Article

Association of solar variability and space weather factors with parameters of clinical chemistry, hematology, hemostasis, inflammatory biomarkers and heart rate variability in a middle-aged to elderly population-based cohort

Tobias Sebastian Pahlen [1, *]

[1] Martin-Luther-Universität Halle-Wittenberg
* Correspondence: tpahlen@icloud.com; Tel.: +41-78-2192559

Abstract: Heliobiological studies investigated the effects of solar variability on human health through epidemiological approaches. Hospital statistics revealed associations between geomagnetic disturbances and blood flow-related pathologies like myocardial infarction or stroke. Further clinical studies, looking at parameters like heart rate variability (HRV), discovered underlying physiological processes, yet they could not explain the biophysical mechanisms. In order to broaden physiological understanding, this study explored changes in the hematovascular system due to dynamics in solar- and geomagnetic activity.

A dataset of 40 blood parameters alongside HRV measures for 1,779 non-hospitalized individuals between 45 and 83 years of age was compared to solar-, cosmic-ray-, and geomagnetic activity indicators during the solar minimum period between years 2007 - 2010. Demographic subgroups regarding age, gender, health scores and certain pathologies were analyzed. Correlations from clinical- and geospace-data were assessed for different time-lags between both datasets, applying signal smoothing methods and Bonferroni correction.

Increased levels for certain differential leucocytes, inflammatory markers, and glycated hemoglobin A1c were observed for long-term periods of increased cosmic-ray intensity paired with reduced geomagnetic activity ($p<0.01$) – which accounts to an increase in cardiovascular disease (CVD) risk factors comparable with other studies during similar periods. Similar correlations were noted in liver and kidney function markers. No significant correlations were found for red blood cell parameters and routine clinical coagulation factors.

For lipid parameters, an increase in the Apolipoprotein B / A1 ratio was found for long-term periods of higher solar radio flux F10.7 ($p<0.01$) – resulting in another increased CVD risk factor. On shorter timescales, peaks in Total- and LDL-Cholesterol were observed following space-weather events after a delay of 6 days ($p<0.01$) – a characteristic time-lag behavior corresponding with similar heliobiological studies.

HRV parameters showed an increase in absolute power across all frequency bands and in SSDN for periods of increased geomagnetic activity with a time-lag of 3 - 4 days. Regarding the interplay of HRV with inflammation factors, connections to the blood parameter findings of present study were established.

Demographic subgroup analysis revealed significant dependances on individual factors: Inflammatory responses were most pronounced in male subjects within the youngest age group (49 – 62 y.). Further, results were more expressed in subjects with a lower KSK-12-health score and suffering from hypertension or stroke / myocardial infarction in the past.

This study established a foundation for heliobiological research on clinical chemistry. It has shown highly significant correlations analyzing blood parameters in a large cohort of elderly participants in the northern hemisphere, which depended significantly on

demographic factors and – as demonstrated by the analysis of solar cycle subwindows - on the solar cycle macrophase, as well.

Keywords: heliobiology; space weather factors; solar activity; geomagnetic activity; solar minimum; human health; human magneto sensitivity; cardiovascular system; autonomic nervous system; blood parameters

1. Introduction

The Sun is the source of energy, and thus life, in our solar system. It constantly emits energetic particles through the solar wind, which pose a threat to satellites, communications, as well as astronauts leading to the development of "space weather" programs. Variability in solar emissions and the interplanetary magnetic field can interact with Earth's magnetosphere leading to space weather events. This would relate to short-term events like solar flares or coronal mass ejections; yet the Sun exhibits also long-term variability, e.g. through the periodic 11-year Schwabe solar cycle (SC).

The effect of solar activity on human health was first studied by A. Tchijevsky, through a process called historiometry (Tchijevsky, 1971). Analyzing historical events, he correlated socio-historical quantitative measures to periodical sunspot activity and found revolutions and periods of fighting to occur predominantly during solar maxima, whereas social stable episodes to correlate with solar minima. Similarly, he applied this analysis to early 20th century`s epidemic cycles, which corresponded with the SC as well (Tchijevsky, 1930). Recent historiometric studies confirmed these hypotheses with independent datasets (Ertel, 1996; Mikulecky, 2007; Putilov, 1992).

More recently, with the development of satellites and ground-based instruments, detailed knowledge of the solar electromagnetic environment was obtained, allowing researchers to explore correlations of specific solar parameters with hospital statistics or physiological parameters like Heart Rate Variability (HRV), Electroencephalography (EEG) or blood pressure. Studies found a response of these physiological parameters to certain periods of geomagnetic activity and an increase of hospitalizations and deaths from cardiovascular diseases (CVD) and strokes, respectively (Alabdulgader et al., 2018; Cherry, 2002; Ghione, Mezzasalma, Del Seppia, & Papi, 1998; Kiznys, Vencloviene, & Milvidaite, 2020; Persinger, 2014; Saroka & Persinger, 2014). Predominantly, heart and brain functions were found to correlate with indices of solar and geomagnetic activity. Heliobiological effects were analyzed on different system scales, from an entire population to a single organ. On the other hand, timescales varied - from several years during the SC to hourly responses.

Many of the analyzed pathologies in heliobiology, e.g. myocardial infarction (MI) or stroke, related to a disturbed blood flow in the cardiovascular or cerebral system. However, only a small number of clinical studies analyzed blood parameters, e.g. the relation between geomagnetic storms and reduced melatonin hormone levels (Burch, Reif, & Yost, 1999). Magnetobiological studies on mice found changes in coagulation factors and thrombocytes applying very low frequency (VLF) electromagnetic magnetic fields similar to geomagnetic oscillations (Gorczynska, 1986; Gorczynska & Wegrzynowicz, 1983; Kazimierska, 2001; Vallejo, Hidalgo, & Hernández, 2019). Furthermore, human magnetobiological studies reported negative effects of VLF fields on pro-inflammatory cytokines for industrial workers (Hosseinabadi, Khanjani, Samaei, & Nazarkhani, 2019).

