Translating scientific results benefits the community: From pancreatitis to COVID-19

Ph.D. Thesis

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PUBLICATIONS RELATED TO THE SUBJECT OF THE THESIS

I. Anikó Nagy, Márk Félix Juhász, Anikó Görbe, Alex Váradi, Ferenc Izbéki, et al. Glucose level independently and dose-dependently worsens acute pancreatitis: a prospective, international cohort analysis of 2250 acute pancreatitis cases. Pancreatology 2021. *in press* IF: 3.799

II. Gombos K, Herczeg R, Erőss B, Kovács SZ, Uzzoli A, Nagy T, Kiss S, Szakács Z, Imrei M, Szentesi A, Nagy A, Fábián A, Hegyi P, Gyenesei A. Translating Scientific Knowledge to Government Decision Makers Has Crucial Importance in the Management of the COVID-19 Pandemic. Popul Health Manag. 2021 Feb;24(1):35-45. doi: 10.1089/pop.2020.0159. Epub 2020 Sep 2. PMID: 32882160. IF: 2.145

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SCIENTIFIC METRICS

Number of publications **related to the subject** of the thesis:	3 (1 first author)
Cumulative impact factor of publications related to the thesis:	8.007
D1: 1, Q1: 2, Q2: -, Q3: -, Q4: -	
Number of **total accepted/published** articles:	8 (1 first author)
Cumulative impact factor of the published articles:	11.385
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Number of total citation by **MTM2:**	273 independent
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I. INTRODUCTION

In this day and age, applying a scientific mindset and the prompt utilization of scientific results are vital, for the appropriate functioning and improvement of near all parts of life. However, the number of scientific publications is increasing at a rapid pace: with 291,806 available on MEDLINE in the year of 1995 and 1,064,266 in 2015 – no doubt too much to be handled on a personal or even institutional level. There is a dire need for a centralized method that aids the incorporation of evidence into daily practice, and that converts it into a language that is understandable and usable not only by scientific professionals, but by governments and the general public as well.

Translational medicine (TM) aims to ensure that scientific results are delivered or 'translated' into general use. In medicine for example, this is done by following up promising basic science results with clinical studies, by standardizing the method of reporting in scientific papers, by updating guidelines as often and as thoroughly as possible, and promoting evidence-based patient management. And not only in medicine, but in any area of life, knowledge acquired this way should be presented both to decision makers and the general public, in a manner that they can best handle the information.

AP is the sudden-onset inflammation of the pancreas, a common reason behind abdominal pain in the adult emergency department. In up to 25-30% of cases, severe disease course will occur, with a mortality rate as high as 40% - both severity and mortality could and should be diminished with improved care of these patients. Recent years' basic science and clinical investigations are focusing on commonly encountered laboratory and anamnestic parameters that could help in establishing AP prognosis and the best choice of treatment on admission: pancreatotoxic agents. Pancreatotoxicity, a dose-dependent relationship with worsening clinical outcomes of AP, is already demonstrated in case of bile acids, alcohol and its metabolites, fatty acids and fatty acid ethyl esters and presumed in case of smoking and several drugs. We set out to examine – in keeping with the mentality of TM – whether such a dose-dependent relationship exists with increasing serum glucose values, since basic science points towards the potential pancreatotoxic effects of hyperglycemia.

However, in December 2019 the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) pandemic hit, causing the Coronavirus Disease 2019 (COVID-19). In little more than one year, there have been around 120 million confirmed cases of COVID-19 worldwide, resulting in almost 3 million deaths, mostly due to respiratory failure. The world was struck unprepared for an outbreak and pandemonium of these measures. This made TM

more necessary than ever: the scientific evidence, amassed in a hurry, needed to be evaluated and summarized in a hurry so that the government could react promptly and appropriately, minimizing the deleterious effects of the pandemic. It also became essential to assess, more swiftly than usual, where the literature was lacking, and design clinical or basic science experiments to fill the inherent voids. Thus, our focus partly shifted towards applying TM research for improving the COVID-19 pandemic.

II. AIMS OF PHD WORK

As the Director-General of Heim Pál National Pediatric Institute and the former State Secretary for Health of Hungary, it is of crucial importance to me that scientific results make their way into patient care as soon as possible. This not only improves the quality of care and helps avoid unnecessary deaths, but also greatly contributes towards building a more cost-efficient healthcare system, which ultimately provides the basis for further improvement and better working conditions.

