptoms in general population have recently received increased attention, as respiratory diseases are associated with a significant proportion of chronic morbidity (1,2). A complex interaction between genetic background and exposure to multiple environmental stimuli is widely recognized in the etiology of many lung diseases (3). The role of genetics is being intensively investigated, using predominately genome screens and association studies. These studies have identified regions of the genome which are linked with the phenotypes of asthma and atopy (4,5), or with the occurrence of chronic obstructive pulmonary disease (COPD) (6). The most important environmental risk factor for the development of respiratory diseases is tobacco smoke inhalation, either among smokers, or non-smokers through passive smoking (7,8). Air pollution, such as exposure to organic or inorganic dusts, fumes, or gasses, is another highly prevalent environmental risk factor.

The most common chronic respiratory diseases are asthma and chronic obstructive pulmonary disease, two distinct inflammatory disorders, with different pathogenesis, clinical courses, and distinct treatment strategies (9,10). Asthma is a very common disorder, affecting people of all ages. Chronic obstructive pulmonary disease is a progressive, slow onset debilitating disease of the airways, characterized by a gradual loss of lung function and reduction in life quality (11-13). The term COPD includes chronic bronchitis, emphysema, or a combination of these conditions. It is a highly prevalent smoking-related condition, thus representing a significant economic burden to the health care system (14).

The aim of this study was to analyze the self-reported prevalence of asthma and other chronic respiratory symptoms in the population of 9 villages on Adriatic islands in Croatia, that also included immigrants to these villages. We also examined geographical variation among the studied villages in the prevalence of these symptoms and the possible relation of respiratory symptoms to

the genetic background inferred on the basis of two-generation pedigrees.

Subjects and methods

Setting

The “1001 Dalmatians” research program was launched with an aim to study multiple small isolated populations of Croatian islands that share a similar environment and lifestyle (15). The data were collected during 2002 and 2003. The details of this program are described elsewhere (16).

Subjects

This study included subjects from the “1001 Dalmatians” research program. Random samples of adult inhabitants were collected from 9 villages on the Adriatic islands of Rab (villages Banjol, Barbat, Lopar, Rab, and Supetarska Draga), Vis (Vis and Komiža), Lastovo, and Mljet, in Croatia (Figure 1). Sampling was based on computerized randomization of the most complete and accessible population registries in the villages. The total sample consisted of 454 men and 547 women. Apart from the village of residence, the sample was divided into sub-samples according to age, gender, and smoking habits. According to age, subjects were divided into three groups: ≤ 35 years, 36 to 64 years, and ≥ 65 years, and into

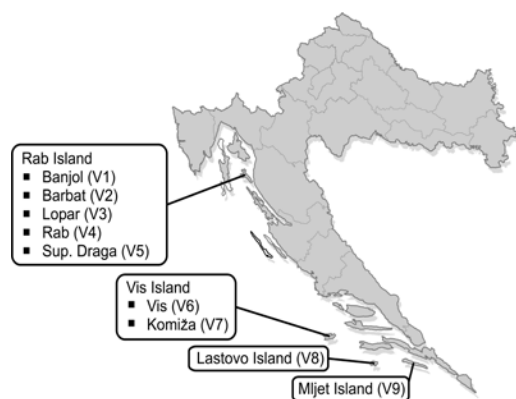


Figure 1. Geographic location of the investigated islands of Rab, Vis, Lastovo and Mljet. Immigrants in the islands originate from the mainland Croatia.

two categories according to smoking habits: non-smokers (including former smokers) and smokers. Subjects were also divided into two regional subgroups, according to geographical position of the studied island in the Adriatic Sea. Northern subgroup included subjects from the villages on the island of Rab, whereas southern subgroup included subjects from the villages on the islands of Vis, Lastovo, and Mljet.

Subjects were then classified into categories according to personal genetic history, based on the two-generation ancestral pedigrees. We classified each subject into one of the 3 categories based on their presumed individual genome-wide heterozygosity. Category "Inbred" included examinees with all four grandparents born in the studied village. Category "Outbred" included examinees with 1 to 4 grandparents born in different small villages on each island. Category "Immigrants" included examinees who had between 1 and 4 grandparents born on the mainland and (majority of examinees were also born on the mainland). Although personal genetic history is not, in strict terms, an ordered categorical variable, we could expect differences among the categories in mean individual genome-wide heterozygosity. The lowest mean value of individual genome-wide heterozygosity would be expected in the category "Inbred", which included individuals who were recently inbred, followed by the categories "Outbred" and "Immigrants."

