Case-control Study of Risk Factors for Lumbar Intervertebral Disc Herniation in Croatian Island Populations

Robert Saftić[1], Matijana Grgić[2], Barbara Ebling[3],

[1]Department of Neurosurgery, Osijek University Hospital, Osijek, Croatia
[2]Institute of Public Health, Zagreb, Croatia
[3] Osijek Health Center, Osijek, Croatia

Aim To investigate the risk factors for lumbar intervertebral disc herniation (L4/L5 or L5/S1) severe enough to require surgery of the lower spine among 9 isolated populations of Croatian islands and to evaluate predictive value, sensitivity, and specificity of a simple screening test based on the understanding of the risk factors in this population.

Methods In a sample of 1001 examinees from Croatian island populations, we identified all subjects who underwent surgery of the lower spine due to lumbar intervertebral disc herniation L4/L5 or L5/S1 and selected 4 controls matched by age, gender, and village of residence for each of them. Odds ratio was computed for the following variables: body mass index, occupation, intensity of physical labor at work, intensity of physical labor at home, smoking index, claudication index, self-assessed limitation in physical activity, level of education, socio-economic status, and family history of lumbar intervertebral disc herniation requiring surgery.

Results Comparison of 67 identified cases with 268 controls revealed the highest odds ratios (OR) for positive family history (OR 4.00; 95% confidence intervals [CI], 1.89-6.11, $P<0.001$), intensity of physical labor at work defined as "hard" (OR 2.94; 95% CI, 1.07-4.81, $P<0.001$), and body mass index of 25.7 or more (OR 2.77, 95% CI, 1.05-4.49, $P=0.002$). A simple screening test based on the presence of any two of these three criteria has 74% sensitivity and 82% specificity to detect persons who underwent lower spine surgery due to lumbar intervertebral disc herniation in the population aged 40 years or more.

Conclusion Occurrence of lumbar disk herniation severe enough to require surgery of the lower spine can be predicted using a very simple set of criteria. This type of screening could reduce the need for surgery in isolated communities through prevention within primary health care.

> **Correspondence to:**

Robert Saftić
Department of Neurosurgery
Osijek Clinical Hospital
Huttlerova 4
31000 Osijek, Croatia
robert.saftic@gmail.com

> **Received:** July 10, 2006
> **Accepted:** July 21, 2006

> **Croat Med J. 2006;47:593-600**

With the increase in life expectancy, the surgery of the lower spine became relatively frequent in most countries (1,2), and in most of the cases it is necessitated by lumbar intervertebral disc herniation (3). This problem is particularly apparent in rural and isolated human populations, in which agriculture and fishery represent the main human activities. Because the physical labor they perform requires working most of the time in bent position that particularly burdens the lower spine, they have an increased lifetime risk of the lumbar intervertebral disc herniation (4,5). This is also often associated with an inadequate access to secondary and tertiary health care in the villages, as well as to surgical treatment, which further aggravates the problem (6).

Most of the research related to spine surgery is focused on the methods and techniques of diagnostics, therapy, and rehabilitation, but hardly anything has been published on disease prevention and avoiding the need for surgery (7). What would be particularly helpful is to understand the risk factors for lumbar intervertebral disc herniation requiring surgery of the lower spine in rural and isolated human communities. A screening method for increased risk could be developed for identifying risk factors very early and thus avoiding the need for spine surgery through counseling within the primary health care and lifestyle modification.

The aim of this study was to investigate risk factors that predispose individuals to lumbar intervertebral disc herniation severe enough to warrant surgery of the lower spine (L4/L5 or L5/S1) among the isolated populations of Croatian islands, and to evaluate predictive values, sensitivity, and specificity of a simple screening test based on the understanding of the risk factors in this population.

