

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

**Data mining of metabolic abnormalities in pediatric and adult
hypertensive populations**

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DATA MINING OF METABOLIC ABNORMALITIES IN PEDIATRIC AND ADULT HYPERTENSIVE POPULATIONS

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Introduction

Hypertension is a prime public health challenge worldwide, whether in children or adults. In adulthood, 54% of patients who suffer a cerebral infarction, 47% of coronary heart disease and 25% of other cardiovascular diseases are attributable to hypertension. However, hypertension indeed is one of the most preventable risk factors for cardiovascular disease and premature death. Global surveys show that over the past four decades, the number of people with hypertension has been gradually increasing in low- and middle-income countries, with a negative impact on disability and mortality rates. Hypertension diagnosed in childhood is as much a public health priority as adult hypertension. With a predictive value of between 19% and 65%, hypertension diagnosed in childhood is a potent risk factor for the adult form. The roots of adult hypertension can probably be traced back to childhood (tracking phenomenon). Therefore, early detection and treatment are urgent. Unfortunately, there is also a clear trend that the number of children diagnosed with hypertension has gradually increased over the last decades. This increase is mainly due to obesity at epidemic proportions, a sedentary lifestyle and, to some extent, excessive salt consumption. These factors are not necessarily in connection with the economic status of a country. Complex metabolic processes influence not only the complications of hypertension but also global cardiovascular risk. This tendency is correct in children and adults as well. Cardiovascular disease is considered the most common cause of death in Hungary. It is also fact-based that the cardiovascular mortality rate in our country is twice the European Union average. This fact in itself reinforces the need to focus on the early detection of hypertension in both children and adults and on the identification of risk factors and co-morbidities as a focus of prevention. Based on the literature review, we could not find a retrospective study of a large population that provided a comprehensive picture of complex metabolic abnormalities in hypertensive patients in the adult or even paediatric population in Central and Eastern Europe. Although data mining is not a common form of epidemiological data processing, it can be considered a pioneering method suitable for laboratory and clinical information analysis. The resulting relevant statistical data undoubtedly provide a basis for prevention and are essential for therapeutic decision-making.

Review of literature

Childhood and adolescent hypertension

Hypertension is often diagnosed during puberty and mostly in adolescents who are overweight or obese. Etiologically, primary and secondary forms are distinguished. Hereditary factors may contribute to primary hypertension in childhood. The inheritance pattern is multifactorial but is adversely affected by environmental factors such as diet, consumption of processed foods and increased sodium intake. A dietary study in Hungary has shown that sodium intake in our country exceeds recommendations, and potassium intake is below the target values. According to a previous multicentre study, the daily energy intake is provided mainly by processed foods when we look at the child population of eight countries, including Hungary. These factors have led to a well-known association between obesity and hypertension in children and adolescents. As in adults, obesity due to poor diet and physical inactivity is a major predisposing factor for the development of metabolic disorders diagnosed in childhood, including dyslipidaemia, hyperinsulinaemia and hyperuricaemia. Insulin resistance and hyperinsulinaemia may also contribute to increased renal sodium reabsorption and excessive sympathetic nervous system activity. The effect of food components on gene expression or fructose intake on uric acid levels may also be associated with abnormal metabolic changes. A previously published study has shown a positive correlation between uric acid, insulin and triglyceride levels and hypertension, particularly in overweight and obese young people. Some other factors may also increase the risk of developing primary hypertension, such as low birth weight, male gender, heredity and even ethnicity. Recent evidence suggests that primary variant hypertension is the leading form of hypertension in children and adolescents, especially among adolescents. In adolescents, the prevalence of primary hypertension accounts for 85-95%, similar to the adult figures. The underlying cause of secondary hypertension is clearly identifiable. The secondary form is common in infants and young children. The causes of hypertension in this aetiological group vary with age. Thrombosis or stenosis of the renal artery, congenital renal abnormalities, aortic coarctation or various endocrinological pathologies such as pheochromocytoma, hyperthyroidism and hyperaldosteronism may be underlying, although diseases affecting renal tissue considered to be the leading aetiological factor. In adolescent girls, oral contraceptive use also contributes to hypertension. We can also mention the use of certain sympathomimetics and the adverse effects of certain dietary supplements. More attention should be paid to screening for hypertension in children, as the relatively low prevalence may lead to misdiagnosis. The diagnosis of hypertension in children and adolescents can be challenging, as maturation leads

to changes in the correlation between standards and definitions. Previous guidelines have proven that stating the uniform definition of hypertension in children and adolescents requires caution. It has made it difficult to define the prevalence of hypertension at a global level in this age group. The European Hypertension Society's Task Force on Childhood and Adolescent Hypertension updated its previous guidelines in 2016. Two decades ago, a cross-sectional, population-based study in Debrecen, a city of 230,000 inhabitants, found the prevalence of hypertension to be 2.53% in adolescents (15-18 years old). However, other studies have estimated the most likely prevalence of hypertension in children and adolescents to be 3.5%. A recently published meta-analysis of 47 papers puts the combined prevalence of childhood hypertension at 4.00% (95% CI, 3.29-4.78%). Nevertheless, a relatively modest amount of data was available from surveys on childhood hypertension in Eastern Europe.

Adult hypertension

In daily practice, whether in primary care or an inpatient setting, hypertension is perhaps one of the most common diagnoses. Etiologically, two main groups are distinguished. The primary form predominates, but clarification of the secondary aetiology is essential if it arises. Previous studies extensively investigated the close correlation between obesity and hypertension. Epidemiological studies have consistently demonstrated a non-threshold, almost linear relationship between body mass index (BMI) and blood pressure elevation. Previous studies have reported significantly higher BMI and abdominal circumference values among hypertensive individuals than among individuals without hypertension. Abdominal obesity affects the endocrine and immune systems. Several determinants of the pathological interaction between obesity and hypertension are known. These include haemodynamic changes, oxidative stress, renal impairment, hyperinsulinemia and insulin resistance, sleep apnoea syndrome and the leptin-melanocortin pathway. In addition to these, although less frequently mentioned, the role of genetics, epigenetics and mitochondrial factors is not negligible. At the cellular level, adipose tissue contributes to endothelial dysfunction by secreting several hormones and paracrine signals, known as adipokines. These molecules play a principal physiological role in the regulation of vascular tone. Obesity is characterised by increased secretion of proinflammatory and vasoactive adipokines such as angiotensinogen, angiotensin II, aldosterone and increased plasma renin activity. In addition, the expression of renin receptors is increased in human visceral adipose tissue. Sleep apnoea is also extremely common in obese patients, with an estimated prevalence of between 40% and 90%. Sleep apnoea increases

