

UNIVERSITY OF PÉCS
FACULTY OF HEALTH SCIENCES
DOCTORAL SCHOOL OF HEALTH SCIENCES

Head of the Doctoral School of Health Sciences: Prof. Dr. Bódis József

Programme leader: Prof. Dr. Bódis József

Supervisor: Dr. Farkas Bálint

**INVESTIGATING THE ASSOCIATION BETWEEN HARMFUL ENVIRONMENTAL
EFFECTS AND PERINATAL FETAL DEATHS**

Doctoral (Ph.D.) thesis

Sarolta Szalai



Pécs, 2023

1.INTRODUCTION

A teratogenic effect is defined as anything that could harm the development of the fetus. These effects may include diseases (viral infections, diabetes), external environmental effects (radioactive radiation, mechanical effects), and medicines administered during pregnancy (valproates, benzodiazepines). Adverse environmental effects may lead to miscarriage, or congenital anomalies. Congenital anomalies are morphological, biochemical, or functional abnormalities that develop during fetal life, and are detected prenatally, at birth, or after birth.

The present study focused on radiation as an environmental risk, and the effects of coronavirus infection on perinatal outcomes in Hungary. In addition, we studied the possible intrauterine consequences of Covid-19 virus, such as early- to mid-term or late fetal loss. The actuality of our study was given by the fact that in 2020 the radiation data from the Chernobyl nuclear power plant explosion in Hungary, which had been unlocked since 1986, were released and in March of the same year the Covid-19 pandemic was also appeared for the first time in Hungary.

1.1. The Chernobyl nuclear reactor explosion

In 1986, on April 26th at 1:23 am, the fourth reactor of the Vladimir Iljics Lenin nuclear power plant located near the Ukrainian city of Chernobyl suffered an open-air meltdown, resulting in the largest nuclear disaster in human history. As a consequence of the incident, a massive quantity of radioactive material was emitted into the atmosphere and then spread expeditiously by wind, polluting the majority of Europe. Radioactive radiation is extremely dangerous to the developing fetus. According to international literature, the Chernobyl nuclear power plant explosion in 1986 led to a significant increase in the incidence of congenital malformations in parts of the Soviet Union.¹ The most common anomalies were multiple congenital anomalies, limb

¹ Lazjuk GI, Nikolaev DL, Novikova IV. Changes in registered congenital anomalies in the Republic of Belarus after the Chernobyl accident. *Stem Cells*. 1997;15 Suppl 2:255-60. doi: 10.1002/stem.5530150734. PMID: 9368311.

deficiencies and polydactyly. Studies have also shown that radioactive radiation from the Chernobyl accident led to chromosomal mutations. The teratogenic effect also increased the incidence of Down's syndrome.

1.2. Radiation data in 1986 in Hungary

For the present study, we gained access to recently released radiation data between 29th April and 10th May 1986 by way of a collaboration with the Department of Physics at the University of Szeged in Hungary. After 34 years of the data being not available, the accessed data were finally became publicly available in 2020. We gained access to the radiation data via our collaboration with the University of Szeged, Department of Physics in Hungary. The available data include measurements of the effects of released radiation conducted as part of a top-secret program that was implemented in Hungary after the incident. We found out how much radiation cloud Hungary was exposed to, which means how much aerosol activity has been detected. Aerosol activity is defined as the activity per unit volume of radioactive material in a medium, measured in Becquerel/m³. The main radioactive isotopes released were ¹³²Te, ¹³²I, ¹³¹I, ¹³⁴Cs, ¹³⁷Cs and ¹⁰³Ru. According to the information contained in previously classified documents, the Hungarian population was exposed to considerable doses of radioactive isotopes following the Chernobyl nuclear disaster.

1.3. Covid19 virus infection

In our research we also explored the possible consequences of coronavirus infection during pregnancy. Covid-19 (Coronavirus disease 2019) is a viral respiratory disease caused by the coronavirus SARS-CoV-2 (Severe acute respiratory syndrome coronavirus 2). The first cases of the virus were detected in December 2019 in the Chinese city of Wuhan, leading to the pandemic outbreak.