Participants and methods

Study population

The study was conducted in 9 villages on Croatian islands of Rab, Vis, Lastovo, and Mljet. The villages were chosen in 2002 to present a range of differing ethnic histories, fluctuations in population size, accessibility of genealogical records and population collaboration in research program. The details on the selection of the villages were given by Rudan et al (8). The field study measuring health variables was performed during 2002 and 2003 by a team from the Andrija Štampar School of Public Health of the Zagreb University School of Medicine and the Institute for Anthropological Research in Zagreb, Croatia. In each of the 9 chosen villages, a random sample of 100 adult inhabitants was recruited. Sampling was based on computerized randomization of the most complete and accessible population registries in each village, which included medical records (Mljet and Lastovo islands), voting lists (Vis island), and household numbers (Rab island). Additional 101 examinees were recruited from the immigrants to all 9 villages who agreed to take part in the study, to form a genetically diverse control population that shares the same environment. 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. All field work methods and procedures were described in detail by Rudan et al (8).

Study design

The design of this study is outlined in the algorithm shown in Figure 1. First, we identified the examinees who underwent surgery of the lower spine due to lumbar intervertebral disc herniation and then we selected 4 controls matched by age, gender, and village of residence (or immigrant status) to each of the cases. We computed odds ratios for 10 selected variables that could act as potential risk factors. Based on the presence of different combination of identified risk factors with highest odds ratios, we defined 3 potential screening tests and applied them to all the examinees of 40 years or older in the sample (n = 835). We tested the validity of the screening tests in

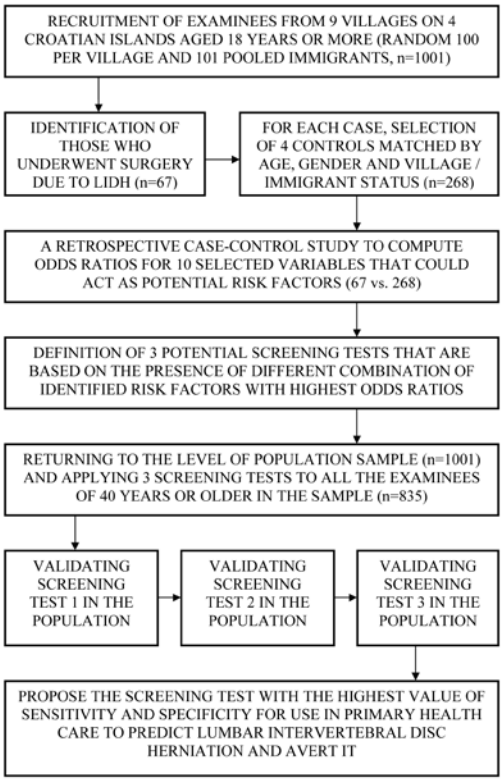

Figure 1. An algorithm showing a design of the study in nine steps.

the population and proposed the screening test with the highest value of sensitivity and specificity to predict lumbar intervertebral disc herniation in primary health care.

Identification of individuals who underwent lower spine surgery

The variable of interest was defined as having a positive history of lower spine surgery. To make this variable as specific and precisely defined as possible, we included only the examinees who underwent the surgery due to lumbar intervertebral disc herniation at the level of L4/L5 or L5/S1. A total of 9 examinees (0.9%) who underwent surgery of the lower spine due to other causes, such as degenerative changes or stenoses were not included in the analysis. Among 1001 examinees included in this study, a careful examination of medical records identified a total of 67 (6.7%) examinees who underwent the operation in secondary or tertiary health care facilities.

The decision whether a person met the case definition was made unanimously by the two visiting medical doctors (field research staff) and the local general practitioner, based on the examinations of medical histories of all the recruited examinees and a subsequent review of the documentation from the secondary or tertiary health care facility in which the surgery was performed. In all cases, medical records were detailed enough for a decision whether the surgery was performed because of lumbar intervertebral disc herniation (L4/L5 or L5/S1).

Choice of controls

For each of the 67 cases, 4 controls were chosen from the reminder of the sample of 1001 examinees. These controls were matched to cases by the village of residence/immigrant status, gender, and age (±3 years). If more than 4 appropriate controls could be chosen based on this set of criteria, then the priority was given to those controls with the age closest to the case. If there were more than 4 possible controls with the same age, gender, and village of residence as the case, then the 4 were selected using the random number tables and based on the last digit of their code number.

