THESES FOR THE DEGREE OF DOCTOR OF PHYLOSOPHY (PhD)

Application of biostatistical methods in population level health risk assessment

LÁSZLÓ KARDOS MD MSc

Tutor: Róza Ádány MD DSc

UNIVERSITY OF DEBRECEN
MEDICAL AND HEALTH SCIENCE CENTER
SCHOOL OF PUBLIC HEALTH

DEBRECEN, 2005

1 Introduction

1.1 The role and significance of biostatistical methods in health related scientific research

Along the course of activities in human medicine, an immense amount of valuable data is generated, the correct analysis and interpretation of which is probably the most fundamental prerequisite, and also incentive, for the development of public health and medical service. It is modern epidemiology that deals as a discipline with the collection, process, analysis, and interpretation of numerical data on health, disease, and factors influencing them, with the ultimate objective of coming to substantiated conclusions of utility in health and public health service planning and evaluation. Health science biostatistics has the primary task of providing methodological support to epidemiology and other disciplines. The application of biostatistics is an indispensable component of epidemiological research and health policy based on results thereof. A discipline of limited recognition and subject sometimes to neglect in everyday epidemiological practice due to lack of preparedness in Hungary, biostatistics is gradually gaining space parallel with the establishment of modern public health in this country.

2 Objectives

This thesis is an overview of the biostatistical aspects of the research practice at the School of Public Health, University of Debrecen; using typical research projects and results thereof, it demonstrates how the application of biostatistical methods helps turn raw masses of data into comprehensive messages that can be utilized in decision making in general and local health policy. It also illustrates the added benefit of analysis based on advanced methods as compared to conventional approaches.

By introducing the use of biostatistical tools through methodological developments in mortality analysis, methods, results, and possible interpretations of a nationwide study of the association between premature mortality from suicide and standard of living will be presented.

Another mortality study carried out on the settlement level in one of Hungary's counties for a more specific reason: a suspect clustering of cancer deaths, an overview will be given of the advantages and importance of Bayesian smoothing of unstable mortality measures, and of geographical information systems.

A third mortality analysis involved a hospital's workforce with elevated cancer mortality and a history of occupational chemical exposure at the workplace. The objective of the study was to assess the level of statistical evidence for the unusual accumulation of deaths, without regard to the presence or absence of a causal link to chemical exposure.

In addition to mortality analyses, a stronger and stronger highlight of our research portfolio is the analysis of morbidity. The country's first general practitioner based morbidity registration system, the General Practitioners'

Morbidity Sentinel Stations Program, commenced operation in 1998 as a joint initiative by the School of Public Health and Hungary's public health authority. Biostatistical aspects of the requirements for operating the system, processing the data, making them interpretable, will be demonstrated.

3 Data and methods

3.1 The application and advantages of Poisson regression

Conventional mortality analyses are based on direct or indirect standardization, a method that partially or completely removes the confounding effect of age, but is incapable on its own to remove confounding by other factors, and – in the case of the indirect method – is even unsuitable for the immediate comparison of mortality between several study populations. In addition to its other benefits, Poisson regression is capable of eliminating these problems. Its application and advantages will be demonstrated via the analysis of a study on the association between Hungary's suicide mortality and standard of living over the period 1994-1999.

Standardized death rates from suicide of Hungarians exceeded the European Union average about three times in men and more than twice in women during 1970-1999. Possible explanations for the phenomenon include the effect of socioeconomic factors, which can be modeled in a framework of per capita annual gross domestic product (GDP) in people's home counties and premature mortality from suicide. Conventional methods are suitable for the calculation of county level suicide mortality figures relative to the national average for visualization along with a map of county GDPs, another possibility being a descriptive comparison of mortality differences relative to the national level between categories of county GDP. To break down these limitations and quantify the potential relationship in the form of an association measure, we examined the connection between GDP and mortality using Poisson regression analysis. The objective of the analysis was to estimate the relative change in mortality associated with a unit increase of GDP. The models were adjusted for age and calendar year separately in 15 to 64-year-old men and women.