In my PhD work I wanted to focus on different aspects of TM. We set out to analyze a prospective, international cohort of AP patients, and establish whether serum glucose predicts worse clinical outcomes or complications – since this information was yet uninvestigated. During the COVID-19 pandemic we provided systematic literature reviews and performed mathematical modelling estimations to aid government decision makers. While exploring the available literature, we identified a gap in knowledge – this led to designing and initiating our randomized controlled trial (RCT), Personalized Health Education Against COVID-19 (PROACTIVE-19), which is the first to investigate and provide a personalized, multicomponent lifestyle intervention program in a telephone-based manner, to help avoid the contraction and severe course of COVID-19.

III. GLUCOSE LEVEL INDEPENDENTLY AND DOSE DEPENDENTLY WORSENS ACUTE PANCREATITIS: A COHORT ANALYSIS

III.1. Introduction

AP is the inflammation of the pancreas, most often caused by alcohol consumption and biliary obstruction. The incidence of AP is gradually increasing worldwide, now reported to be 4.6-100/100,000 in the general population.

Hyperglycemia is an established independent risk factor in numerous diseases. Furthermore, not only the acute elevations in serum glucose are of interest – studies describe chronic glucose dysregulation to be prognostic for mortality after acute myocardial infarction, both in diabetic and non-diabetic patients. In AP, the exact role of glucose dysregulation and its laboratory indicators is yet to be described.

Our goal was to examine the presence of dose-dependency between glucose dysregulation and clinically important outcomes of AP in a large, multicenter, prospective cohort.

III.2. Methods

This study presents a post-hoc analysis of a prospective, international, multicenter registry of AP patients, maintained by the HPSG. In the present analysis, we included 2,461 participants with available data on (1) HbA1c any time during the hospitalization with AP and/or (2) on-admission serum glucose measurement and/or (3) at least two serum glucose measurements during hospitalization. Glucose measured only within the first 24 hours was accepted as on-admission glucose level. HbA1c measured any time during the hospitalization was accepted for this analysis.

Three variables were taken into account in dividing our examined cohort into subgroups. To observe the role of the glucose homeostasis preceding the admission with AP – 'before AP' (BAP) – participants were divided into five groups based on their HbA1c: ≤6.50; 6.51-7.00; 7.01-8.00; 8.01-9.00; ≥9.01%. To reflect the on-admission state – 'on-admission AP' (OAP) – seven groups were formed based on on-admission serum glucose levels: ≤3.99, 4.00-5.99, 6.00-7.79, 7.80-11.09, 11.10-14.99, 15.00-19.99, ≥20.00 mmol/L. Seven groups were formed based on peak serum glucose during the hospital stay – 'during AP' (DAP) – among those patients who had at least two glucose measurements: ≤3.99, 4.00-5.99, 6.00-7.79, 7.80-11.09, 11.10-14.99, 15.00-19.99, ≥20.00 mmol/L. These boundaries were chosen to reflect already established cut-offs (6.5% and 7% for HbA1c, 7.8 mmol/L and 11.1 mmol/L for glucose (38), participant and event numbers to maintain statistical power and equal increments to avoid the possibility of arbitrary cut-off selection.

For the descriptive analysis of categorical variables, case number and percentage were computed, while in the case of continuous variables, patient number, mean, standard deviation (SD), median, 25% and 75% quartiles (IQR) were calculated. To identify the three subcohorts' representativeness, we used the Chi-squared test in case of categorical data, the Student's t-test for normally distributed variables, and the Mann-Whitney U-test for non-normally distributed

variables. The dose-dependent effects of HgA1c, on-admission and maximum glucose levels on the investigated outcomes, were tested using the Cochran-Armitage test for trend (in case of categorical variables) and the Jonckheere-Terpstra trend test (in case of continuous variables).

To detect the predictive accuracy of HbA1c, on-admission glucose level and maximum glucose level on the mortality and severity, the Receiver Operating Characteristic Curve (ROC) was applied. Odds ratios (OR) with 95% CI were calculated for severe AP cases and mortality. Binary logistic regression was used to test the independent prognostic role of the three investigated variables. All calculations were performed with the statistical software R, version 4.0.2 (R Core Team, 2020, Vienna, Austria) using the coin (v1.3-4; Hothorn et. al., 2008), rcompanion (v2.3.27; Mangiafico, 2021), DescTools (v0.99.39; Signorell et. al., 2020), PMCMRplus (v1.9.0; Pohlert, 2021) and pROC (v1.17.0.1; Robin et. al. 2011) packages.