Choice of variables representing potential risk factors

From the information collected during the field work, we chose 10 variables that could represent potential risk factors for lumbar intervertebral disc herniation requiring lower spine surgery. The choice was based on previous reports on the role of the chosen variables as risk factors for lower back pain (5,6,9-13), or because they seemed as plausible potential risk factors among the available information collected during the field study. These included body mass index, occupation type, intensity of physical labor at work, intensity of physical labor at home, smoking index, clau-

dication index, self-assessed limitation in physical activity, level of education, socio-economic status, and family history of lower spine surgery. Age, gender, and village of residence/immigrant status were not considered as potential risk factors, as these were the variables for which matching was performed.

All variables were defined as dichotomous ordered categorical variables, so that the odds ratio could be easily computed and a simple screening test subsequently developed based on the results of the risk factor analysis. In all cases, higher category value of each variable was defined as presumably associated with an increased risk for lower spine surgery due to lumbar intervertebral disc herniation. Examinees were classified as normal if they had body mass index up to 25.6 or overweight if they had body mass index of 25.7 or more (14). Occupation type was divided into sitting or standing occupations (including clerks, lawyers, economists, tailors, waiters, cooks, salespersons, teachers, policemen, electricians, and housewives) and occupations involving hard physical activity (agriculture workers, soldiers, construction workers, mechanics, and fishermen). All occupations were recorded as those before eventual lower spine surgery. Three more variables were derived from the standard WHO questionnaire for chronic non-communicable diseases (15): intensity of physical labor at work (defined as sitting, easy, or moderate vs hard), intensity of physical labor at home (defined as sitting, easy, or moderate vs hard), and smoking index (defined as non-smokers vs smokers or former smokers). Claudication index was based on the standard WHO claudication questionnaire (16). It is a score ranging between 0 (maximum health) and 8 (very poor circulation flow and clogged blood vessels). The variable was defined categorically as a value of 0-3 vs value of 4-8.

The next variable was self-assessment of limitations in physical activity of bending from the SF-36 questionnaire (17), defined categorically as "no limitation or small limitation" vs "considerable limitation". The level of education was defined as "no education beyond elementary (8 grades completed)" vs "more than elementary (9 or more grades)". Socio-economic status was defined according to the questionnaire tailored specially for the examined populations. The questionnaire assessed the possession of material goods and technical appliances in the household (ie, a car, a washing machine/dryer, a color TV set, and duration of their possession). The examinees with the score of 0-2 were classified as less wealthy, whereas those with the score of 3-4 were classified as more wealthy. Finally, a positive family history was defined as having a parent who underwent spine surgery.

Statistical analysis

We calculated the odds ratio for each of the 10 potential risk factors and to determine its statistical significance. The latter was performed using a χ^2 test for independent samples with one degree of freedom.

Sensitivity (Se), specificity (Sp), positive predictive value (PPV), and negative predictive value (NPV) of the proposed screening method were also calculated.

Results

The study involved 67 cases who underwent surgery for lumbar intervertebral disc herniation and 268 controls (4 controls for each case). The controls were matched by age, gender, and village of residence to the cases. There were 4 investigated variables that reached the statistical significance (Table 1): positive family history of lower spine surgery (OR 4.00, $P<0.001$), self-perceived intensity of physical labor at work defined as "hard" (OR 2.94, $P=0.001$), body mass index 25.7 or more (OR 2.77, $P=0.002$), and occupation as agriculture workers, soldiers, construction workers, mechanics, or fishermen (OR 1.94, $P=0.038$).