3.2 Geographical information system based analysis of cancer mortality in Fejér County using empirical Bayes estimates

General practitioners of some settlements around lake Velencei, Fejér County, noted unusual developments in the mortality of citizens in their service area in the 1990s: a suspect rise in the number of cases of cancer deaths was observed. It became a priority to judge whether the accumulation can be reasonably considered to be beyond random fluctuation, and we joined forces with the county office of the national public health authority to design and execute an epidemiological study to clarify the question. Along with an approach based on numerical indicators, the tools of geographical information systems were put to use in the analysis. The study was about the mortality during 1994-1999 of Fejér County inhabitants aged 15 to 64. Mortality differences relative to the national average were examined in deaths from malignancies of the digestive system, other cancers, and non-malignant diseases. Settlement level standardized mortality ratios (SMR) were calculated using conventional methods. A smoothing technique based on Bayesian statistical theory was used to adjust extreme ratios found usually in small settlements. To render the mortality situation visually, settlement specific adjusted SMR data were used as estimation points for the fitting of a continuous county surface, which was mapped.

3.3 Cancer mortality in hospital workers potentially exposed to ethylene oxide

Hungarian authors in the mid 1990s reported a conspicuous accumulation of cancer cases among workers of the county hospital in Eger, Heves County. Of candidate explanation theories for the phenomenon, attention became focused on an ethylene oxide (ETO) gas sterilizer operated on hospital premises in violation of safety regulations. In our study, we analyzed cancer mortality in workers of the hospital to assess statistical support for the presumed rise in incidence.

Before starting the analysis, raw data had to be subjected to a multiple step conversion procedure into a record arrangement that, on one hand, is suitable both in terms of structure and detail for the calculation of mortality indexes without losses to the original information content, and, on the other hand, appreciates the fact that cancer cases and deaths due to occupational exposure may appear years, even decades after the end of employment. In practice, this meant that in addition to the existing workforce at any time, previous employees too had to be considered at risk all along.

We used indirect standardization in the mortality analysis for the period 1987-1999 involving women employees only. National, Eger City, and Heves County mortality were all used in the calculation of standardized mortality ratios and their exact Poisson confidence intervals.

3.4 Population level analysis of morbidity: the General Practitioners' Morbidity Sentinel Stations Program

Launched in 1998 with the participation of 74 general practitioners (GP) in four Hungarian counties (Győr-Moson-Sopron, Hajdú-Bihar, Szabolcs-Szatmár-Bereg, Zala), the county offices of the national public health authority, and the School of Public Health, the General Practitioners' Morbidity Sentinel Stations Program is carried on to date as the country's first sentinel station based GP-level morbidity registration system. Its objective is the prevalence and incidence monitoring of chronic non-infective diseases of the highest public health importance. The first level of the collection of morbidity data is the GPs acting as sentinels, who report the data to their county offices of the national public health authority, where a preliminary processing takes place before forwarding to the School of Public Health. It is a strategic intention of the program to separate inventive intellectual work (design, interpretation of results, communication of findings, coding software, etc) from repetitive, algorithmic tasks, to fully automate the latter, thereby liberating human capacities for creative activity. The highly protocolized nature of the study including strict regulations of data structure makes this goal attainable. Writing code in the high level programming language of the professional statistical and data processing package we use, we developed automatic computer software systems that render specifically targeted analysis output based on the latest updates of raw data. Such targets include the identification of extremely high or low disease incidences for direct quality control, the calculation of age specific county average prevalences or incidences in the disease groups, or the preparation of practice specific feedback to participating general practitioners.

4 Results

4.1 The application and advantages of Poisson regression

Using conventional methods to examine the association between GDP and differences relative to national average in suicide mortality or mortality from other causes, a trend of decrease in SMR is seen with the increase of GDP in men, reflecting more favorable mortality situations in counties with higher standards of living. The phenomenon is more accentuated in suicide mortality. At the same time, no similar association is observed in women: there is no causal group in which the mortality ratios change along an unbroken trend with GDP categories. In map-based comparisons, it is men's suicide mortality that has the areas of the highest levels most prominently overlapping with counties of low economic output, and vice versa. The association suggested by the women's suicide mortality map with county GDP is far less obvious. In other causes of death, differences of mortality from the national average are less wide, their approximate match with the GDP map is seen to some extent in men, much less in women.

