

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

**Inequalities in mortality due to cardiovascular disease and preventive medication among the Hungarian population, analysed using spatial epidemiological methods**

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## 1. INTRODUCTION

### 1.1. *The socioeconomic status*

Socioeconomic status (SES) indicates the position of an individual or group in a given society. A relevant approach to characterise SES is the measurement of deprivation. Deprivation, a form of exclusion, a feature of modern poverty, is a multidimensional concept. Multidimensional poverty studies have been working on methodologies for measuring and quantifying deprivation since the 1960s and have achieved considerable results. The importance of these researches was further enhanced by the increasing attention of the European Union, the United Nations and its Children's Fund (UNICEF) to social exclusion, which deprivation measures aimed to determine, from the 1970s onwards.

The findings of several international and national epidemiological and health sociological studies have shown that wide income and socioeconomic inequalities have an impact on life opportunities, the risk of morbidity and mortality, and life expectancy at birth. Socio-economic deprivation is a risk factor for many diseases, and it is also associated with inequalities in mortality. The efforts to reduce these inequalities - in the documents, recommendations and guidelines of the European Union (EU), the United Nations, the World Health Organisation - have been particularly highlighted.

In the mid-80s, the role of the level of education on mortality was highlighted as the most important SES determinant. In England, men in the lowest educational strata, even if they did not smoke or drink more alcohol than men in other strata, had one and a half times higher risk of death due to acute myocardial infarction compared with men with higher educational qualifications and higher employment status.

The relationship between deprivation and health status in Hungary was also revealed by stratified studies in the mid-80s, followed by further studies analysing inequalities in the socioeconomic and cultural status of the Hungarian population. These studies also showed that the prevalence of circulatory system diseases was more than 3.6 times higher in the deprived population than in the non-deprived one. The most disadvantaged socioeconomic areas were previously identified in the industrial areas of Hungary, which are now predominantly rural, small rural areas, often with a higher representation of Roma population than average.

Many studies - at different spatial levels - have focused on investigating the relationship between various socioeconomic factors and mortality and morbidity, and on determining the economic

development of particular regions. These studies have shown that deprivation is associated with a higher risk of mortality, and have highlighted that in Hungary it is the primary factor of premature mortality, including cardiovascular mortality.

It is essential to distinguish between poverty and deprivation, although they are often used synonymously. It is generally accepted that if people lack the financial resources to meet their needs they are living in poverty, whereas if people lack access to other types of resources, they are deprived. Deprivation is a term used to describe the unmet needs of people, while poverty is a term used to describe the lack of resources to meet those needs. It is important, therefore, that the measurement of deprivation should not be limited to material resources, but should cover a wide range of social and living conditions.

One of the principles of EU policy is to reduce inequalities between the Member States (European Pillar of Social Rights, 2017) and to ensure a healthy environment at community, national and regional level. Reducing poverty, ensuring effective healthcare for citizens, and improving quality of life are all long-term development goals aimed at maintaining social, economic and regional cohesion in the EU. Despite this principle, the regional problems, including health inequalities, have increased in many Eastern European countries following accession to the EU. The Marmot report and a recent joint publication by the OECD and the European Commission on health and access to health services showed that there are significant health inequalities between and even within the EU Member States. The health status of the population of Member States that joined the European Union in 2004 and afterwards (EU13 countries) is less favourable than that of the population of Member States that were members of the EU before 2004 (EU15 countries).

It should be noted that the high prevalence of risk factors of health behaviour (smoking, excessive alcohol consumption, lack of physical activity, unhealthy diet, etc.) is a serious problem in terms of chronic disease prevention in Hungary. Additionally, it is important to note that, particularly among the Roma population living in more deprived areas, smoking and unhealthy diets are 1.5 to 3 times more common than in the general Hungarian population. The lower prevalence of lifestyle factors associated with a healthy lifestyle is also observed among people with less education, lower incomes and older people living in deprived small settlements. The Hungarian government has introduced several policies and social policies (anti-smoking legislation, new taxes on 'unhealthy' foods such as sweetened, salty and fatty products) to promote positive changes in health behaviour, but in this perspective, the most significant action for the Roma population has been most certainly the quadrupling of public work employment expenditure between 2010 and 2015.

### ***1.2. The association between antihypertensive preventive medication and SES***

According to the most recently available international data, the average relative risk of premature adult (25-64 years) mortality due to cardiovascular diseases (CVDs) is 2.96 times higher in the EU13 compared to the EU15, and particularly high in Bulgaria (5.25), Latvia (4.30), Lithuania (3.98), Romania (3.54) and Hungary (3.33). Although these data demonstrate that the effectiveness of preventive interventions targeting CVD is inadequate in these countries, there is a lack of studies to justify preventive measures. It is generally accepted that, in addition to interventions that influence lifestyle, significant benefits can be derived from the use of preventive medication. Aspirin and lipid-lowering drugs are widely used in the primary prevention of CVD.

Since high blood pressure is a major risk factor for CVD, antihypertensive treatment is particularly important. In a recent paper by Vrijens and colleagues, based on data from a survey of people with hypertension and discussions of a European expert group on the current state of drug adherence, they concluded that 'achieving satisfactory adherence can have a much greater impact than any other intervention to improve antihypertensive treatment and health systems have to evolve to address this challenge'.

The prevalence of hypertension in different social groups has been studied in a nearly comprehensive manner, and contradictory results have been reported in several cases on the relationship between SES and hypertension. Using PubMed, ProQuest and Cochrane databases in a systematic meta-analysis of observational studies on the association between hypertension and SES, the authors reported that the overall risk of hypertension increased among the population with the lowest socioeconomic status in terms of income, employment and education.

The results of studies investigating the association between SES and the use of antihypertensives can only be interpreted with rigorous restrictions. A systematic review and meta-analysis of studies on the association between SES and nonadherence to antihypertensive medication found that only seven of 32 studies examined more than one component, while none performed a multivariate assessment. Although the results of the pooled adjusted risk estimate showed associations between nonadherence to medication instructions and SES (0.89; 0.87-0.92 95% confidence;  $P < 0.001$ ), it was also noted that some of the studies included in the meta-analysis did not find a strong association between low (unfavourable) SES and nonadherence to antihypertensive medication. They noted that common uncertainties in the assessment of SES are identified in nearly all studies and emphasised the need for future studies that use a comprehensive measure and estimate of SES to determine if there is a true association between SES and medication utilisation.

### **1.3. *The association between antithrombotic preventive medication and SES***

CVDs cover a wide range of diseases, including thromboembolic diseases. Based on the results of several studies, an inverse relationship between SES and morbidity/mortality in thromboembolic diseases seems to have been identified. A nationwide study in the Netherlands found that areas with a more favourable SES had a lower incidence of venous thromboembolism. Another nationwide study in Sweden concluded that high educational qualifications and certain occupations requiring high educational qualifications were inversely associated with the incidence of venous thromboembolism.

For the secondary prevention of thromboembolic diseases, in addition to aspirin, lipid-lowering and antihypertensive drugs, which are also used in primary prevention, the use of antiplatelet agents and anticoagulants is strongly recommended, which act by blocking the pathways of platelet aggregation and the coagulation cascade. Clinical trials have demonstrated the safeness and effectiveness of antiplatelet drugs in the prevention of non-cardioembolic stroke, while anticoagulants are accepted for the prevention of cardioembolic stroke, atrial fibrillation and thrombotic complications associated with various cardiac conditions, including, in particular, atrial fibrillation. Long-term, sustained use of these preventive drugs is common, and guidelines define which preventive drugs are recommended for which levels of risk.

The Prospective Urban Rural Epidemiology (PURE) study found that across country groups by income (low, lower-middle, upper-middle, and high), the average use of medicines, including antiplatelet drugs, for secondary prevention of CVD is low, especially in low-income countries. Subsequent analysis based on the results of the PURE study revealed significant differences between countries. Although country-level data on secondary prevention and their availability are essential for defining national health system health policy goals and planning interventions that can reduce early CVD mortality and morbidity, only a few studies have examined the relationship between the preventive utilisation of antiplatelet drugs and anticoagulants (hereafter antithrombotic agents) and socioeconomic status.