Table 1. Odds ratios for investigated risk factors for lower spine surgery in Croatian island populations*

Risk factor	Cases (n = 67)	Controls (n = 268)	Odds ratio (95%CI)	χ^2_1	*P*
Body mass index 25.7 or more	55 (82.1%)	167 (62.3%)	2.77 (1.05-4.49)	9.38	0.002
Occupation: agriculture workers, soldiers, construction workers, mechanics or fishermen	22 (32.8%)	54 (20.1%)	1.94 (0.13-3.75)	4.92	0.027
Intensity of physical labor at work: "hard"	21 (31.3%)	36 (13.4%)	2.94 (1.07-4.81)	12.18	0.000
Intensity of physical labor at home: "hard"	5 (7.5%)	13 (5.0%)	1.58 (0.00-4.49)	0.72	0.396
Smokers or former smokers	36 (53.7%)	145 (54.1%)	0.99 (0.00-2.70)	0.00	1.000
Claudication index 4 or more†	12 (17.9%)	48 (17.9%)	1.00 (0.00-3.01)	0.00	1.000
Self-assessed limitation in physical activity: "considerable"‡	16 (23.9%)	39 (14.6%)	1.84 (0.00-3.77)	3.40	0.065
Level of education: "8 grades completed or less"	20 (29.9%)	82 (30.6%)	0.97 (0.00-2.76)	0.01	0.920
Socio-economic status index value 0-2§	23 (34.3%)	82 (30.6%)	1.19 (0.00-2.95)	0.35	0.554
Positive family history of spine surgery	15 (22.4%)	18 (6.7%)	4.00 (1.89-6.11)	14.82	0.000

*A total of 67 cases underwent surgery and were matched by age, gender, and village of residence/immigrant status to 268 healthy controls.
†Based on WHO claudication questionnaire ref. 16.
‡Based on SF36 questionnaire, ref. 17.
§Based on a simple questionnaire tailored for this population, ref. 8.

Table 2. Validity of the screening test based on the three most significant identified risk factors, when applied in the larger sample of the examinees aged 40 y or more from 9 studied villages (n = 835)*

Validity parameters	No. (%) of examinees
No. of examinees in the larger sample aged 40 y or more	835 (100.0)
No. of examinees who underwent lower spine surgery (L4/L5 or L5/S1)	58 (6.5)
No. of examinees who did not undergo lower spine surgery (L4/L5 or L5/S1)	777 (93.5)
Validity of screening test based on the presence of all 3 risk factors:	
underwent surgery, test positive	18 (2.2)
underwent surgery, test negative	40 (4.8)
no surgery, test positive	7 (0.8)
no surgery, test negative	770 (92.2)
sensitivity	31
specificity	99
positive predictive value	72
negative predictive value	95
Validity of screening test based on the presence of at least 2 of 3 risk factors:	
underwent surgery, test positive	43 (5.1)
underwent surgery, test negative	15 (1.8)
no surgery, test positive	141 (16.9)
no surgery, test negative	636 (76.2)
sensitivity	74
specificity	82
positive predictive value	23
negative predictive value	98
Validity of screening test based on the presence of at least 1 of 3 risk factors:	
underwent surgery, test positive	55 (6.6)
underwent surgery, test negative	3 (0.4)
no surgery, test positive	628 (75.2)
no surgery, test negative	149 (17.8%)
sensitivity	95
specificity	19
positive predictive value	8
negative predictive value	98

*Body mass index 25.7 or more, intensity of physical labor at work defined as "hard," and positive family history of spine surgery.

Based on this set of identified risk factors, we investigated the validity of a simple screening test for identifying the individuals who would likely develop lumbar intervertebral disc herniation (L4/L5 or L5/S1) requiring lower spine surgery. We used only the first three identified risk factors: family history of lower spine surgery, self-perceived intensity of physical labor at work, and body mass index 25.7 or more. The occupation type was left out because it was likely to be dependent from self-perceived intensity of physical labor at work, which showed much higher odds ratio and statistical significance. Therefore, we only used the three remaining and mutually largely independent variables to develop the screening test.