The set of relationships recovered by separate Poisson regression modeling in suicide and other cause mortality indicated that increase in standard of living is associated with favorable changes of mortality in both causal groups, but this relationship is greater in effect size in itself in suicide mortality, and also gets significantly steeper and steeper as age advances. A doubling of GDP entails a reduction of other cause mortality to 84% regardless of age, and of suicide mortality to 71% in the youngest age group, and progressively to even less in older age groups – to less than 63% in the oldest. The relative difference in mortality between the two extremes of the GDP range is about 70% in suicide and 40% in other causes. The differences are strongly significant, the confidence intervals are narrow, indicating similar interpretations over their entire ranges. In

women, however, as a striking contrast to the above, neither suicide nor other cause mortality seems to be associated with county GDP. This is unequivocally true in all age groups.

4.2 Geographical information system based analysis of cancer mortality in Fejér County using empirical Bayes estimates

Judging by mortality maps, an accumulation of deaths due to cancers of the digestive system in males aged 15 to 64 is substantiated in the area north and east of lake Velencei. The suspicion of accumulation was raised before the study primarily in the settlement of Kápolnásnyék. Through mapping, however, the involvement of the immediate neighboring settlements Pázmánd, Vereb, Vértesacsa is made evident, even though only a part of this contiguous area would be identified by a conventional method as having significantly elevated mortality. Deaths from cancers of the digestive system are about 1.5 times to twice as common as the national average. Other differences worthy of attention are seen in the greater part of the county's southern half, and also in the northwest sector of the Mór area. An almost contiguous territory of high mortality spreading from the Mór area through the Székesfehérvár area down south and reaching up northeast to include the Dunaújváros area is also observed to overlap with settlements identified by conventional methods as having significantly high mortality to a limited extent only.

4.3 Cancer mortality in hospital workers potentially exposed to ethylene oxide

Individual records from the original data collection were converted into an aggregate database containing mid-year numbers, national, Heves County, or Eger city age specific death rates, observed and expected numbers of cases (the latter calculated as the product of mid-year numbers and death rates), in all strata defined by calendar years and five-year age groups of women ever employed at the hospital's pediatric ward during the time of potential ETO exposure.

After a summation of observed and expected numbers of cases, the division of the former by the latter yields the standardized mortality ratio, a measure of risk in the study subjects relative to the reference population. Whichever of the three different reference populations is used in the analysis, the SMRs calculated over a 13-year period for the female workforce of the hospital's pediatric ward indicate a significantly elevated level (SMR: 251 to 273%) of cancer mortality. The confidence intervals are fairly wide but suggest a higher incidence of cancers even at their lowest extremes.

4.4 Population level analysis of morbidity: the General Practitioners' Morbidity Sentinel Stations Program

Thanks to continuous development efforts, algorithmic tasks in the program are now performed by a wide range of multifunctional software routines. The full explanation of their operations or the listing of source codes is not possible here, instead, some typical examples of numerical and graphical output produced by the system will be used to demonstrate its importance. From what is initially an incomprehensive mass of data unsuitable for conclusions due to its sheer volume, derived output ready for immediate interpretation or further process (graphing etc) is generated through restructuring and collapsing, merging with information from other counties, and various other steps. As an example, automatically generated tables help investigators identify and compare age group specific prevalence and incidence estimates in monitored diseases over participating counties in males and females.

Result from the data collection program can supply valuable information to public health policy and practice. At the same time, coordinators find it very important to feed results back to the primary sources of data. All participating GPs obtain annually the graphical summaries of latest incidence estimates pertinent to their own practices in a format facilitating comparison to home and other county averages. These also are generated by the School of Public Health statistical workstation using software routines developed by us specifically for the task without human interference and at minimal human resource costs.

5 Conclusions

In the previous chapters, an overview was given about examples of the application of biostatistical methods in such important components of epidemiological research as data analysis, evaluation of statistical support for research hypotheses, and algorithmic process of high volumes of data.

The multiple regression method used in the study of the association between premature suicide mortality and standard of living yielded association measures and, for ease of interpretation, confidence intervals, while conventional methods calculate stratum specific indexes only, the comparison of which can lead to no more than hypotheses as any ratios between them will be rendered uncertain due to potential confounding by differences of age distribution between compared populations. These limitations are not relieved by the fact that stratum specific SMRs have confidence intervals because those represent the uncertainty around estimates of differences of local mortality from the national average, and not that around an association measure between outcome and the factor defining the strata. Conventional methods too make possible the construction of stratified output of differences of men's suicide mortality relative to national average detailed for every ten-year age group and any desired number of GDP categories, but this approach often leads to strata so thin that even otherwise existing, strong associations might prove difficult to prove statistically.