A study in China found more than 70% lower antiplatelet use among lower SES patients, while another study in Sweden showed that the odds of being prescribed warfarin (a vitamin K antagonist oral anticoagulant) were remarkably higher among men and women living in high SES neighbourhoods than among those living in low SES neighbourhoods - men: odds ratio (EH) = 1.44 (95% confidence interval (CI) 1.27-1.63); for women: EH = 1.19 (95% CI 1.05-1.36). Persons living in low SES areas are more likely to be inadequately treated, and less warfarin utilisation than recommended is detected among those with a need for it due to atrial fibrillation and possibly other cardiovascular diseases. In contrast, a recent study in Wales (UK), which followed up linked primary and secondary care data over a six-year study period (2004-2010) based on an electronic cohort of people aged 20 years and over, showed no significant inequalities in adherence to recommended medications to primary and secondary prevention of coronary heart

disease by quintile of the Welsh Index of Multiple Deprivation (an area-based measure of socioeconomic inequality).

## 2. LITERATURE REVIEW

### 2.1. *Spatial epidemiology methods in public health studies*

Spatial epidemiology, supported by sophisticated statistical methods and spatial analysis techniques, provides an opportunity to assess and analyse the spatial distribution of geocoded events and risk factors that indicate or are associated with health status, as well as their relations. Due to data collection limitations or the privacy of personal data, most spatial epidemiological studies use aggregated data at the spatial level.

#### 2.1.1. Indicators

Standardisation allows the consideration of the potential effects of known confounders such as age, gender or socioeconomic status.

The direct standardised indicator indicates the level of mortality/morbidity of the population in the study area if its age distribution corresponded to the age distribution of the standard population. The directly standardised rate is an index indicator, and its value is fictive. Changing the age structure of the standard population used also changes the value of the age-standardised rates. The index allows direct comparisons using the same standard population, the extent depending on the standard population chosen, but requires a significant number of cases and an accurate measure of the age-specific distribution of the observed study population. For rare diseases or small geographical areas (small populations), the number of cases is usually so small that the observed age-specific rate - and ultimately the index itself - may be statistically unstable, and therefore the indirect standardisation approach is the preferred method in spatial epidemiology.

The most widely used index for mapping disease risks is the indirect standardised morbidity/mortality/prevalence ratio (SH). Indirect standardisation compares the number of observed cases in the study population with the number of expected cases determined by using the age-specific rates of the standard population weighted by the stratum size of the study population. The expected number of cases shows the numbers of cases in the study population if the stratum-specific rates were the same as the rates in the standard population. The ratio indicates the percentage difference between the mortality/morbidity of the population under study and the mortality/morbidity of the standard population for a given period and disease group.

When, in the studied population group, the

SH = 1.00 then there is no difference from the standard level,

SH < 1.00 then below the standard level,

SH > 1.00 then the level of frequency is above the standard level.

Indirect standardised ratios for the population of different study areas can be directly compared with the mortality/morbidity/prevalence level of the population used as a standard, and the difference can be compared accurately. However, the indirect standardised ratios of the population of the different study areas cannot be compared to each other unconditionally if the age structure of the population of the study areas is different, since the method employs different weightings for each area in the determination of the ratios (as the weights depend on the age and sex distribution of the population of the study areas).

The confidence intervals, as the uncertainty of the point estimate, need to be displayed with the calculated indicator. The calculation of confidence intervals is based on the assumption of the approximately normal distribution of the risk indicator or an appropriate mathematical transformation (e.g. logarithmic). While for large numbers of cases the assumption of approximate normality is reasonable, for small numbers of cases this assumption is not appropriate; thus, for low numbers of cases, a Poisson statistical approach is preferred.

### 2.1.2. Spatial pattern analysis

Examining the spatial distribution of health status indicators allows public health analyses to identify high-risk areas by examining patterns of spatial distribution, using non-focused or focused cluster analysis or disease mapping. In the epidemiological approach, clustering is the spatial accumulation of cases in the population at risk concerning its size. Spatial clustering occurs when there is residual spatial risk variation beyond that explained by the background population. This residual variation may be due to a true clustering of cases in one or more areas, or to a correlation between observations. Clustering may be due to several factors, such as lifestyle, environmental risk, infectious agent, or genetic variability.

According to Waldo Tobler's first law of geography, 'everything is linked to everything else, but the link between near things is stronger than the link between distant things'. This law is also the basis for the concept of spatial autocorrelation, which expresses the fact that indicators and characteristics of areas that are nearer to each other are related (either positively, i.e. similar, or negatively, i.e. opposite). Statistical analysis of autocorrelation measures and characterizes these spatial relationships and their magnitude, helping to determine the pattern of spatial distribution objectively. One commonly used indicator is Moran's I, which can take values between  $-1 \leq I \leq 1$ .

In case the indicator is

$I > -1/(N-1) (\approx 0)$ , then there is positive,

$I = -1/(N-1) (\approx 0)$ , then there is none,

$I < -1/(N-1) (\approx 0)$ , then there is negative autocorrelation.

where  $N$  is the number of area units

In the case of positive autocorrelation, the spatial distribution is characterised by clustering. In the absence of autocorrelation, the spatial distribution of the analysed variable can be described as random, while in the case of negative correlation, the spatial distribution is dispersed.

Cluster identification techniques are based on hypothesis-testing methods, whereby the study area is scanned by placing several circular (or elliptical) windows to identify the group of adjacent areas with the highest or lowest risk. The test statistic is determined using the Monte-Carlo simulation.

### 2.1.3. Disease mapping

When using aggregated areal data, it should not be ignored that it masks the heterogeneity and variability within the study area. The higher the resolution of the study, i.e. the smaller the spatial, population units, the more ecological bias due to within-area heterogeneity can be reduced. Studies at the small area scale allow local effects to be taken into account.

However, not careful map visualisation can be very misleading in high-resolution studies. For small area analyses, it may occur that small populations often have few observed and expected cases, resulting in unstable risk estimates. The variance of the indirectly standardised ratio is inversely related to the expected number of cases, so small populations contribute to the high variability of risk with very high statistical uncertainty. The smaller the number of cases, the greater the spatial variability of the maps, reflecting near-random variation; resulting in 'noisy' maps that are difficult to interpret.

Bayesian hierarchical models provide remarkable help and approach for dealing with problems due to small numbers of cases. The Bayesian theorem underlying Bayesian statistics describes the probability of an event, based on prior knowledge of the event's potentially related information (prior probability distribution). The result of the estimation is a posterior probability distribution that depends on the prior probability distribution and the conditional probability of the data. The Bayesian smoothing approach results in less smoothed risks in areas with higher case/population values (e.g. urban areas) than in areas with higher variability of risks (typically with low case numbers), and thus results more stable estimates of the spatial distribution of risk,

One of the Bayesian smoothing options is the Poisson-lognormal model (Heterogeneous- HET), which deals with spatially unstructured random effects, using smoothing to the "global" mean across the entire study area. The other is the Intrinsic Conditional Auto-Regressive (ICAR) model, which incorporates spatially structured random effects that account for spatial autocorrelation, smoothing to the "local" mean using information borrowed from neighbouring areas, revealing the spatial correlation of risk. The most commonly used model in public health is the hierarchical Bayesian convolution model (BYM model) proposed by Besag et al., which includes both spatially unstructured, heterogeneous and spatially structured random effects that account for spatial autocorrelation, allowing a combination of 'local' and 'global' smoothing. The degree of smoothing can be controlled by a specification of the so-called hyperprior parameters. The Deviance Information Criterion (DIC) and the Watanabe-Akaike Information Criterion (WAIC) methods and measures help to select and employ the best-fitting model from a variety of models.

Hierarchical models can enable multivariate, joint analyses, so that the joint effects and correlations of several indicators can be investigated. The development of statistical methods over the last decades has also provided to extend disease mapping models with the time dimension, providing estimations of spatial and temporal variation in risk in high-resolution studies.

#### 2.1.4. Statistical uncertainty

The uncertainty of the point estimate is also determined in spatial epidemiology and can be displayed on maps whenever appropriate. For Bayesian approaches, the 95% Bayesian credible interval of the risk can provide information on the uncertainty related to the estimated risk.