endothelin levels through neurohormonal dysregulation, endothelial dysfunction, inflammation and repeated hypoxic episodes, which ultimately causes elevated blood pressure. Hyperlipidemia is a metabolic abnormality commonly recognised in hypertensive patients. In atherogenic dyslipidaemia, high triglyceride and low high-density lipoprotein cholesterol (HDL-C) levels are considered to be characteristic alterations associated with normal to slightly elevated low-density lipoprotein cholesterol (LDL-C) levels and a predominance of small, dense LDL particles. This abnormal condition is mainly associated with overweight, obesity and carbohydrate metabolism disorders. In addition to an elevated BMI and diabetes mellitus, high glucose and HbA1c values are common laboratory abnormalities in the findings of hypertensive patients, contributing to the development of atherogenic dyslipidemia. In addition to these findings, elevated total cholesterol and LDL-C levels are also common abnormalities in hypertensive individuals, according to the literature. It should be emphasized, that the co-existence of hypertension and dyslipidemia has a synergistic effect on both mortality and cardiovascular morbidity. There is a significantly higher risk factor for these two conditions together than separately. In addition to these factors, elevated uric acid levels are another potent contributor to metabolic processes. On one hand, in hypertension, renal blood flow is reduced, resulting in urate reabsorption. Persistently high blood pressure values cause chronic microvascular damage. Local tissue damage occurs due to hypoxia, which raises uric acid levels. We cannot forget the side effects of antihypertensive drug therapy. Thiazide-type diuretics contribute to elevated serum uric acid levels by stimulating proximal tubule reabsorption. On the other hand, elevated uric acid activates the renin-angiotensin-aldosterone system and reduces circulating nitric oxide levels, thus inducing vasoconstriction. In addition, high uric acid levels increase smooth muscle cell proliferation, which is the basis of secondary arteriosclerosis. The latter adversely affects electrolyte transport via the kidneys, leading to a further increase in blood pressure. The renal aetiology of hypertension is accepted. Hypertension is both a cause and a consequence of chronic kidney disease and is associated with its progression. In individuals with chronic kidney disease, the development of hypertension is due to a multifaceted pathomechanism. These include increased sympathetic tone, overactivity of the renin-angiotensin-aldosterone system leading to salt and water retention, increased salt sensitivity and endothelial dysfunction. These ultimately result in marked vascular stiffness. Once hypertension has already developed, many factors, including relative renal hypoxia and increased oxidative metabolism, subsequently stimulate further deterioration of renal disease. Obesity or overweight, insulin resistance, type 2 diabetes mellitus

(T2DM), hypertension and hyperlipidaemia are often associated with non-alcoholic fatty liver disease (NAFLD). Elevations in glutamate oxaloacetate aspartate aminotransferase (GOT), glutamine pyruvate alanine aminotransferase (GPT) and gamma-glutamyl transferase (GGT) are markers of liver cell damage and are common abnormalities in patients with liver disease, including NAFLD. Given this, we have to monitor these markers in hypertensive individuals. Among the risk factors of hypertension, we can find some pliable, while others cannot be modified. The latter category includes gender, age, ethnicity and genetics. Modifiable risk factors include obesity and overweight, salt, potassium or saturated fat and alcohol consumption, stress and physical inactivity. The epidemiology of adult hypertension is relatively well-documented chronologically and geographically. According to 135 population-based studies of 968 419 adults from ninety countries, the global age-standardised prevalence of hypertension in 2010 was 31.1%, slightly higher in men (31.9%) than in women (30.1%). The highest prevalence was reported in Eastern Europe and Central Asia (39.0%). As stated in the publication of the Prospective Urban Rural Epidemiology (PURE) study, 40.8% of subjects in a study of 153 996 people aged between 35 and 70 years in 628 rural and urban communities in economically and geographically diverse countries between 2003 and 2009 had hypertension. There was a higher prevalence in favour of men (41.4%). However, the measured prevalence in women was 37.7%. If we want to analyse epidemiological data in Hungary, we can use information from the Hungarian Hypertension Register and the Hungarian Central Statistical Office. In 2011, the estimated prevalence of hypertension in Hungary was 35%, with a male/female ratio of 47/53%. Hungary has joined the May Measurement Month (MMM) programme. The results of the MMM showed that 1286 (46.5%) of 2766 Hungarian participants had hypertension. According to the European Society of Cardiology database, the prevalence of hypertension in Hungary was 30% in 2021, associated with a 26.4% prevalence of obesity. The 2018 ESC/ESH and Hungarian Hypertension Society professional guidelines provide more details on the adult hypertension diagnosis.

Data mining

Data mining is the discipline of science that aims to find and investigate unambiguous relationships in large data sets. It has been known and used since the 1980s and is a method based on machine learning derived from classical artificial intelligence. We can use this technique in expansive fields, including telecommunications, genetics, biomedical sciences and astronomy. The method revolves around statistics. The main question in statistical analysis is

when the sample is representative, while in data mining large amounts of information are already available. In the latter case, the leading dilemma is how to analyze to obtain relevant answers of value. Several publications support the view that data mining of clinical big data can provide practitioners with valuable knowledge and is essential for accurate clinical decision-making and risk assessment. Our previous work has also demonstrated that various data mining methods built on the processing of bulk health data are ideal for screening for the diagnosis of hypertension and even other health conditions.

Aims

- I.** In our retrospective study, we set out to use a data-mining approach to assess, across regions and among a large population of children
- of hypertension in a large population of children,
 - the prevalence of the most common comorbidities, and
 - the prevalence of the most common metabolic disorders associated with hypertension.

In addition, we aimed to compare the results obtained with data available in the international literature.