One should bear in mind also that these preliminary studies would be ill-suited as means of finding proof of causal links between exposure and outcome. Even in light of the powerful statistical support for the association, jumping to the conclusion that drawing deprived counties' standards of living nearer to that of leading ones will solve Hungary's suicide problem would be wholly unsubstantiated. We cannot even indisputably say, though it is suggested by the

results, that men are more sensitive in terms of suicide to low standards of living and destitute socioeconomic conditions than women. It cannot be excluded that macroeconomic indicators such as GDP are only proxy variables of factors in true causal links to suicide mortality. The clarification of this issue requires further studies in analytical epidemiology, and the question why this proxy behavior is present so prominently in men but not at all in women is likewise subject to further investigation.

The advantages of advanced methods, however, do not mean that simpler approaches should be forgotten and avoided. Simple standardized mortality ratios in the Eger hospital cancer deaths investigation adequately answered the research question with no need for regression analysis – it became evident that it would not be plausible to attribute the presumed clustering of cases to the work of chance. In the absence of factors that could have been used as explanatory variables, such as level of ETO exposure (now hopeless to recover retrospectively), Poisson regression would have lead to results identical with those delivered by the traditional procedure.

The preliminary exploration in Fejér County also lacked any explanatory variable (environmental exposure, lifestyle and other socioeconomic factors) to warrant the use of multiple regression modeling for the evaluation of its effect. It is advantageous in terms of further investigations in this setting that there exist methods for the identification of spatial clusters capable both of Bayesian smoothing of unstable mortality estimates and of adjustment for confounding variables. The study period can be extended to the years beyond 1999 subject to availability of data. The inclusion of neighboring counties is called for simply by the presence of clusters seen close to the county's borders. The approach used in the analysis is not specific to Fejér County, and similar accumulations of deaths are most probably present in various disease groups in other territories of

the country. These methods can be the basis for explorative studies on the county and area level, the compilation of which can be regarded as a comprehensive, demonstrative national mortality mapping effort based on contemporary methodology.

In addition to a diverse set of epidemiological conclusions from the morbidity registration program, it can be stated, from a biostatistical point of view, that the automation of data processing by statistical programming saves a lot of time and effort, thereby making possible the generation of output that would not normally be considered essential in a study. Data monitoring programs in which the flow of information is one-way from collectors to analysts are not uncommon. This is not the case in the General Practitioners' Morbidity Sentinel Stations Program, and for participating GPs – as evident from their reactions – the epidemiological summary information they obtain of their own practices is of crucial importance. This is true even in practices with fully computer based management.

Considering the international history and contemporary reputation of biostatistics, the recent rapid development of epidemiology in Hungary, and the public health challenges faced by the country, the intuition that a period of rising esteem for the discipline is imminent seems well substantiated. Nevertheless, no graduate level biostatistical training is currently offered by any university in Hungary – those in the country with degrees all obtained them abroad. One of the most important medium term tasks of our public health education system is to establish the conditions for the tuition of the requisite number of professionals, that is, to prepare for the launch of biostatistical education in Hungary.

6 Appendix

6.1 List of publications fundamental to the theses

Kardos L, Széles Gy, Gombkötő Gy, Szeremi M, Tompa A, Ádány R: Cancer deaths among hospital staff potentially exposed to ethylene oxide: an epidemiological analysis. Environ Mol Mutagen 42:59-60, 2003

IF: 2,000

Széles Gy, Vokó Z, Jenei T, Kardos L, Bajtay A, Papp E, Pásti G, Kósa Zs, Molnár I, Lun K, Ádány R. A preliminary evaluation of a health monitoring program in Hungary. Eur J Public Health, in press

IF: 1,281

Kardos L, Papp Z, V Hajdú P, Ferencz P, Ádány R. Spatial analysis of cancer mortality using empirical Bayes estimates in Fejer County, Hungary (submitted for publication in Magyar Onkológia)

6.2 Other publications

Treszl A, Ádány R, Rákosy Z, Kardos L, Bégány A, Gilde K, Balázs M. Extra copies of c-myc are more pronounced in nodular melanomas than in superficial spreading melanomas as revealed by fluorescence in situ hybridisation. Cytometry 60B:37-46, 2004

IF: 2,095

Kardos L, Széles Gy, V Hajdú P, Bordás I, Ádány R. Morbidity and mortality of the diseases of the digestive system in Hungary. In: Ádány R (ed): Hungary's health at the turn of the century. Medicina, Budapest, 2003.