Pregnant women and their fetuses are at a high risk from the potentially harmful effects of the coronavirus, so extra care is needed to protect them. During pregnancy, the immune system is partially compromised, increasing the risk of disease and even fetal death. Various studies have shown that many pregnancies can lead to an increase in

the activity of blood coagulation factors, which can even lead to the risk of a blood coagulation disorder. If a thrombus blocks the blood flow to the fetus, it does not get enough oxygen and nutrients. Studies have shown that the incidence of pregnancy-related thromboembolic events was significantly higher after the appearance of SARS-CoV-2 coronavirus infection in 2018 and 2019.²

2.OBJECTIVE

We hypothesize that

- In Hungary the number and rate of early fetal deaths increased significantly between 1986 and 1987, as a consequence of the Chernobyl nuclear reactor explosion.
- The impact of the Chernobyl nuclear disaster in Hungary resulted in a significant increase in the number and rate of late fetal deaths between 1981 and 1991.
- A review of the National Registry of Congenital Anomalies (*Veleszületett Rendellenességek Országos Nyilvántartása, VRONY*), database for the period 1981-1991 would show significant increased trend for each group of congenital anomalies.
- In Hungary, the number and rate of early fetal deaths increased significantly during the four epidemic waves due to Covid.
- In Hungary, the number and rate of abortions increased significantly during the four epidemic waves, as a consequence of Covid pandemia.

3.MATERIALS AND METHODS

² Gabrieli D, Cahen-Peretz A, Shimonovitz T, Marks-Garber K, Amsalem H, Kalish Y, Lavy Y, Walfisch A. Thromboembolic events in pregnant and puerperal women after COVID-19 lockdowns: A retrospective cohort study. *Int J Gynaecol Obstet.* 2021 Oct;155(1):95-100. doi: 10.1002/ijgo.13777. Epub 2021 Jul 29. PMID: 34077561; PMCID: PMC9087693.

3.1. Data collection on fetal deaths between 1981 and 1991

A retrospective analysis of perinatal statistical data, including abortion (spontaneous and voluntary), stillbirth, and livebirth rates between January 1, 1981 and December 31, 1991 were conducted. Data were obtained from the Hungarian Central Statistical Office (*Központi Statisztikai Hivatal, KSH*). This study was approved by the Ethical Board of the University of Pecs, Hungary. For the period 1981-1991, the size of our study sample was 2.543.848 pregnancies. The number of live births during the observed period was 1.413.796 newborns, the number of abortions was 925.935, and the number of early, mid-term and late fetal loss was 204.117.

There were 149.377 early fetal deaths in Hungary between 1981 and 1991, of which 14.107 occurred in the year of the disaster.

Fetal loss between 12nd and 24th weeks of pregnancy was found to be 45.638 between 1981 and 1991. In 1986, the year of the Chernobyl nuclear reactor explosion, there were 4187 mid-term fetal losses detected.

During the period covered by our study, a total of 925.935 voluntary abortions were performed in Hungary at the request of the mother, of which 83.586 occurred in 1986.

3.2 Congenital anomalies data collection 1981-1991

Congenital anomaly incidence data were obtained from the National Registry of Congenital Anomalies (*Veleszületett Rendellenességek Országos Nyilvántartása, VRONY*), a nationwide medical registry of confirmed congenital anomalies in Hungary. VRONY has been operating for 50 years. Data were acquired by examination of photographic pathology records of second-trimester abortions, fetuses that succumbed to intrauterine death, and clinical or pathological newborn examination records. The VRONY distinguishes among the following 50 anomaly types. In our research, we grouped radiation-related congenital disorders into 12 classes according to the organ(s) affected:

1. Nervous system disorders
2. Cardiovascular developmental disorders

3. Respiratory disorders
4. Gastrointestinal disorders
5. Urinary tract disorders
6. Skeletal developmental disorders
7. Musculoskeletal disorders
8. Integument (skin) disorders;
9. Endocrine organ disorders;
10. Chromosomal abnormalities
11. Minor anomalies;
12. Multiplex anomalies

3.3. Data collection on fetal deaths 2018-2021

From the KSH, we received data about the the number and percentage of pregnancies, live births, intrauterine fetal deaths before week 12 of pregnancy, abortions and all fetal deaths (early- mid-term and late) between 2018 and 2021. The statistics were not available before summer 2022 and are therefore the first to be published.

The sample size for our 2018-2021 study was 525.471 embryos or fetuses. The number of live births during the study was 364.377 newborns, the number of voluntary first trimester abortions were 98.532, and the number of early- to mid-term and late-term fetal losses were 62.562.

In our study we presented a retrospective analysis of 1000 births. This study was approved by the Ethical Board of the University of Pecs, Hungary.

The data reported by KSH were grouped according to the four Covid waves and compared with the equivalent preCovid periods.

