Óbudai Egyetem

Doktori (PhD) értekezés tézisfüzete

Two Applications of Biostatistics in the Analysis of Pathophysiological Processes

by

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1 Background of the Research

The application of biostatistical tools is indispensable in many current medical research. As medicine became more and more empirically oriented in the last centuries, and as it became more and more model-oriented in the last decades, the mathematical and – specifically – biostatistical methods received special attention. The application of such apparatus is necessary to the precise investigation of many questions, and can also help to raise new ones. The present dissertation shows two examples for this. It also demonstrates how informatics and applied informatics supports the modern biostatistical investigations.

1.1 Effect of Obesity on Laboratory Parameters

The first thesis group deals with the topic of obesity, more specifically, pediatric obesity. Obesity (Andersen 2003) is considered an epidemic in most parts of the developed world. As an example: it has been long time since overweight and obese people became the majority in the United States' population; according to the latest data, the prevalence of overweight is 34.2%, the prevalence of obesity and extreme obesity is 39.5% among adults aged 20 and over (Ogden and Carrol 2010b). The speed of progress is even more frightening, especially as far as obesity is concerned: the same prevalence was only 14.3% in 1960 (Ogden and Carrol 2010b). Situation is similar in Hungary: the prevalence of overweight is 34.1%, the prevalence of obesity is 19.5% (Organization for Economic Co-operation and Development 2012).

The same applies to pediatric obesity as well, although the available information is less detailed (Wang and Lobstein 2006; Ogden, Yanovski, et al. 2007). In the United States, the prevalence of obesity among children and adolescents aged 2-19 is 16.9% (Ogden and Carrol 2010a), in Hungary, the same prevalence is estimated to be about 5-10% (Kern 2007; Antal et al. 2009).

Obesity is in the focus of public health for decades, as – in addition to its continuously increasing prevalence – it also increases all-cause morbidity and mortality (Flegal et al. 2013; Visscher and Seidell 2001; Pi-Sunyer 2009). Type 2 diabetes (formerly known as non-insulin dependent diabetes, which is typically adult-onset), various cardiovascular diseases (including ischaemic heart disease), asthma, gallbladder disease, various malignant tumors are examples for diseases with increased occurrence casually linked to obesity(Guh et al. 2009). These have been described in children too (Burke 2006; Nyberg et al. 2011).

It is well-known that obesity, and even overweight, causes systematical changes in the laboratory results. The reasons of these changes are complex. On one hand, many change

is a more or less direct consequence of the manifestly altered homeostatic equilibrium induced by obesity, like elevated serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels found in obese adults (Ruhl and Everhart 2003), and in children as well.

However, in some cases, the change in the laboratory parameters can not be attributed to a single physiological alteration, or even to any well-defined alteration that causes manifest obesity-related finding at all at the moment the laboratory parameter is already changed. A notable example is C-reactive protein (CRP) which is used even predicatively (Bo et al. 2009; Juonala et al. 2011; Ong et al. 2011) because of this reason.

1.2 Modeling and Evaluating the Performance of Tight Glycemic Control Protocols

The second thesis group also considers a problem of an intensively researched topic: it deals with the objective evaluation and examination of the so-called tight glycemic control protocols that are used in critical care.

Stress induced hyperglycemia is a significant issue in critical care, affecting up to 30-50% of patients and increasing morbidity and mortality (Krinsley 2003; McCowen, Malhotra, and Bistrian 2001). Controlling glycemia has proved difficult due to the associated risk of hypoglycemia when highly dynamic patients are treated with exogenous insulin (Griesdale et al. 2009). Both extremes, as well as glycemic variability, have been independently linked to increased morbidity and mortality (Bagshaw et al. 2009; Egi et al. 2006; Krinsley 2008), creating a difficult clinical problem.

More specifically, inter- and intra- patient metabolic variability drive outcome glycemic variability and hypoglycemic risk (Chase, Compte, et al. 2011) making good control difficult. In particular, sudden and large rises in insulin sensitivity can result in a hypoglycemic event when exogenous insulin is given over a typical 3-4 hour measurement interval. It is critical to determine the size and likelihood of these intra-patient variations, to enable a more complete understanding of the inherent risks in glycemic control.

Very few studies have examined time-varying evolution of insulin sensitivity and its variability in the critically ill. Langouche et al. (2007) noted that insulin sensitivity rose between days 1 and 5 over their large cohorts, but provided no daily or diagnostic specific evolution. Lin et al. (2008) showed that hour to hour changes for a clinically validated model-based insulin sensitivity metric could be quite large as a function of current insulin sensitivity level for a medical Intensive Care Unit (ICU) cohort that covered all diagnostic categories and days of ICU stay. However, no studies to date have explicitly described the evolution of intra-patient insulin sensitivity and its variability on a daily basis, or for

different diagnostic categories.