The validity of three different variants of the screening test was tested among the examinees in the larger sample from 9 villages, aged 40 years or more (n = 835, Table 2). The first variant of the test, which required the presence of all 3 risk factors to predict the history of lower spine surgery, had a very high specificity (99%), but rather low sensitivity (31%), with the positive predictive value of 72% and negative predictive value of 95%. Therefore, we decided to relax the criteria and require only the presence of any 2 of the 3 identified risk factors, as the second variant of the screening test (Table 2). This decreased the specificity of the test to still acceptable 82%, but improved the sensitivity to 74%. Further relaxation of the criteria (requiring only one of the three risk factors), which is the third variant of the test (Table 2), increased the sensitivity to 95%, but reduced the specificity to only 19%.

Discussion

This study identified several risk factors for lumbar intervertebral disc herniation requiring surgery of the lower spine in Croatian island populations. The prevalence of the history of the lower spine surgery in a random sample of 1001 examinees from 9 villages was 6.7%, and the comparison of 67 cases with 268 controls revealed that the highest odds ratios were associated with positive family history of lower spine surgery, self-perceived intensity of physical labor at work defined as "hard," and body mass index of 25.7 or more. These three risk factors were reasonably independent from each other. Whereas the first captures hereditary factors, the second is entirely environmental, and the third one results from the combination of genetic and environmental factors. The high importance of family history found in this study emphasizes the suitability of isolated populations to detect such effects, as their reduced genetic and environmental diversity enables detecting these effects more easily than in the outbred diverse general population (18-20).

The study also convincingly showed that factors such as smoking, socio-economic status, level of education, cardiovascular morbidity (assessed through claudication index), and intensity of physical work at home did not contribute significantly to the risk of lumbar intervertebral disc herniation in these populations. For most of these variables, the prevalence of risk exposure was almost exactly the same among the cases and the controls, which in a way controls for confounding effects and implies that the sampling was adequately performed and that the observed positive results of this study are likely to be genuine.

Based on identified risk factors, a simple screening test was devised to assist primary care workers in isolated human populations to identify persons in the community who would be at risk of lumbar intervertebral disc herniation requiring lower spine surgery. A possible concern over the suggested screening test is that screening methods are mainly useful when an intervention is available to reverse the risk. In such individuals, preventive activities (such as exercises for the lumbar spine and lifestyle change) could then be introduced to delay or defer the need for the surgery (3). We tested the validity of screening tests based on the presence of 3, 2, or 1 risk factor. We showed that a very simple screening test, based on presence of any two of these three risk factors, has a sensitivity of 74% and specificity of 82% to detect persons who underwent lower spine surgery because of lumbar intervertebral disc herniation in the population aged 40 years or more. This test could be very useful, as it allows identification of a large majority of the individuals who will develop lumbar intervertebral disc herniation requiring surgery and applying indicated interventions to prevent the need for surgery, without involving many of the individuals who would never have lumbar intervertebral disc herniation.

Effective screening test is of particular public health importance in rural and isolated populations with limited access to secondary and tertiary health care. The incidence of the problem peaks at fifth decade of life (6), with increasing likelihood of the rupture of the posterior ligaments of the spine and herniation of intervertebral disc (21). The problem decreases with age, as the turgor and elasticity of intervertebral disc are decreased among the elderly (22).

A number of factors could have interfered with the validity of our results. We excluded the examinees who underwent surgery of the lower spine due to other causes (eg, degenerative changes, stenoses) from the cases, although they reflected mere continuum of degenerative spinal disease with disk height changes, herniation, microinstability, ligamentous hypertrophy, stenosis, and others. However, inclusion of these early changes would greatly reduce the specificity of the case definition and lead to numerous misclassifications. We wanted to investigate only the most severe end of the spectrum in order to reduce misclassification as a potential bias. In addition, the

most severe cases were also more likely to reveal the true underlying risk factors and were also of the greatest practical significance in considering a preventive public health action.