3.4. Statistical analysis

Statistical analyses were performed in R software (R Core Team 2021; R Foundation for Statistical Computing, Vienna, Austria). All variables are presented as number of observations, as percentages and as a rate per thousand births. Poisson values were

calculated for incidence rates. Incidence estimates are shown with 95% confidence intervals (CIs). Event rates were compared between time points with Proportion and Chi-squared tests. The statistical significance criterion was $p < 0.05$.

4.RESULTS

4.1 Early pregnancy loss between 1981 and 1991

Trend analysis revealed a linear increasing rate of early pregnancy loss in Hungary during the observation period. There were similar numbers of recorded spontaneous abortions in the year before the nuclear catastrophe (1985: 13.782), and the year following it (1987: 13.684). Although the number of spontaneous abortions appears to be higher for the year of the incident than in the preceding year (1985: 13.782 vs. 1986: 14.107) and the subsequent year (1986: 14.107 vs. 1987: 13.684), the values did not differ significantly ($p=0.9$).

4.2. Mid-term fetal death between 1981 and 1991

Trend analysis of fetal death between the 12th and 24th weeks of pregnancy in Hungary during the observed time demonstrated a linearly decreasing rate. Despite this continuously decreasing tendency, direct pairwise comparisons among the year before (1985: 4.288), the year of (1986: 4.187), and the year after (1987: 4.018) the catastrophe did not yield significant differences ($p= 0.9$).

4.3. Voluntary abortions between 1981 and 1991

Trend analysis of the voluntary abortion rates in Hungary during the observed period revealed a linearly increasing rate. Despite this continuously increasing tendency, the

year before (1985: 81.970), the year of (1986: 83.586), and the year after (1987: 84.547) the catastrophe did not differ significantly from one another ($p= 0.9$).

4.4. Congenital anomalies between 1981 and 1991

According to VRONY data, during the decade of 1981–1991, there were 28.714 registered neonatal congenital anomalies, with an average annual incidence of 1.97% (28.714 per 1.459.434 births).

Analyzing congenital anomalies according to the 12 major groups defined in the Methods, we found that stable or slightly decreasing congenital anomaly incidences throughout the 1980s, with no signs of a spike in relation to the nuclear catastrophe in 1986, including in the following years (Figure 1). Although there appeared to be a linear increase in chromosomal anomalies, the nuclear pollution did not have a detectable significant impact ($p= 0.1$) on the incidence of chromosomal anomalies (Figure 1).