A major advantage of the Bayesian framework is that the full posterior probability distribution is obtained for the parameter in interest. In the Bayesian approach, the Credible interval explicitly indicates the posterior probability that the estimated parameter is within its limits. Following the same rationale, Bayesian inference can make any probabilistic prediction on parameters; for example, it is easy to calculate the posterior probability that the estimated parameter is greater (or less) than a selected threshold. This probability is often used in epidemiological studies, assuming that the estimated parameter is the relative risk/risk of disease (or mortality). In this case, the density function (posterior probability distribution) estimated for a given area can be used to determine the probability that the risk value is greater than 1. If at least 80% of the area under the relative mortality density function is above 1, then there is at least an 80% probability that the relative risk is greater than 1. Richardson et al. have shown that using this decision rule  $D(0.8, 1)$  for BYM models, areas of elevated risk can be identified with high specificity and acceptable sensitivity

### 2.1.5. Ecological regression

The ecological regression models allow for the investigation of spatial relationships between risk factors and health outcomes. By extending the disease mapping models with the spatial risk factor, it is also feasible to take into account the assumed effect of residual spatial autocorrelation as an 'unmeasured risk factor'. Ignoring this component may lead to biased estimates of regression coefficients, underestimation of uncertainty, i.e. - falsely - to the estimation of narrower confidence intervals.

There are many computational methods and software available for fitting Bayesian hierarchical models and for the estimation of the parameters. For example, WinBUGS and OpenBUGS, which fit models using Markov chain Monte-Carlo simulation (MCMC), or INLA, which fits models using an integrated nested Laplace approximation. The advantage of the INLA approach is that it takes significantly less time to estimate the model fitting.

The application of epidemiological methods, in addition to individually designed studies, with the reduced computation time, provides a basis for the development and maintenance of detailed and methodologically correct public health information systems.

## ***2.2. Overview of a history of socioeconomic indicators***

The results of numerous international and national epidemiological and health sociological studies have now demonstrated the links between unfavourable socioeconomic status and the poor state of health (mortality, morbidity).

socioeconomic inequalities can be reflected in health inequalities, and understanding health inequalities, their determinants and their relationships are essential in reducing them. Examining the spatial distribution of socioeconomic status and examining its correlations can be a first step in achieving these objectives. Although high-resolution, area-based studies are appropriate to examine the spatial distribution and inequalities of specific SES indicators, the development and application of composite or multidimensional indices of deprivation have become more common. The majority of these indices are based on census data.

The first such index was Jarman's Underprivileged Area (UPA) score, developed primarily to measure primary healthcare needs. The indicators included unemployment, the proportion of unskilled workers, the proportion of single-parent households, proportion of under-fives, pensioners living alone, ethnicity, frequency of moving in the past year and the lack of a car.

The Townsend and Carstairs indices are primarily developed to measure material deprivation. Similar methodologies were followed to calculate both indices, but while the Townsend index used indicators of unemployment, lack of cars, overcrowding and the proportion of people not owning their own home, the Carstairs index combined indicators of male unemployment, lack of cars, overcrowding and low social class.

Forrest and Gordon have designed two different indices to measure material (MATDEP) and social (SOCDEP) deprivation. The MATDEP took into account overcrowding, the comfort of housing (bathrooms, central heating) and lack of cars, while the SOCDEP took into account unemployment (both in the active and the 16-24-year-old population), single-parent households, single-person households, pensioner households, people with long-term chronic illnesses and people with dependents.

Deprivation indices were developed in New Zealand and Belgium at the turn of the millennium, and multiple composite indexes in the UK. The UK index is constructed by combining and aggregating 39 indicators in seven main domains (income, unemployment, education, health, crime, housing and environment) and is updated every 5 years.

Studies on the relationship between deprivation and health status have also been carried out in Central and Eastern European EU countries, such as Slovenia and the Czech Republic. In Western Europe, in France and Spain, extensive studies have investigated the relationship between socioeconomic status and health status. Other studies have also been implemented in Germany, Denmark, Cyprus, Switzerland and overseas in the USA and Canada. Most deprivation indices include indicators related to income, employment, education, housing and ownership of certain goods or objects, and family.

The methodological basis for index calculation is the normalisation of the data and the computation of the Z-score. Normalisation (usually log-transformation) transforms the distribution of variables into a normal distribution, and the Z-score allows the combination of variables by transforming different variables into the same scale.

Different weights can be used to sum up the Z value; the weights could be of equal values or based on empirical measurements/observations. Expert opinions, empirical evidence(s), policy focus, societal needs can be used to determine the weights. In most cases, weights are determined using a type of factor analysis or regression analysis. The most commonly used data reduction techniques are Principal Component Analysis and Factor Analysis. The principal component analysis is based on the analysis of the total variance, while factor analysis is used to analyze the shared variance.

A recent form of index building is the employment of hierarchical Bayesian factor analysis, which helps to deal with the uncertainty arising from small numbers of cases (e.g. in the case of small settlements) and also to determine the measurement uncertainty of the indices as well.

Although the objective determination of weights is helped by factor analysis techniques, it is not reproducible in time and space, because indicator values change over time, so their relationships and the weights also change. This is also true when index construction is carried out based on the same indicators for different areas (e.g. countries) since the weights are probably different.

### ***2.3. Territorial inequalities in the socioeconomic status of the Hungarian population based on the developed Deprivation Index 2011.***

The aim - based on the available data - was to develop an area-based, multidimensional indicator reflecting both material and social deprivation, which can be used to characterise the socioeconomic status of Hungarian municipalities with a composite indicator, and by identifying inequalities could provide a wide contribution to understanding several public health problems, and also provide opportunities to identify possible strategies for addressing inequalities.

Employing national and international literature, an SES index was developed using a combination of selected socioeconomic status indicators at the municipality level, derived from the integrated database of the National Spatial Development and Planning Information System (TEIR), including the data of the Central Statistical Office of Hungary from the 2001 Census and the data of the Tax and Financial Control Office (2011).

#### **2.3.1. The indicators selected**

The chosen indicators are:

**Income** (per capita taxable income);

**Low education level** (proportion of the population aged 15 years and over with 8 or fewer years of primary education, whether completed or not);

**Unemployment** (the proportion of unemployed among the productive age population);

**Single-parent families** (percentage of women raising children alone in families);

**Large families** (proportion of two-parent families with three or more children as a percentage of families);

**The density of housing** (persons per room);

**Car ownership** (number of cars per 100 persons).

### 2.3.2. Forming the index

Data were transformed by normalisation (log-transformation) and standard values were determined. For standardisation, the Z-value was determined based on the observed value ( $X$ ) of the indicator, the mean of all observed values ( $\bar{X}$ ) and their standard deviation ( $s$ ):  $Z = \frac{X - \bar{X}}{s}$

For income and car ownership reversed:  $Z = \frac{\bar{X} - X}{s}$

The standardisation provided a standard normal distribution of each indicator ( $\bar{X}=0$ ,  $s=1$ ). The weighting of each indicator before aggregation was based on the statistical relationship between them. The weights were determined using principal component analysis. The municipality-specific index was determined by summation of the weighted Z-scores of the indicators for a given municipality:

$$\text{Deprivation index} = \sum (\text{weight}_i \times Z - \text{value}_i)$$

Negative values indicate less deprived areas, positive values indicate more deprived areas. Overall, higher values represent deeper/more deprivation.

### 2.3.3. Spatial distribution of deprivation

Based on our results, we identified two major contiguous areas of deprivation in Hungary, one in the North-East and East and the other in the South-West of the country, based on the DI deprivation. The coherent deprived area in the north-eastern part comprised the whole of Borsod-Abaúj-Zemplén and Szabolcs-Szatmár-Bereg counties, the northern border part of Nógrád county and the south-eastern corner of Heves county, joined by the deprived areas found in the eastern part of Jász-Nagykun-Szolnok county. Other connected deprived areas can be found in the eastern part of the country, such as Hajdú-Bihar county, except for Debrecen and its surrounding area, which also appeared as a deprived area connected to the above-mentioned areas, and this more deeply deprived part also extended into the northern part of Békés county. In the case of Békés county, it should be noted that the Storm Corner is also one of the most deprived areas in the country.