Another possible problem is more general relevance and applicability of the findings in our chosen population (rural, isolated). This selection was based on the assumption that hard physical labor underlies much of the episodes of lumbar intervertebral disc herniation at the level of population. We did so despite of the "similarity" in the prevalence of lumbar intervertebral disc herniation surgery in urban and rural areas, which is likely to be mainly due to a larger number of surgeons available and larger number of surgeries generally performed in urban areas. Therefore, the indication for surgery in urban areas is likely to be more permissive than in rural areas. This is precisely why we chose to undertake our study in the isolated rural area, because the prevalence of the problem is certainly considerably greater there due to their harder physical labor in agriculture and fishery and maintaining difficult bending positions for long periods of time, in combination with the low accessibility of tertiary sector health care. So, it is more useful to have a screening method in rural rather than in urban areas, and the results of our study are not invalidated by the potential confounding factor of health care accessibility in any way.

Besides those general concerns, there are also some more specific ones. A statistically significant investigated variable was based on self-assessment (the intensity of physical labor), and there could be a variation in self-perceived intensity of their work. Furthermore, the second important predictor of lumbar intervertebral disc herniation requiring surgery – positive family history of lower spine surgery, could also reflect shared environment as well as shared genetics, as there may be risky behaviors within a family which were not directly investigated. As for the third significant risk factor (body mass index), a possibility of reverse causality should be considered, ie, that people gained weight and developed higher body mass index as a consequence of restricted activity and altered lifestyle caused by severe lower spinal problems and the surgery. Similar problem does not extend to the fourth significant risk factor, occupation type, as all occupations were recorded as those before surgery.

Our findings are in line with the results of the previous studies of risk factors for lumbar intervertebral disc herniation. It is known that the incidence is greater in men, 12.8 per 1000, as opposed to 6.6 per 1000 in women after the age of 28 years (4). Body mass index was already considered an important risk factor, although predominantly among men (3). Hard physical work involving lifting and carrying heavy objects and bending was also proposed as a risk factor (5). Injuries of the spine contribute to small structural damage and acceleration of degenerative changes, which increases the risk in persons who had spinal injury (11). The effect of smoking is controversial, and this study supports the previous studies in which the effect was not noted (13). The role of genetic factors was also confirmed in twin studies, where it was assessed that genetic factors contributed at least 20% to the incidence of the disorder (23).

This study showed that lower intervertebral disc herniation requiring surgical treatment could be predicted in advance to some extent, using a very simple set of criteria. These criteria rely on 3 identified risk factors (positive family history, intensity of physical labor at work defined as "hard", and body mass index 25.7 or more), and this screening could reduce the need for surgery in isolated communities through prevention within primary health care.

Acknowledgments

The study was partially supported through the grants from the Ministry of Science, Education and Sport of the Republic of Croatia (No. 0108330), and the grants from The British Council, The Wellcome Trust, The Royal Society, and Medical Research Council. The authors collectively thank to very large number of individu-

als (medical students of the Zagreb University School of Medicine, Croatia; local general practitioners and nurses in study populations; the employees of several other Croatian institutions, including but not limited to the University of Rijeka and Split, Croatia; Croatian Institute of Public Health; Institutes of Public Health in Split and Dubrovnik, Croatia; and the Institute for Anthropological Research in Zagreb, Croatia) for their individual help in planning and carrying out the field work related to the project.

References

1 Christensen FB, Bunger C. Stabilisation surgery for chronic low back pain: indications, surgical procedures, and outcome. Scand J Rheumatol. 2004;33:210-7. Medline:15370714

2 Kwon BK, Vaccaro AR, Grauer JN, Beiner J. Indications, techniques, and outcomes of posterior surgery for chronic low back pain. Orthop Clin North Am. 2003;34:297-308. Medline:12914269

3 Battie MC, Videman T, Parent E. Lumbar disc degeneration: epidemiology and genetic influences. Spine. 2004;29:2679-90. Medline:15564917

4 Zitting P, Rantakallio P, Vanharanta H. Cumulative incidence of lumbar disc diseases leading to hospitalization up to the age of 28 years. Spine. 1998;23:2337-43. Medline:9820915