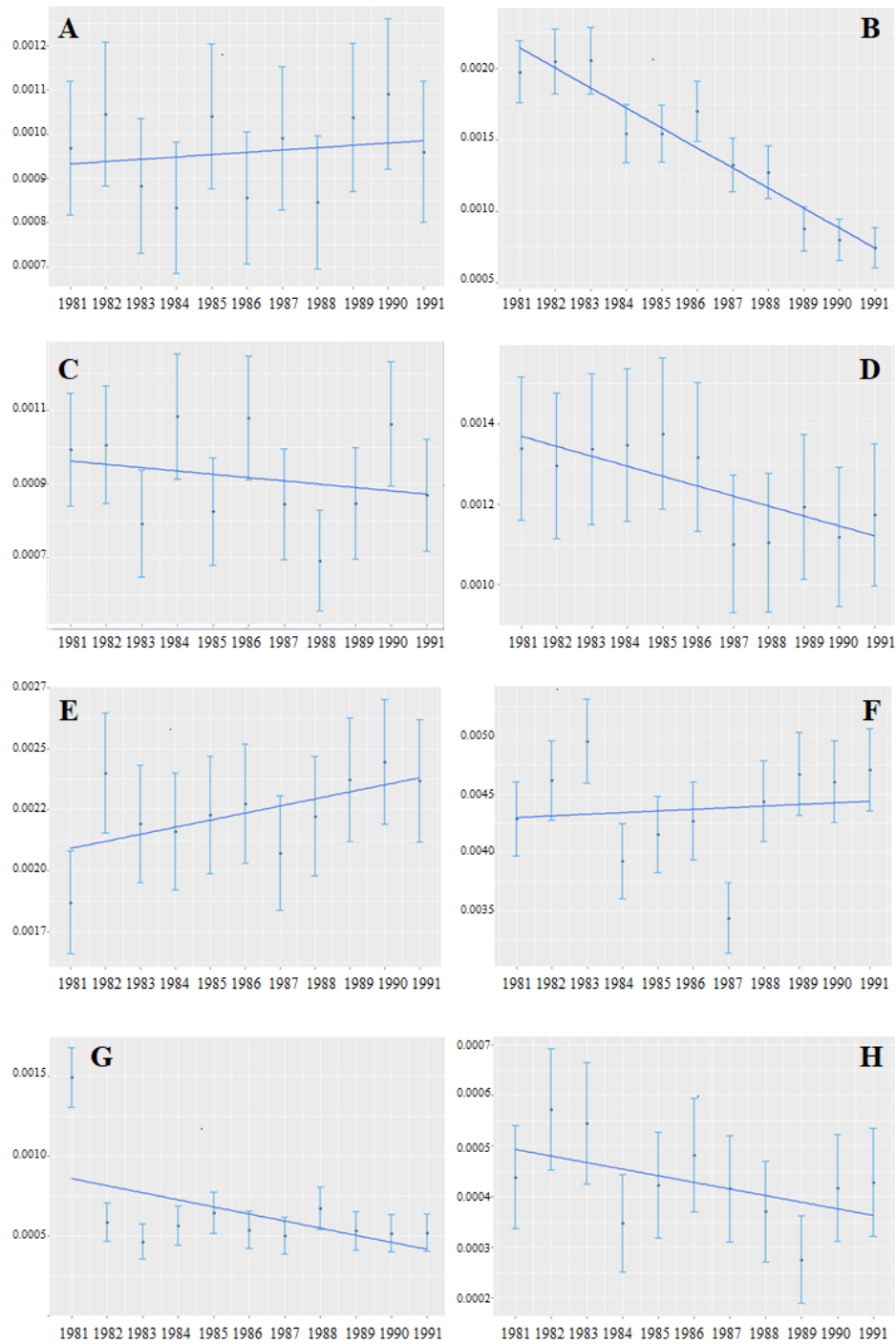


Figure 1: (A) Chromosomal anomalies. (B) Nervous system congenital defects. (C) GI tract congenital defects. (D) Respiratory tract congenital defects. (E) Uro-genital tract congenital defects. (F) Cardiovascular tract congenital defects. (G) Skeletal anomalies. (H) Muscular anomalies.

4.5 Voluntary abortions per thousand births during each Covid wave

In our study, Poisson trend analysis showed a decreasing rate of voluntary abortions in Hungary during the four observed Covid epidemic waves, relative to the equivalent PreCovid periods.

The number of abortions in the first Covid wave decreased by 1.13% compared to 2018. In the second Covid wave, the number of abortions was 1.1% lower (7195) than in 2018 (7955) in the same period. In the third wave of Covid, the number of abortions decreased by 1.4% (7730), compared to 2018 (9607). In the fourth wave caused by the delta variant, the number of abortions was 1.2% fewer (6649), compared to 2018 (7955). Our results showed that the values were not significantly different ($p = .2$)

4.6. Early, mid-term and late fetal loss per thousand births during each Covid wave

Using Poisson trend analysis, we found a steadily decreasing trend in total fetal mortality in our country during all four Covid epidemic waves, relative to the equivalent PreCovid periods. The number of fetal deaths in the first Covid wave (5234) decreased by 1.08% compared to 2019 (5634) (Figure 2.A). In the second Covid wave (4688), the number of fetal deaths decreased by 1.1% compared to 2018 (5168) (Figure 2.B). February to May 2021 (5127) also saw a 1.1% decrease in fetal deaths compared to the 2019 term (5658) (Figure 2.C). In the fourth Covid wave (4747), caused by the delta variant, there was also a 1.1% decrease in fetal deaths compared to the 2018 data (5168) (Figure 2.D). Our analysis showed that the number and proportion of fetal deaths did not differ significantly during any of the epidemic waves ($p = 0.1$).