- II.** Furthermore, based on data mining in a large adult patient population, we aimed to
- to assess the prevalence of hypertension,
 - analyse the associated characteristic metabolic abnormalities,
 - document the proportion of comorbidities associated with hypertension.

In addition, we aimed to evaluate the results obtained for their relevance to clinical practice.

Materials and methods

Screening of the child and adolescent study population

The source data included the complete medical records of the clinical centre from January 1, 2007, to December 31, 2021. In the study, we evaluated the data of every child between the ages of 3 and 18 who visited the Clinical Center of the University of Debrecen during the aforementioned 15-year study period (total number of children aged 3-18 $n = 92,198$; boys/girls: 44,255/47,943; 48/ 52%). The Ethics Committee of the University of Debrecen and the Scientific and Research Ethics Committee approved the study. In the case of the examined patient population, paediatricians, predominantly specialists working as endocrinologists and nephrologists, established the clinical diagnosis of hypertension. The colleagues set the diagnosis of hypertension based on the international guidelines available at the time. Our specialists performed the measurements with validated devices. We established the diagnosis of hypertension on textual medical history data recorded in the source data (searched for the word “hypertension” and its synonyms) and hypertension diagnosis codes (International Statistical Classification of Diseases and Health-Related Problems 9th and 10th revised editions, WHO).

Screening of adult study population

For software development, the Clinical Center of the University of Debrecen provided access to anonymous health documentation from the North-Eastern Hungarian region between January 1, 2001 and December 31, 2021. During the 20-year study period, we collected data from patients over 18 years of age treated as inpatients or outpatients ($n=937,249$; male/female: 42.9/57.1%). The Ethics Committee of the University of Debrecen and the Scientific and Research Ethics Committee approved the study. The specialists working at our clinic established the diagnosis of high blood pressure based on the international standards in force at all times. They measured blood pressure with validated tools and methods specified in the recommendation. In connection with health data processing, we relied on data mining. On one hand, the text medical history data contained information. We searched for "high blood pressure" and its synonyms. On the other hand, we used the codes for the diagnosis of hypertension according to the International Classification of Diseases (BNO version 10), which can also be found in the source documents.

Data mining - the method

Database generation

The data mining software that forms the basis of our study is a result of a collaboration born between clinicians, IT specialists and statisticians. Through the Clinical Center of the University of Debrecen, we had access to anonymous clinical data collected in Northeastern Hungary for software development. Our research group and cooperation partner, Black Horse Group Ltd., launched a data mining project. We also received permission to use Black Horse's medical framework, called "AescuLab". Considering both study populations, we processed several decades of data from the Clinical Center of the University of Debrecen. It was essential to unify the data, convert it into the appropriate format and then clean it. Without all these steps, it would not have been possible to use the IT commands and the planned algorithms appropriately. The data extracted from the clinical records were subjected to a multi-step procedure. Anonymity was ensured to protect patient data and patient information was separated from real persons. Since the documents came from inpatient or outpatient care providers, many health professionals had access to the patients' documentation and could modify the data content and add new information to it. Based on all of this, the challenge was that the information duplication that occurred regarding a patient might be heterogeneous, not clearly interpretable data content. The developed program also provided a solution to these emerging problems. The solution to these complex tasks is open-source tools, namely <https://numpy.org/> and <http://pandas.pydata.org/> and with other proprietary scripts and solutions developed for data cleaning and filling in missing or incorrect data. The complete data containing laboratory cases, anamnesis, diagnosis codes and patients' statistical data was obtained from previously separate data. Furthermore, we built an integrated database. We have corrected the elements judged to be incorrect and stored numbers as numbers, dates as UTS or Python date format, and text data as "utf-8" encoded text in a uniform format. Data were registered in PostgreSQL 13.x database tables as part of the preprocessing process.

Data processing

Further structuring of the data was necessary to be able to work with accurate and reliable information. The terms provided by us were identified and sorted into specified groups utilizing parsing, stemming, stop word filtering, BOW modelling and ranking of terms (TF-IDF, W2V - Keras framework, <https://keras.io/>). Search terms and their frequency of occurrence are defined as histograms by BOW models and the sequential structure is not taken into account. In contrast,

the context and the sequential system are taken into account by W2V models. By definition, expressions are written as elements of a vector space defined by a neural network. This unambiguous language model identifies the elements of a sequence using contextual terms and using the structure of the sequence. The two models can be applied equally effectively to determine the significance of given words/phrases and rank them based on their IDF values or perplexity. For even more precise data cleaning, we compiled a list of professional vocabularies and used string-matching algorithms to manage misspellings and restore damaged concepts from fragmented data. The data obtained in this way resulted in a finite set of terms, in which the occurrence rate of each term per document appeared, as well as a secondary value that indicated the previously performed medical examinations. Our original list first ran into several million items, but using the aforementioned methods, we ended up with a much more practical list of 250,000 terms. By linking cases, patient record data and diagnoses, the patient histories were displayed as a time series of events closely related to the patients, a format that enabled the recognition of patients with hypertension. Since the compiled data sets had different data structures, we created a common representation that enables statistical analysis. With this structure, specific "attributes" can be decoded. For example, the concept of hypertension can appear in the text-based data set in the form of various words or parameters and derived data from real measurements. We developed several different data mining tools and ran them through the source data. Data cleaning was another challenge, as we had to fill in missing or incorrect data fragments, and each incorrect data had to be handled differently. For example, the method of using "gap-filling" binary variables with a mean value does not give clear results. All similar unique cases were interpreted as normal expressions. To handle the extremely large amount of data, we developed additional serialization and streaming techniques, thus optimizing the final query engine capable of handling partial data and attribute deduction for identification. These methods included parsing (morphological analysis), stemming (word stemming), stop-word filtering and creating a dictionary based on unigrams and bigrams after manual cleaning of phrases/words. Using TF-IDF (term frequency/translated document frequency) and word embedding techniques, we surfaced the data containing the terms. The word embeddings in Hungarian were based on traditional corpora, so we had to carry out further linguistic processing partly with the help of language models taught by ourselves and partly with the help of already-known language models. For this subtask, we used the NLTK (version 3.x) Python library. We used the BERT (Bidirectional Encoder Representations from Transformers) and GRU (Gated Recurrent Unit) models for our language models. GRU is a

feedback neural network in which cleaned unigrams and bigrams form dictionaries. Finally, the data were arranged in a matrix, which assigned the examined characteristics and their corresponding continuous (e.g. laboratory value) and discrete (e.g. hypertension - yes/no) variables to a given patient/case. A given regular expression was identified or given a high probability flag if it was interpreted as an expression by the language model or as laboratory measurement data.