The other coherent area was the western half of Baranya County, Somogy County - except for the county capital and the municipalities along Lake Balaton - and the north-western third of Tolna County.

More deprived areas were also spread in Zalaszentgrót and its surroundings, Ajka and its surroundings, the municipalities in the northern and north-western part of Kiskunság, the border

municipalities of south-eastern Bačka, Szentes and the surroundings of Makó in Csongrád County and the municipalities in the south-eastern part of Pest County.

#### ***2.4. Demonstration of the association between the health status of the Hungarian population and the socioeconomic status based on the developed DI (the use of DI in research)***

##### **2.4.1. The association between premature mortality and deprivation**

Using ecological regression (spatial regression), the results of the association between premature adult (25-64 years) mortality and DI for the years 2015-2019 identified a significant positive association for both sexes, for overall mortality and all major mortality groups; i.e., the risk of mortality increased with increasing deprivation. The results of the regression analysis also showed a significant positive association between mortality before age 1 year and mortality due to infectious diseases (BNO-10: A00-B99) (for age groups 0-X years) and increasing deprivation.

##### **2.4.2. Association between the incidence of malignant neoplasms and deprivation**

The association between premature (25-64 years) risk of morbidity and mortality due to malignant neoplasms and DI was also investigated using spatial regression. A positive significant association between deprivation level and the risk of morbidity and mortality from malignant neoplasms was in general found for both sexes.

Analysed by cancer type, this association was strongest for lung cancer, oral cavity cancer and cervical cancer. It should be emphasised that increasing levels of deprivation increase the risk of dying from cancer considerably more than the risk of morbidity. It is also important to highlight the fact that deprivation significantly increased the risk of death even in cancer types (colorectal cancer, pancreatic cancer) in which the increased risk of morbidity was not statistically significant concerning deprivation. A significant inverse association with the spatial distribution of socioeconomic deprivation was found in only one case, breast cancer, but the risk of mortality was also significantly higher for breast cancer associated with deprivation.

##### **2.4.3. Association of childhood leukaemia survival (0-15 years) with deprivation**

During the 45-year study period from 1971-2015, 3157 cases of childhood leukaemia and myelodysplastic syndrome were recorded by the Hungarian Childhood Cancer Registry. During follow-up, 1432 death cases were recorded.

The results of a Cox regression model stratified by sex, age, type of leukaemia and period of diagnosis showed that deprivation at the municipality level was a significant prognostic factor for the survival probability of leukaemia patients. Children with leukaemia diagnosed in more deprived areas had a higher risk of dying than children with leukaemia living in areas with a more favourable SES.

### 3. RESEARCH OBJECTIVES

1. The principal aim of the research was to investigate the association between the socioeconomic situation of the Hungarian population and the spatial distribution of premature (25-64 years) mortality due to diseases of the circulatory system for the years 2015-2019.

Considering the importance of antihypertensive and antithrombotic preventive medication in the prevention (or at least delay) of cardiovascular disease mortality, we also aimed

1. To investigate the mortality and morbidity due to cardiovascular diseases and the utilisation (prescription/redemption rates) of antihypertensive drugs in relation to socioeconomic situation, in particular by examining and comparing their spatial distributions.
2. To analyse the relationship between prescription and redemption rates of antithrombotic (antiplatelet and anticoagulant) drugs and deprivation, and to identify potential anomalies in the utilisation antithrombotic medicines.

### 4. DATA AND METHOD

#### 4.1. Data sources

#### **Deprivation index**

The source of the indicators used for the determination of DI at the municipal and district level was the database of the Central Statistical Office (KSH) and the National Spatial Development and Planning Information System (TEIR).

#### **Mortality data**

Mortality data were provided by the HCSO as follows:

Data on mortality from diseases of the circulatory system (BNO-10: I00-I99), by the municipality, for the years 2015-2019, for 25-64-year-olds, by sex, in 5-year age groups were available.

For the analysis of the use of antihypertensive drugs, mortality due to diseases of the circulatory system (BNO-10: I00-I99), ischaemic heart disease (BNO-10: I20-I25), cerebrovascular disease (BNO-10: I60-I69), and hypertension (BNO-10: I10-I15) was available for 2012, by sex and 5-year age group, at the district level, for 35-64-year-olds.

To examine the use of antithrombotic drugs, data on mortality from thromboembolic diseases, namely cerebral infarction (BNO-10: I63, I64), arterial embolism and thrombosis (BNO-10: I74), phlebitis and thrombophlebitis (BNO-10: I80) and other venous embolism and thrombosis (BNO-10: I82) mortality were available for 2016 at the district level, 40-X years of age, by sex and 5-year age group.

### **Prevalence data**

The district-level prevalence data, used in the study of the utilisation of antihypertensive drugs, include ischaemic heart disease (BNO-10: I20-I25), cerebrovascular disease (BNO-10: I60-I69), and hypertension (BNO-10: I10-I15) data were derived from the KSH National Statistical Data Collection Programme (Patient Flow and Morbidity Data of General Practitioners and General Pediatric Practices) database, by district level, for the years 2011-2013, for 35-64-year-olds, by sex and 10-year age group.

### **Drug utilisation data**

Data on the utilisation of medicines (prescriptions and redemptions) by General Practitioners (GP) were obtained from the National Health Insurance Fund Administration of Hungary (NEAK) database.

The number of antihypertensive drugs prescribed and redeemed by drugs, as diuretics, beta-blockers, calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and combinations of ACE inhibitors and ARBs with diuretics, were available by GP practice for the year 2012, ages 0-X years.

Data on the prescription and redemption of antithrombotic drugs by groups of agents commonly used in secondary cardiovascular prevention, such as vitamin K antagonists (coumarin derivatives, acenocoumarol - Syncumar; Warfarin), Factor Xa inhibitors (rivaroxaban-Xarelto), and platelet aggregation inhibitors (Clopidogrel), were available for the year 2016, for the age group 40-X years, by 5-year age group and by sex, per GP practice.

## **Population data**

The source of the population data (population for the years studied, by 5-year age group and sex) was the Central Office for Administrative and Electronic Public Services.

## **District level aggregation**

Since DI, mortality, prevalence and population data were not available by GP practice, and due to the free choice of a GP practice in Hungary, data were aggregated to district level when grouping the data into the same study unit to minimise the probability of misclassification, but to maintain the highest possible spatial resolution.

### **4.2. Methodology**

#### **4.2.1. Deprivation index**

The DI was calculated according to the method described in section 2.3.2 Index calculation. The DI for each district was determined by the weighted average of the municipality-level DI, weighted by population size.

#### **4.2.2. Rapid Inquiry Facility**

The ecological studies were carried out using the Rapid Inquiry Facility – RIF 3.2 software developed by the Small Area Health Statistics Unit SAHSU - Department of Epidemiology and Public Health, Imperial College London and further developed in collaboration with the Centers for Disease Control and Prevention, CDC, USA.

#### **4.2.3. Spatial inequality**

In mortality analyses, either because of the high spatial resolution, the short study period or the low number of cases (also observed at district level), the instability of the relative indicators can be stabilised using hierarchical Bayesian models, which provide more stable estimates and more easily interpretable maps of the spatial distribution of mortality risks.

In our studies, spatial distribution of inequalities was analysed using relative indicators, indirectly standardised ratios by age and sex, smoothed by hierarchical Bayesian methods, using the "diseasemapping" function of RIF 3.2. RIF 3.2 implements all the three hierarchical Bayesian models (HET, CAR, BYM). The model diagnostic parameters (DIC, WAIC) were used to select

the best supported model with the lowest predictive error, which was the BYM model for all studies.

The uncertainty related to the estimated relative risks was measured by the posterior probability (UV) exceeding 1, which shows the probability that the estimated risk of a given area is greater than 1. The maps were marked with areas - interpreted as sufficient statistical evidence that the relative risk has increased - where the estimated relative risk value is greater than 1 with a probability of at least 80%. Furthermore, when examining the spatial distribution of premature (35-64 years) deaths due to diseases of the circulatory system in 2012, areas where the risk of death was estimated to be 80-90%, 90.01-95% and >95% with probability greater than 1 were marked separately.

