SHORT THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PHD)

The characteristics of avoidable premature mortality and their association with the socioeconomic status in Hungary

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UNIVERSITY OF DEBRECEN
DOCTORAL SCHOOL OF HEALTH SCIENCES

Debrecen, 2021

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The PhD Defense is held online and starts at 10:00 on 16th November, 2021.

Publicity is provided online. If you wish to participate, please indicate it in a message sent to the e-mail address nagy.csilla@nfo.bfkh.gov.hu by 2 p.m. on 15 November, 2021 latest. After the deadline it is no longer possible to coı to the PhD defense due to technical reasons.

1. INTRODUCTION

For decades, the extremely poor health status of the Hungarian population has been known by international comparison and is most evident in the high rate of premature mortality. It has been a problem that needs to be solved by health policy. Health policy is forced to set prevention priorities, mainly because of its limited resources. This requires evidence-based identification of interventions to reduce mortality in the working-age population (25-64 years), which is the largest loss to society. These priorities identify and rank public health needs, and plan interventions through strategies to reduce inequalities.

Consequently, the descriptive epidemiological studies most found in the public health literature are concerned with characterising the health status of the population, with particular emphasis on the investigation of the inequalities in morbidity and mortality and the identification of the factors that influence them. Mortality analyses (also because of the high quality and easy availability of basic data) are of crucial importance, and studies that focus on the analysis of the avoidability of premature deaths are definitive. Avoidable mortality is based on the concept that premature deaths from certain conditions should be rare (typically before the age of 65), and ideally should not occur if there are timely and effective healthcare or public health interventions.

A wide range of international and national studies emphasises the crucial importance of avoidable mortality. Furthermore, indicators on avoidable mortality are now available in OECD and EUROSTAT databases because of extensive and comprehensive international research by the World Health Organisation and the European Union.

The revision of the concept of avoidable mortality has intensified in recent decades; the most relevant change is the differentiation such complex groups as the total avoidable deaths influenced by health service activity (Mortality Amenable to Health Care: MAHC) and by primary prevention (Preventive Avoidable Mortality: PAM).

The MAHC indicator makes the premature mortality of the population assessable in terms of 'healthcare', and several studies have used and continue to use MAHC mortality to characterise the performance of healthcare systems, while the other ('PAM') analyses premature mortality in terms of the achievement or implementation of 'society's goals and objectives', including the effectiveness of primary prevention.

Furthermore, a very significant number of research studies have now also supported a strong and significant association of avoidable mortality with socioeconomic factors. Several studies have also established the association between mortality due to chronic liver disease (one of the most important causes of death in the PAM group) and mortality due to diabetes (in the MAHC group) and high deprivation.

Considering that in our country both MAHC and PAM mortality contribute significantly to the social burden, despite their declining trends, our study investigates

the characteristics of avoidable mortality in the working-age Hungarian population. We aim to investigate the spatial distribution of avoidable deaths from MAHC/PAM (and within these groups, mortality due to diabetes and alcoholic liver disease) and their association with socioeconomic status using modern spatial epidemiological methods.

Evolution of the concept of avoidable mortality to the present day

A significant proportion of deaths - at a defined lifetime period - could be avoided with the current advances in medicine (especially preventive medicine) and with the appropriate use of the available primary prevention, screening, diagnostic and treatment services. Thus, avoidable mortality data are useful indicators for characterising the quality of healthcare, considering that there are factors (e.g., socioeconomic status, municipality size) that have a significant impact on the quality of healthcare, not directly but indirectly.

Since the concept of avoidable mortality developed in 1976, both the meaning and terminology have undergone enormous changes. In the initial concept, causes of death were considered avoidable only if they could be postponed or should not have occurred with timely and effective healthcare. Since the early 1990s, the classification of indicators of avoidable mortality has been significantly refined and the indicator groups were defined in terms of their place within the healthcare system principles or public health policy. The causes of death were divided into two main groups. First, causes of mortality amenable to medical intervention, healthcare, secondary and tertiary prevention actions (e.g., treatable conditions or mortality amenable to healthcare), and second, causes of deaths amenable to primary prevention actions (e.g., preventable conditions).

Since the beginning of the 2000s, both the World Health Organization and the European Union (EU) have included several revisions to the list of indicators of mortality amenable to healthcare within a framework of comprehensive, wide-ranging, international research. One of the key reasons for such amendments was the increased demand from health policy for comparability, monitoring and assessing the performance of healthcare in the light of limited financial resources for maintenance of the healthcare system. The contribution of healthcare system deficiencies to total mortality is 10%, assuming a relatively effective, satisfactory, accessible healthcare system. In cases where the healthcare system is poor (e.g., low expenditure and inadequate resource allocation); however, its role and contribution to overall mortality will increase.

Past international and national studies have focused on levels, spatial and temporal distributions of mortality amenable to healthcare, and contributions to the years of potential life lost. In addition, a significant number of studies have shown the association between mortality amenable to healthcare and the factors of socioeconomic status (SES).

The definitions and revisions of specific deaths in the avoidable mortality groups are based on the availability of (public) health evidence, but the scope and level of scientific evidence for 'avoidability' are widening as science and technology develop. More and newer screening opportunities, treatments and interventions are becoming available that are increasingly making more and more diseases, or a particular disease in an extended lifetime, more avoidable. It follows that the lists of avoidable deaths need to be systematically updated as the latest, most recently available, and accessible medical practice, health service or effective primary prevention (e.g., preventive medication) becomes available. The consequence is that all lists are specific to a given period, i.e., only valid for a limited time. The list of diseases and groups of illnesses, as defined by international researchers who have done excellent work on the subject, is therefore never constant, but continuously evolving and developing over time.
The age limit for avoidable premature deaths (the upper age limit) has also been revised several times in recent decades. For several diseases, the upper age limit of 65 years has been raised to 75 years, reflecting the increase in life expectancy at birth of the population of economically developed countries. Furthermore, since the concept was first conceived, the chances of survival have increased for many diseases (e.g., certain malignancies, stroke, or IHD) due to innovations in healthcare. Also, death coding in the 65-75 age groups is now even more accurate. Nevertheless, concerning the possibility of further increasing the upper age limit, some experts emphasise that above the age of 75, the 'avoidability' of deaths is less evident and the exact identification of deaths (due to diseases that affect several organ systems) may also become problematic.