The ethical approval for this research was obtained from appropriate research ethics committees in Croatia and Scotland. Informed written consent was obtained from all participants in the study.

Respiratory symptoms

Data on respiratory symptoms and diseases were obtained from the European Union respiratory health questionnaire (17), and World Health Organization (WHO) non-communicable diseases questionnaire (18). All subjects were asked about acute dyspnea, chronic dyspnea, airway

narrowing, acute and/or chronic cough, asthma, asthma therapy, and allergy symptoms. Data on smoking habits included the number of cigarettes smoked per day and the number of smoking years, expressed as pack-years. Pack years were counted as the number of cigarettes smoked daily, multiplied by years of smoking and divided by 20. Acute dyspnea was defined as occasional dyspnea during the last 12 months, whereas chronic dyspnea was defined as regular dyspnea in the last 12 months. Airway narrowing was recorded if the subject had the feeling of airway narrowing in the morning during the last 12 months. Acute cough was defined as occasional cough during the last 12 months and chronic cough as daily cough in the morning or during the day over the last two years. Subjects were considered to have asthma if they had difficulties in breathing and/or asthma attack with reduction in lung function. Asthma therapy was defined as taking of asthma medications on a regular basis. Allergic symptoms related to environmental (atmospheric or food) pollutants were also recorded.

Statistical analysis

Differences in frequencies of respiratory symptoms and diseases between subgroups were tested using χ^2 test. Age differences were tested by univariate analysis of variance (ANOVA). Association of respiratory symptoms and diseases with multiple risk factor variables was assessed by logistic regression analysis. Analyses were performed by SPSS 10.0 statistical package for Windows (SPSS Inc., Chicago, IL, USA), with statistical significance set at $P < 0.05$.

Results

In the initial analysis, based on descriptive methods, we investigated gender differences in respiratory symptoms. Age and prevalence of smoking were not significantly different between genders, but significant differences in smoking habits were recorded. Men smoked longer and more

Table 1. Basic characteristics (mean \pm standard deviation, range) of 1001 subjects from Croatian Adriatic villages in 2002-2003

| Characteristics | Gender | | P* |
|---|------------------------------|------------------------------|--------|
| | men (n=454) | women (n=547) | |
| Age (y) | 55.0 \pm 15.5 (18-87) | 55.0 \pm 14.1 (19-88) | 0.945 |
| Current tobacco smokers prevalence (n; %) | 103 (22.7) | 121 (22.1) | 0.445† |
| age (y) | 47.9 \pm 15.2 (18-79) | 46.2 \pm 11.7 (20-73) | 0.343 |
| smoking intensity (cigarettes/d) | 21.8 \pm 12.8 (1-50) | 16.9 \pm 10.8 (1-60) | 0.002 |
| smoking duration (y) | 25.0 \pm 13.9 (1-62) | 21.3 \pm 8.9 (3-45) | 0.016 |
| pack-years‡ | 27.4 \pm 21.8 (0.10-90.00) | 18.8 \pm 16.3 (0.25-90.00) | 0.001 |

*ANOVA.

†Fischer exact test.

‡Pack years were counted as the number of cigarettes smoked daily multiplied by years of smoking and divided by 20.

Table 2. Respiratory symptoms and diseases by gender in 1001 subjects from Croatian Adriatic villages in 2002-2003

| Respiratory symptoms | No. (%) of subjects | | P* |
|----------------------------|---------------------|---------------|-------|
| | men (n=454) | women (n=547) | |
| Acute dyspnea | 108 (23.8) | 164 (30.0) | 0.032 |
| Chronic dyspnea | 56 (12.3) | 70 (12.8) | 0.849 |
| Airway narrowing | 54 (11.9) | 79 (14.4) | 0.262 |
| Acute and/or chronic cough | 75 (16.5) | 133 (24.3) | 0.003 |
| Asthma | 5 (1.1) | 23 (4.2) | 0.003 |
| Asthma therapy | 11 (2.4) | 25 (4.6) | 0.087 |
| Allergy symptoms | 66 (14.5) | 98 (17.9) | 0.170 |

*Fischer exact test.

intensively and had higher pack-years count (Table 1). The prevalence of respiratory symptoms also exhibited a certain difference between genders (Table 2). Women had higher prevalence of all respiratory symptoms, with significantly higher findings for acute dyspnea, acute and/or chronic cough, and asthma. Among age groups, there were no significant differences in respiratory symptoms (Table 3).

Smoking was significantly associated with the occurrence of acute and chronic dyspnea in men smokers, whereas other respiratory symptoms and diseases did not show significant association with smoking (Table 4).