Laboratory analysis

Routine laboratory parameters such as glucose, urea, creatinine, uric acid, GOT, GPT and GGT were determined at the Institute of Laboratory Medicine of the University of Debrecen using standard laboratory methods using Cobas c501 and Cobas c600 analyzers (Roche Ltd, Mannheim, Germany). Serum total cholesterol and triglyceride concentrations were determined using an enzymatic, colorimetric method, in the case of HDL-C and LDL-C, a homogeneous, enzymatic method (Roche HDL-C plus 3rd generation and Roche LDL-C plus 2nd generation). ApoA1 and ApoB100 and their values were measured using the immunoturbidimetric method (Tina-quant Apolipoprotein A-1 ver.2, Tina-quant Apolipoprotein B ver.2). HbA1c was measured using high-pressure cation exchange liquid chromatography-HPLC. In all cases, the tests were carried out according to the recommendations given by the manufacturer.

Statistical methods

The anonymous patient data used for the statistical calculations were obtained from the computer system of the Clinical Center of the University of Debrecen. Our partner provided access to the data source in HL7 format; he also cleaned and pre-processed the data, which thus became suitable for use in the data mining and machine learning project. By rationalizing the database, we eliminated the potential system errors resulting from the original data recording method, which affected the entire patient registry database of the Clinical Center for several years, including all text, and various diagnostic and laboratory data. The data was queried from the PostgreSQL 13.x database. The resulting large text files were interpreted as the starting database for the subsequent statistical analysis. Statistical analysis was performed using data mining packages supported by Python. We used the operating systems Python 3.8, IPython 7.29, Cython 0.29, Pandas 0.23 and Numpy 1.22 in the Conda 4.10 environment, with Dask in the data cleaning and processing phases. Collection of clinically relevant data and complex text analysis was performed using machine learning using SciKit-Learn 1.0 and Pytorch 1.09.

Significance was calculated using an unpaired t-test, where we determined a significance level of 95%. The statistical figures were compiled with the help of the Matplotlib 3.5 software package and related libraries.

Results

Child population

Identification of hypertensive children and adolescents

Based upon the data source containing laboratory cases, textual history data, diagnosis codes and patient statistic data, we evaluated each child from ages 3 to 18 years that visited the University of Debrecen Clinical Center's hospital during the 15-year study period (total number of 3 to 18-year-old children $n = 92,198$; boys/girls: 44,255/47,943; 48/52%). We identified a total of 3,687 children with hypertension (2,107 boys and 1,580 girls), which means that the calculated prevalence of hypertension in the whole study population is 4%, a higher prevalence in boys (4.7%) as compared to girls (3.2%). We divided the study population into five age groups (3-6 years; 6-9 years, 9-12 years, 12-15 years and 15-18 years). The 3-6 year-old age group was defined as the period above the age of 3 years and below the age of 6 years. We found an increasing prevalence in the consecutive age groups in the whole study population (1.54; 2.64; 4.0; 5.49 and 5.56%, respectively), and in the boys (1.66; 2.6; 4.57; 6.48 and 8.22%), while in girls the highest prevalence was identified in the 12-15-year-old age group (1.39; 2.69; 3.4; 4.6 and 3.8% was found, respectively). We found a strong linear correlation between age and the number of children diagnosed with hypertension in the whole study population ($R^2 = 0.93$), in boys ($R^2 = 0.91$) and in girls ($R^2 = 0.93$). Likewise, an exponential correlation was detected between the cumulative number of children in various age groups diagnosed with hypertension in the whole study population ($R^2 = 0.97$), in boys ($R^2 = 0.98$) and girls ($R^2 = 0.96$).

Comorbidities

We also evaluated the prevalence of the most significant concomitant diseases. We found a markedly and significantly higher prevalence of obesity (49.7 vs. 6.16%), diabetes mellitus (7.17 vs. 1.27%), renal diseases (2.81 vs. 0.51%) and thyroid diseases (8.74 vs. 6.22%) in hypertensive children as compared to normotensives. Obesity was the most prevalent concomitant disease in all patient groups, with the highest prevalence documented in the 6-9-year-old and the 9-12-year-old age groups (65%). Moreover, we found higher BMI values in hypertensive children as compared to the normotensive group in all studied patient groups

(25.6; 26.7; 28.1 and 29.7 vs. 20.1; 21.4; 22.6 and 24.6 kg/m² in the 6-9-year-old, 9-12-year-old, 12-15-year-old and 15-18-year-old groups, respectively).

Examination of serum glucose, lipid, uric acid and kidney function parameters

We found significantly higher total cholesterol (4.27 ± 0.95 vs. 4.17 ± 0.88 mmol/L), LDL-C (2.62 ± 0.79 vs. 2.44 ± 0.74 mmol/L) and triglyceride ($1.2(0.85-1.69)$ vs. $0.94(0.7-1.33)$ mmol/L), and lower HDL-C (1.2 ± 0.3 vs. 1.42 ± 0.39 mmol/L) levels in children with hypertension compared to the normotensive children in the whole study population and in all age groups. Except for the first age group, total cholesterol level was higher in hypertensive children compared to the normotensive group. Furthermore, significantly higher serum uric acid levels were found in children with hypertension (299.2 ± 86.1 vs. 259.9 ± 73.3 μ mol/L). There were no reportable differences in glucose, urea and creatine levels between the hypertensive and normotensive groups throughout the various age groups.

The prevalence of several secondary causes resulting in hypertension such as hyperthyroidism, hyperaldosteronism, Cushing syndrome, pheochromocytoma, hyperparathyroidism and chronic renal disease was a shade higher in the most hypertensive age groups, but because of the scarcity of cases, we could not perform statistical analysis. Indeed, the documentation of rare causes of secondary hypertension appears to be insufficient and inaccurate.