International and national evolution and characteristics of mortality amenable to healthcare (MAHC) and preventable avoidable mortality (PAM)

When the concept of avoidable mortality is reviewed, MAHC mortality has become much more the focus of investigation than PAM mortality. Despite the recent significant interventions to reduce the number/rate of avoidable deaths in all European countries, there are still significant differences between the EU-27 Member States. There are considerable regional differences not only between the Member States but also within the Member States, i.e., even in countries with relatively lower levels of avoidable mortality, a wide range of analyses showed important regional inequalities.
Most of the research on ***MAHC mortality*** has focused on the level of mortality, its temporal trends and spatial distribution, and its role in life expectancy at birth. In 2017, Hungary was among the countries with the most unfavourable indicators in the EU-28, together with Slovakia, Romania, Latvia, Estonia, and Lithuania. In 2016, based on EUROSTAT standardised mortality indicators, the national MAHC mortality rate was also about twice (1.9 times) the EU-27 average, which is considered unfavourable. The mortality rate of the Hungarian population was the fifth highest (176th of 100,000), but

it should be noted that mortality rates above the EU-27 average were also characteristic of mortality rates in former socialist countries with a similar socio-cultural and historical background to Hungary.
A positive fact about the time trend in MAHC mortality is that there is evidence to confirm that it is continuously decreasing across Europe. In our country, a range of studies has already shown this change in MAHC mortality, which is decreasing in trend but still about twice as high as in developed Western European countries. Karanikolos and colleagues examined the direction and rate of change in trends in standardised mortality and mortality due to other causes of death in 28 countries in Europe. Their findings showed that in all EU countries, the level of mortality had dropped and the average rate of change in MAHC mortality was more intense than that of other mortality.
The average annual rate of decline for mortality due to MAHC was only 0.4% in Lithuania and 5.6% in Ireland (for males) and 1.8% in Lithuania and Italy and 5.0% in Ireland (for females).
The results of a national study also confirmed that declining cardiovascular mortality was behind the declining MAHC mortality. In our country between 2012 and 2018, the national MAHC mortality rate was characterised by a decreasing trend in all counties for both sexes, and 11 counties had a mortality rate higher than the Hungarian rates for males and 10 counties for females. It is important to note that the Hungarian mortality rate was more than twice the EU-27 average at that time, and the relative mortality rate was two and a half times higher for males in Borsod-Abaúj-Zemplén, Nógrád and Békés counties and twice the relative mortality risk for females in Békés, Borsod-Abaúj-Zemplén and Jász-Nagykun-Szolnok counties.

The Preventable Avoidable Mortality (PAM) includes deaths in the premature life period that can be affected or avoided primarily by effective and widely organised (population level) primary prevention and targeted health policy decisions and interventions.
In Europe, the trend in standardised mortality rates, as defined by the common OECD/EUROSTAT list of MAHC and PAM, has been declining over the past almost 20 years, but the level of PA mortality has much exceeded that of MAHC. In our country, in 2017, the PAM rate was 1.9 times the MAHC rate, but in Austria, Finland and Slovenia this relative mortality was more than twice and two and a half times higher, respectively. The standardized mortality indicators show that from 2001 the Estonian, Latvian, and Lithuanian populations had higher PAM than the Hungarian PAM, and from 2003 to 2015 only the Latvian and Lithuanian populations had higher mortality. Furthermore, in 2016, the PAM of the Hungarian population was significantly higher than the EU-27 average.

PAM (like MAHC) showed a declining trend between 2012 and 2018 and in 2017, this mortality was higher in 12 counties for males and 10 counties for females than the Hungarian mortality rate. In addition, the Hungarian PAM rate in 2017 was more than twice the EU-27 average. And the 2,5 times higher relative mortality rates for males and females in Borsod-Abaúj-Zemplén county and females in Jász-Nagykun-Szolnok county compared to the EU-27 average are remarkable.

According to Nolte and McKee's classification (and in the OECD/EUROSTAT statistics based on Nolte and McKee classification), mortality due to chronic liver diseases and cirrhosis (ICD-9: 571), as well as mortality related to excessive alcohol consumption (ICD-10: K70, K73, K74.0-K74.2, K74.6-K74.9, K85.2, K86.0) has one of the highest proportions within the complex group of PAM.

It is no surprise that alcohol-related health and social problems are major global problems, which can be prevented primarily through a targeted alcohol policy and alcohol prevention strategy within a country. In Central Europe, the excessive consumption of alcohol is the second most important risk factor for disease and injury. And although mortality due to chronic liver diseases and cirrhosis is on a reducing trend in Europe, Hungary is still characterised by a premature mortality rate in 2015 that was almost four times higher for males and almost three times higher for females compared to the EU-15 average. Within our country, the spatial distribution of mortality due to alcohol-related liver diseases has been analysed in several studies. High mortality risk among the working-age Hungarian population, especially among males, was observed in the northeast-southwest axis of Hungary. The fact that excessive alcohol consumption is the etiological factor underlying more than 80% of mortality due to chronic liver disease in Hungary indicates a significant 'alcohol exposure' of the Hungarian population, which is further contributed to by the quality of alcohol consumed (mainly of questionable origins).

The factors affecting avoidable mortality

The characteristics of avoidable mortality are particularly important because their causes are related to the performance of health services. Such deaths are defined as deaths due to selected diseases/states that could be avoided in their totality or at the very least to a significant proportion, according to the current state of medical and (public) healthcare evidence, by the use and utilization of timely and adequate medical/(public) health interventions in specific age ranges.

According to this definition, however, the criteria can be defined, both from the point of view of the healthcare and the individual, which, if they are satisfied, can be termed 'avoidability'.

The influencing factors from the healthcare side are the following:

- the quality of health services;
- access to health services.

The influencing factors on the individual side:
- the use of health services;
- socioeconomic situation.

The quality of health services is the most important influence on MAHC from the care side, and consequently, the factors that cause avoidable deaths may point to deficiencies in health services. Although the international studies recommend care and careful interpretation of their direct and simple use as indicators of healthcare quality, they do not deny that they can provide an indication and insight into problems in the healthcare system.

In a major international study published in 2018, Kruk and colleagues found that in the 137 low- and middle-income countries they studied, approximately 8 million people die each year due to lack of access to high-quality care. Furthermore, 8.6 million people die from healthcare-related causes, and it is particularly remarkable that 5 million of these people have accessed healthcare services but have received low/poor quality healthcare. In these countries, deaths attributable to poor-quality healthcare accounted for 58% of all deaths that had occurred. It is concluded that raising access and coverage to health services in these countries will no longer solve the problem of reducing these deaths, but that improving the quality of the healthcare system should be an immediate priority.