This study comprehensively explored possible health effects of solar variability on a biochemical level by analyzing a wide range of blood parameters together with HRV-measurements. Medical records from the German epidemiologic CARLA study (Hassan et al., 2022) were compared to geospace data from NASA Goddard Space Centre and Finland's University of Hulu Observatory. A group of 40 blood parameters, including blood counts, lipids, coagulation parameters, inflammatory-, routine biochemical- and

cardiovascular markers was analyzed. The participants of the CARLA study were not hospitalized with health conditions according to an average age of 67 years, including age-related increased cardiovascular risk factors.

The timespan of medical data covered years 2007 – 2010, restricting the study period to a solar minimum between two SC with generally less variability in solar parameters. However, a less active solar phase does not imply less expressed effects on biological life. It is important to consider that galactic cosmic rays are shielded by both the Sun's heliosphere and Earth's magnetosphere. Both of these protecting fields are at their lowest during a solar minimum, allowing more galactic cosmic rays to penetrate Earth's atmosphere. In the context of a weakening Earth's magnetic field, its accelerating decay and anomalies (Pavon-Carrasco & De Santis, 2016) and the fact that we are statistically overdue for a geomagnetic reversal (Turner, 1995), it is crucial to understand implications of low solar- and geomagnetic activity on human health. Civilized humans have not yet experienced such a reversal and its possible health impacts.

In addition, recent publications suggest an upcoming grand solar minimum during the next 30 years (Zharkova, Shepherd, Popova, & Zharkov, 2015) within a long-term 400-year solar cycle based on solar magnetograph analysis. Thereby, periods of low solar activity could become a new normal.

Considering that the shielding effect of Earth's magnetosphere decreases with lower latitudes, most heliobiological studies were conducted in northern latitudes of Europe or North America, compared to a limited number of studies in southern latitudes(Cabrera, Mindell, Toledo, Alvo, & Ferro, 2016; Mendoza & de la Pena, 2010), which showed generally less expressed effects on health. For this reason, present study`s analysis at the mid-high latitude of Germany can be regarded as a conservative approach.

2. Materials and Methods

Dataprocessing

Geospace and medical data were obtained and curated in order to perform the correlation analysis.

Geospace data

Daily averages for following geospace parameters were obtained from *NASA/Goddard Space Flight Centre* Space Physics Data Facility and corrected for time-zone, except for Neutron Count Rate, which was obtained from *Finland's University of Oulu's Sodankyla Geophysical Observatory*:

Solar Activity
- Sunspot Number
- F10.7 Solar Radio Flux

Geomagnetism / Space Weather
- Kp-Index
- Ap-Index
- Solar wind (Plasma) speed
- Geomagnetic Polar Cap (North) Index (PCN)

Galactic Cosmic Rays
- Corrected Neutron Count Rate (ground-based indirect measure of cosmic rays corrected for atmospheric pressure)

Medical data

Medical data was obtained from the epidemiological CARLA-Study (Cardiovascular Disease, Living and Ageing in Halle) conducted by *Institut für Medizinische Epidemiologie, Biometrie und Informatik (IMEBI), Medizinische Fakultät, Martin-Luther-Universität in Halle-Wittenberg, Germany (Hassan et al., 2022)*. The study was conducted between 2002 and 2013 and involved blood samples, ECGs and medical examinations of 1779 men and women aged between 45 and 83 years. It consisted of a baseline examination and two follow-up examinations. Data was requested from the first follow-up, which was conducted between 2007 and 2010, since only this examination included blood sample analysis. Following parameters were analyzed in this study:

Clinical chemistry and hematology
- Complete and differential Blood count
- Erythrocytes (RBC) [exp 12/l]
- Mean Corpuscular Volume (MCV)
- Mean Corpuscular Hemoglobin (MCH)
- Mean Corpuscular Hemoglobin Concentration (MCHC)
- Red Blood Cell Distribution Width (RDW)
- Hematocrit
- Hemoglobin [g/dl]
- Leukocytes (WBC) [exp 9/l]
- Lymphocytes [%]
- Lymphocytes [exp 9/l]
- Basophile Granulocytes [%]
- Basophile Granulocytes [exp 9/l]
- Eosinophile Granulocytes [%]
- Eosinophile Granulocytes [exp 9/l]
- Monocytes [%]
- Monocytes [exp 9/l]
- Neutrophile Granulocytes [%]
- Neutrophile Granulocytes [exp 9/l]

Inflammation parameters
- C-reactive protein (CRP) [mg/l]
- Interleukin 6 (IL-6) [pg/ml]
- Soluble tumor necrosis receptor R1 factor (TNF-a) [pg/mL]

Lipids
- Cholesterol [mmol/l]
- HDL-Cholesterol [mmol/l]
- LDL-Cholesterol (Friedewald) [mmol/l]
- LDL-Cholesterol [mmol/l]
- Small dense LDL (Denka Saike) [mmol/l]
- Triglyceride [mmol/l]
- Apo A1 [g/l]
- Apo B [g/l]

Hemostasis
- International Normalized Ratio (INR)
- Platelets (PLT) [exp 9 /l]
- Mean Platelet Volume (MPV)

Clinical Routine
- GPT (ALAT) [ukat/l]
- GOT (ASAT)[ukat/l]
- GGT [ukat/l]

- Creatinine (enzymatic) [umol/l]
- Glucose [mmol/l]
- Hemoglobin A1c [%]
- Hemoglobin A1c [g/dl]
- pNTroBNP [pg/ml]

Electrocardiography

- ECG / Heart rate variability
- SD1
- SD2
- Heartrate (ECG)
- VLF
- LF
- HF
- Normalized LF
- Normalized HF
- LF/HF Ratio
- Standard Deviation of Normal-to-Normal Intervals (SDNN) (ms)
- Minimal Normal Interval (ms)
- Maximal Normal Interval (ms)
- Mean Absolute Successive-Normal-Interval-Differences (ms)

Along with these medical parameters, blood pressure readings, interviews and questionnaires were obtained from the study participants to quantify aspects of health and social situation. Following aspects were considered in the analysis of this study:

- Age at follow-up
- Drug exposition (General)
- Hypertension (Blood pressure reading >= 140/90 or blood pressure lowering medication)
- SF12 (Mental health score)
- SF12 (Physical health score)
- CES-D Depression Score
- Stroke history within Carla study period
- Myocardial infarction in past

Statistical Methods

Analyzing potential impacts of geospace factors on biological parameters, statistical methods were applied to identify significant results and exclude random correlations.