Ethical approval for the registry was granted in 2012 by the Scientific and Research Ethics Committee of the Medical Research Council (22254–1/2012/EKU). All participants provided written, informed consent for participation.

III.3. Results

BAP: pre-existing disturbance of glucose metabolism shows a trend of increasing AP severity and local complications.

While no statistically significant differences were noted (p=0.394), a trend of increasing HbA1c and increasing AP severity was observed. AP severity was highest in Group 4 (21.4% moderate, 5.8% severe). HbA1c was directly associated with the length of hospitalization (LOH) ($p<0.001$) and maximal CRP ($p<0.001$), both peaking in group 4 probably due to the higher proportion of moderate cases, but not with mortality, which was the greatest in Group 2 (7.1%) (Figure 2).

OAP and DAP: on-admission and peak glucose levels demonstrate a dose-dependent association with worse AP outcomes (severity, mortality, complications, LOH, maximal CRP).

A dose-dependent association was seen between on-admission glucose levels, peak in-hospital glucose levels and: severity ($p<0.001$ in both OAP and DAP), mortality ($p<0.001$ OAP and DAP), LOH ($p<0.001$ OAP and DAP), maximal CRP ($p<0.001$ OAP and DAP) (Figure 2), systemic complications ($p<0.001$ OAP and DAP; Figure 3) and local complications ($p<0.001$ OAP and DAP; Figure 4).

The group with a peak in-hospital glucose ≥20 mmol/L (Group 7) noted the highest severity (37.5% moderate, 25.0% severe), mortality (12.5%), systemic (43.8%) and local

complications (62.5%). While similarly, on-admission glucose Group 7 saw the highest rate of local complications (36.6%), Group 6 (serum glucose 15 – 19.99 mmol/L) had the highest severity (38.2% moderate, 8.8% severe), mortality (8.8%), and rate of systemic complications (14.7%).

The binary logistic regression established both on-admission and peak in-hospital serum glucose to be independently associated with mortality (OR=1.133 (95% CI: 1.064-1.204), p<0.001 and OR=1.089 (95% CI: 1.020-1.161), p=0.006, respectively) and severity (OR=1.131 (95% CI: 1.078-1.186), p<0.001 and OR=1.093 (95% CI: 1.039-1.152), p<0.001, respectively) (Tables 7-8). The ROC analysis showed on-admission glucose to be a poor predictor of mortality (AUC=0.636 for an estimated cut-off of 10.635 mmol/l) and severity (AUC=0.671 for an estimated cut-off of 9.435 mmol/l). An on-admission glucose >10 mmol/l had an OR of 3.140 (95% CI: 2.106-4.682) for severe AP and an OR of 2.666 (95% CI: 1.587-4.478) for mortality. The ROC analysis indicated that peak in-hospital glucose is a fair predictor of mortality (AUC=0.703 for an estimated cut-off of 6.665 mmol/l) and severity (AUC=0.732 for an estimated cut-off of 7.355 mmol/l). A peak in-hospital glucose >7 mmol/l had an OR of 14.490 (95% CI: 4.443-47.264) for severe AP and an OR of 4.750 (95% CI: 1.370-16.476) for mortality.

III.4. Discussion

Our study is the first to focus on how alterations of the glucose homeostasis affect clinically relevant outcomes of AP. We found on-admission and peak in-hospital serum glucose concentrations to have a statistically significant dose-dependent relationship with AP severity, mortality, LOH, maximal CRP, systemic and local complications. Both these variables are independently (accounting for DM, age, gender and etiology) associated with AP severity and mortality, a peak in-hospital glucose >7 mmol/l making severe AP almost 15 times and death almost five times more likely. While statistically significant dose-dependency was only identified with LOH and maximal CRP in case of HbA1c, a trend of increasing severity and rate of local complications was also noted. In light of the currently available scientific literature on the matter, these findings strongly suggest that glucose has a direct pancreatotoxic effect.

Implications

Prevention: Increased HbA1c was associated with higher severity and a higher rate of local complications. Maintaining a normal glucose homeostasis might reduce the risk of these events.

Prognosis: Increased on-admission glucose has a dose-dependent association with increasing severity, mortality, LOH and complications of AP.

Prompt treatment: High peak glucose is dose-dependently associated with a higher rate of severe cases, mortality, systemic complications and increased LOH. Hyperglycemia does not necessarily present on admission, monitoring serum glucose during the course of AP is crucial. Adequate in-hospital control of hyperglycemia can greatly contribute to the treatment of AP.