Nolte and McKee examined MAHC mortality in 16 high national income countries and found that 21% of deaths under 75 years for males and 30% for females were related to high-quality healthcare. Although these data are not methodologically comparable with the results of Kruk et al., who found that ESST deaths accounted for 55% of all avoidable deaths, the discrepancy may suggest that the low/poor quality of healthcare systems is a larger barrier to improving the health status of the population in 'poorer' than in 'richer' countries.

From the perspective of the individual, one of the major influencing factors is the use of the service. Some countries have supported the view that expanding health insurance coverage would facilitate higher utilisation of health services whose non-use has a significant impact on MAHC.

Although the availability of insurance tends to increase the use of services, the evidence on its mortality-reducing effect is not consistent. Escobar et al. found that in only three out of nine low- and middle-income countries were an increase in health insurance coverage associated with better health outcomes. In the USA, on the other hand, there is a positive association between health insurance coverage and self-reported improved health status, and in a recent study, it was also associated with a decrease in mortality.

Concerning the role of poor quality of health services and utilisation, Kruk and his colleagues found that in low- and middle-income countries, poor quality of health services contributed to more deaths than non-utilisation (5.0 million deaths were attributed to poor quality of healthcare and 3.6 million to non-utilisation). Poor quality was associated with higher mortality than non-utilisation in 14 of the 17 geographical

regions and 115 of the 137 countries studied. A modelling exercise based on their findings showed that if low-income countries can only finance low-quality care, deaths from poor-quality health services will account for nearly two-thirds of all deaths.

The interactions between socioeconomic status and health services are interdependent. Hence, research on the relationship between avoidable mortality and socioeconomic inequalities is based on two approaches: first, the contribution of health services to the development and evolution of socioeconomic inequalities of health and mortality; and second, the impact of a socioeconomic position (whether favourable or unfavourable) on the use of healthcare, mainly via access to care. The conclusions of these investigations have highlighted that the detection of avoidable deaths and the socioeconomic differences in the contributing factors can inform the strategy for reducing health inequalities and for acting on these strategies.

Several studies have found relevant ethnic and gender differences (in terms of socio-economic factors) in MAHC avoidable mortality. A mortality excess was identified for African Americans and males in the USA, and ethnic and gender differences were also found in a study in Singapore. In addition, research using education (as the only factor) to characterise socioeconomic status has been conducted and concluded that the association between education and avoidable mortality can be demonstrated in all European countries. This is especially the finding in Central and Eastern Europe and the Baltic countries where low educational qualifications are associated with significantly higher MAHC mortality rates.

Further studies, using composite indices of socioeconomic status, deprivation indices (DI), have shown that avoidable mortality rates are related to deprivation. One study examined the relationship between MAHC and deprivation among the population of 16 cities in Europe (including capital cities). A positive association between the two factors was found in the majority of the cities studied. Furthermore, they found that avoidable mortality was often, but not always, higher in deprived areas within a city where there was a greater social difference between males than females. In Hungary, before the turn of the millennium, studies analysing avoidable mortality were mainly trend studies, which did not explore the relationship with socioeconomic (SES) factors. In the first decade of the second millennium, the research on the relationship between SES factors and different mortality and morbidity did not typically include avoidable mortality in the scope of the analysis. The results of this Hungarian correlational study identified high mortality due to all-cause and cardiovascular diseases especially in the most deprived areas of the country (north-east and south-west and along the connecting axis).

About 10 years ago, researchers started to investigate the spatial inequalities in MAHC and the association between this mortality risk and the spatial distribution of the area-based multidimensional DI indicator developed by us. The results found a strong,

significant, positive association between MAHC and spatial inequalities in socioeconomic status. High MAHC risk within the country was identified in the area of the band connecting the north-east and south-west regions, but after adjusting for socioeconomic status, the high relative risk indicators were disappearing in the north-east and east, which means that the high risk can be partly explained by the deprivation level of the population. In contrast, in the western part of Hungary, the high mortality risks in the area remained after adjustment for socioeconomic stratification, suggesting that in these areas, in addition to deprivation, other factors may be influencing mortality risk. It was highlighted that these factors may also be related to health services (both quality and availability), although it was emphasised that further detailed studies are needed to identify the potential explanations.

2. AIMS

The main objective of the research is to explore the spatial inequalities of MAHC within our country using the Nolte and McKee concept and to analyse the association between MAHC and socioeconomic status using a multidimensional area-based DI indicator based on available data for the period 2015-2019.

Furthermore, we investigated the spatial inequalities of type 2 diabetes mortality (within the MAHC complex group) (2018-2019) and metformin utilisation (prescription, redemption and redemption rates) for diabetes prevention and their association with socioeconomic status in the Hungarian population aged 20 years and older.

The aim was also to map the premature mortality due to alcoholic liver disease and cirrhosis (BNO-10: K70) (2015-2019) and to identify the association between this mortality risk and socioeconomic status. Alcoholic liver disease and cirrhosis (BNO-10: K70) is one of the most important causes of death within the complex group of preventable mortality as conceptualised by Nolte and McKee.

3. MATERIALS AND METHODS

Data sources

The mortality data (MAHC and mortality due to alcoholis liver diseases and cirrhosis) at municipality level, by sex and 5-year age bands for 2015–2019, were acquired from the Hungarian Central Statistical Office. Population data also at the municipality level, by sex and 5-year age bands for the years 2015-2019, were obtained from the Central Office for Administrative and Electronic Public Services.

The diabetes mellitus (ICD-10: E10–E14) mortality data at the district level, for the years of 2018 and 2019 were obtained from the Hungarian Central Statistical Office, whilst the Central Office for Administrative and Electronic Public Services provided us

population records for districts. Both mortality and population data were stratified by five-year age bands and sex.

The data of prescriptions for metformin and the data of redeemed metformin prescriptions were obtained from the National Health Insurance Fund Administration of Hungary for each primary healthcare practice for the entire years of 2018 and 2019. Metformin prescriptions and redemptions were collected only for patients who received metformin as monotherapy for prediabetes. The data were aggregated at the district level and stratified similarly to the mortality data (i.e., by five-year age bands and sex).