Since the outcome of a probability estimate is a density function, if the estimated relative mortality risk value for an area exceeds 1 with a probability of no more than 20%, it can be reasonably said to be less than 1 with a probability of 80%. For the 2015-2019 analysis of the municipality-level spatial distribution of premature adult (25-64 years) mortality due to diseases of the circulatory system and the 2016 analysis of the spatial distribution of mortality due to thromboembolic diseases, these low mortality risk areas were also highlighted as low risk areas.

#### **4.2.4. Risk analysis**

The relationship between DI and mortality, morbidity and drug utilisation was investigated by using the RIF 'risk analysis' function, by defining direct and indirect standardised indicators for groups of municipalities and districts classified by quintiles or tertiles of the Index. For the direct standardisation, the age distribution of the European standard population (2013) was used as standard, and for the indirect standardisation, the national sex- and age-specific (by 5-year age groups) rates for the period under study were used as standard. In the analysis of data on the utilisation of antihypertensive drugs, where data by age group were not available, adjustments were performed using the proportion of the population aged 60 years and over in the districts as a categorical covariate in the risk estimate. For the frequency calculations, the population aged 30 years and older were used. To compare the relative indicators (group medians of socioeconomic status) obtained as quintile or tertile DI, i.e. to statistically analyse the relationship between the observed variable and deprivation,  $\chi^2$  homogeneity tests and  $\chi^2$  linearity trend tests were performed. In the analysis of the utilization of antihypertensive drugs, the districts were grouped into tertiles according to deprivation. In this way, we were able to ensure the robustness of our analysis even for relatively small numbers of cases (such as deaths from hypertension). We performed a negative binomial regression analysis (used to analyse case-count type data) to examine the association between deaths due to thromboembolic diseases and the prescription and redemption of antithrombotic drugs with deprivation. We used negative binomial regression

instead of Poisson regression to address the overdispersion identified by the Pearson 2 goodness-of-fit test. The use of the district-level expected cases for age group 40-X years, sex, 2016, determined by indirect standardization, as an offset variable in the regression without a coefficient, allowed the elimination of differences due to the different size, sex and age group distribution of the populations at risk, ensuring comparability of the cases by deprivation group and interpretation as a coefficient effect. Using the data from the least deprived group as a reference, the Incidence Rate Ratio (IRR) was estimated by deprivation category.

## 5. RESULTS

### ***5.1. Secular trends, spatial disparities and spatial distribution of mortality from diseases of the circulatory system and its association with deprivation in the Hungarian population.***

The premature (25-64 years) mortality from diseases of the circulatory system in the Hungarian population followed a declining trend and showed marked regional disparities in the 2015-2019 study period.

It should be noted that, comparing the premature mortality rates of the V4 Member States based on the standardised rates for age composition of the European Standard Population 1976 used by the WHO (WHO, 2021), the premature mortality of the Hungarian population is almost twice for both sexes that of the Czech Republic (1.85 for women and 1.88 for men) according to the latest available data for 2017. The premature mortality of Hungarian women is similar to the previous one (1.76) and exceeds the Polish premature mortality for women, while for men the Hungarian mortality excess one and half times higher than the Polish mortality. Slovakian mortality is also more favourable than the mortality of the Hungarian population for both sexes, with Hungarian female premature mortality 34% higher, while male premature mortality is 52% higher than Slovakian female, male mortality respectively.

In terms of spatial distribution, the population living in the north-eastern and south-western parts of the country, and along the axis connecting these two areas, is the most disadvantaged in terms of mortality.

The location of the areas with an elevated risk of premature mortality, although with different rates for each sex, was similar to the areas estimated by the DI as being more deprived. The results of the risk analysis showed a statistically significant ( $\chi^2_{\text{homogeneity}} = 1284.40$ ,  $P = 0$ ,  $\chi^2_{\text{linearity}} = 1249.18$ ,  $P = 0$ ) positive association between increased deprivation and increased indirect standardised premature mortality due to circulatory system diseases for both sexes. Based on the DI, the overall mortality (Standardised Death Rate) in the top quintile (most deprived group) municipalities was 200% higher for men and 260% higher for women than in the lowest quintile (least deprived group) municipalities. In the most deprived areas, premature mortality was 50%

higher than the national premature mortality rate for men and 87% higher for women, while premature mortality in the least deprived areas was 27% lower than the national rate for both sexes.

## **5.2. Association between the utilisation of antihypertensive drugs for the treatment of hypertension and deprivation in Hungary**

### **5.2.1. The spatial distribution of premature mortality and the prevalence of selected cardiovascular diseases as well as their association with deprivation**

Deprivation index values defined by districts varied widely from  $-3.76$  to  $+5.83$ , which indicates a high level of socioeconomic inequalities in the country. The tertiles based on the DI values were defined as ranges of  $-3.76 \leq DI \leq -0.6$  with an average of  $-1.32$  (tertile I);  $-0.6 < DI \leq 0.58$  with an average of  $-0.04$  (tertile II); and  $0.58 < DI \leq 5.83$  with an average of  $1.59$ . The distribution of the DI values shows that the least-favoured districts were found in the northeastern and southwestern part of Hungary in 2011. The least deprived districts of the country were localized in the northwestern region of Hungary, in the capital city of Budapest and its neighbouring areas. The spatial distribution of premature mortality due to diseases of the circulatory system in Hungary was characterized by significant inequalities, the areas of highest SMRs were found in the eastern part of the country, and along the north-eastern border of Hungary.

The resultant pattern of excess risks caused by the examined causes of premature mortality showed a correlation with the spatial pattern of deprivation. The results of the risk analysis showed a significant association between the risk of premature cardiovascular mortality and deprivation ( $\chi^2_{\text{homogeneity}} = 229.21$ ,  $P = 0$ ,  $\chi^2_{\text{linearity}} = 226.91$ ,  $P = 0$ ); between the risk of cerebrovascular premature mortality and deprivation ( $\chi^2_{\text{homogeneity}} = 33.38$ ,  $P = 0$ ,  $\chi^2_{\text{linearity}} = 33.12$ ,  $P = 0$ ); between the risk of chronic ischaemic heart diseases and deprivation ( $\chi^2_{\text{homogeneity}} = 191.1$ ,  $P = 0$ ,  $\chi^2_{\text{linearity}} = 182.58$ ,  $P = 0$ ); and between the risk of hypertensive diseases and deprivation ( $\chi^2_{\text{homogeneity}} = 23.8$ ,  $P = 0$ ,  $\chi^2_{\text{linearity}} = 23.7$ ,  $P = 0$ ). Premature mortality in the areas of the highest deprivation tertile exceeded the national average mortality by 25% for mortality due to diseases of the circulatory system, by 22% for mortality due to cerebrovascular disease, and by 28%—with a wider confidence interval - for mortality due to hypertensive diseases.

Regarding the relative prevalence values, the results of the risk analysis also showed a significant association between the relative prevalence of chronic ischaemic heart diseases and deprivation ( $\chi^2_{\text{homogeneity}} = 41872.22$ ,  $P = 0$ ,  $\chi^2_{\text{linearity}} = 41072.6$ ,  $P = 0$ ); between the relative prevalence of cerebrovascular diseases and deprivation ( $\chi^2_{\text{homogeneity}} = 8823.8$ ,  $P = 0$ ,  $\chi^2_{\text{linearity}} = 8241.2$ ,  $P = 0$ ); and between the relative prevalence of hypertensive diseases and deprivation ( $\chi^2_{\text{homogeneity}} =$

7085.9  $P = 0$ ,  $\chi^2_{\text{linearity}} = 5755.9$ ,  $P = 0$ ). For hypertensive diseases, fewer differences were found in morbidity associated with deprivation. In the areas of the highest deprivation tertile, morbidity exceeded the national average by only 4%.