5 Magora A. Investigation of the relation between low back pain and occupation. IV. Physical requirements: bending, rotation, reaching and sudden maximal effort. Scand J Rehabil Med. 1973;5:186-90. Medline:4272614

6 Kelsey JL, Ostfeld AM. Demographic characteristics of persons with acute herniated lumbar intervertebral disc. J Chronic Dis. 1975;28:37-50. Medline:1110263

7 Weiss HR, Weiss G, Schaar HJ. Conservative management in patients with scoliosis – does it reduce the incidence of surgery? Stud Health Technol Inform. 2002;91:342-7. Medline:15457752

8 Rudan I, Biloglav Z, Vorko-Jovic **A, Kujundzic-Tiljak** M, Stevanovic **R, Ropac D, et al. Effects of inbreeding,** endogamy, genetic admixture, and outbreeding on human health: a "1001 Dalmatians" study. Croat Med J. 2006;47:601-10. Medline: 16909458

9 Kelsey JL, Hardy RJ. Driving of motor vehicles as a risk factor for acute herniated lumbar intervertebral disc. Am J Epidemiol. 1975;102:63-73. Medline:1155438

10 Riihimaki H, Viikari-Juntura E, Moneta G, Kuha J, Videman T, Tola S. Incidence of sciatic pain among men in machine operating, dynamic physical work, and sedentary work. A three-year follow-up. Spine. 1994;19:138-42. Medline:8153819

11 Riihimaki H, Wickstrom G, Hanninen K, Luopajarvi T. Predictors of sciatic pain among concrete reinforcement workers and house painters – a five-year follow-up. Scand J Work Environ Health. 1989;15:415-23. Medline:2533392

12 Manninen P, Riihimak H, Heliovaara M. Incidence and risk factors of low-back pain in middle-aged farmers. Occup Med (Lond). 1995;45:141-6. Medline:7605976

13 Heliovaara M, Knekt P, Aromaa A. Incidence and risk factors of herniated lumbar intervertebral disc or sciatica leading to hospitalization. J Chronic Dis. 1987;40:251-8. Medline:3818881

14 Weiner JS, Lourie JA. Human biology – a guide to field methods. Oxford: Blackwell; 1969.

15 Pardell H, Roure E, Drygas W, Morava E, Nussel E, Puska P, et al. East-west differences in reported preventive practices. A comparative study of six European areas of the WHO-CINDI programme. Eur J Public Health. 2001;11:393-6. Medline:11766479

16 Leng GC, Fowkes FG. The Edinburgh Claudication Questionnaire: an improved version of the WHO/Rose Questionnaire for use in epidemiological surveys. J Clin Epidemiol. 1992;45:1101-9. Medline:1474406

17 Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992;30:473-83. Medline:1593914

18 Rudan I, Campbell H, Rudan P. Genetic epidemiological studies of eastern Adriatic island isolates, Croatia: objectives and strategies. Coll Antropol. 1999;23:531-46. Medline:10646227

19 Rudan I, Rudan D, Campbell H, Carothers A, Wright A, Smolej-Narancic N, et al. Inbreeding and risk of late onset complex disease. J Med Genet. 2003;40:925-32. Medline:14684692

20 Rudan I, Smolej-Narancic N, Campbell H, Carothers A, Wright A, Janicijevic B, et al. Inbreeding and the genetic complexity of human hypertension. Genetics. 2003;163:1011-21. Medline:12663539

21 Adams MA, Hutton WC. Prolapsed intervertebral disc. A hyperflexion injury 1981 Volvo Award in Basic Science. Spine. 1982;7:184-91. Medline:7112236

22 Spangfort EV. The lumbar disc herniation. A computer-aided analysis of 2,504 operations. Acta Orthop Scand Suppl. 1972;142:1-95. Medline:4516334

23 Heikkila JK, Koskenvuo M, Heliovaara M, Kurppa K, Riihimaki H, Heikkila K, et al. Genetic and environmental factors in sciatica. Evidence from a nationwide panel of 9365 adult twin pairs. Ann Med. 1989;21:393-8. Medline:2605032