Correlation Coefficients

The Pearson correlation coefficient (r) was calculated to quantify linear relationships, ranging from -1 (perfect negative correlation) to 1 (perfect positive correlation), with 0 indicating no correlation. A stronger physiological response to geospace data should result in a larger correlation coefficient. Statistical significance was assessed with the p-value, with values below 0.01 considered significant (1% probability of random occurrence).

Key assumptions for valid p-values include independence of data pairs and normal distribution of variables. While independence was ensured by the fact that medical observations were taken from different patients every day, perfect normality was not assumed due to limited sample size. To address distributional concerns, the Spearman correlation coefficient—which ranks data monotonically without accounting for linearity—was used as a validation method. Since rank-ordering in Spearman correlations loses information,

Pearson's correlations remained the primary analysis method for the interval-scale based measurements in this study.

Bonferroni Correction

Bonferroni correction was applied as a further statistical significance test to prevent false positives due to multiple comparisons of the hypothesis tests (Napierala, 2012), since correlation coefficients of a given medical parameter were repeatedly calculated for 7 different (but not completely independent) geospace parameters and for 13 different time lags. A simplified approach of the Bonferroni correction was used, which multiplies the smallest p-value by the number of tests (Alabdulgader et al., 2018). For N analyses, with the most significant result having a p-value of P, this would imply:

$$P_{corr} = N \times P$$

It has to be noted, that this correction increases the probability of producing false negatives, because it reduces statistical power. Furthermore, the Bonferroni correction can be overly conservative, if test statistics are positively correlated (Moran, 2003; Nakagawa, 2004).

Time-Lag Analysis

Medical parameters, especially blood parameters, may take a certain amount of time to respond to changes in the environment. For this reason, it is not sufficient to analyze medical parameter correlations in-phase with geospace data. Instead, by shifting medical data in time behind geospace data, i.e. introducing time-lags in the correlation analysis, a delayed medical response can be tested.

On the other side, a number of studies observed an anticipatory physiological reaction that occurred several days before the onset of a Geomagnetic Storm (GMS) with significant alterations in participants' blood pressure, HRV, heart rate, skin conductance and by exhibiting certain pathologies (Dimitrova, Stoilova, & Cholakov, 2004; Dmitreva, Khabarova, Obridko, Ragulskaja, & Reznikov, 2000; Khabarova, 2004; Khabarova & Dimitrova, 2009).

This anticipatory reaction was already observed by Tchijevsky, who suggested unknown radiation produced by the sun was likely responsible (Khabarova, 2004) - prior to any available solar measurements, e.g. x-ray- or F10.7-flux. The increased solar radiation Tchijevsky referred to could be associated with solar flares, which suddenly emit highly energetic radiation, often accompanied by Coronal Mass Ejections (CME) emitting large amounts of plasma. The radiation of a solar flare takes ca. 8 minutes to travel to Earth as opposed to a CME plasma stream, requiring up to 3 days before reaching Earth `s magnetosphere, possibly resulting in a GMS. (Khabarova, 2004) suggested that a mechanism for the anticipatory effects may be related to a reorganization of ionosphere currents due to increased solar radiation.

To test for these anticipatory effects, this study included negative time lags of up to -3 days.

Correlation Analysis

In the first step of the data analysis, the medical and environmental data were cleaned from uncomplete entries and daily averages of the individual medical measures were formed. In average, ca. 4-5 participants had been examined each working day during the CARLA study, except for breaks and holidays. Each examination day yielded an average value for the medical parameters from the randomly called participants. Correlations were performed using daily averages of medical parameters instead of following single

participants, because every patient had attended the study only once within the three-year period. Therefore, the actual number of participants, which is higher than the number of medical data points, is not reflected in the statistical analysis. Individual differences between participants on a single day were assumed to be averaged to a certain degree.

In the following step, daily averages of medical parameters were compared to daily averages of geospace data by calculating Pearson linear correlation coefficients. Additionally, p-values were calculated according to the sample size of each data set. Since geospace parameters were not assumed to be independent variables, internal correlation coefficients were calculated for these parameters (Appendix A). Geomagnetic parameters showed the largest correlation coefficients with each other (R= 0.65 - 0.95). Daily averages of KP-Index and AP-Index, both derived from the three-hourly KP-Index, were most significantly correlated. Furthermore, Sunspot Number and F10.7 were significantly correlated. The Neutron Count Rate, a measure for the intensity of cosmic rays, showed a negative correlation with geomagnetic indices, e.g. with Plasma Speed (R=-0.58). Medical parameters showed considerably less pronounced inter-correlations, compared to environmental parameters. Because of the large number of included blood parameters and the complex biological systems they represent, their internal correlations were not further analyzed.

To quantify possible time-lags in the correlation, medical data was shifted in daily steps from 3 days before to 10 days after geospace data.

Data smoothing of environmental parameters

The geospace parameters, especially geomagnetic indices, showed high fluctuations on daily timescales, with variances of more than 100% on successive days. A common method of data processing in astrophysics is to smooth such data. In present analysis, smoothing was also meaningful on a biophysical level, because the human body may respond differently to a sudden change in solar activity, compared to long-term trends of the solar data envelope. By smoothing geospace data, blood values were correlated to a running average of adjacent geospace data points, instead of single-day data. With increasing size of smoothing windows, information about longer timescale correlations could be obtained.

Geospace parameters were visually inspected to verify suitable data smoothing methods, before calculating correlation coefficients with medical parameters. Inspecting geospace parameters over the study timespan, it could be seen that many indices were continuously wiggling across their entire range (Fig. 1), so that their long-term trend was hardly visible in the raw data. For solar- and cosmic ray parameters, the variability was comparably less expressed (Fig. 2).