IV. TRANSLATIONAL MEDICINE IN THE COVID-19 PANDEMIC

The arrival of the COVID-19 pandemic and the ensuing humanitarian crises immediately shifted our focus. Through tremendous efforts, we formed an interdisciplinary team applying the methods of TM. Our ultimate goal was to aid the Hungarian government in this desperate and seemingly hopeless situation to best handle the pandemic, so together, we can achieve the best possible medical and economical results. We mathematically modelled intensive care unit (ICU) capacity, regional differences, Gross Domestic Product (GDP) loss, etc. and forwarded the information to policy-makers. During our systematic review of the available literature, we noted the need for RCTs testing telephone-based lifestyle interventions. We designed and initiated the PROACTIVE-19 trial to fill this void.

IV.1. TRANSLATING SCIENTIFIC KNOWLEDGE TO GOVERNMENT DECISION MAKERS: MATHEMATICAL MODELLING STUDY

IV.1.1. Methods

To support the epidemiological decision-making process, we performed several scientific data analyses and formulated them into three chapters: 1) results, 2) problems, 3) suggestions.

Mathematical modeling of the COVID-19 epidemic in Hungary

To predict the possible outcome over time for various R metrics, data was collected on the 8th of April 2020 from the official Hungarian data resource site (koronavirus.gov.hu). The model was generated both for the whole country and separately for all its main regions.

Modeling the regional differences in Hungary: the complex health distance index (CHDI)

For the measurement of the regional differences of health status in Hungary, we adopted and restructured the approach of the functional distance index from the economic analyses.

Modeling the GDP loss, economic crisis management, and competitiveness

Our mathematical model focuses on quantifiable variables, and takes into account data of the previous years and currently available data. To model the GDP loss for the five main Hungarian regions, GDP was corrected and normalized by the estimated death rate.

Modelling the impact of closing and reopening elementary schools

Classic SIR (susceptible-infected-recovered) simulation using EpiFire 3.34 API software was applied to model contact network of epidemic transmission using the 'small-world-like' model to compare epidemic scenarios for closing and reopening schools in the current COVID-19 pandemic.

Modeling the optimal screening strategy in Hungary

A Hungarian-specific model was developed to estimate the optimal screening strategies, i.e. the number of screening tests needed for recommendations to keep R under a required level. The calculation was made in R software .

IV.1.3. Results

First we modeled different scenarios to the decision-makers in which we estimated the number of deaths in relation to the predicted number of new cases (number of people infected) together with the modeled numbers of available and occupied ICU beds. The best case scenario for the whole country, using R metrics estimated on the 8th of April, 2020, shows that maintaining the restriction would result in a total of 20,000 new cases at its peak, there would still have enough number of ICU beds to cover the needs for the most serious cases, and therefore, the total death would be kept under 1,500. The worst case scenario was modeled for higher R metrics (R=2.2). The numbers indicate that within three weeks there would not be enough ICU beds, as we would have been sort of 40,000 at the peak, the number of infected cases would have reached 550,000 and the number of deaths was predicted to be 70,000.

Then we investigated the regional differences in Hungary. Our mathematical models clearly indicated that Hungary could not be handled as a whole, but rather regional differences should be taken into account. It was clearly seen when we looked for each region separately the regional distribution of people over 65 years, the differences between the ICU capacities, the estimated GDP loss due to lack of labor force, and the inequalities in CHDI. Therefore the earier modeled best case scenario was also modeled for each region separately. The worst case scenario for each region separately indicates that none of the region would have enough ICU bed capacity.

Next we provided disease transmission simulations to help crucial decisions on closing and reopening elementary schools. According to our calculations for Budapest in the case of the R=2.2 or higher, large epidemic size classes are prone to face fast disease transmission with relatively high frequency. In this case, the chance for an effective health policy intervention to suppress or mitigate the epidemic cycle is very low. Thereby we don't suggest early or complete release of school closures, moreover we support a prolonged and stepwise opening towards the contact education in the elementary schools.

Since it was earlier suggested that higher number of tests results in a lower rate of mortality, we compared the number of tests performed in different countries. We can clearly conclude that the amount of daily testing highly determines the rate of subsequent mortality.

Internationally available data show that Germany is one of the most efficient European countries to keep the mortality rate low. Using this number as a reference point, we have estimated the optimal number of tests needed in Hungary.