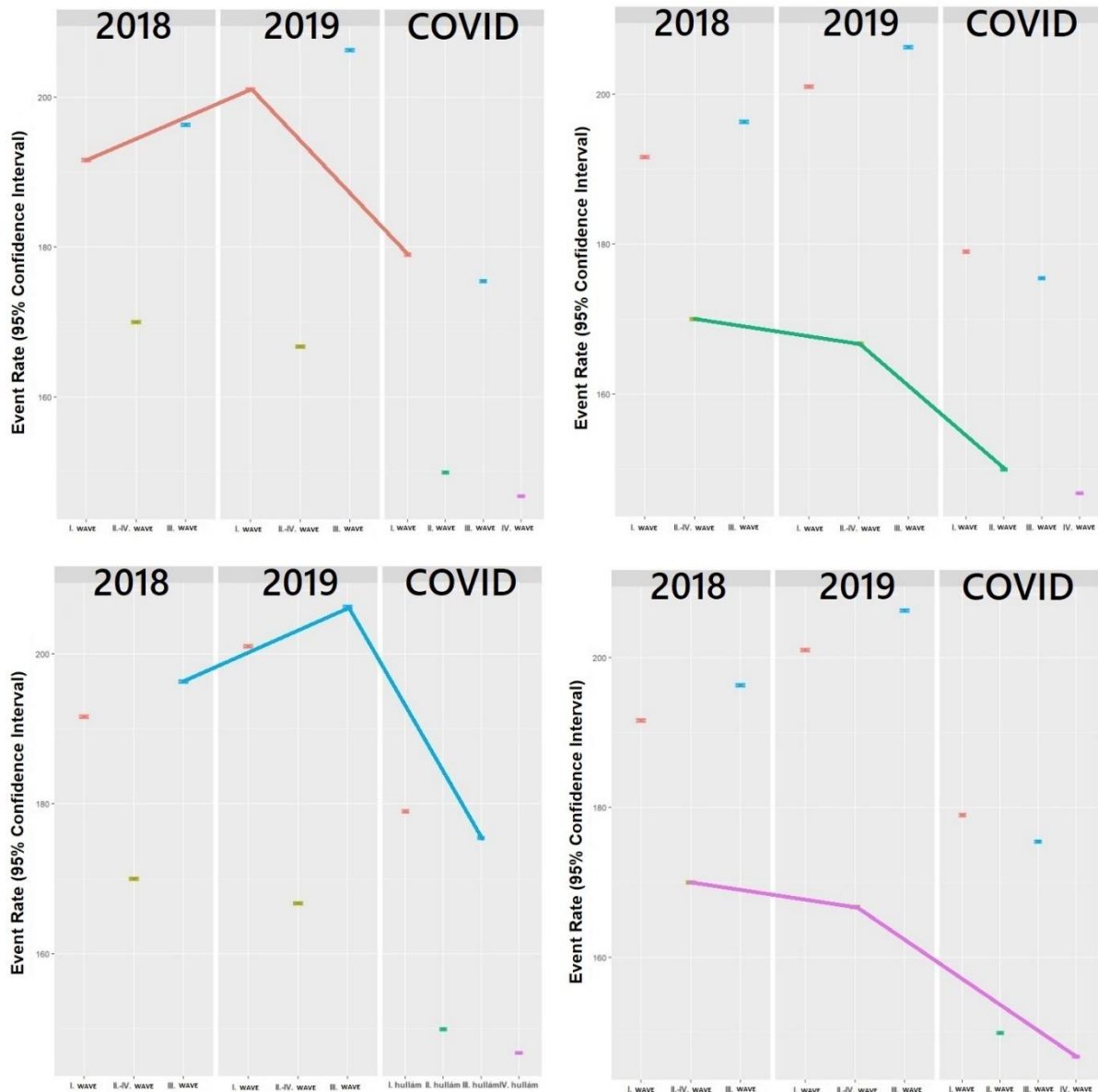


Figure 2: A. Trends in fetal mortality during the **first** Covid wave compared to the equivalent PreCovid period per 1000 births.
 B. Trends in fetal mortality during the **second** Covid wave compared to the equivalent PreCovid period per 1000 births.
 C. Fetal mortality trends during the **third** Covid wave compared to the equivalent PreCovid period per 1000 births.
 D. Fetal mortality trends during the **fourth** Covid wave compared to the equivalent PreCovid period per 1000 births.

5.CONCLUSION AND DISCUSSION

After examining the various teratogen effects, we concluded that neither radiation nor viral infection had any negative impact on the perinatal outcomes.

5.1. The perinatal effects of the Chernobyl nuclear power plant explosion in Hungary

Following a three and half decade period of data related to the Chernobyl disaster being unavailable to the public, we carried out a retrospective investigation focusing on the potential obstetrical impact of the disaster. We did not find significant increases in the occurrence of pregnancy losses or congenital anomalies within Hungary in relation to the Chernobyl catastrophe. Meanwhile, we observed a gradual decline in late pregnancy loss over the target decade that may be attributable to improving prenatal diagnostics.

Based on the measured radiation levels and the present data, it can be concluded that the perinatal effects of the Chernobyl accident in Hungary were negligible, similar to other European countries.