Area-based, (municipality and district level) Deprivation Index (DI) values are available to provide information about the socioeconomic status for 2011, the year of the last census in Hungary. The method for calculating DI was described previously and successfully used in several studies. Briefly, the calculation of DI is based on seven municipality level socio-economic indicators (income, education level, unemployment rate, representation of one-parent families, that of large families, density of housing and car ownership) and was evaluated using the principal components analysis. The district-level deprivation was determined using the population-weighted average of DI.

The areas with positive index values are municipalities/districts with a lower socioeconomic status compared with the national average (more deprived), and the converse was shown in municipalities/districts with negative index values (less deprived).

In the investigation, the areas (municipalities, districts) were divided into quintile groups for municipalities and tertile groups for districts, based on the DI value of the given areas.

Methods and indicators

The mortality amenable to healthcare analyses is based on the Avoidable Deaths Complex Group, developed by the most widely referenced researchers in the international literature (*Martin McKee and Ellen Nolte*) and published in 2004. This concept defined healthcare-associated deaths as deaths in the 0-74 age group that could be avoided by adequate and timely utilization and application of healthcare interventions. The list of 34 health-care-avoidable deaths, identified by Nolte and McKee, includes a total of 34 deaths that are avoidable through healthcare at a range of different age groups; however, the analysis was carried out consistently for the population aged 0-74 years.

Time trends analysis of mortality

The time trends in premature (25-64 years old) mortality due to MAHC and alcoholic liver disease and cirrhosis (BNO-10: K70) were characterised using Standardised Death Rates (SDR) per 100,000 population at a national level for the period 2007-2019. SDRs

were calculated directly standardized for the European standard population age distribution (2013).

Spatial epidemiological analysis

Mortality

The spatial distribution analysis was performed using Rapid Inquiry Facility (RIF) Software and INLA. Using the 'disease mapping' option in the RIF the spatial patterns of MAHC for the age group 0-74, and mortality due to alcoholic liver diseases and cirrhosis (ICD-10: K70) for the age group 25-64 years, were examined and visualized at the municipality level in 2015-2019. Furthermore, the mortality due to T2DM (ICD-10: E10-E14) was analyzed for the 20+ age group at the district level for 2018-2019. Hierarchical Bayesian adjusted indirect standardised mortality ratios (SMRs, relative risks) were calculated for the Besag, York and Mollie model using the INLA method based on the expected incidence of age-specific mortality rates and visualized with posterior probabilities at the municipality level for the Hungarian population. The maps for each

Health outcomes show the relative risks and exceedance posterior probabilities.

Disease-mapping methods deal with the estimation of the spatial distribution of disease risk. The use of raw indirectly standardized mortality ratios (SMRs) to estimate disease risks in small areas such as municipality areas is problematic as SMRs can become numerically unstable with small populations and low counts of observed/expected cases which leads to both extreme risks being associated with low populated areas and increased uncertainty.

Mapping the SMRs can produce a 'noisy' map, which does not allow spatial patterns to be easily detected. One way of addressing these problems is smoothing by Bayesian hierarchical methods. We used the hierarchical Bayesian model for disease mapping proposed by Besag et al., which is widely used in practice (it will be denoted as the BYM model named after Besag, York and Mollie). These hierarchical Bayesian models shrink unstable risks towards the global mean risk and the local mean risk, accounting for spatial autocorrelation, by 'borrowing' information between adjacent areas. Maps based on these estimates are more informative and more easily interpretable with an observed spatial structure more likely resulting from either risk factors or unmeasured confounders.

Standard deviations of components of the hierarchical Bayesian model were also calculated in all cases and uncertainty was shown by the posterior probability of an excess risk for areas. On the maps were highlighted where the posterior probabilities were >0.8 or <0.2. Using these PP values, areas of real increase or decrease can be identified with acceptable sensitivity, and the estimated mortality risks can be said to have at least an 80% probability of being different from the mortality of the reference population.

Metformin utilization

The frequency of metformin prescriptions and redemptions in the 20+ age group for 2018–2019 was determined concerning the national average, and their ratios for compliance were also depicted using RIF. The redemption rates (the number of redemption per number of the prescription) for metformin were used to characterize the level of primary non-compliance. The results were analyzed by metformin monotherapy for deprivation tertiles at the district level.

Ecological study, risk analysis
(the effect of socioeconomic status as a health determinant)

Using the risk analysis in the RIF, the association between deprivation and the spatial distribution of premature mortality, due to amenable mortality to healthcare, alcoholic liver diseases and T2DM, was calculated. Based on the DI values, we have classified the groups of areas into 3 (district level study) and 5 (municipality level studies). Then, the association between the median DI values of these categories and the absolute (SDR) and relative mortality (SMR) of the population of the categories was examined. Homogeneity and linear trend tests were carried out to check whether the risk is statistically homogeneous across bands and to test the global association of the DI and the relative risk of premature mortality due to MAHC, alcoholic liver diseases and T2DM.

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Association between the risk of MAHC, of premature mortality due to alcoholic liver disease and cirrhosis (BNO-10: K70) and socioeconomic status

The RIF was used to identify the association (2015-2019) between the spatial distribution of DI and MAHC (Nolte and McKee conceptualisation) of the Hungarian population aged 0-74 years. Both the SDRs (stratified by the age distribution of the European standard population in 2013) and the SMRs indicators were calculated according to the categories based on the DI quintile.

In this part of the ecological investigation, the association between premature mortality from alcoholic liver disease and liver cirrhosis and socioeconomic status was also investigated for Hungarian municipalities in 2015-2019. The association between median DI values and mortality (SDR/SMR) of the population of the 5 categories of municipalities were examined.

The methodology of the association study between diabetes mortality (BNO-10: E10-E14) and preventive metformin medication utilisation and socioeconomic status

The frequency of prescriptions for metformin, redeemed prescriptions, and the ratios for compliance concerning the national average was also mapped using the RIF, and their association with deprivation was defined using tertiles of DI as a district-based

categorical covariate. Chi-square tests for homogeneity and trend analysis were also implemented to investigate associations.
It is defined (per DI tertile):

- the relative risk of mortality (compared to the national average),
- the average number of prescriptions and redemptions per year,
- the relative frequency of prescriptions and redemptions (compared to the national average),
- the relative redemption rate (compared to the national average),
- the prescription and redemption rates per 100 persons aged 20 and over, and
- the redemption rate (in %).