### **5.2.2. Antihypertensive drug utilization (prescription and redemption rates)**

In Hungary, altogether, 41,221,460 antihypertensive regimens were prescribed in 2012, and only 64.85% of those (26,732,297) were redeemed. The frequency of prescription was 6.111 [6.108–6.112] and the frequency of redemption was 3.963 [3.961–3.964] per person aged >30- year-old. The redemption rate of different types of antihypertensive drugs differed significantly. The redemption rates of beta-blocking agents, ACE inhibitors, calcium channel blockers, diuretics, and ARBs were approximately 70%, while the redemption rates of ACE inhibitors and ARBs combined with diuretics were significantly lower (46.46 and 36.43%, respectively). Furthermore, the lowest frequencies of prescription and redemption per person aged >30-year-old were found for ARBs combined with diuretics, and the highest frequencies were shown for beta-blocking agents.

The proportion of ACE inhibitor (with and without diuretics) prescription and redemption was the highest (about one-third of the total) in each deprivation group (tertiles I-III.), while the prescription and redemption of beta-blocking agents was the second highest, and the prescription and redemption of calcium channel blockers was the third highest.

Representation of these drugs' prescription and redemption increased by deprivation level; proportions of ARB prescription in the most deprived tertile were lower (by approximately 2%) than that in the least deprived tertile (12.05 vs. 14.14%). The same trend was observed in the case of ARB redemption (its representation in the most deprived tertile: 10.07%; and in the least deprived tertile: 11.55%).

Areas of the highest deprivation showed high frequencies of ACE inhibitors in midwestern, northeastern, eastern and southwestern parts of Hungary. However, in those parts of the country, low relative frequencies of prescriptions for ARBs were found, while in the midwestern and northwestern part of Hungary was associated with high relative frequency values.

The results of the risk analysis showed a linear association of the relative frequency of prescriptions for almost every drug with its redemption and deprivation. However, varying associations were found regarding ARBs and ARBs in combination with diuretics.

A reverse J-shaped association was detected between the relative frequency of ARB prescriptions and deprivation. In the highest deprivation tertile, it was lower than the national average by 3% (relative frequency: 96.77% [96.53–97.02]). The relative frequency of the prescriptions and redemptions for ARBs in combination with diuretics showed a J-shaped association with deprivation.

The frequency of prescription for all antihypertensive drugs in the lowest tertile (i.e., in the least deprived tertile) was 5.7273 [5.7244–5.7302], which was 7% (relative frequency: 93% [93.72–93.82]) lower than the Hungarian average, whilst the frequency in tertile III (i.e., in the most deprived tertile) was 6.5809 [6.5769–6.5850], which exceeded the national average by 7% (relative frequency: 107% [107.04–107.17]). Furthermore, the frequency of redemption for all antihypertensive drugs in the lowest tertile was 3.6038 [3.6015–3.6061], which was 10% lower than the national average (relative frequency: 90% [90.37–90.49]), and in the highest tertile, the frequency was 4.6047 [4.6013–4.6081], which was 15% higher (relative frequency: 15% [114.71–114.88]) than the national average. Similar linear associations were found in the relative frequency for almost every drug, except the ARBs in combination with diuretics prescription.

When the number of redeemed prescriptions and that of the prescriptions for antihypertensive drugs were compared, the redemption rate was found to be higher as the deprivation became more pronounced, i.e., better compliance was observed in tertile II than in tertile I, and the highest rates (independent from the types of drugs) were always associated with the districts with the highest deprivation.

### ***5.3. The association between the utilisation of antithrombotic drugs preventing deaths from thrombotic diseases and deprivation in the Hungarian population***

#### **5.3.1. The spatial distribution of mortality caused by different thromboembolic diseases in connection with deprivation**

The spatial distribution of mortality due to thromboembolic diseases could be characterized by significant inequalities, and the areas of highest standardized mortality ratios (SMRs) were detected in the northwestern, western, northeastern, and southeastern regions of the country. However, a cluster consisting of five counties with high mortality caused by thromboembolic diseases was detected in the northwestern and western parts of the country, where the majority of the least-deprived districts were localized, while a cluster consisting of two counties that were highly deprived with low mortality figures was localized in the northeastern region.

The results of the regression analysis presented that deprivation was a significant but non-linear determinant of mortality due to thromboembolic diseases in deprivation quintiles III-IV, and it was found to be higher by approximately 30–40%, while in quintile V, it was approximately 30% higher than that in the least-deprived region (quintile I).

### **5.3.2. Prescription and redemption rates of antithrombotic drugs and their relationships with deprivation**

In Hungary, 1,729,058 clopidogrels, 1,024,233 Syncumar, 447,050 warfarin, and 165,816 Xarelto prescriptions for 28 days/one month were issued by general practitioners in 2016. The highest frequencies of both prescription and redemption per person aged 40+ years old were noticed for clopidogrel, and the lowest frequencies were shown for Xarelto. The redemption rate of the four types of antithrombotic drugs differed significantly. The redemption rate of Syncumar prescriptions was the highest, 76.24%, while the redemption rate of clopidogrel was the lowest, only 54.4%.

The frequency of clopidogrel prescriptions concerning the national average was higher in districts in the southwestern and northeastern parts of Hungary. The frequency of Syncumar prescriptions also had a similar spatial pattern with a higher relative prescription rate in the middle of the country. The districts with a higher relative frequency of warfarin prescriptions were located in the northeastern, southern, and western parts of Hungary. Districts with a higher relative prescription ratio for Xarelto were located along the axis in the southwestern and southeastern parts of the country.

The spatial patterns of relative redemption ratio were very similar to the prescription ratio for each anticoagulant drug, respectively.

### **5.3.3. Prescription and redemption patterns of antithrombotic drugs and their relationships with deprivation levels**

Concerning the total number of drugs utilized, clopidogrel prescription and redemption were the highest (approximately half of the total prescriptions and 40.7% of the total redemptions), followed by the prescription and redemption of Syncumar, warfarin, and Xarelto. The proportions of clopidogrel and Syncumar prescriptions and redemptions were increased by deprivation level, while the proportion of warfarin and Xarelto prescriptions and redemptions showed an opposite trend, i.e., in the most deprived quintile, the proportions were much lower than in the least deprived quintile. The most remarkable differences between the least-deprived and the most-deprived quintiles were observed for Xarelto prescription and redemption (6.22% vs. 3.53% and 6.14% vs. 3.87%, respectively).

A significant association was discovered between the frequency of clopidogrel prescriptions per 100 persons aged 40+ years and deprivation. The incidence rate ratios in the highest deprivation quintile (quintile V) were 60.7% higher than those in the lowest quintile area (quintile I). A similar association was found in the case of Syncumar prescriptions, with 25.342 prescriptions/100 persons in the most deprived quintile (Table 3). The results show that deprivation is a significant but non-linear determinant of the frequency of warfarin prescriptions, and no association was found between Xarelto prescription frequency and deprivation. Similar but stronger, positive associations were detected between deprivation and redemption regarding clopidogrel, Syncumar, and warfarin, but no association was found for Xarelto.

When the number of redeemed prescriptions and that of the prescriptions for antithrombotic drugs were compared, the frequency of redemption and the redemption rate were shown to be increased as the deprivation became more pronounced, i.e., better primary compliance was observed in quintile V than in quintile I, and the highest rates (independent of the types of drugs) were always associated with the districts with the highest deprivation.

#### **5.3.4. Identification of Anomalies in Preventive Medication in a Cluster with High Mortality in the Less Deprived Region of the Country**

The cluster with high mortality (standardized mortality ratio: 1.393) caused by thromboembolic diseases in the northwestern part of the country, consisting mainly of counties with the highest socioeconomic performance, was further analyzed, and it was shown that both prescription and redemption rates for each drug were less favourable than the country average. To better demonstrate the extent of the discrepancy between socioeconomic development and thromboembolic disease mortality, as well as preventive medication, further analysis was performed. Prescription and redemption rates, as well as the relative redemption rate, were defined for each drug for an eastern Hungarian region consisting of two highly deprived counties with significantly lower mortality than the country average (standardized mortality ratio: 0.747, and all the rates were found to be significantly higher than that in the northwestern cluster, close to or even better than the national average values).