Széles Gy, Vokó Z, Jenei T, Kardos L, Bajtay A, Hamburger I, Kósa Zs, Pénzes M, Tokár Zs, Paul Zs, Papp E, Menyhárt I, Parragi K, Horváth G, Ertner S, Esenszki B, Fodor M, Molnár I, Lun K, Ádány R. Design, launch and management of a general practitioners' morbidity data collection program in Hungary. The prevalence of hypertension, diabetes mellitus and liver cirrhosis. Orv Hetil 144:1521-9, 2003

Nagygyörgy E, Kardos L, Széles Gy, V Hajdú P, Ádány R. Local differences of mortality in Borsod-Abaúj-Zemplén County, 1994-1996. Népegészségügy 81:60-67, 2000

Authoring contribution: Ádány R, V Hajdú P. Dictionary of epidemiology. Medicina, Budapest, 2003.

V Hajdú P, Kardos L, Ádány R. Mortality from diseases of the circulatory system in Hungary. In: Ádány R (ed): Hungary's health at the turn of the century. Medicina, Budapest, 2003.

6.3 Participation in national and international conferences

6.3.1 Presentations and posters in the theses' thematic

Kardos L, Ádány R. Analysis of mortality in Vas County, 1994-1996. Public Health Scientific Society (Hungary), General Assembly IX, Hévíz, 2000.04.13-15. (oral presentation)

Kardos L, Széles Gy, Gombkötő Gy, Szeremi M, Tompa A, Ádány R. Cancer deaths among hospital staff potentially exposed to ethylene oxide. Public Health Scientific Society (Hungary), General Assembly XI, Nyíregyháza, 2002.04.11-13. (oral presentation)

Kardos L, Széles Gy, Balázs B, Jenei T, Ádány R. Case control study into the etiology of chronic liver disease. Public Health Scientific Society (Hungary), General Assembly XIII, Szekszárd, 2004.04.11-13. (oral presentation)

6.3.2 List of other presentations and posters

Kardos L, Kériné Fülöp I, Ádány R. Progress of mortality from chronic liver disease and cirrhosis in Hungary and other countries of Central and Eastern Europe between 1980 and 1998. Public Health Scientific Society (Hungary), General Assembly X, Gyula, 2001.04.26-28. (oral presentation)

Kardos L, Széles Gy, V Hajdú P, Bordás I, Ádány R. Progress and local inequalities of the morbidity of diseases of the digestive system in Hungary, 1996-2001. Public Health Scientific Society (Hungary), General Assembly XII, Hévíz, 2003.04.24-26. (oral presentation)

Kardos L, Ádány R. Training and beyond: establishment of the first regional Health Observatory under the auspices of the School of Public Health in Hungary. 26th Annual Conference, Association of Schools of Public Health of the European Region (ASPHER), "Training for Public Health in Europe: old and new paradigms", Caltanissetta, Italy 2004.09.11-14. (poster)

Pocsai Zs, Széles Gy, Kardos L, Tóth E Zs, Paragh Gy, Bajtai A, Paller J, Pásti G, Kósa Zs, Papp E, Kvarda A, Ádány R. Distribution of genetic polymorphisms predisposing to cardiovascular diseases in a sample representative to the general Hungarian population and in hypercholesterolemic patient groups. A symposium titled "Challenges and opportunities of public health in the century of postgenomics" organized by the Prevention Committee of the Medical Department and the Epidemiology Working Committee of the Hungarian Academy of Sciences, the National Institute of Chemical Safety, and the School of Public Health, University of Debrecen; Hajdúszoboszló, 2004.04.23-25. (oral presentation)

Pocsai Zs, Széles Gy, Kardos L, Tóth E Zs, Paragh Gy, Bajtai A, Paller J, Pásti G, Kósa Zs, Papp E, Kvarda A, Ádány R. Apolipoprotein E allele frequency distribution in the Hungarian general population and hypercholesterolaemic group. Public Health Scientific Society (Hungary), General Assembly XIII, Szekszárd, 2004.05.05-08. (oral presentation)