4. RESULTS

Trends and spatial distribution of mortality due to amenable to healthcare (MAHC) and its association with socioeconomic status in the Hungarian population (2007-2019)

Trends

The trend of standardized mortality amenable to healthcare has been continuously decreasing between 2007 and 2019. During this period, the mortality rate declined by approximately one fifth (78% for males and 79% for females). As a result of the reduction in the mortality rate for both sexes, the relative risk of avoidable mortality due to amenable to healthcare between males and females remained unchanged (1.8 times the risk for males than females).

Spatial distribution of mortality

The spatial inequalities of the ESZT mortality (the geographical distribution of the SMRs smoothed by the full Bayesian estimation) can be characterised as follows: the distribution of mortality risks higher than the national level was similar for both sexes; the eastern part of Hungary was covered almost fully (except Nyíregyháza, Eger, Szeged, and the northern part of Hajdú-Bihar county). In Central Hungary, for both sexes, Budapest, and the north-western agglomeration of the capital, as well as the Danube, were the areas with lower mortality risk than the national average.

For the West-Hungary region, the distribution of areas at high risk of mortality was similar by sex, but differences in mortality compared to the national average were more pronounced for males. In this part of Hungary, in the largest part of Győr-Moson-Sopron county and the areas around Lake Balaton, lower mortality risks than the national average could be identified.

The association between mortality and socioeconomic status

A strong significant positive linear association between mortality due to amenable healthcare and deprivation was identified for both sexes (Males: χ^2Homogenity= 938,39, p=0, χ^2Linearity= 933,73, p=0; Females: χ^2Homogenity= 511,46, p=0, χ^2Linearity= 507,76, p=0). Rates of mortality amenable to healthcare in the upper quintile band (i.e., the most deprived, V. quintile) exceeded the mortality in the lowest quintile (i.e.the least deprived, I. quintile) band by 88% in males and by 69% in females. Furthermore, while the mortality in the areas of the lowest deprivation (I.) quintile was by 25% for males and 20% females lower than the national level, the mortality in those areas of highest deprivation (the most deprived, V. quintile) exceeded the national average by 41% for males and 36% for females.

Trends and spatial distribution of mortality due to alcoholic liver diseases and cirrhosis and its association with socioeconomic status in the Hungarian population (2007-2019)

Trends

Between 2007 and 2019, premature mortality due to alcoholic liver disease and cirrhosis showed a continuously decreased trend. The mortality rate has dropped by approximately two thirds (61% for males and 62% for females). Because of similar rates of reduction for both sexes, the three and a half times higher risk of mortality for males (compared to females) has remained the same over the period 2007 to 2019.

Spatial distribution of premature mortality

Stratifying by age, for both sexes, areas at high risk of mortality were mainly located in the western part of the country (for females, the border areas of Baranya, Győr-Moson-Sopron and Vas counties were excluded). Additional areas with a high risk of premature mortality were identified in counties along the north-eastern border, in the south-eastern part of Pest county and the western part of Bács-Kiskun county for males, and females in the whole of Borsod-Abaúj-Zemplén county and the western part of Bács-Kiskun county. It is remarkable that while the high mortality risk for males was found only in the south-eastern part of Pest county, the premature mortality for females was higher than the national average in the south-eastern districts of Pest county and Budapest.

The association between mortality and socioeconomic status

A statistically strong, significant positive linear association was found between premature mortality due to alcoholic liver disease and cirrhosis and deprivation for males (Males: χ^2Homogenity= 119,70, p=0, χ^2Linearity= 107,98, p=0). For the same relationship also for females, but statistically weaker than we found for males (Femalés: χ^2Homogenity= 20,24, p=0,001 χ^2Linearity= 10,33, p=0,01). The premature mortality rate in quintile V (most deprived category) exceeded the mortality rate observed in the least deprived (I) quintile (67% for males and 21% for females). The premature

mortality in the least deprived (I. quintile) was 21% lower than the national average for males and 10% for females, while in the most deprived category (V. quintile) the mortality was 32% higher than the national average for males and 11% for females.

Spatial distribution of mortality due to T2DM, as well as the preventive metformin medication monotherapy and their association with socioeconomic status in the Hungarian population (2018-2019)

Spatial distribution of mortality and its relationship to SES

The districts of highest mortality risk due to T2DM were found at the southwestern (Somogy, Tolna, Baranya) and northeastern (Borsod-Abaúj-Zemplén) counties, as well as in an additional county (Fejér) located in the middle part of Hungary. Most districts with the highest mortality risks seem to be localized in the more deprived areas of the country. This is supported by the results of the risk analysis showing a significant association between relative mortality and deprivation. The results of risk analysis showed a significant (no linear) association between the relative mortality due to T2DM and deprivation ($\chi 2$ homogeneity = 98.83, p = 0, $\chi 2$ linearity = 23.56, p = 0). In comparison with the country average T2DM mortality risk was found lower by approximately 6% in deprivation tertile I. (Relative $\text{Mortality}_{\text{DI I.}}$: 0.939; confidence interval [CI: 0.902–0.978]) and by 7.5% in deprivation tertile II (Relative $\text{Mortality}_{\text{DI II.}}$: 0.925; [0.886–0.965]). The mortality risk between tertiles I and II does not differ significantly, while in the most deprived tertile (III) the risk of mortality was significant, by approximately 24% (Relative $\text{Mortality}_{\text{DI III.}}$: 1.236 [1.178–1.296], higher than the country average.

Metformin utilization

In Hungary, 1,720,137.5 metformin prescriptions were prescribed per year in 2018–2019, and only 1,118,983.5, i.e., 65.1% of them (confidence interval, CI: 64.967–65.137) was redeemed. The frequency of prescription was 20.901/100 persons (CI: 20.879–20.923) and the frequency of redemption was 13.597/100 persons (CI: 13.579–13.615). These values served as a reference in district/county-level analysis.

The spatial distribution of districts with a higher relative frequency of metformin prescriptions and redemptions showed a similar pattern as territorial inequalities. The frequency of prescription and redemption was higher in the northeastern, eastern and southwestern parts of Hungary. In these areas, higher relative compliance was found also, while in the middle part of Hungary (Budapest (capital city), Pest and Fejér counties) lower relative redemption rates were observed. It is noted that the districts with lower relative redemption rates were shown the territorial inequalities of areas with a lower frequency of metformin prescription.