IV.1.3. Discussion

Importantly, it seems that the analyses described here and presented to the National Epidemiological Policy-Making Body could have major impact on governmental decision-making since several of these suggestions has already taken effect before we have done the analysis. For example:

(1) previous considerations of the possible lifting of restrictions during the Easter holidays were rejected and lifting the restrictions were postponed for approximately a month,

(2) regional variations of the epidemic have been introduced; restrictions will be eased in less densely populated areas while Budapest and surrounding area will remain under a more strict control,

(3) the importance of increasing the number of testing has been recognized by the authorities,

(4) a representative population screening study was recently initiated which involves more than 10000 volunteers and the concerted effort of the country's four medical university.

In conclusion, in times of epidemics, the formation of interdisciplinary research groups is essential for policymakers, as none of the disciplines can model the complex problems that arise during an epidemic alone. The establishment, research activity and participation in decision-making of the KETLAK group can serve as a model for other countries, researchers and policymakers not only in managing the challenges of COVID-19, but in future pandemics as well.

IV.2. PERSONALIZED HEALTH EDUCATION AGAINST COVID-19 (PROACTIVE-19): PROTOCOL OF A RANDOMIZED CONTROLLED TRIAL

Our main objective is to evaluate the effects of a personalized multicomponent lifestyle intervention aiming to improve the outcomes of COVID-19 infection in the population over 60 years in a randomized clinical trial. The main hypothesis of PROACTIVE-19 is that the personalized multicomponent lifestyle intervention reduces the rate of our composite outcome

consisting of the need for intensive therapy, hospitalisation, and mortality in the COVID-19 population.

IV.2.2. Methods

Design

The study protocol is structured following SPIRIT 2013. PROACTIVE-19 is a pragmatic, randomized controlled clinical trial with adaptive "sample size re-estimation" design. This design allows interim analyses and necessary modifications of the sample size of the ongoing trial to ensure adequate power. Ethical approval: Scientific and Research Ethics Committee of the Hungarian Medical Research Council (IV/2428- 2 /2020/EKU).

Inclusion and exclusion criteria

The inclusion criteria of our selective primary prevention programme are: (1) age over 60 years (that is, high-risk individuals), (2) informed consent to participate. The exclusion criteria are: (1) confirmed COVID-19 (active or recovered); (2) hospitalisation at screening for eligibility; (3) someone was already enrolled in the study from the same community/household (to avoid potential crosstalk between the study arms).

Interventions

Participants will be randomized into two groups: (A) general health education; (B) personalized health education. They will go through questioning and recommendations in 5 domains: (1) mental health, (2) smoking habits, (3) physical activity, (4) dietary habits, and (5) alcohol consumption. Both groups will receive the same line of questioning to assess habits concerning these domains.

Group A: questioning will be done in the order as mentioned above, followed by a general health education aiming towards improvement of these factors with general recommendations (the expected mean duration is approximately 10 min).

Group B: questioning will be done in the same structured order, but an assessment of each domain will be followed by personalized recommendations (the expected mean duration is approximately 20 min).

After the first contact, there will be follow-up calls in both groups, with a matching schedule: every week in the first month, every second week in the second month, then monthly. During these encounters, all change in all five domains since the last call will be assessed.

The operators will have received any healthcare education. Before enrolling participants, the operators will have to complete a standard training program consisting of seminars on the interventions held by medical professionals, followed by practice of scenarios.

The operators will be trained not to give additional healthcare advice, and we will not secure other information sources, including electronic and printed material.

Outcomes

Based on literature data , **the primary endpoint** will be defined as the composite of any of the followings in COVID-19 cases (an accredited laboratory should verify positivity) the rate of:

1. ICU admissions
2. hospital admissions (longer than 48 hours) for the following reasons
    - arrhythmia (causing hemodynamic instability and requiring continuous monitoring and/or cardiac support, as indicated by mean arterial pressure <65 mm Hg, and/or serum lactate >2 mmol/L) and/or
    - ARDS (severe hypoxemic respiratory failure indicated by a PaO_2/FiO_2 <300 mm Hg according to the Berlin definition) and/or
    - circulatory shock (the requirement of continuous vasopressor support to maintain mean arterial pressure ≥65 mmHg and/or serum lactate ≤2 mmol/L) and/or
3. deaths.

Secondary endpoints are the followings:

1. the number of general practitioner visits,
2. the number of emergency, hospital, and intensive care admissions;
3. the LOH and ICU stay,
4. the number of organ dysfunctions and failures (central nervous system, cardiovascular, respiratory, renal, liver, hematological),
5. the measurable lifestyle changes (including physical and mental health),
6. the costs of care.