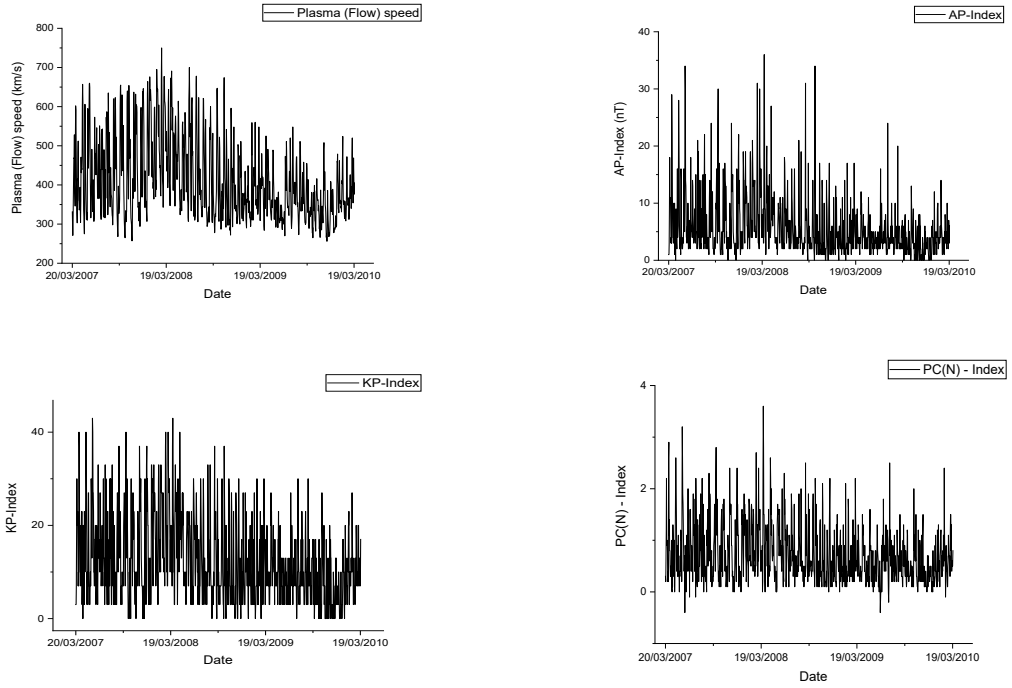

Figure 1: Geomagnetic parameters: Plasma speed, AP-/KP-Index and Polarcap (North)-Index raw data for the entire study timespan.

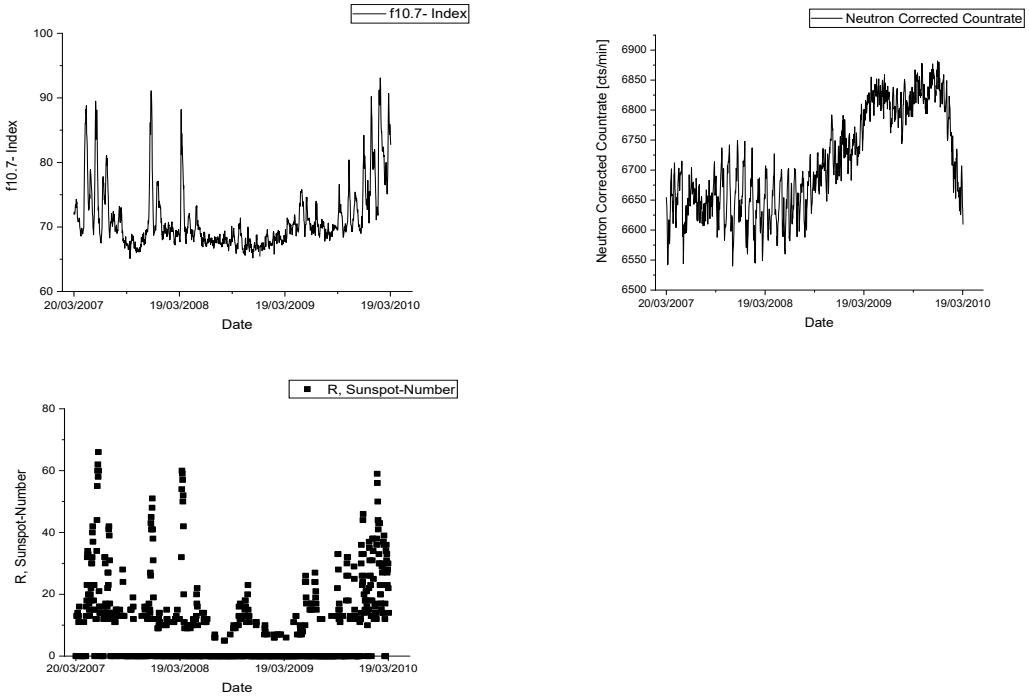

Figure 2: Solar-/ cosmic ray parameters: F10.7 Radio Flux, Sunspot Number and Neutron Count Rate raw data for the entire study timespan.

As smoothing methods, a polynomial approach of the Savitzky–Golay Filter (Savitzky & Golay, 1964) and the conservative method of Adjacent Weighted Average smoothing were applied.

The Adjacent Weighted Average method showed not to be as sensitive as the polynomial method, as it could not reproduce high gradient fluctuations in the data. However, it robustly reproduced long-term trends of the data. With the Savitzky–Golay Filter, misinterpretations at extrema of the geospacer data occurred in several cases. Examples of the smoothing process are provided in Appendix A.

Comparing both methods for different data window sizes, it was decided to use the Adjacent Weighted Average method with a 25-days sampling window in further analysis.

Medical subgroups analysis

To investigate correlation dependences on demographic and medical criteria of the subjects, the participants of the study were grouped into subpopulations according to age, gender, health status, previous illnesses and medications. The following sections illustrate subgroup characteristics, with value N representing the absolute number of participants in a subgroup, whereas N* representing the number of processed examination days, i.e. data points, from daily averaging. Because of differing participant numbers in each subgroup (sample sizes for different subgroups ranged from N*=94 to N*=545), p-values were calculated individually for each subgroup. Geospace parameter correlations were included in the results, if they showed a minimum 3σ-significance.