Risk analysis

The risk analysis showed a significant positive linear association between relative frequency of prescriptions, that of redemptions, as well as redemption rate of metformin

and deprivation (for prescription: χ^2 homogeneity = 40,610.63, p = 0, χ^2 linearity = 40,434.71, p = 0; for redemption: χ^2 homogeneity = 63,371.83, p = 0, χ^2 linearity = 62,787.78, p = 0; for redemption rate: χ^2 homogeneity = 8513.32, p = 0, χ^2 linearity = 7773.41, p = 0). In the less deprived areas the frequency of metformin prescription was lower than the national average by 12% (Relative $\text{Frequency}_{\text{DI I.}}$: 88,0%; [MT: 87,8-88,1), while in the most deprived (III.) tertile by 16% was higher than national level (Relative $\text{Frequency}_{\text{DI III.}}$: 116,0%; [MT: 115,7-116,2]). Moreover, redemption frequency in the least deprived tertile approximately by 17% was lower (Relative $\text{Frequency}_{\text{DI I.}}$: 83,2%; [MT: 83,0-83,4]), than national average, while in the most deprived areas by 27% was higher (Relative $\text{Frequency}_{\text{DI III.}}$: 127,4%; [MT: 127,0-127,7]).

The same significant positive linear relationship between the redemption rate and deprivation was identified. In the most deprived category (III), we observed a relative frequency of the redemption rate approximately 10% higher than the national average. (Relative Frequency $_{\text{DI III.}}$: 109,9%; [MT: 109,6-110,2]).

In the areas with high deprivation (tertile III) 24.211 ($\text{CI}_{\text{DI III.}}$: 24,175-24,248) per 100 persons metformin prescriptions were found, i.e., the relative prescription frequency was higher than the national average by 16%. In the same tertile the frequency of redemptions was 17.297/100 persons, i.e., higher than national level by 27%, while the redemption rate was 71.5% (Redemption Rate $_{\text{DI III.}}$: 71,485%; [CI: 71,393-71,578]), i.e., higher than national redemption rate by 10% (Redemption Rate $_{\text{DI I.}}$: 61,462%; [CI: 61,374 – 61,550]).

To demonstrate the variation in the relationship between socioeconomic status and T2DM mortality, as well as metformin medication, further analysis was carried out at the county level. Some counties were found where the relative mortality risk and frequency of metformin prescription and redeeming, as well as redemption rate, were found to be higher than the national average, and these counties are localized in the most deprived region of the country (e.g., Borsod-Abaúj-Zemplén and Baranya counties). Contrarily, despite its unfavourable socioeconomic status, a single county with lower relative mortality risk and lower metformin medication than the national average was also detected (Hajdú-Bihar county). Furthermore, an area was identified among counties in the less deprived tertile with significantly higher T2DM mortality, but with significantly lower relative metformin medication (Fejér county and Eastern part of Tolna county—forming together a cluster in the midwestern part of Hungary). In general, it can be accepted that socioeconomic deprivation is associated with increased T2DM mortality and a higher level of metformin utilization, but exceptions to this statistical correlation in both respects can be identified.

6. DISCUSSION

Interpreting our findings

Despite a continuously declining trend since the millennium, mortality amenable to healthcare (MAHC) in Hungary was still around twice the EU-27 average in 2016. Several international and national studies reviewing the evolution of mortality amenable to healthcare highlight that, although trends are declining, the high relative mortality compared to the European Union average or some populations with low mortality is not unique to our country. The mortality trends of the population of former socialist countries, which are sociocultural and historically alike to Hungary, are similar. In addition to the results of these trend studies, a knowledge of the spatial inequalities of mortality avoidable and the associated factors (mainly socioeconomic status) provide important information for national and local health policy. The knowledge of the spatial patterns of health status and the factors influencing them is also important because they have a key role to play in the identification of public health priorities and the planning and organisation of health services.

Considering this, in the aim of the present study we mapped the spatial inequalities of MAHC (as conceptualised by Nolte and McKee) and within this group, T2DM mortality, as well as premature mortality due to alcoholic liver disease and cirrhosis, which are preventable, avoidable cause of death. Furthermore, for all these indicators, we also characterised their relationship with socioeconomic status. We also described the characteristics of the spatial distribution of prediabetes medication treatment, i.e. metformin use for diabetes prevention, and its relationship with socioeconomic status in the context of diabetes mortality, a major public health concern.

The findings of our spatial inequalities research have confirmed the findings of other previous studies in Hungary that the high mortality risk for all examined mortality outcomes is clustered in the eastern, north-eastern and south-western regions of Hungary, and have provided new evidence that this spatial inequality is an epidemiological representation of socioeconomic inequalities.

The present findings are consistent with those of our previous research on the use of drugs for the preventive medication of non-communicable diseases. This was because in our studies of antihypertensive therapies for hypertension, which has a high morbidity rate, and anticoagulant medications for the secondary (and rarely primary) prevention of mortality due to arterial and venous thrombotic diseases, we also found higher prescription and redemption rates in these areas. It should be noted, on the contrary, that the frequency of statin prescription was lower than the national average in these areas.

In analysing spatial inequalities of mortality, we also identified differences in the spatial distribution of mortality by sex. Although the distribution of the high mortality risk of MAHC in Western Hungary was similar by sex, the unfavourable differences of

mortality compared to the national average were more pronounced among males. Differences in premature mortality due to alcoholic liver disease and cirrhosis by sex were also observed in the central region, as we have reported in our previous study. We also examined the role of socioeconomic status in our research. Nowadays, the results of numerous studies support that this factor also has an impact on an individual's health status and, as for ultimate outcomes of health deterioration, on mortality. Thus, a significant volume of evidence confirms the association between socioeconomic status (as a factor outside healthcare) and MAHC, and the similar relationship to mortality due to alcoholic liver disease and cirrhosis.

Our previous studies also show that socioeconomic status is associated not only with mortality but also with the use of different medicines to prevent diseases of major public health priority. In agreement with these findings from the literature, we also identified a strong significant linear same direction association (the poorer the socioeconomic status, the higher the mortality) between deprivation and MAHC, and premature mortality due to alcoholic liver disease and cirrhosis, for both sexes. For these two indicators, the results showed that mortality rates for populations in the most deprived areas were well higher than those observed for the least deprived. While in the least deprived quintiles, both sexes had lower mortality than the national average, there was a significant increase in the relative risk of mortality in the most deprived areas. It should be mentioned concerning MAHC that socioeconomic status not only influences mortality intrinsically but also through the population's use of healthcare, most especially access to care (e.g. large distances, the difficulty of transportation).