In the northern group of islands there was significantly higher prevalence of all respiratory symptoms and diseases, except for asthma and asthma therapy (Table 5). We recorded significant differences in personal genetic histories background for the total and regional samples. Slightly more than a half of the total sample was inbred, with higher percentage of inbred subjects in the southern group. Immigrants were equally represented in both groups (Table 6).

Multivariate logistic regression analysis was initially performed, using a full model which included gender, age, smoking status, region of residence, and genetic background (Table 7). Gender was the strongest predictor for acute and/or chronic cough and asthma, and smoking was the strongest risk factor for acute and chronic dyspnea and airway narrowing. Region was a significant risk factor for all the symptoms, except for asthma, whereas genetic background was a significant predictor only for allergy symptoms with odds ratio of 1.97 associated with being immigrant.

In the extended analysis, personal genetic histories-by-region interaction was included with

Table 3. Respiratory symptoms and diseases by gender and age groups in 1001 subjects from Croatian Adriatic villages in 2002-2003

| Respiratory symptoms | No. (%) of subjects per age group (y) | | | | | | | |
|----------------------------|---------------------------------------|---------------|-------------|-------|---------------|---------------|-------------|-------|
| | men (n=454) | | | | women (n=547) | | | |
| | <35 (n=61) | 36-64 (n=240) | >65 (n=153) | P* | <35 (n=53) | 36-64 (n=331) | >65 (n=163) | P* |
| Acute dyspnea | 8 (13.1) | 59 (24.6) | 41 (26.8) | 0.096 | 15 (28.3) | 91 (27.5) | 58 (35.6) | 0.175 |
| Chronic dyspnea | 5 (8.2) | 31 (12.9) | 20 (13.1) | 0.572 | 5 (9.4) | 43 (13.0) | 22 (13.5) | 0.733 |
| Airway narrowing | 7 (11.5) | 31 (12.9) | 16 (10.5) | 0.759 | 5 (9.4) | 45 (13.6) | 29 (17.8) | 0.253 |
| Acute and/or chronic cough | 9 (14.8) | 37 (15.4) | 29 (19.0) | 0.604 | 9 (17.0) | 85 (25.7) | 39 (23.9) | 0.387 |
| Asthma | 0 | 4 (1.7) | 1 (0.7) | 0.435 | 1 (1.9) | 14 (4.2) | 8 (4.9) | 0.635 |
| Asthma therapy | 0 | 7 (2.9) | 4 (2.6) | 0.409 | 1 (1.9) | 16 (4.8) | 8 (4.9) | 0.616 |
| Allergy symptoms | 11 (18.0) | 34 (14.2) | 21 (13.7) | 0.702 | 8 (15.1) | 68 (20.5) | 22 (13.5) | 0.135 |

* χ^2 test.

Table 4. Respiratory symptoms and diseases by gender and smoking habits in 1001 subjects from Croatian Adriatic villages in 2002-2003

| Respiratory symptoms | No. (%) of subjects | | | | | |
|----------------------------|-----------------------|-------------------|-------|-----------------------|-------------------|-------|
| | men (n = 454) | | | women (n = 547) | | |
| | non-smokers (n = 351) | smokers (n = 103) | P* | non-smokers (n = 426) | smokers (n = 121) | P* |
| Acute dyspnea | 74 (21.1) | 34 (33.0) | 0.017 | 124 (29.1) | 40 (33.1) | 0.432 |
| Chronic dyspnea | 37 (10.5) | 19 (18.4) | 0.040 | 53 (12.4) | 17 (14.0) | 0.645 |
| Airway narrowing | 37 (10.5) | 17 (16.5) | 0.119 | 58 (13.6) | 21 (17.4) | 0.307 |
| Acute and/or chronic cough | 55 (15.7) | 20 (19.4%) | 0.368 | 106 (24.9) | 27 (22.3) | 0.632 |
| Asthma | 4 (1.1) | 1 (1.0) | 0.999 | 21 (4.9) | 2 (1.7) | 0.130 |
| Asthma therapy | 10 (2.8) | 1 (1.0) | 0.469 | 22 (5.2) | 3 (2.5) | 0.322 |
| Allergy symptoms | 55 (15.7) | 11 (10.7) | 0.265 | 76 (17.8) | 22 (18.2) | 0.999 |

*Fisher exact test.