Health scores

The internationally established *KSK/PSK12 scores* assess health status on a range from 0 to 100, based on a set of 12 questions (Ware Jr, 2000), where higher KSK-scores reflect a better physical- and higher PSK-scores reflect a better mental health status. Two equal sized subgroups were formed for each score by splitting the population at its median value (Tab. 1).

Table 1: Health score distribution (N_{total} = 1349). Subgroup criteria:
KSK12 >= 45.6 (*N=398); KSK12 < 45.6 (*N=427)
PSK12 >= 53.4 (*N=407); PSK12 < 53.4 (*N=419)

Data	Mean	Standard Deviation	Minimum	Median	Maximum
KSK12 - score	44.09	9.92	16.32	45.60	67.14
PSK12 - score	49.40	11.36	3.57	53.41	68.31

Pathologies

a) Depression score

The *Centre for Epidemiologic Studies Depression Scale (CES-D)* assesses depression status on a range from 0 to 60, higher scores suggesting subject is suffering from depression pathologies. Participants were grouped according to their CES-D according to the criterion for a depressive person to score at least a CES-D value of 23 (Lewinsohn, Seeley, Roberts, & Allen, 1997). The total number of participants/ data points in this subgroup was N= 104/ N*=94.

b) Stroke / Myocardial infarction

Participants, who had suffered from a Stroke or Myocardial infarction in the past were considered as a subgroup. The total number of participants/ data points in this subgroup was N=171/ N*=134.

c) Hypertension

Participants, who had a blood pressure reading of at least 140/90 mmHG in their examination or were taking blood pressure lowering drugs were considered as a subgroup. The total number of participants/ data points in this subgroup was N=1084/ N*=511.

Medication

Participants, who were not regularly taking medications defined a subgroup, with corresponding health scores (Tab. 2) slightly higher compared to the entire sample (Tab. 3).

Table 2: Characteristics of participants, who were not regularly taking medication (N=162, N*=150)

Data	Mean	Standard Deviation	Minimum	Maximum
Age	60.7	7.6	50.3	86.8
KSK12 - score	50.1	7.9	16.3	67.1
PSK12 - score	50.9	10.3	10.3	65.5
CES-D Depression Score	8.4	8.3	0.0	52.0

Gender

The cohort was divided by gender, with 790 male and 646 female subjects marking two subgroups. The male subgroup showed slightly better health scores in all categories compared to the female subgroup (Appendix A)

Age

The age of participants ranged from 49 - 87 years. Participants were split into three age subgroups with comparable age intervals: Group 1 (Age: 49 - 62 years), Group 2 (Age: 63 - 75 years) and Group 3 (Age: 76 - 87 years). Demographic and health scores were examined for each group (Appendix A), with physical health scores decreasing for higher ages. Concerning mental health scores no comparable tendency was observed.

Summary

The average age of participants was 67 years, with average KSK/PSK12 scores in a middle range (Tab. 3) and a drug exposition of 89%. The average CES-D score of 9.9 was well below the clinical criterion for depression (CES-D> 25). The distribution of genders was balanced, with 45% females. Based on health and demographic parameters, the selection of CARLA study participants was not biased, except for the restriction to a higher age group.

Table 3: Demographic and general health data of the CARLA study cohort (N= 1436, N*= 545)

Data	Mean	Standard Deviation	Minimum	Maximum
Age	67.30	9.70	49.94	87.20
KSK12 - score	44.09	9.92	16.32	67.14
PSK12 - score	49.40	11.36	3.57	68.31
CES-D Depression Score	9.89	8.25	0.00	54

3. Results and Discussion

The correlation coefficients for a given medical parameter with seven geospace parameters were evaluated as a function of time-lag. Horizontal lines indicate the threshold for p-values of 2σ- and 3σ significance. P-values above the 3σ threshold were considered to be significant correlations in this study. To rule out correlation artefacts caused by distributional violations in the data sets, Spearman' s correlation coefficients and their

significance were evaluated, as well. In summary, the significant Pearson's correlations could be confirmed with Spearman's method. Each group of medical parameters was examined separately, and significant results were further analyzed using smoothing methods in order to differentiate between short- and long-term correlations for selected medical parameters.

For the demographic subgroup analysis, 21 blood parameters were selected due to their significant correlation and medical implications. Several blood parameters, which did not show significant correlations, were still included to provide a complete picture of the corresponding lab profile. For each blood parameter group, a time-lag of either 0 days or 6 days was selected and applied for subgroup analysis, since these time-lags showed the highest significance in general.

In the last part, a geospace data subwindow was analyzed in order to investigate the impact of the specific period within the SC phase the data was collected in.

Red blood cells, Hemoglobin and Hematocrit

The time-lag analysis for RBC parameters showed significant correlations for Hemoglobin, MCHC and RDW, slightly exceeding three-sigma significance (Fig. 3-5). For Hemoglobin and MCHC, a peak was visible after 4 - 5 days for geomagnetic parameters (KP-, AP- and PC(N)-Index), whereas no general trend of correlation throughout the 13-days window was visible - results changing from being positively to negatively correlated. However, a significant and general trend could be observed for Hemoglobin/ Neutron Count - specifically after smoothing (Fig. 5). A similar - but less expressed - trend appeared for the correlation of RDW with Neutron Count after smoothing. Applying Bonferroni correction to the most significant correlation (Hemoglobin/ Neutron Count; 10 days lag), its significance decreased from 3.5 σ to 2 σ.