Pocsai Zs, Széles Gy, Kardos L, Tóth Zs, Paragh Gy, Bajtai A, Paller J, Pásti G, Kósa Zs, Papp E, Kvarda A, Ádány R. Apolipoprotein E allele frequency distribution in the Hungarian general population and hypercholesterolaemic group. 15th International Symposium Drugs Affecting Lipid Metabolism (DALM), Venice, Italy, 2004.10.24-27. (poster)

Pocsai Zs, Széles Gy, Kardos L, Tóth Zs, Paragh Gy, Bajtai A, Paller J, Pásti G, Kósa Zs, Papp E, Kvarda A, Ádány R. Paraoxonase 55/192 allele frequency distribution in the Hungarian general population and hypercholesterolaemic group. 15th International Symposium Drugs Affecting Lipid Metabolism (DALM), Venice, Italy, 2004.10.24-27. (poster)

Széles Gy, Vokó Z, Bajtay A, Hamburger I, Erdő Gy, Ertner S, Fodor M, Kósa Zs, Pénzes M, Papp E, Menyhárt I, Parragi K, Jenei T, Kardos L, Molnár I, Ádány R. 1999 incidence data and experience from quality control measures of the General Practitioners' Morbidity sentinel stations Program in the framework of a collaboration between the School of public Health and the national public health and medical officer service in Hungary. Public Health Scientific Society (Hungary), General Assembly IX, Hévíz, 2000.04.13-15. (oral presentation)

Széles Gy, Vokó Z, Jenei T, Kardos L, Molnár I, Ádány R. Experiences and impact of the first hungarian General Practitioners' Morbidity sentinel stations Program in the framework of a collaboration between the School of public Health and the national public health and medical officer service in Hungary. XXII Annual Conference of the Association of Schools of Public Health in the European Region. 2000, Aarhus, Denmark (oral presentation)

Széles Gy, Vokó Z, Bajtai A, Hamburger I, Erdő Gy, Ertner S, Fodor M, Kósa Zs, Pénzes M, Papp E, Menyhért I, Parragi K, Jenei T, Kardos L, Molnár I, Ádány R. Results of the two year (1999-2000) incidence data analysis of the first Hungarian general practitioners' morbidity sentinel stations program. Public Health Scientific Society (Hungary), General Assembly X, Gyula, 2001.04.26-28. (oral presentation)

Széles Gy, Vokó Z, Jenei T, Kardos L, Bajtai A, Hamburger I, Pásti G, Fodor M, Kósa Zs, Tokár Zs, Papp E, Menyhárt I, Parragi K, Horváth g, Pintér A, Ádány R. Results of the two year (1999-2000) incidence data analysis of the first Hungarian general practitioners' morbidity sentinel stations program and the methodology of the unknown morbidity survey. XXIII Annual Conference of the Association of Schools of Public Health of the European Region. 2001, Hortobágy, Hungary (oral presentation)

Széles Gy, Vokó Z, Jenei T, Kardos L, Ádány R, Kósa Zs, Tokár Zs, Paul Zs, Papp E, Menyhárt I, Parragi K, Horváth G, Lun K. Unknown morbidity survey in the framework of the Hungarian general practitioner's morbidity sentinel stations program. Public Health Scientific Society (Hungary), General Assembly XI, Nyíregyháza, 2002.04.11-13. (oral presentation)

Széles Gy, Vokó Z, Paller J, Hamburger I, Pásti G, Fodor M, Esenszki B, Kósa Zs, Tokár Zs, Kvarda A, Menyhárt I, Parragi K, Horváth G, Városi Zs, Lehoczki K, Sz. Huszár E, Grosschmid S, Földesi Zs, Csajági S, Jenei T, Kardos L, Bujdosó L, Ádány R. Progress report on incidence results and developments of the Hungarian general practitioner's morbidity sentinel stations program. Public Health Scientific Society (Hungary), General Assembly XIII, Szekszárd, 2004.04.11-13. (oral presentation)

Vokó Z, Kósa Zs, Tokár Zs, Paul Zs, Papp E, Menyhárt I, Parragi K, Horváth G, Széles Gy, Jenei T, Kardos L, Ádány R. Unknown morbidity survey in the framework of the Hungarian general practitioner's morbidity sentinel stations program. XXIV Annual Conference of the Association of Schools of Public Health of the European Region. 2002, Zagreb, Croatia (oral presentation)