Adult population

Identification of hypertensive adults

We evaluated data from 937,249 adults over 18 years old who visited the University of Debrecen Clinical Center's hospital throughout the 20-year study period (males/females 42.9/57.1%). We identified a total of 292,561 adults with hypertension (male/female: 45.4/54.6%), with a 31.2% calculated prevalence of hypertension in the whole study population and a higher prevalence in males (33%) compared to females (29.9%). We found an increasing prevalence in consecutive age groups both in males and females up to the age of 80. The ratio of males with hypertension was higher from 18 to 65 years of age, while it was lower above 65 years of age.

Body mass index

Markedly higher body mass index (BMI) values were found in hypertensive patients as compared to non-hypertensives in the entire study population (29.5 ± 6.3 vs. 26.57 ± 5.6 kg/m², $p < 0.001$) and in all age groups up to 80 years of age, with a highest mean value in the 35–49-year-old age group (30.92 ± 7.3 kg/m²).

Lipid parameters

Interestingly, we could not find significant differences in total cholesterol and LDL-C levels in the entire patient population (5.1 ± 1.2 vs. 5.0 ± 1.2 mmol/L and 3.1 ± 0.99 vs. 3.1 ± 1.0 mmol/L, respectively). Moreover, significantly lower serum total cholesterol and LDL-C levels were found in age groups 35–49 years, 50–64 years, and 65–79 years in hypertensives as compared to normotensives. The serum total cholesterol level was significantly higher in the hypertensive >80-year-old age group compared to normotensives. A significantly higher triglyceride level was found in hypertensive adults compared to non-hypertensives in the entire study population ($1.46(1.06–2.07)$ vs. $1.19 (0.82–1.73)$ mmol/L, $p < 0.001$). Regarding the consecutive age groups, serum triglyceride levels were higher from 18 to 80 years of age. Serum HDL-C levels were significantly lower in hypertensive subjects compared to normotensives in the entire study population (1.36 ± 0.4 vs. 1.46 ± 0.6 mmol/L, $p < 0.001$). Furthermore, lower serum HDL levels were detected in all age groups. A significantly higher ApoB100 level was found in hypertensive adults compared to non-hypertensives in the entire study population (0.99 ± 0.3 vs. 0.93 ± 0.33 g/L, $p < 0.001$, respectively). In addition, higher ApoB100 levels were found in most age groups (from 18 to 80 years of age). Serum ApoA1 levels were significantly lower in hypertensive subjects compared to normotensives in the whole study population. Similarly, we found lower serum ApoA1 levels in all age groups except for the 65–79-year-old age group.

Correlation between body mass index and lipid parameters

Serum triglyceride and ApoB100 levels showed a significant positive correlation with BMI ($R=0.18$; $p<0.001$ and $R=0.05$; $p<0.01$, respectively), while HDL-C and ApoA1 levels showed a significantly negative correlation with BMI in the entire hypertensive population ($R=-0.24$; $p<0.001$ and $R=-0.15$; $p<0.001$).

Identification of statin users

Based on our data, the ratios of statin users in hypertensive subjects as compared to normotensives were markedly higher in all age groups.

Examination of serum glucose, hemoglobin A1c and uric acid levels, kidney function and liver function parameters

Significantly higher serum glucose levels (5.8 (5.2–6.9) vs. 4.7 (4.6–5.8) mmol/L, $p < 0.001$) were found in subjects with hypertension compared with the non-hypertensive subjects in the entire study population, as well as in all age groups. HbA1c levels were also significantly higher in hypertensives in all patient groups except for the 65–79-year-old age group. Furthermore, serum uric acid levels were significantly higher (321 ± 96.6 vs. 278 ± 88.2 $\mu\text{mol/L}$, $p < 0.001$) in subjects with hypertension compared with non-hypertensive subjects in the entire study population, as well as in all age groups. Moreover, significantly higher urea and creatinine levels were found in the entire hypertensive group compared to normotensives (5.78 (4.6–7.5) vs. 4.6 (3.7–5.7) mmol/L, $p < 0.001$ and 76 (64–92) vs. 69 (59–81) $\mu\text{mol/L}$, $p < 0.001$, respectively) and in most age groups. AST activity was significantly higher in HT patients compared to non-HT subjects only in the 18–34-year-old age group. ALT was significantly higher in most age groups, while GGT was higher in HT patients compared to normotensives in all age groups.

Comorbidities and vascular complications

The prevalence of obesity, diabetes, and renal diseases was markedly higher in hypertensive patients compared to non-hypertensives. Furthermore, the prevalence of atherosclerotic vascular complications including cardiovascular, cerebrovascular, and peripheral artery diseases were significantly higher in hypertensive subjects as compared to normotensives. In hypertensive patients the highest obesity prevalence was found in the 35–49 and 51–65 y age groups (37.2 and 37%), the lowest was in the >80 y group (21.4%). The diabetes prevalence was the highest in the 65–74 y age group (22.8%), while the lowest in the 18–34 y age group (5.1%). The prevalence of cardiovascular disease gradually increased in the consecutive age groups from 17.8 to 53.4%. The prevalence of cerebrovascular disease dramatically increased in elderly patients (26.9 and 29.8% in 65–79 y and >80 y, respectively). The prevalence values of peripheral arterial disease were relatively low in all age groups and varied between 2.2 and

6.2%. Interestingly, the highest prevalence was found in the 35–49 y age group. The prevalence of renal diseases gradually increased from 4.4 to 24.8% in the consecutive age groups. Similar tendencies have been found in the non-hypertensive population, but the prevalence values were approximately ten times lower compared to hypertensive patients.

Distribution of laboratory parameters of the study population according to severity grades of hypertension

Hypertensive patients were divided into three groups based on the grade of hypertension. Grades were defined according to the 2018 ESC/ESH Guidelines for the management of arterial hypertension. Grade 1 was defined as systolic blood pressure (SBP) 140–159 mmHg and/or diastolic blood pressure (DBP) 90–99 mmHg; Grade 2 was defined as SBP 160–179 mmHg and/or DBP 100–109 mmHg; Grade 3 was defined as SBP $\geq$ 180 mmHg and/or DBP $\geq$ 110 mmHg. Several metabolic parameters including triglyceride, glucose and uric acid levels were significantly higher in higher grades of hypertension. Renal function showed worsening in the consecutive grade categories.