## **6. DISCUSSION**

### **6.1. Discussion**

This study investigated the association of cardiovascular disease mortality and preventive medication with deprivation using a DI developed to characterise socioeconomic status. The DI

is a complex, multidimensional index that includes both material and social factors. Our studies aimed to define an index measuring the socioeconomic status of the population at the municipal level in Hungary, using both international and national references, and to examine the relationship between inequalities defined by the DI and premature adult (25-64 years) mortality due to cardiovascular disease in the Hungarian population.

We also aimed to assess the association between cardiovascular mortality and spatial inequalities in the utilisation of certain groups of drugs used for preventive medication, i.e. whether cardiovascular mortality is associated with the utilisation of preventive medication.

The developed index is the first multidimensional, composite index in Hungary that can be applied for municipal-level analysis, and this study summarises the results of the first comprehensive study analysing the association between socioeconomic status and the prevalence of CVD, CVD mortality and the utilisation of antihypertensive and antithrombotic drugs. The relevance of the study is enhanced by considering that our country is one of the EU Member States in Central and South-Eastern Europe, which are former post-communist states, with a population characterised by an excessively high relative risk of premature CVD mortality.

Risk analysis showed a significant association of the risk of premature cardiovascular and cerebrovascular mortality with deprivation. The spatial pattern of prevalence values for different diseases was similar to the distribution of their relative risk of mortality; however, inequality was less dramatic for hypertensive diseases. Based on the fact that the prevalence of hypertension exceeded the national average by only 4% in the areas of the highest deprivation tertile, while the prevalence of chronic ischaemic heart diseases and cerebrovascular diseases was higher than the national average by approximately 30% and 20%, respectively, it is reasonable to suppose that in a significant number of cases, hypertension remains unknown until the manifestation of its complications, i.e., late diagnosis. This result itself highlights the importance of screening for hypertension.

This assumption is supported by the findings that the frequency of prescriptions for all antihypertensive drugs is 7% higher than the national average, while the frequency of redemption is 15% higher than the national average in the regions with the highest deprivation. The higher frequency of prescriptions may indicate that fewer hypertensive patients can be controlled on monotherapy, i.e., more patients require more than one antihypertensive medication for blood pressure control, while the significantly lower level of primary non-compliance may indicate that the patients take medical advice when symptoms of hypertensive crisis appear or in comorbid conditions.

The patterns of antihypertensive drugs prescription and redemption significantly differ by DI tertile; although the differences expressed in a percentage seem to be small, they are statistically

significant due to a large number of observations. In areas of the highest deprivation, higher relative frequencies of ACE inhibitors, beta-blockers and calcium channel blocker prescriptions and lower relative frequency of ARB prescriptions were found. The representation of ARBs among the antihypertensive medications used was increased with the improvement of socioeconomic status. These findings concur with the observation of a registry-based study on the types of antihypertensive medications used in ambulatory settings in Finland that high-income patients were more likely to use ARBs, while low-income patients were more likely to use beta-blockers and ACE inhibitors.

Concerning the history of hypertension treatment from the discovery of blood pressure-lowering effect of thiazides and thiazide-like compounds more and more potential pharmacological targets became known and these findings lead to the development and introduction of novel antihypertensive medicines. The milestones on this process are the multicentre randomized placebo-controlled clinical trials which were designed not only to clinically test some newly discovered drugs but also to characterize and compare their effects on CVD morbidity and mortality. The recently completed SPRINT study showed a huge reduction in mortality (25%) and CVD events (30%) in the group with a systolic blood pressure goal of 120 mmHg. Large randomized clinical trials have provided strong evidence that antihypertensive treatment substantially reduces the risk of overall mortality, especially that of cardiovascular diseases as stroke and coronary heart diseases. Based on results obtained in the meta-analysis of data published on the effect of antihypertensive treatment on secondary prevention of CVD events and all-cause mortality among persons without clinically defined hypertension it could be concluded that even among patients with a clinical history of CVD but without hypertension, antihypertensive treatment is associated with decreased risk of stroke, congestive heart failure, composite CVD events, and all-cause mortality.

Different types of antihypertensive drugs show different effectiveness for the treatment of hypertension. When perindopril as a new ACE inhibitor drug was introduced among patients with stable coronary heart disease it was shown in the EUROPA study that perindopril treatment can significantly improve outcome, namely, it results in a 20% additional risk reduction. The study group concluded that 'treatment with perindopril, on top of other preventive medications, should be considered in all patients with coronary heart disease.' Angiotensin II receptor blockers (ARBs) as 'recent advances in risk reduction' were interpreted based on results obtained in the ONTARGET trial in which the ACE inhibitor ramipril and the ARB telmisartan were found equally effective in reducing the incidence of cardiovascular death, myocardial infarction, stroke, and hospitalization for heart failure in patients at high risk for cardiovascular disease. Despite new and new drug discoveries a large scale study designed to compare the effectiveness of thiazide diuretic (TD), ACE inhibitors, ARBs and calcium channel blocker (CCB) monotherapies for the treatment of hypertension on 565,009 patients the authors found that patients who took TDs experienced a lower risk of clinical events compared with patients who took ACE inhibitors,

ARBs and CCBs. These results provide a strong rationale for choosing TDs as first-line monotherapy for the control of hypertension.

In a carefully designed meta-analysis of publications on the relationship between SES and hypertension, Leng et al. could identify only a single publication from the CESEE countries, and even this report lacked considerable merit. This single study was carried out among central Slovakian adults with a small sample size of 100 probands (50 males and 50 females) in which only 14 participants with low SES were identified; among them, hypertension was found to be less frequent than in the group of participants with high SES ( $n = 15$ ). Concerning the sample size, this finding could not be considered substantial even if the authors themselves did not report, in the very same paper, a conflicting result; namely, when the group was stratified by educational level, the prevalence of hypertension was found to be highest in the least educated group. Studies on Roma, the most disadvantaged ethnic population of the European Union that is accumulating in the CESEE countries, did not reveal significant differences by ethnicity regarding hypertension between Roma and the host populations in Slovakia and Hungary, but the prevalence of hypertension in the Bayash Roma population was significantly lower than what is usually reported for the general population of Croatia. Only a single report mentions a higher prevalence of hypertension among Slovakian Roma than in the general population.

Among the four preventive drugs, the redemption rate of Syncumar prescriptions was the highest, 76.24%, while the redemption rate of clopidogrel was the lowest, only 54.4%. The frequency of prescription for these drugs (except for Xarelto) was positively associated with deprivation. As the deprivation became more pronounced, the redemption rate was noticed to increase, irrespective of the types of drugs. However, the interactions between prescription/redemption measures and mortality due to thromboembolic diseases among districts were not consequent in Hungary. In a cluster of high mortality caused by thromboembolic diseases in the northwestern part of the country, consisting mainly of counties with the highest socioeconomic performance, prescription and redemption rates for each drug were found to be less favourable than the country average. In contrast, an eastern Hungarian region consisting of two highly deprived counties with significantly lower mortality than the country average had significantly higher prescription and redemption rates than this northwestern cluster. The reason why these discrepancies exist cannot be squarely defined. It is reasonable to suppose that a study on healthcare access and performance would be able to—at least partly—clarify the background of these unexpected inequalities. There are 36 stroke units in Hungary, of which performance is assessed by the thrombolysis rate (national thrombolysis rate is 13%). Only a single stroke unit (Veszprém) in the northwestern cluster slightly overperformed (14%) compared to the average, lagging behind the performance of centres in Budapest and Debrecen responsible for the healthcare of the population of the eastern cluster with significantly better mortality rates of thromboembolic diseases and better coverage in preventive medication. Such deficiency in healthcare performance might be explained by human resource deficits in the northwestern cluster caused by increased out-migration and,

consequently, the attrition of physicians after the EU accession of Hungary. In addition, a significant portion of physicians living in the northwestern part of the country is cross-border commuters working in Austrian healthcare institutions, especially in the bordering province of Burgenland, where, in certain hospitals, the proportion of commuting Hungarian doctors reaches 23%. This fact became known due to the connection with the COVID-19 pandemic.