The primary and secondary outcomes will be assessed upon the conclusion of the trial, at least one year after the enrollment of the last participant.

IV.2.3. Discussion

Neither the worldwide climax of the COVID-19 pandemic can be foreseen nor the potential repeated outbreaks. Although efforts of primary prevention (i.e. vaccine development) are promising, it is expected to take 12-18 months from now on. Better lifestyle has its unquestionable advantages not only for infectious but also for common chronic diseases

including diabetes mellitus, chronic heart failure or malignant tumours. Considering the recent low numbers of reported cases and the expected trajectory of the epidemic in Hungary, it seems that we are still on time to seek for personalized and easily available public health interventions applicable for the target population.

While in the United States, "remote" consent via telecommunication may be possible, the Hungarian laws have not allowed such initiatives until now. An outbreak imposes new challenges to the process of ethical approval. Most importantly, the instant reaction of both the researchers and the ethical committees is essential, while preserving the validity of scientific content.

Based on the results of the current study, such strategies could be introduced in other countries. Lifestyle counselling is expected to reduce mental distress, smoking and alcohol consumption, increase physical activity and favourably change the body mass (along with the body composition). As the main results of all these, the interventions may boost the body's cardiovascular and pulmonary reserve capacities, leading to improved resistance against the damage caused by COVID-19. Consequently, lifestyle changes can reduce the incidence of life-threatening conditions and attenuate the detrimental effects of the pandemic seriously affecting the older population.

V. SUMMARY AND NEW DISCOVERIES

Chapter III. Glucose level independently and dose-dependently worsens acute pancreatitis: A cohort analysis

- We established that increasing on-admission and peak in-hospital glucose is associated with increasing AP severity and mortality, independently of age, gender, DM and AP etiology.
- We saw a dose-dependent association not only with severity and mortality, but also with LOH and complications. In light of the available literature, this suggests that serum glucose might be a pancreatotoxic agent.
- A trend was seen with increasing HbA1c and AP severity and complications
- Based on these conclusions, we formulated the following implications for practice:
    - 1. Prevention: Maintaining a normal glucose homeostasis might reduce the risk of severe AP and local complications.
    - 2. Prognosis: Increased on-admission glucose has a dose-dependent association with increasing severity, mortality, LOH and complications of AP.

- 3. Prompt treatment: High peak glucose is dose-dependently associated with a higher rate of severe cases, mortality, systemic complications and increased LOH. Hyperglycemia does not necessarily present on admission, monitoring serum glucose during the course of AP is crucial. Adequate in-hospital control of hyperglycemia can greatly contribute to the treatment of AP.

Chapter IV. Translational medicine in the COVID-19 pandemic

- We formed an interdisciplinary team (KETLAK) to help contain the COVID-19 pandemic in Hungary – we think that formation of such teams is crucial to aid government decision makers. No single discipline can tackle such a complex problem alone.
- We analyzed the international state of the COVID-19 pandemic, performed mathematical models for the course and dynamics, also accounting for territorial patterns, economic, social and healthcare related factors.
- These information were regularly delivered to the government and policy makers to help combat the pandemic.
- The KETLAK group could serve as a model for other countries and for future epidemics as well.
- Noticing a gap in the available evidence, we planned and initiated a RCT. The PROACTIVE-19 trial will show the benefits of a telephone-based, personalized, multicomponent lifestyle intervention in COVID-19.
- Based on positive results, a similar strategy could be applied in other countries, not only for COVID-19, but for other diseases as well.

VI. AUTHOR'S OWN CONTRIBUTIONS

In all three articles used in the thesis, the author played a key role in designing the concept and structure of the investigations, in performing the analyses and writing the manuscript.

Additional contributions:

VI.1. Nagy et al. Pancreatology, 2021

The author drafted the original concept, and conducted the majority of data interpretation, wrote the manuscript.

VI.2. Gombos et al. Popul Health Manag, 2020

The author played a central role in coordinating the interdisciplinary team and in maintaining a continuous channel of communication with the governing body's pandemic board, led by the

prime minister. The author also made significant contributions in interpreting and analyzing the data and writing the manuscript.

VI.3. Erőss et al. Trials, 2020

Next to a key role in designing the study structure, writing and providing critical revisions for the manuscript, the author took part in overviewing the available literature and registered trials in the field of question.

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