Summary of novel findings

Using data mining method, we investigated for the first time the frequency of occurrence of childhood hypertension and its co-morbidities, as well as typical metabolic abnormalities.

Based on our results:

- The incidence of childhood high blood pressure in our region is 4%.
- The diagnosis of hypertension in adolescent boys (between the ages of 15 and 18) was more than twice the regional average (8.22%), so we have to put a spotlight on this age group in terms of screening for hypertension.
- We measured significantly higher serum triglyceride levels in all hypertensive age groups of children, with lower HDL-C and higher LDL-C levels, which indicates the early onset of complex lipid metabolic disorder.
- Based on the data, the documentation of the secondary causes of the child's hypertension in the medical records deserves more attention.

In the Eastern-Central European region, we assessed the complex metabolic background of adult hypertension in a large population using data mining for the first time.

Based on our results:

- In our region, the calculated prevalence of adult hypertension is 31.2%.
- Our results support the association of cardiovascular risk factors in adult hypertensive patients.
- Our results confirmed the frequent occurrence of cardiovascular diseases in hypertensive patients.
- Based on our results, data mining may be worth applying in everyday clinical research to determine prevalence data and explore complex relationships with specific lesions.

Discussion

Child and adolescent population

Data mining techniques gained ground in clinical diagnostics, and we can use them for several purposes, including research in the biomedical and healthcare fields. Since data on childhood hypertension in the Eastern European regions are scarce we aimed to investigate a 15-year period and a large pediatric patient population to calculate the estimated prevalence of childhood hypertension and its concomitant diseases using data mining methods. Our data suggest that the calculated prevalence of childhood hypertension in Hungary, at least in our region, is 4%. It is comparable to the data of other European countries and is in line with the result of a recent meta-analysis. In agreement with the literature data, the prevalence of hypertension increases with age from 1.54% up to 5.56%, showing gender differences and a markedly higher ratio of hypertension in boys. In adolescent boys (from 15 to 18 years), the prevalence of hypertension was more than twice the average (8.22%), highlighting the importance of screening in this subpopulation. As far as hypertension etiology is concerned, the traditional separation is primary and secondary classification. Primary hypertension in children is mainly hereditary. The inheritance pattern is multifactorial and modified by environmental factors and diet, such as highly processed food and sodium intake. Although we could not extract data on these parameters, a recent study reported that sodium intake exceeds while potassium does not reach dietary recommendations in Hungary. A multicenter paper proved that almost half of the daily energy intake of children from eight European countries including Hungary came from ultra-processed foods. A significant connection between obesity and hypertension is well-documented among children. Our data also highlight the importance of obesity in this patient population: we found significantly higher BMI values and markedly higher obesity prevalence in hypertensive children. As in adults, obesity due to poor diet and inactivity is the most important predisposing factor for metabolic abnormalities in childhood, including dyslipidemia, hyperinsulinemia and hyperuricemia. Insulin resistance and hyperinsulinemia might contribute to enhanced renal sodium reabsorption or increased sympathetic nervous system activity. We found that the prevalence of diabetes was significantly higher among children with hypertension in all age groups. The impact of diet components on gene expression or fructose intake on uric acid levels also contributes to harmful metabolic changes. Although we have no data on diet components and fructose intake of the study population, serum uric acid levels were significantly higher in the hypertensive groups

compared to the normotensive children. A former study found a positive association between uric acid and blood pressure, insulin and triglycerides in overweight and obese youths. We also found significantly higher serum triglyceride levels in all hypertensive age groups accompanied by lower HDL-C and higher LDL-C levels, indicating the complex disturbance of lipid metabolism. While dyslipidemia is common in adulthood, especially in overweight and obese population, its early appearance associated with childhood hypertension is astonishing and alarming, highlighting the importance of immediate laboratory screening at the moment of recognition. Although the pharmacological management of childhood dyslipidemia should be reserved for special situations, lifestyle intervention can be indicated at any age. In secondary hypertension, there is an identifiable cause in the background. Secondary hypertension is relatively common in infants and young children. The causes of hypertension vary with age. Renal artery thrombosis or stenosis, congenital renal malformations, coarctation of the aorta or various endocrinological disorders can be the underlying cause of hypertension, although renal abnormality is the leading problem. Our data also demonstrated a higher prevalence of renal diseases in hypertensive children. Although we could not identify children with renal artery occlusion/stenosis or aortic coarctation, we found that the prevalence of several endocrine disorders was significantly higher in the hypertensive groups indicating their possible pathogenic role in hypertension. In adolescent females taking oral contraceptives is associated with hypertension. Unfortunately, data on the medication of adolescents enrolled in the study is not accessible. Our study is not without some limitations. Hospitalgoers, both children and adults, represent a population that differs from the average population. Therefore, our calculations might overestimate the prevalence of hypertension, for example, the frequency of some secondary forms. The University of Debrecen Clinical Center is a regional centre for pediatric endocrinology and nephrology care that provides specialized, multidisciplinary care to children and adolescents with endocrine and renal disorders. We studied a relatively large cohort of children, which may not directly represent the total pediatric population in our region but may provide data. Unfortunately, we were unable to assess data on family history, diet and lifestyle habits. Additionally, a larger population is needed to define the contribution of secondary causes leading to childhood hypertension since their recording in medical documentation is precarious and inaccurate. Furthermore, we also collected data on patients' antihypertensive medication. However, we could find only a few children treated with antihypertensive agents. In general, pediatricians administered beta-blockers and ACE-inhibitors in severe cases but primarily suggested lifestyle modification to the patients and their

parents. We could not provide statistical data due to the low number of cases. Still, we believe that our data mining method verified their impact on the diagnostic process of childhood hypertension. The rising prevalence of pediatric hypertension carries problematic global health dimensions. Childhood hypertension is no longer a condition characterized by elevated blood pressure values but rather a chronic disease associated with metabolic complications at presentation. Therefore, timely screening and interventions for these early metabolic complications are essential to prevent morbidity and mortality in the future.