In line with our findings, insufficient anticoagulant treatment and its link with SES have been reported by several studies. Prescribing was less frequent with older age and in patients born in other Nordic countries or countries outside of Europe than in those born in Sweden. University education and higher income were associated with higher levels of oral anticoagulant prescription. In an Italian study based on the Italian geographical macro-regions (North, Central, South), data on medication adherence of nonvalvular atrial fibrillation patients were analyzed to assess whether socioeconomic conditions might also influence medication adherence. Regional disparities exist in drug prescriptions. In high-risk patients, oral anticoagulants were more likely to be prescribed in northern and central patients than in high-risk southern patients. Additionally, medication adherence was noticed as a progressive decrease from North to South.

A review presented 47 articles concerning anticoagulant therapy on patients' perspectives and patients' adherence. The findings through five interacting dimensions of adherence were synthesized: patient-related factors, therapy-related factors, condition-related factors, health system factors, and social, economic factors. Overall, one-fifth of the studies in the review examined the impact of patients' background in social and economic aspects on their perception of and adherence to warfarin therapy. The financial burden of warfarin to patients is dependent on healthcare service costs to individuals and the extent to which these medicines are subsidized by the governments or insurance companies in those countries where they are available. Concerning warfarin, only two studies stated that a small number of patients were financially burdened by further expenses associated with managing the therapy.

In Hungary, the higher redemption rate of the antithrombotics—including the high-cost Xarelto—in deprived districts might be explained by the broad access to prescription exemption certificates. In contrast, the vitamin K antagonist warfarin applied in acute thromboembolic diseases as anticoagulant therapy could cause similar redemption patterns across quintiles.

The effectiveness of oral anticoagulants is critically dependent on patients' adherence to intake regimens. Lee et al. underlined the significant role of promoting medication adherence for risk reduction, especially in low-income patients with CVDs.

Contrary to the approach of 'the lower social, economic status associated with lower adherence', our study indicates that a more complex relationship exists between socioeconomic factors and medication adherence. There is a need to address medication nonadherence, which is an important cost driver in healthcare expenditures and inequalities, as an interconnected network. Beyond policies targeting health behaviour (new taxes on 'unhealthy' food, such as sweetened, salty, and fatty products, anti-smoking legislation) that were introduced by the Hungarian government,

actions to facilitate favourable changes in inequalities in health services are necessary. For example, financial incentives are effective tools to achieve a major contribution to the reduction in inequalities in the delivery of clinical care related to area deprivation. Additionally, it can be supposed that underlying problems exist at the level of service provision and/or access to health services in certain clusters given the fact that low prescription and redemption rates occur together with high SES.

## **6.2. *Proposals***

The municipality-based DI defined for Hungary as a whole is applicable for public health investigations. On one hand, it can be used in studies exploring the spatial distribution of health status indicators, and on the other hand, it can be used as a categorical covariate in multilevel stratified statistical models adjusted for socioeconomic status in public health and environmental health studies to control for potential bias, allowing the examination of the relationship between other risk factors and the risk associated with them separately from socioeconomic status.

Our results have again drawn attention to the fact that inequalities due to socioeconomic factors may be reflected in spatial inequalities in health status characteristics. These findings can be used to develop prevention strategies or design local health promotion programmes to reduce health inequalities, following the Health and Consumer Strategy and the EU's proposed action programme. Understanding all this is crucial for the planning of focused interventions, but the study also underlines the fundamental importance of overall societal engagement and support for public health programmes.

The development and application of the DI contribute to the investigation of social and spatial disparities in premature mortality from diseases of the circulatory system and a better understanding of this important public health problem. It offers an opportunity to consider potential approaches to address such inequalities. The study draws attention to the importance of public responsibility in understanding, investigating and mitigating health inequalities.

In future, particular attention should also be focused on the study of health system determinants. Information should be collected on all the factors that may influence the drug adherence of patients to understand and address the low relative prevalence rates. For example, it is worth considering and investigating the reimbursement of particular medicines, or the attitudes of the general public regarding particular drugs, or the presence or change in the professional knowledge of general practitioners. Overall, it is concluded that the analysis of the spatial distribution patterns of mortality concerning relevant preventive medication will also allow the identification of populations that are assumed to be inadequately treated, including by preventive medication.

Overall, spatial data analysis can contribute to the identification of gaps in health services and thus to the reduction of preventable and avoidable mortality.

## 7. KEY FINDINGS

The area-based DI, defined for Hungary at the municipal level, is suitable for application in public health studies.

Our results have highlighted and provide further evidence that inequalities determined by socioeconomic factors may be reflected in spatial inequalities in health status characteristics.

The prescription and redemption of antihypertensive drugs varies significantly by DI tertile; although the differences in percentage terms appear small, they are highly statistically significant due to a large number of observations. Higher relative prescribing frequencies were identified in the more deprived areas for ACE inhibitor, beta-blockers and calcium channel blocker antihypertensives, while these areas were characterised by lower relative ARB prescribing frequencies. The representation of ARBs among the antihypertensive drugs used increased with increasing socioeconomic status.

Among the four preventive antithrombotic drugs, Syncumar had the highest redemption rate of 76.24%, while clopidogrel had the lowest redemption rate of only 54.4%. The prescription frequency of these drugs (except Xarelto) showed a positive correlation with deprivation. Irrespective of the type of drug, the prevalence rate also increased with increasing deprivation. However, the relationship between mortality from thromboembolic diseases and the spatial distribution of prescription/prevalence rates is not consistent. In the northwest of the country, in the best socioeconomic counties, a high risk of death from thromboembolic diseases was observed, associated with a significantly lower prescription and redemption rate than the national average. In contrast, two counties in Eastern Hungary, which are more deprived than the national average, had a significantly more favourable mortality risk and a higher prescription and redemption rate than the North-Western cluster.

In the future, particular attention should also be devoted to the study of health system factors. Information should be collected on factors that may influence patients' adherence to medication to understand and address the low relative redemption rates.

## 8. SUMMARY

Mortality due to cardiovascular diseases (CVDs) has been declining but, despite this, the relative risk of premature death in our country is still very unfavourable, almost three times higher than the EU15 average. Preventing (or at least delaying) CVD mortality is a key issue for interventions that influence lifestyle, but there are also considerable potential benefits of using preventive medication. Regarding CVD, antihypertensive and antithrombotic preventive medication is particularly important.

The socioeconomic status not only influences CVD mortality/morbidity, but also the prevention and preventive medication. Thus, beyond the spatial inequalities in CVD mortality, our research has focused on the association between the developed area-based Deprivation Index (DI) and CVD mortality/morbidity and preventive medication use.

Our research results showed a significant positive association between deprivation and premature mortality/prevalence due to circulatory system diseases, ischaemic heart disease, cerebrovascular disease and hypertension. Higher relative prescribing frequencies for ACE inhibitors, beta-blockers and calcium channel blockers were found in deprived areas, while these areas were characterised by lower relative ARB prescribing frequencies. The representation of ARBs among the antihypertensive drugs used increased with increasing socioeconomic status. The redemption rate improved with increasing deprivation, i.e. the most deprived group had the highest redemption rate for all agents.

Regression analysis by a quintile group of districts based on DI deprivation was a significant non-linear correlated determinant of mortality from thromboembolic disease. A significant positive association was identified between the frequency of prescription and redemption of antithrombotic drugs and deprivation, except for Xarelto. For all drugs, the redemption rate increased with increasing levels of deprivation. However, the relationship between mortality from thromboembolic diseases and the spatial distribution of prescription/redemption rates is not consistent. The risk of death from thromboembolic diseases was higher in the North-West, in the less deprived counties, and this was associated with a much lower prescription/redemption rate than the national average. In contrast, two counties with more deprived populations in Eastern Hungary were characterised by a lower mortality risk and higher prescription/redemption rates than the North-Western cluster.

Overall, it can be concluded that the analysis of the spatial distribution of mortality concerning the relevant preventive medication also provides an opportunity to identify populations that are assumed to be inadequately treated, including with preventive medication.



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## 9. KEYWORDS

socioeconomic status, deprivation, health inequalities, cardiovascular mortality, preventive medication, antihypertensives, anticoagulants, prescription, redemption

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