5.2 The perinatal effects of the Covid-19 pandemic in Hungary

In our study, we assessed the potential fetal mortality of the Covid-19 pandemic in Hungary between 2018 and 2021. Our results show a decreasing trend in fetal deaths during all four epidemic waves, which may be a result of pregnant women's increased attention to healthy lifestyles.

Analysing the impact of the new coronavirus disease on perinatal mortality, we can conclude that fetal mortality, although declining, has continued on a similar trend to the years before the pandemic in our country.

No significant differences were found, which means that the pandemic had no important perinatal impact in Hungary.

As we do not have strong enough evidence that Covid does not cause perinatal complications, it would be advisable to continue the research.

Our results from this study could even form the foundation for a prospective analysis. In the longer term, we would be more likely to detect the possible prenatal effects of the pandemic.

6.SUMMARY OF NEW RESULTS

1. The results of our research show that in 1986 and 1987 there was a non-significant, but increasing trend in the absolute number and percentage of spontaneous abortions in Hungary.
2. Between 1981 and 1991, we found a decrease in late fetal deaths in Hungary, although the difference was not statistically significant.
3. Reviewing the VRONY database from 1981 to 1991, no significant differences in the prevalence of congenital anomalies were found.
4. The Chernobyl nuclear accident had no statistically relevant effect, and no significant impact on the perinatal outcome in Hungary, so no new effect was detected.
5. No significant difference were found in the trends in fetal mortality in Hungary between 2018 and 2021, which means that the new Covid-19 disease did not have a major impact on perinatal mortality.
6. We found an upside on the Covid 19 pandemic, as the number of fetal losses decreased following the pandemic outbreak compared to the average in the PreCovid years. In all four epidemic waves, the number of spontaneous abortions and voluntary abortions per thousand births were lower.

7.ACKNOWLEDGEMENTS

Firstly I would like to thank my supervisor, **Dr. Bálint Farkas**, who has consistently inspired my work throughout the three years. I thank him for his time, his valuable advices, and his support, which contributed to the production of my thesis.

I am also thankful to **Dr. Béla Veszprémi**, my previous programme leader, who helped me get started on my road and gave me a lot of professional direction.

Thank you also **Dr. Viktoria Prémusz**, the coordinator of the Doctoral School, who was always available to answer my questions.

István Szittyai from the Department of Physics of the University of Szeged also contributed to my research, helping to obtain the classified 1986 radiation data.

Dr. Gabriella Vukovich, President of the Central Statistical Office of Hungary (Központi Statisztikai Hivatal, KSH), provided me with considerable help in collecting data for my research. Additional scientific and friendly help in providing data was received from **Melinda Csáky-Szunyogh**, who is the Acting Head of the National Registry of Congenital Disorders (Velezületett Rendellenességek Országos Nyilvántartása, VRONY).

Thanks also to the work of **Dr Kornélia Borbásné Farkas**, who assisted in the preparation of statistical tests and graphs.

I am also grateful to **my parents** for their patience, support, and inspiration.

The thesis and the scientific results presented in this study were prepared with the support of the Richter Gedeon Talentum Foundation established by Richter Gedeon Plc. (headquarters: 1103 Budapest, Gyömrői út 19-21.) in concordance with the framework of the **Richter Gedeon PhD Scholarship**.

8. PUBLICATIONS

1. Farkas B.; **Szalai S.**; Bodis J.; Varjas T.; Varnagy A.; Godony K., Szenczi A.; Sulyok E.; Expression of mRNAs for DNA-methyltransferases and Histone Deacetylases in Granulosa Cells and Follicular Fluid of Women Undergoing in vitro Fertilization, RESEARCH SQUARE : PREPRINT PLATFORM 1 : 1 p. 1 (2023)
2. **Szalai S.**; Farkas N.; Veszpremi B.; Bodis J.; Kovacs K; Farkas B.; Assessment of the potential impacts of the Chernobyl nuclear disaster on maternal and fetal health in Hungary. JOURNAL OF MATERNAL-FETAL & NEONATAL MEDICINE 35: 25 pp. 9481-9488. , 8 p. (2022)
3. Bitá L.; Szalai Z; **Szalai S.**; C típusú distalis radius törések kezelése variábilis szögállású szögstabil lemezzel, MAGYAR TRAUMATOLÓGIA ORTOPÉDIA KÉZSEBÉSZET PLASZTIKAI SEBÉSZET 59 : 3-4 pp. 115-124. , 10 p. (2016)

Total impact factor: 2,398