However, 'access/availability' of services is not the only factor that influences avoidable mortality. The level of knowledge (health intelligence, health literacy) of individuals about health and its determinants (including health determinants and healthcare) is also important and these factors can influence service utilisation independently of its availability. Regarding premature mortality due to alcoholic liver disease and cirrhosis, it should be noted that although several studies have confirmed the role of SES in uncontrolled alcohol-related excess mortality, some studies have not detected a significant spatial rearrangement of high mortality risk areas after adjustment for socioeconomic factors. This suggests that the high risk of mortality in the area is not exclusively explained by the extremely unfavourable socioeconomic status (or a health behaviour problem). Therefore, further detailed epidemiological studies focusing on risk factors are needed to confirm the associations found in our present study.

Further results of our risk analysis showed a significant positive linear association similar to those described above, for metformin use to prevent T2DM, i.e. each relative frequency of medication use (prescription, redemption, redemption rate) rose with increasing depth of deprivation. Although the number of studies analysing the association between metformin use and socioeconomic deprivation worldwide is small, one American study of prediabetes patients described that metformin use varied by sex,

race, poverty/income or education, but the prevalence of metformin treatment in people with prediabetes was only 0.7%.

It should also be highlighted that in the ecological part of the study on metformin use, the spatial distribution of metformin prescribing/redeeming rates only partially covered districts/counties with a high risk of mortality due to T2DM. These results show that, while on the whole, deprived areas with a high risk of mortality due to T2DM are not associated with either metformin under using or less favourable primary compliance (i.e. redemptions rates), but we did identify areas where low metformin prescribing/redeeming rates were associated with high T2DM mortality. This included the less-favoured areas of the country, some of the districts in the central-western part of Hungary (mainly in Fejér County). In these areas, the risk of mortality due to T2DM was high, but all relative medicines using frequency indicators were lower than the national average. This result shows that our methodology can be used not only to characterise socioeconomic status and spatial inequalities of mortality, as well as related factors in general but also to identify regions where significantly higher than average mortality is associated with inadequate preventive services. A comparative analysis of the distribution of mortality and preventive medication would justify a review and improvement of prevention practices, which could also lead to significant improvements in avoidable mortality.

Conclusion

Identifying areas at high risk of mortality, our results clearly showed the population at risk of avoidable MAHC, mortality due to alcoholic liver disease and T2DM. Awareness of these spatial inequalities helps national and local decision-makers and sectoral managers to define public health priorities to reduce mortality in Hungary and to target the development of healthcare services based on these priorities.

In addition to a comprehensive understanding of the performance of the healthcare system, detailed knowledge of the factors influencing mortality is needed to improve healthcare. This also requires an analysis of the factors influencing and behind the spatial inequalities in mortality (and thus mortality due to amenable to healthcare).

Although the results of mortality amenable to healthcare clearly show a likely lack of healthcare, further investigation is required to identify possible causes. Clarifying the context of the inequalities identified within and above the socioeconomic factors is necessary for targeted interventions and measures. These more detailed investigations could also verify the supposed role of unhealthy lifestyles, risky health behaviours (smoking, excessive alcohol consumption, poor diet, lack of exercise). This justifiably highlights the need for future epidemiological studies (e.g. related to mortality avoidable by primary prevention, well-designed, professionally based health surveys, morbidity studies).

Already in 2011, the main objective of the European Commission-funded AMIEHS (Avoidable Mortality in the European Union) study was to establish a new and evidence-based definition of mortality amenable to healthcare (MAHC). The European efforts to define a single MAHC, avoidable mortality indicator group are well documented and the updating of the lists provides adequate results that can be compared. In Hungary, although the adaptation to two internationally accepted concepts in the NEKIR epidemiological database has been done, despite the international examples to be followed, a separate, 'country-specific' MAHC list has not yet been developed in Hungary. And even though the avoidable mortality indicator of the MAHC is proposed to measure the performance, efficiency and quality of healthcare systems only with a circumspect, carefully interpretation, an avoidable mortality list harmonising with a widely accepted concept, but also taking into account national specificities and priorities, would ensure international comparability of the Hungarian healthcare system. Establishing such a set of 'country-specific' indicators could be a first step towards mapping the performance of national health services and ensuring comparability of the effectiveness of individual systems, even within the country. Several studies have highlighted that this 'first step' can identify priorities for healthcare development (including human resource development) and can be a starting point for quality control of health system services, assurance and development.

Regarding mortality due to T2DM, studies from the US suggest that only about half of the family physicians have a positive attitude towards prediabetes as a diagnostic construct and even if the academic family practitioners (clinicians) consider prediabetes screening, diagnosis and management are important health issues, according to the electronic charts of the patients' clinicians suggested most patients with prediabetes counselling on physical activity, but less than one third of them reported prescribing metformin. Similar study was none-third out among Hungarian general practitioner similar), but based on the results of our survey by the involvement of 34 Hungarian GPs it was shown that in 64% of individuals registered in the GPs' practices the regular health check legally specified as once every three years (51/1997. Decree of the Ministry of Welfare) was not completed. The fasting blood glucose measurement whose once every two years frequency is also legally specified is performed only in 34% of practice clients. It is reasonable to suppose that the missing financial incentives for prevention services in primary care strongly hamper service provision regarding prediabetes screening as well. Although detailed guideline for practitioners on diabetes screening was published by the Hungarian Diabetes Federation almost ten years ago, not simply the prediabetes screening is insufficient, but even monitoring the achievement of fasting blood glucose and HbA1c target values in case of diabetic patients is largely incomplete (proportion of uncontrolled subjects was 43–45% in 2016). To prevent the development of T2DM, if lifestyle modification is not successful and/or does not lead to results, metformin treatment with a normal lifestyle will reduce

or delay the onset of diabetes. In this context, there is a need to increase knowledge of preventive medication, including metformin treatment, in primary care in the home and to make the prescribed use of preventive medication widespread. A national study has also demonstrated that the mortality burden of diabetes in Hungary is significantly higher, about 2.5 times higher than official mortality statistics, and it is of crucial importance that diabetes prevention (covering not only preventive medication but also screening, treatment, care, prevention, screening and management of complications) should be a public health priority.