Such information would provide insight into the risk of hypoglycemia by diagnostic category and day of ICU stay. Additionally, insight into the likelihood of glycemic variability resulting from greater or lesser intra-patient variability of insulin sensitivity could be attained.

This thesis presents the first rigorous statistical analysis of inter- and intra- patient insulin sensitivity variability as a function of diagnostic category and day of stay. It is also the first to examine the long-term behavior of insulin sensitivity.

The significance of these can be understood in the light of glycemic control, especially tight glycemic control (TGC). TGC protocols aim to address specifically this issue. Glycemic control can reduce negative outcomes (Krinsley 2004; Chase, Shaw, et al. 2008), but has proven difficult (Casaer et al. 2011; Brunkhorst et al. 2008). Only Chase, Shaw, et al. (2008) reduced both mortality and hypoglycemia.

2 Directions and Goals of the Research

2.1 Effect of Obesity on Laboratory Parameters

Previous researches in this topic mostly focused on univariate questions (as exemplified by the above citations). In other words, they were rather association-oriented findings, i.e. they described changes of a certain laboratory result in obese subjects (as opposed to the healthy state). To my best knowledge, no investigation addressed the question how obesity affects the laboratory results from a multivariate perspective (i.e. what is the effect of obesity if not only individual changes, but also alterations in the correlation structure of the laboratory results is considered), especially not in children.

Therefore, my primary aim was to investigate how pediatric obesity influences the uni- and multivariate structure of common laboratory parameters in a precise, uniform way for all parameters.

The principal novelty of my research lies in the fact that I present a methodology that integrates the handling of different levels of overweight and obesity using advanced statistical apparatus.

2.2 Modeling and Evaluating the Performance of Tight Glycemic Control Protocols

One of the key tasks of such protocols is the prediction of the patients' insulin sensitivity. Within this thesis group, I have developed a biostatistical method, which makes it possible

to model the evolution of a patient's insulin sensitivity in the context of the predictions provided by the protocol. The method explicitly incorporates the patient's diagnosis and the length-of-stay in the intensive care unit, which can fundamentally influence the evolution of the insulin sensitivity. The method thus makes it possible to quantitatively assess the protocol, furthermore it can also provide (even clinical) suggestions on how to improve the protocol, considering different goals.

3 Materials and Methods of Investigation

3.1 Effect of Obesity on Laboratory Parameters

In the first thesis, I created a novel biostatistical methodology to fulfill the aim defined above. This thesis also involves the actual implementation of this methodology as a computer program to provide informatics support in applying this methodology to real-life databases.

This methodology quantifies the degree of overweight/obesity by the so-called standardized BMI (or Z-BMI) in order to take the effect of growth into account (Cole et al. 2005). The Z-BMI score is explicitly incorporated in both the univariate and the multivariate analysis.

In the univariate analysis, the joint probability density function of the investigated laboratory parameter and the Z-BMI is estimated by kernel density estimation (Wand and Jones 1995; Silverman 1986), from which a conditional distribution is obtained for the investigated Z-BMI level. Necessary univariate indicators can be obtained from this conditional distribution through numerical methods. The univariate association is characterized with Spearman-ρ non-parametric correlation coefficient (Maritz 1995). To assess significant associations, Holm–Bonferroni-correction is employed (Holm 1979).

The multivariate analysis follows similar lines, but in that case a three-dimensional joint distribution is estimated (two investigated laboratory parameters and Z-BMI) with kernel density estimation, from which a "conditional correlation matrix" is reconstructed element-by-element. Possible nonpositive eigenvalues are eliminated through smoothing (Wothke 1993). On this correlation matrix, principal components analysis (Jolliffe 2002) and cluster analysis (Everitt and Hothorn 2011) is performed.

In the second thesis, I applied this methodology to two concrete, relevant databases: a representative, large-sample US survey, the so-called NHANES (Centers for Disease Control and Prevention, National Center for Health Statistics 2013) and a non-representative Hungarian study, which we performed specifically for this end [F-4], and which – to our best knowledge – is the first Hungarian survey addressing this question.

3.2 Modeling and Evaluating the Performance of Tight Glycemic Control Protocols

To investigate this question, I used the SPRINT protocol, which identifies hourly, model-based insulin sensitivity (SI) values. SPRINT is a model-based, clinically validated tight glycemic control (TGC) protocol that provides explicit control for both nutrition intake and insulin input (Chase, Shaw, et al. 2008). Based on clinical data from $n = 390$ patients (47 836 hours) in the SPRINT medical ICU cohort (Chase, Shaw, et al. 2008) hour-to-hour changes are evaluated for the cohort over all days of ICU stay using a stochastic model (Lin et al. 2008) that provides kernel density estimation-based distributions of $SI\,(n+1)$ values (in terms of predicted distribution, i.e. $\widehat{F}_{SI_{n+1}}$) for each current $SI\,(n)$ value using all 47 836 data points.