Table 5. Respiratory symptoms and diseases by region in 1001 subjects from Croatian Adriatic villages in 2002-2003

| Respiratory symptoms | No. (%) of subjects per region | | |
|----------------------------|--------------------------------|-----------------|-------|
| | South (n = 467) | North (n = 534) | P* |
| Acute dyspnea | 110 (23.6) | 162 (30.3) | 0.019 |
| Chronic dyspnea | 46 (9.9) | 80 (15.0) | 0.017 |
| Airway narrowing | 51 (10.9) | 82 (15.4) | 0.040 |
| Acute and/or chronic cough | 79 (16.9) | 129 (24.2) | 0.005 |
| Asthma and asthma therapy | 18 (3.9) | 24 (4.5) | 0.639 |
| Allergy symptoms | 55 (11.8) | 109 (20.4) | 0.001 |

*Fisher exact test.

gender, age, and smoking as predictor variables. Among the studied respiratory symptoms and diseases, the interaction was significant only for allergy symptoms (OR, 1.32; 95% CI, 1.17-1.48). Stratification to four interaction items (region-by-genetic background) indicated that the highest odds ratios were recorded in immigrant group from the northern islands (OR, 3.20), followed by outbred group from the northern islands (OR, 1.73) and immigrant groups from the southern islands (OR, 1.12). Outbred group from the southern islands exhibited the lowest odds ratio (OR, 0.74), relative to all inbred examinees.

Discussion

This study describes respiratory findings in the population of selected Croatian island villages. Interestingly, men and women exhibited the same prevalence of smoking, although men smoked longer and more frequently than women, which resulted in significantly higher pack-years count.

However, women exhibited higher prevalence of acute dyspnea, acute/chronic cough,

Table 6. Genetic background in the total sample and by region of residence in 1001 subjects from Croatian Adriatic villages in 2002-2003

| Samples | No. (%) of subjects | | |
|-------------------------|---------------------|------------|------------|
| | inbred | outbred | immigrants |
| Total sample (n = 1001) | 529 (52.8) | 382 (38.2) | 90 (9.0) |
| Regional samples: | | | |
| South (n = 467) | 267 (57.2) | 153 (32.8) | 47 (10.0) |
| North (n = 534) | 262 (49.1) | 229 (42.9) | 43 (8.0) |

*P=0.004, χ^2 test.

and asthma. Watson et al (19) demonstrated that gender plays an important role in the prevalence of COPD. In their study, despite significantly lower number of pack-years of smoking, women were more likely to report severe dyspnea than men. Similarly, French et al (20) demonstrated that women with chronic cough were more inclined to seek medical help than men, because their health-related quality of life was more adversely affected and because they were more apt to suffer from physical complaints. Hardie et al (21), who studied respiratory symptoms in men and women, showed that these symptoms occurred half as likely in men as in women, indicating that female gender was a predictor of dyspnea, current asthma, and chronic bronchitis.

Higher prevalence of respiratory symptoms was found in the villages on northern islands. Benner et al (22) investigated the prevalence of asthma and wheezing in the population of two different climate areas of Saudi Arabia and reported major differences between the coastal and inland areas. Similar study was carried out in Germany (23), reporting the significant differences among elderly inhabitants in the preva-

Table 7. Multivariate screening for predictor variables for respiratory symptoms by logistic regression analysis

| Independent variable | Predictors (OR, 95% CI)* | | | | | |
|-----------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| | acute dyspnea | chronic dyspnea | airway narrowing | acute and/or chronic cough | asthma and its therapy | allergy symptoms |
| Gender: | | | | | | |
| male (referent) | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| female | 1.42 (1.06-1.90) P=0.018 | 1.04 (0.71-1.53) P=0.846 | 1.31 (0.90-1.91) P=0.161 | 1.69 (1.23-2.33) P=0.001 | 2.00 (1.00-4.01) P=0.049 | 1.24 (0.87-1.76) P=0.231 |
| age (y) | 1.03 (1.01-1.04) P<0.001 | 1.02 (1.01-1.04) P=0.004 | 1.02 (1.00-1.03) P=0.026 | 1.01 (1.00-1.02) P=0.052 | 1.01 (0.99-1.04) P=0.269 | 0.99 (0.98-1.01) P=0.287 |
| Smoking: | | | | | | |
| nonsmokers (referent) | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| smokers | 1.98 (1.40-2.83) P<0.001 | 1.90 (1.21-2.99) P=0.006 | 1.84 (1.18-2.87) P=0.007 | 1.23 (0.83-1.81) P=0.310 | 0.51 (0.19-1.36) P=0.180 | 0.82 (0.53-1.27) P=0.370 |
| Region: | | | | | | |
| South (referent) | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| North | 1.62 (1.20-2.17) P=0.001 | 1.80 (1.21-2.68) P=0.004 | 1.63 (1.11-2.40) P=0.012 | 1.69 (1.22-2.32) P=0.001 | 1.18 (0.62-2.22) P=0.616 | 1.89 (1.32-2.71) P<0.001 |
| Genetic background: | | | | | | |
| inbred (referent) | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| outbred | 0.92 (0.68-1.25) P=0.606 | 0.95 (0.63-1.42) P=0.785 | 0.93 (0.63-1.38) P=0.723 | 0.86 (0.62-1.20) P=0.374 | 1.37 (0.69-2.72) P=0.364 | 1.23 (0.86-1.77) P=0.264 |
| immigrants | 1.02 (0.60-1.73) P=0.940 | 1.48 (0.77-2.85) P=0.238 | 0.80 (0.39-1.65) P=0.546 | 0.80 (0.44-1.43) P=0.446 | 2.41 (0.94-6.18) P=0.067 | 1.97 (1.13-3.43) P=0.017 |