Adult population

Our study among adult hypertensive individuals is unique because it assessed the complex metabolic state of hypertensive patients in a large population in the East-Central European region over a 20-year period. Our results prove the unequivocal association of cardiovascular risk factors, including metabolic changes, in the case of patients with already-known complications. But these changes can already be seen in persons dealing with chronic consequences not yet diagnosed. According to our hypothesis, the prevalence of high blood pressure in our region correlates with international data. However, due to the low level of health awareness, we expected a relatively high prevalence of accompanying metabolic disorders, which may explain the outstanding cardiovascular morbidity and mortality rates in our country. Based on our study, the calculated prevalence of hypertension is the same as the international results and is consistent with some previous data found in Hungarian registers. If we compare the outcome of our study with the European Society of Cardiology (ESC) statistics on cardiovascular diseases in 2021, the median age-standardized prevalence of hypertension among adults in Hungary was 30% in 2015. During the 20-year examination period defined in our study, the disease was diagnosed in a total of 292,561 adults out of 937,249 hospital-goers. Therefore, the calculated prevalence of hypertension is 31.2%. Data from 2015 confirmed that the prevalence of hypertension was lower in women than in men in all ESC member countries. According to the statistics, we also documented a higher prevalence in men (33%) compared to women (29.9%). It was part of our preliminary research plan, but we could not compare all our results with the ESC data due to the different test methods. Regardless of this, the assumption is that data mining is considered a reliable statistical analysis method based on its own results that correlate with international data. We have read about the positive correlation between progressively increasing BMI, obesity and high blood pressure disease in numerous publications. Our data also supported the mentioned observations. The average body mass index

of hypertensive patients was 26.9 kg/m^2 , according to data from a 2019 domestic program. The values we documented were significantly higher than this. Based on this, the domestic impact of the obesity pandemic, which is growing yearly, can be clearly perceived. Hypertension, atherogenic dyslipidemia, elevated body mass index and diabetes mellitus are all protagonists of an interrelated matrix characterized by characteristic laboratory abnormalities. Elevated total cholesterol and LDL-C levels are often measured in hypertension. However, we did not find any significant differences in the latter parameters between hypertensive and non-hypertensive patients at the level of the entire population. Although cholesterol and LDL-C levels were lower in hypertensive patients compared to normotensive individuals, but only in the 35-79 age group. It did not differ significantly in other age groups and the whole population. Higher levels of ApoB100-containing VLDL particles (as indicated by higher triglyceride levels) may explain the higher serum ApoB100 concentrations in hypertensive patients despite similar LDL-C levels. Lower LDL-C levels are most likely the consequence of a surprisingly different ratio of statin use in favour of hypertensive patients. Patients with high blood pressure often struggle with comorbidities of the cardiovascular system, where the basic therapy includes statins. This phenomenon can explain the lower total cholesterol and LDL-C levels. Moreover, due to close patient care, better adherence and perhaps also the administration of fixed-dose combination antihypertensive therapy with statin content in recent years, lipid levels tend to approach target values in hypertensives. The total cholesterol level turned out to be lower than 5.5 mmol/L published in the Hungarian Hypertension Register. We must highlight the age group over 80 years in our study population. total cholesterol level was higher in HT patients compared to non-HT subjects in the $>80 \text{ y}$ age group. On the one hand, statin use was very low in this age group, and we also hypothesize that the statin adherence might be lower as well, since age is a key factor in statin adherence. On the other hand, total cholesterol both in HT and non-HT patients were lower in $>80 \text{ y}$ age group compared to younger patient groups. The BMI of these elderly patients is also lower, which might be responsible for the lower total cholesterol levels. This unintentional weight loss in elderly populations is well documented in the literature. Nonmalignant diseases are more common causes, but malignancy accounts for up to one-third of cases of unintentional weight loss. Medication use and polypharmacy can interfere with the sense of taste or induce nausea as causative factors. Social factors such as isolation and financial constraints may also lead to unintentional weight loss in the elderly. Furthermore, patients with higher total cholesterol may pass away at a younger age compared to those with cardiovascular diseases. A significantly higher triglyceride level and a significantly lower HDL-C level were

measured in hypertensive individuals compared to non-hypertensive individuals, which was in line with international data. This fact alone highlights the importance of treating hypertriglyceridemia, as well as the cardinal importance of effective therapy for underlying obesity and diabetes mellitus. Elevated triglyceride, LDL-C and low HDL-C levels are typical factors of atherogenic dyslipidemia, which today is an area that requires special attention regarding the treatment and prevention of cardiovascular diseases. Optimally adjusted blood pressure reduces the chance of developing cardiovascular events by approximately 25%, while effective lipid reduction can bring even more direct benefits. Based on all of this, the main goal of the preventive strategy of cardiovascular events is to optimize the combined treatment of hypertension and dyslipidemia. The lower ApoA1 levels measured in the study population did not bring new results, because ApoA1 is the main structural protein of HDL, which is proportional to the number of HDL particles. Body mass index and age have been proven to have the greatest influence on the chance of the co-occurrence of hypertension and hyperlipidemia. Based on our results, the correlation of triglyceride and HDL-C levels with BMI highlights the clear positive role of physical activity, maintaining optimal body weight and the correct education of patients. The measured triglyceride and HDL-C levels correlate with previous data from the Hungarian Hypertension Register. An elevated uric acid level is both a cause and a consequence of the development of high blood pressure through several pathomechanisms. In correlation with the literature results, we also measured significantly higher serum uric acid levels in subjects suffering from hypertension in our study population. The mutual cause-and-effect relationship between kidney diseases and hypertension is also a widely researched topic. The progression of kidney disease harms blood pressure values; blood pressure that is not optimally adjusted sooner or later leads to deterioration of renal function. In our study, we found significantly higher urea and creatinine levels in the hypertensive group compared to the normotensive group. Furthermore, we also verified a higher prevalence of kidney diseases among people living with high blood pressure compared to the normotensive population. Insulin resistance, T2DM, high blood pressure, hyperlipidemia, obesity or overweight, and non-alcoholic fatty liver disease (NAFLD) are all conditions characterized by pathological differences that can be detected simultaneously in a large percentage of the patient population. Here, our test results correlated with previous publications; in particular, GGT levels were significantly higher in hypertensives compared to normotensives. NAFLD is a metabolic disorder that may be associated with high blood pressure in the studied population, so it would be beneficial to organize the screening of these patients in the future. By the results