The investigations for SI variability will be based on the accuracy of the predictions provided, i.e. we will call a patient variable if the predictions are not accurate (the actual values are not following the predicted distribution). First, the present insulin sensitivity ($SI\,(n)$) is identified, then, the cohort model is used to predict the distribution of insulin sensitivity at the next time-point ($\widehat{F}_{SI(n+1)}$) for the given $SI\,(n)$. The actual (identified) $SI\,(n+1)$ value might be away from the median of this distribution, and this difference over time going forward is the variability in which we are interested. For this end, predicted SI distribution ($\widehat{F}_{SI_{n+1}}$) will be confronted with actual SI of the next hour (SI_{n+1}). Thus, variability was defined by the position of the realized eventual $SI\,(n+1)$ value relative to its predicted distribution $\widehat{F}_{SI(n+1)}$.

I defined two metrics to characterize this variability. The so-called quadratic penalty measures overall variability, while one-sided threshold penalty measures the potentially hypoglycemia inducing sudden rises in SI.

To describe these, I use a linear mixed effects model (Pinheiro and Bates 2000; Brown and Prescott 2006) that includes both time spent in intensive care unit and diagnosis group of the patient. After performing ANOVA to assess the significance of main effects, post-hoc testing on significant effects was carried out using Tukey's Honestly Significant Differences (HSD) method (Hsu 1996), providing the correction that takes the multiple comparisons situation into account.

4 New Scientific Results

Thesis group 1: Effects of obesity on laboratory parameters.

Thesis 1.1:

> ***Thesis 1.1***
> **I have developed a biostatistical methodology (and an associated computer program) to investigate the effect of obesity on laboratory parameters. This methodology provides a way to analyze both the uni- and the multivariate structure of the laboratory parameters, making the effect of obesity explicit during the process.**

Thesis 1.2:

> ***Thesis 1.2***
> **I have provided clinical interpretations for the effects of obesity on laboratory parameters based on a representative international survey and a non-representative survey that was performed on Hungarian adolescents specifically for the aims of the present investigation. I discuss results pertaining to both the uni- and the multivariate structure of the investigated variables.**

Relevant own publications pertaining to this thesis group: [F-1; F-12; F-7; F-2; F-4; F-21; F-3; F-9; F-5; F-10; F-14; F-13; F-6; F-11; F-18; F-19; F-20; F-17].

Thesis 2. Modeling and Evaluating the Performance of Tight Glycemic Control Protocols.

> ***Thesis 2***
> **I have developed a novel methodology to evaluate and model the insulin sensitivity variability and its evolution over time for patients in different diagnosis groups. This also makes the more thorough investigation of the performance of tight glycemic control protocols possible.**

Relevant own publications pertaining to this thesis group: [F-15; F-8; F-16].

5 Discussion and Practical Applicability of the Results

5.1 Effect of Obesity on Laboratory Parameters

Univariate examination of laboratory results sheds light on the pathophysiological alterations that are associated with obesity. While these changes were mostly already well-known for particular parameters, I now performed a comprehensive, uniform investigation for 33 routinely measured blood tests.

The analysis of the multivariate structure of the laboratory results reveals groups of variables that exhibit similar stochastic behavior, pointing to shared physiological background. On the other hand, this analysis also demonstrated that the correlation structure of the laboratory parameters is largely unaffected by the degree of obesity and sex.

The method I proposed for the analysis of the multivariate structure (obtaining conditional correlation matrices through KDE element-by-element with smoothing being applied afterwards, and the analysis of these matrices with PCA or CA) lived up to expectations and was demonstrated to be a useful tool in similar tasks.

These results can be used to deepen our understanding of the pathophysiology of overweight and obesity, and how these diseases affect the human body. Such understanding can be then in turn used to optimize prevention and therapy, which has a direct significance from the public health point of view.

5.2 Modeling and Evaluating the Performance of Tight Glycemic Control Protocols

Inter-patient variability in insulin sensitivity peaks on day 1 across diagnostic groups and metrics. Operative – All other patients are more predictable after day 4 than an all patients and days of stay model accounted for, shown by conservative coverage. The distribution of overall intra-patient variability assessed per-patient and the mixed-effects model shows there are distinctive differences between diagnosis groups, irrespective of the time spent in the ICU. In particular, the Non-operative – Gastric group exhibits the smallest variability, while Cardiac groups are amongst the most variable. Clinically, these results show decreasing risk of hypoglycemia as length of stay increases, as well as some reduction in glycemic variability when all else is equal. The overall results can be used to guide the design and implementation of glycemic management specific to diagnosis group and ICU day of stay to improve control and reduce risk.

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