In terms of avoidable premature mortality due to alcoholic liver disease and cirrhosis, the fact that alcohol consumption is the second highest risk factor for diseases and injury in Central Europe is a severe problem. Although mortality due to chronic liver disease and cirrhosis is on a declining trend in Europe, including in Hungary, the risk of premature mortality was still almost four times higher for males and almost three times higher for females in 2015 compared to the EU-15 average. Several studies have analysed the spatial distribution of mortality due to alcoholic liver disease in our country. In the Hungarian working-age population, especially for males, high mortality risk has been found along Hungary's north-east-south-west axis. The fact that excessive alcohol consumption is the etiological factor underlying more than 80% of mortality due to chronic liver disease in Hungary indicates a significant 'alcohol exposure' of the Hungarian population, which is further contributed to by the quality of alcohol consumed (mainly of questionable origins). This confirms the need for further detailed epidemiological studies for risk factors (quality and origin of alcohol).

7. MAIN FINDINGS AND RESULTS

The research (2015-2019) identified the spatial inequalities of mortality due to MAHC, alcoholic liver disease and cirrhosis, as well as T2DM within our country and explored the association of these mortality rates with socioeconomic status. In addition, by aggregating data for the years 2018 and 2019, spatial inequalities and relative prevalence of metformin prescription, redemption and redemption rates for T2DM prevention, as well as the relationship between the use of the medication and socioeconomic status, were determined.

On this basis, the main findings of the research are:

- In terms of spatial inequalities, the high risk of mortality due to both alcoholic liver disease and cirrhosis and T2DM was clustered in the eastern, north-eastern and south-western regions of Hungary. The districts in these areas had higher rates of metformin prescriptions and redemptions, as well as higher relative rates of redemptions.

- We conclude that socioeconomic factors are important determinants of the high mortality risk investigated (MAHC, premature death from alcoholic liver disease and cirrhosis, and T2DM), with the mortality burden being highest in the most deprived areas.
- Of the findings of the ecological study on metformin use, the most important finding is that there is only a partial overlap between the spatial distribution of metformin prescribing/redeeming frequencies and areas at high risk of T2DM mortality. These results highlight that, although the high risk of mortality due to T2DM cannot be fully explained by metformin 'underuse' nor by less favourable primary compliance (i.e. prescription redemption rates), there are areas where high T2DM mortality is associated with low metformin prescription/redemption rates.
- Using a spatial epidemiological methodology, with adequate methodological limitations and a moderate interpretation of the results, this research represents a new approach to the investigation of MAHC, providing valuable information for a critical (explore the gap-finding) analysis of health system performance, access to and utilisation of services.
- To reduce alcohol-related mortality in the working-age Hungarian population (taking into account inequalities), our results can support national or local decision-makers and policy-makers in the development of the missing alcohol policy strategy, including the targeted planning, organisation and implementation of health promotion programmes to influence the quantity and quality of alcohol consumption.
- It is also of particular importance that the results confirm the strong influence of unfavourable SES on health status, including mortality, and that (national/local) health policy should take this evidence into account when considering programmes to improve the health status of the population. Furthermore, these significant inequalities identified by the SES should also be taken into account when planning measures to improve the performance, quality and efficiency of health services.

8. SUMMARY

For several decades, the Hungarian population has been known for its poor health by international comparison, characterised by extremely unfavourable premature mortality rates. The trend of avoidable mortality within premature mortality, both MAHC and PAM, has been continuously decreasing since 2000, but even in 2017, it was almost three times higher than the avoidable mortality of the Swedish population. Nowadays, a wide evidence base confirms the role of socioeconomic factors as the strongest determinant of high premature mortality. Thus, this study aimed to investigate the characteristics of avoidable mortality in the working-age Hungarian population, in addition to the spatial distribution and trends of avoidable mortality (and within these, mortality due to diabetes and alcoholic liver disease) using modern, spatial epidemiological methods to identify the relationship between the indicators and socioeconomic status.

The results showed that for the spatial inequalities of premature mortality (MAHC/PAM, T2DM, due to alcoholic liver disease), the high risk of mortality was clustered in the eastern, north-eastern, and south-western regions of Hungary and showed a significant linear positive association with deprivation. This suggests that the relevant socioeconomic conditions are important determinants of the high risk of premature mortality found, with the mortality burden concentrated in the most deprived areas. Furthermore, districts located in these areas of the country had a higher frequency of metformin prescription and redemption, as well as a higher relative redemption rate. The results clearly show that, although the spatial distribution of metformin prescription/redemption frequency and areas at high risk of T2DM mortality show only partially overlapping patterns. Thus, the high risk of T2DM mortality cannot be fully explained by either metformin 'under-use' or less favourable primary compliance; there are areas where high T2DM mortality is associated with low metformin prescription/redemption rates.

To summarise, the strong influencing of socioeconomic determinant on mortality means that this effect should be considered when planning programmes to improve the health status of the population and that in the same context, measures to improve the quality and efficiency of health services can only be effective if combined with a reduction in the severe inequalities determined by socioeconomic status.

Keywords: avoidable mortality, epidemiology, socioeconomic status, prescription and dispensing, preventive medication, primary prevention

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Nyilvántartási szám: DEENK/119/2021.PL
Tárgy: PhD Publikációs Lista

Jelölt: Nagy Csilla
Doktori Iskola: Egészségtudományok Doktori Iskola

A PhD értekezés alapjául szolgáló közlemények

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A közlő folyóiratok összesített impakt faktora: 40,368
A közlő folyóiratok összesített impakt faktora (az értekezés alapjául szolgáló közleményekre): 7,956

A DEENK a Jelölt által az iDEa Tudóstérbe feltöltött adatok bibliográfiai és tudománymetriai ellenőrzését a tudományos adatbázisok és a Journal Citation Reports Impact Factor lista alapján elvégezte.

Debrecen, 2021.03.26.

DEBRECENI EGYETEM * Egyetemi és Nemzeti Könyvtár *

9. ACKNOWLEDGEMENTS

First and foremost I am extremely grateful to my friend and colleague, Attila Juhász, for all his help and support.

I would also like to my supervisors, Róza Ádány (MD, PhD, DSc) for her invaluable advice, continuous support, and patience during my PhD study.

Additionally, I would like to express gratitude to my co-authors for their contributions,

In addition, I would like to thank my co-authors for their contributions, with special thanks to Linda Beale (PhD), Piroska V. Hajdú (PhD), and Dr Anna Páldy (PhD).

I thank to Zoltánné Koós and Zsuzsanna Oláh for their technical support.

Finally, I would like to thanks my husband, parents and my friends, for their understanding and encouragement in the past few years.