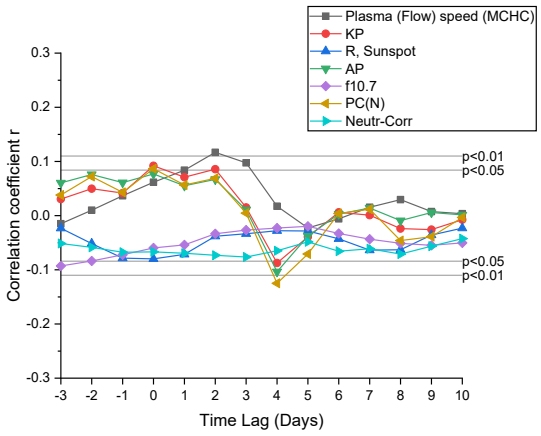

Figure 3: MCHC correlations time-lag analysis

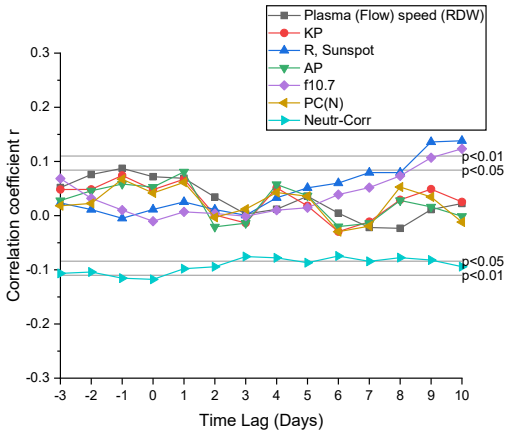

Figure 4: RDW correlations time-lag analysis

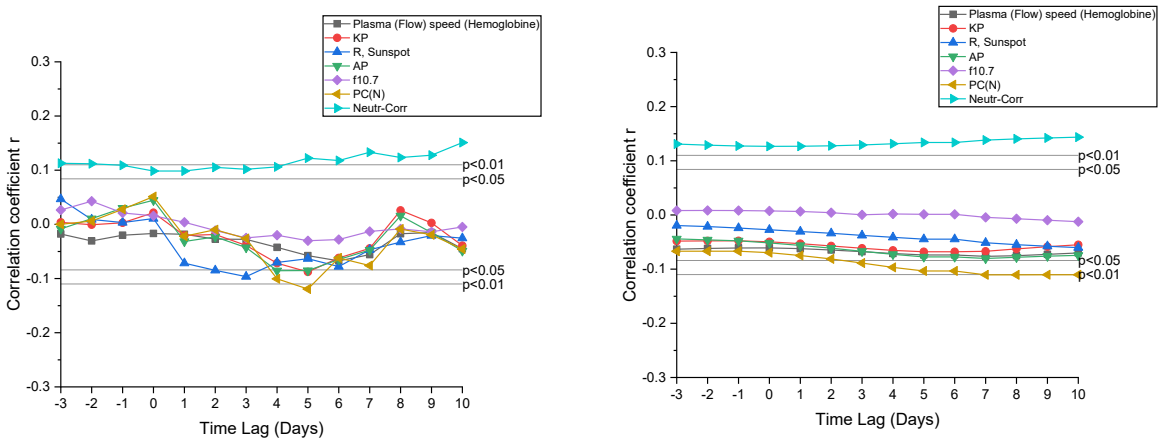

Figure 5: Hemoglobin [g/dl] correlations time-lag analysis (left: unsmoothed, right: smoothed with 25 days window

The observed response could imply lower blood levels of Hemoglobin for periods of low cosmic ray- and high geomagnetic intensity (anti-correlated geospace parameters, Appendix A). The increase in significance after smoothing indicated this effect to be more pronounced on longer timescales. In clinical terms, lower levels of Hemoglobin could indicate a tendency towards anemia. Together with the elevated RDW this could imply a possible tendency to anisocytosis.

White blood cells

The analysis revealed no significant correlations for total leukocytes, neither in raw- nor smoothed data (Fig. 6).

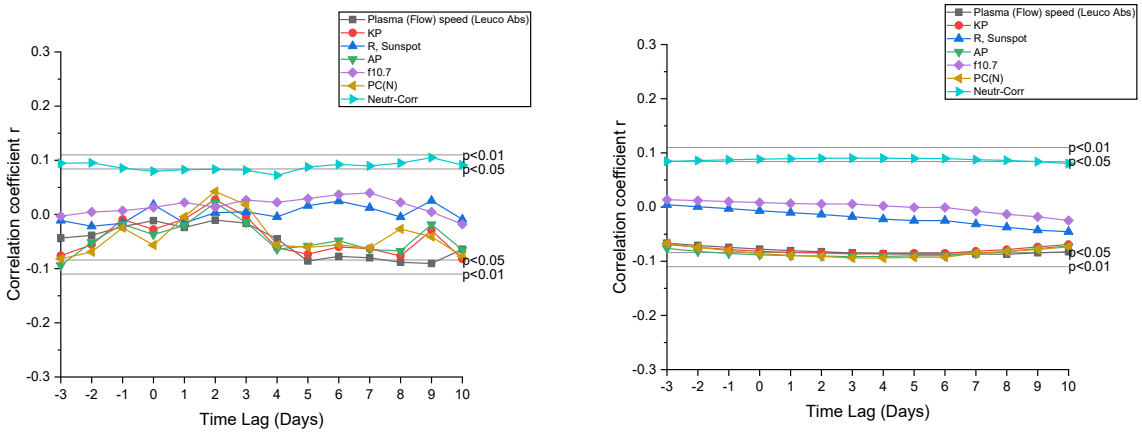

Figure 6: Leukocyte absolute number [exp 9/l] correlation time-lag analysis (left: unsmoothed, right: smoothed with 25 days window)

Yet, significant correlations for differential leukocyte counts, especially for lymphocytes and monocytes, were found both in relative- and absolute concentration measurements (Fig. 7 - 10). Generally, correlation coefficients for differential leukocytes were

higher in absolute number as compared to relative number. This could be due to an amplification of latent correlations in the number of total leukocytes. Minor correlations ($p<0.05$) present in total leukocyte count, would not be reflected in percentage differential leukocyte counts. On the other side, they would be reflected in absolute differential count correlations, which could explain their higher significance as compared to their percentage differential counterparts.