of a previous study, we also found that in the case of severe hypertension, the entire metabolic state, including kidney and liver function, progressively deteriorates. Due to the complex metabolic changes detailed above, the incidence of atherosclerotic vascular complications was inevitably significantly higher among hypertensive individuals compared to normotensives. These differences were also reflected in the incidence of cardiovascular diseases, which we subsequently observed in all age groups. Cerebrovascular diseases have an extremely high prevalence, especially in the older hypertensive population. The latter result may be attributed to the synergistic effect of hypertension and, among other things, lipid metabolism disorder. The unexpectedly low prevalence of PAD may indicate deficiencies in screening. The unexpectedly low prevalence of PAD indicates the shortage of screening, which is also common worldwide since PAD has been historically underappreciated by healthcare professionals and patients.

Data mining - evaluation of the method

Data mining is the process of complex analysis of large information sets. As a result, we can gain insight into prestigious databases. With the help of this novel classification method, we can explore previously unknown relationships in an enormous data set. That process leads to rational data summarization. The basis of the method is connected to explosive development in the world of IT. In data mining, we used medical data to identify specific parameters and examined the child and adult populations. In this way, we created predictive models which may lead to effective clinical decision-making and treatment approaches. The method has a clear place in clinical research. The most convincing argument is that data mining has already been successfully used to disclose metabolic abnormalities not only in hypertension but also in hyperlipidemia and metabolic syndrome. It should be noted, that data mining cannot be considered a "superior" method compared to epidemiological studies, but rather an additional possibility to obtain even more relevant information from mass data.

Summary

Early recognition and correct management of childhood hypertension are fundamental to long-term cardiovascular outcomes. The global prevalence of hypertension in these age groups is gradually increasing. However, in Eastern Europe, it has been only sporadically studied. Therefore, the first objective of our study was to explore the prevalence of childhood hypertension and associated metabolic disorders using data mining methods. We processed the data of 92,198 children who attended the University of Debrecen Clinical Centre in a 15-year-long retrospective study. We identified a total of 3687 children with hypertension. The calculated prevalence of hypertension was 4% in the entire population, with a higher prevalence in boys. We measured significantly higher BMI values in hypertensive children compared to normotensive individuals and in all age groups. In addition, we measured significantly higher total cholesterol and triglyceride and lower HDL-C levels in children with hypertension. Furthermore, significantly higher serum uric acid levels were documented in hypertensive children, while glucose levels did not differ significantly between study groups. Cardiovascular diseases are the leading cause of death in the adult population. Achieving optimal blood pressure levels and managing the associated metabolic disturbance are prominent issues in its prevention. No comprehensive study has previously investigated the complex metabolic status of hypertensive patients in Central and Eastern Europe. Therefore, another objective of our work was to assess the prevalence of hypertension and associated metabolic disorders in our region using data mining methods. During the 20-year study period, we analysed 937,249 patients' data. We detected 292,561 hypertensives in total. The overall calculated prevalence of hypertension was 31.2%. We found significantly higher body mass index values in hypertensive patients than in the non-hypertensive group. We reported markedly higher triglyceride and lower HDL-C levels in adults between 18 and 80 years. Furthermore, we measured notably elevated serum glucose and uric acid levels in hypertensive patients. In addition, we assessed the correlation between lipid parameters and BMI, the prevalence of comorbidities, the proportion of statin use among our subjects, and the distribution of the most common laboratory abnormalities in hypertension severity grades and the overall population. Our study suggests that the calculated prevalence of hypertension and associated metabolic disorders in children and adults is comparable with international findings and highlights the diverse metabolic abnormalities underlying the disease. The availability of reliable national statistics is essential for planning regional public health strategies and optimising resource allocation. It underpins efforts to screen and educate patients and supports everyday clinical decision-making strategies.

Data mining is an excellent but not widely used tool to determine prevalence in large patient populations. It is also considered a niche method to obtain accurate statistical data on baseline and comorbidities, metabolic status and various risk factors in our patients. Our results suggest that early detection and prompt treatment of hypertensive patients' cardiometabolic risk factors are essential to improve quality of life and life expectancy.

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List of publications related to the dissertation

1. **Kovács, B.**, Németh, Á., Daróczy, B., Karányi, Z., Maroda, L., Diószegi, Á., Harangi, M., Páll, D.:
Assessment of Hypertensive Patients' Complex Metabolic Status Using Data Mining
Methods.
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Harangi, M., Páll, D.: Determining the prevalence of childhood hypertension and its
concomitant metabolic abnormalities using data mining methods in the Northeastern region of
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List of other publications

3. Harangi, M., **Kovács, B.**: Lipidcsökkentő kezelés hypertóniában: mit, mennyit, mikor?
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4. **Kovács, B.**, Cseppekál, O., Diószegi, Á., Lengyel, S., Maroda, L., Paragh, G., Harangi, M., Páll, D.:
The Importance of Arterial Stiffness Assessment in Patients with Familial
Hypercholesterolemia.
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5. Nádró, B., Diószegi, Á., **Kovács, B.**, Paragh, G., Páll, D., Harangi, M.: A magasvérnyomás-betegség előfordulása és kezelése frissen diagnosztizált familiáris hypercholesterinaemiás betegekben.
Hyperton. nephrol. 25 (1), 7-11, 2021.
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7. Juhász, L., Balogh, I., Madar, L., **Kovács, B.**, Harangi, M.: A Rare Double Heterozygous Mutation in Low-Density Lipoprotein Receptor and Apolipoprotein B-100 Genes in a Severely Affected Familial Hypercholesterolaemia Patient.
Cureus. 12 (12), 1-5, 2020.
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Vessel Plus. 3 (6), 1-6, 2019.
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