*Abbreviations: OR – odds ratio; CI – confidence intervals.

lence of allergic symptoms. The authors suggested that non-specific causes related to different lifestyles played an important role in the pathogenesis of respiratory symptoms.

A possible explanation to the North-South difference would be indoor pollution. Various risk factors from the indoor environment, such as heating and cooking installations, use of a humidifier, treatment air system or ventilation systems, wooden floor, oil fume contamination, smoke, pets, and wall-to-wall carpets have been associated with the occurrence of respiratory findings (24,25). Women exposed to bio-fuel smoke and passive cigarette smoke suffered more from respiratory illnesses and had decreased pulmonary functions (26-28). Some of these factors might be variably expressed on southern and northern islands, thus causing higher prevalence of respiratory findings among inhabitants of the northern islands.

Multivariable analysis revealed that gender was significantly associated with the prevalence of acute dyspnea, and the prevalence of acute and chronic cough. Borderline significance was recorded in case of asthma and asthma therapy. Age as a predictor variable was significantly as-

sociated with acute and chronic dyspnea, and airway narrowing, whereas borderline significance was recorded for acute and chronic cough. Smoking was associated only with acute and chronic dyspnea and airway narrowing. However, the highest number of significant findings was obtained with region as a predictor variable: all findings except asthma yielded significant results. Finally, personal genetic histories were significantly associated only with the occurrence of allergy symptoms, and borderline significance was recorded with the occurrence of asthma. This is in line with the familiar occurrence of various allergy and asthma symptoms, often occurring in the subtle interaction between genetic and environmental factors (3,4).

A combination of residence on the northern islands and the immigrant background in a stepwise regression model was associated with the highest risk of respiratory allergy. This was an unexpected finding, as inbreeding is expected to act as a depressor of various physiological functions (29). A possible explanation could be related to previous environmental exposure of the immigrant group to polluted air (30). Unfortunately, it is well beyond the scope of this

study to investigate previous environmental exposure.

The main shortcoming of the present study was the use of self-reported data on the respiratory symptoms, as there might have been a various degree of recall bias. Personal genetic histories might not have been correct in all cases, as genealogical data are prone to various levels of uncertainty.

Nevertheless, this study suggests an association between gender and the respiratory symptoms and pathology. There are geographical differences in the occurrence of respiratory findings between northern and southern Adriatic islands. Various dependent variables were significantly associated with the occurrence of respiratory symptoms and diseases, but genetic effects could be only linked to the presence of allergy symptoms. Personal genetic histories were not significantly associated with occurrence of other respiratory symptoms.

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ANNOUNCEMENT

Symposium: Recent Advances in Endemic Nephropathy The Role of Toxins in an Environmental Disease

October 20-22, 2006, Zagreb, Croatia

Organized by:

University of Zagreb, School of Medicine, Zagreb, Croatia;
State University of New York at Stony Brook, NY, USA;
Croatian Center for Endemic Nephropathy, Slavonski Brod, Croatia

Chairs:

Nada Čikeš, Arthur P. Grollman, Bojan Jelaković

Main topics:

The etiology of endemic nephropathy and its associated urothelial cancer,
with an emphasis on connecting basic and clinical science with public health.
Recent studies on the role of nephrotoxic and carcinogenic agents (ochratoxin A and aristolochic acid).

Official language:

English

Contact:

Dr. Živka Dika
Department for Nephrology and Arterial Hypertension
University Hospital Center Zagreb
Kišpatičeva 12, Zagreb, Croatia
zivkadika@yahoo.co.uk
www.endemic-nephropathy.mef.hr