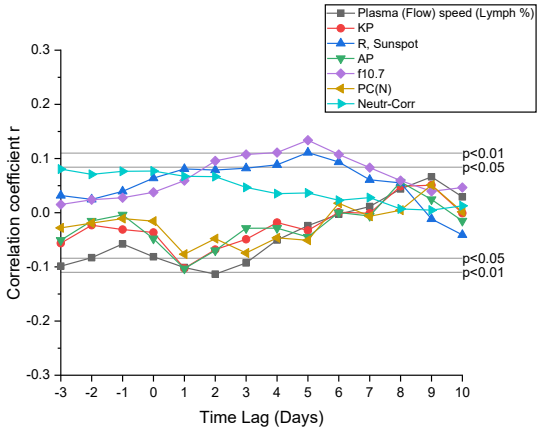

Figure 7: Lymphocyte percentage [%] correlations time-lag analysis

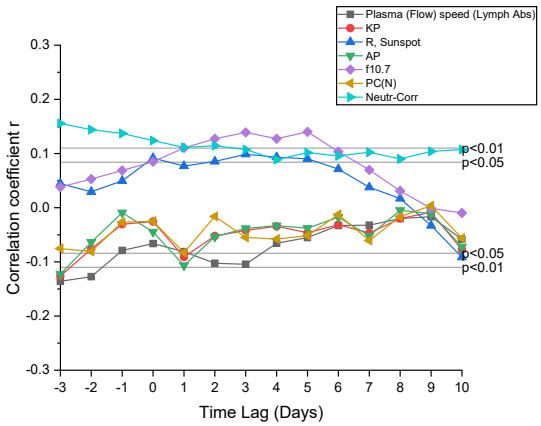

Figure 8: Lymphocyte absolute number [exp 9/l] correlations time-lag analysis

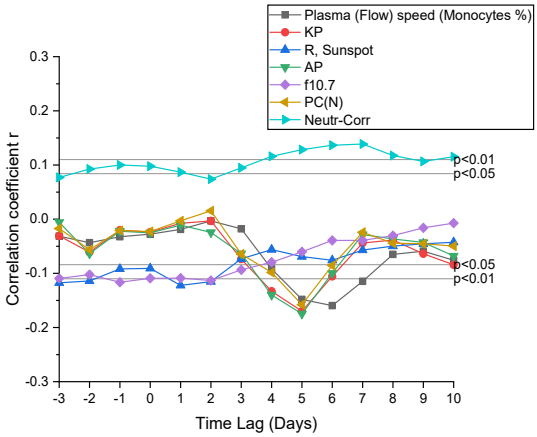

Figure 9: Monocyte percentage [%] correlations time-lag analysis

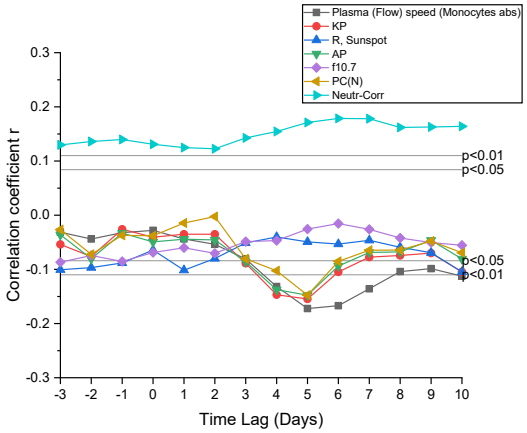

Figure 10: Monocyte absolute number [exp 9/l] correlations time-lag analysis

Lymphocytes

For lymphocytes, a significant correlation with Neutron Count and F10.7 was found (Fig. 11). Applying Bonferroni correction (Lymphocytes Abs. / Neutron Count; -3-day time-lag), significance decreased from 3.5 σ to 2 σ. The correlations were broad in the time domain, with maximum values at a time-lag of 3 to 5 days for F10.7 and –3 to 0 days for Neutron Count. Within geospace data, Neutron Count was generally anticorrelated with geomagnetic parameters like Plasma Speed (Appendix A), which could explain corresponding behavior of medical parameter`s correlations.

In an interpretation, a reaction to geomagnetic parameters at -3 days could have been caused by solar events, e.g. solar flares often accompanied by CMEs. A CME releases energetic particles traveling with the solar wind for 3 days before reaching earth. A solar flare releases energetic radiation, which reaches earth nearly instantaneously and is characterized by wavelengths as F10.7, as F10.7 measurements were correlated with lymphocyte counts at 1-to-5-day time-lags. Combining both, a solar event involving energetic radiation and -particles could be responsible for two distinct medical reactions separated by several days in time. Although frequency and intensity of solar eruptions is generally reduced during solar minima periods as in this study, they were still present: For instance, in January 2009 – in the center of SC minimum- 23 CMEs were observed (Arge, 2009). Considering these solar events, the distinct lymphocyte time-lags at -3 days to geomagnetic parameters, respectively +1 days to F10.7 would be plausible.

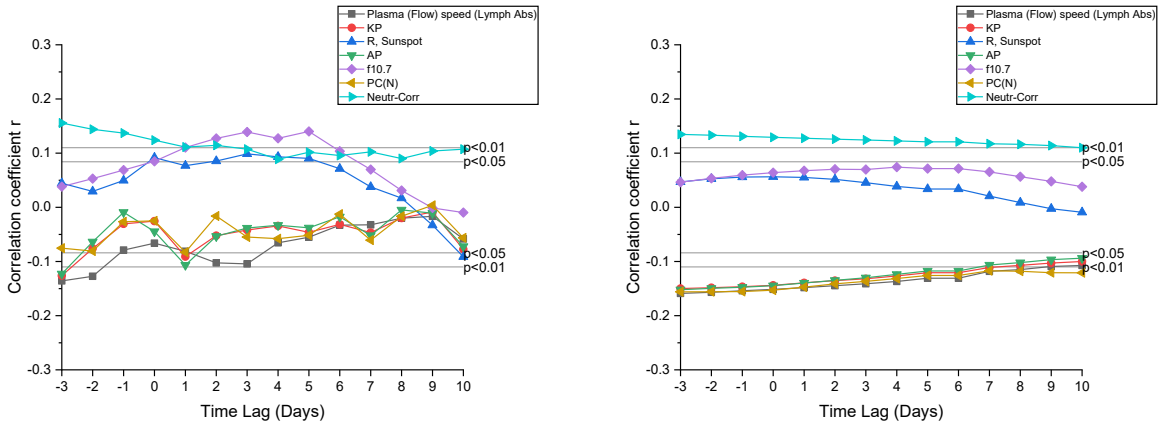

Figure 11: Lymphocytes absolute number [exp 9/l] correlation time-lag analysis (left: unsmoothed, right: smoothed with 25 days window)

Applying data smoothing, lymphocyte`s correlation with F10.7 at 4-to-6-day time-lags decreased below significant levels (Fig. 11). At the same time, the significance of the Neutron Count correlation and the anti-correlation with geomagnetic parameters increased throughout the entire time-lag span. The most significant values in the smoothed data were found at negative time-lags, which could be again related to solar energetic events involving CMEs.

Monocytes

The monocytes correlations were most significant for all white blood cell parameters, particularly with Neutron Count and Plasma Speed. Applying the Bonferroni correction for highest correlation (Monocytes Abs./ Neutron Count at 5 days), significance decreased from 4 σ to 3 σ. The Neutron Count correlation was broad in the time domain (Fig. 12), whereas the Plasma Speed correlation showed a more expressed time-lag dependence with its highest value at a 5-day time-lag.

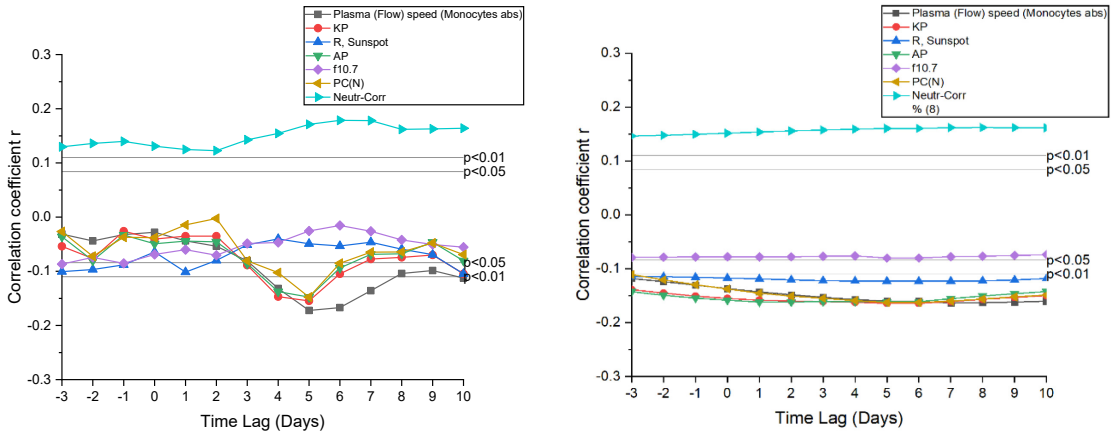

Figure 12: Monocytes absolute number [exp 9/l] correlation time-lag analysis (left: unsmoothed, right: smoothed with 25 days window

Applying smoothing, geomagnetic- and Neutron Count correlations flattened and became more significant throughout, underlining their robustness and long-term characteristics for periods of high cosmic ray intensity and low geomagnetic activity.

Medical subgroups

Monocyte and lymphocyte correlations were analyzed in the subgroups with a time-lag of 6 days due to monocyte peak values at 5-6 days, which were the most significant results in all white blood cell parameters.

For monocytes, Plasma Speed and Neutron Count correlations showed predominantly significance in the lower- and medium age group with a maximum $\Delta\ \sigma = 2.5$ between age groups (Tab. 4 and Appendix B). Comparing health scores, the lower physical health score (KSK) group showed significant and considerably lower p-values compared to its counterpart ($\Delta\ \sigma \leq 1.5$), whereas the higher psychological health score (PSK) group showed lower p-values compared to its counterpart for the geospace parameters ($\Delta\ \sigma \leq 1$). In genders, male subgroup monocyte absolute number correlations were more significant than in the female division for all analyzed parameters ($\Delta\ \sigma \leq 2$). For pathologies, only the *hypertension* group maintained the initial significant correlations with Plasma Speed and Neutron Count, with a slight decrease ($\Delta\ \sigma \leq 0.5$) in both measures of monocytes.

Table 4: Monocyte absolute number [exp 9/l] medical subgroups' correlations significance compared. P-values with 3σ significance and above are highlighted.

Parameter: Monozytes [Exp 9/L]			Timelag (Days): 6	
Subgroup	**Plasma Speed**	**Kp**	**Ap**	**Neutron Count**
Complete	**6.65e-05**	1.02e-02	3.57e-02	**2.37e-05**
Agegroup 1	1.80e-02	1.02e-01	2.04e-01	**4.14e-06**
Agegroup 2	**1.84e-04**	3.29e-01	3.29e-01	**1.84e-04**
Agegroup 3	2.42e-02	1.00e+00	5.37e-02	2.62e-01
Male	**3.31e-04**	**1.16e-02**	**1.16e-02**	**8.50e-06**
Female	**5.65e-03**	1.42e-01	1.99e-01	2.72e-02
No Medication	**8.33e-04**	1.13e-01	2.23e-01	**1.13e-04**
Stroke/Mi	1.07e-01	1.00e+00	1.00e+00	7.31e-01
Hypertension	**2.82e-04**	2.38e-02	4.20e-02	**6.70e-04**
KSK Low	**7.79e-05**	**9.07e-04**	**1.88e-03**	**3.75e-03**
KSK High	**2.70e-03**	6.91e-01	6.91e-01	**1.37e-04**
PSK Low	**7.71e-03**	1.02e-01	1.02e-01	2.43e-02
PSK High	**2.62e-04**	6.97e-02	1.07e-01	**5.73e-04**
Depression	5.03e-01	3.88e-01	4.43e-01	3.38e-01

For lymphocytes, although in the full cohort all correlations were below the 3σ-threshold at a time-lag of 6 days, in subgroups several correlations` significance increased above the threshold, e.g. for F10.7 and Neutron Count. However, changes were marginal ($\Delta \sigma \leq 0.5$) and trends not clear, except for the *hypertension* subgroup with clearly increased significance in both lymphocyte counts.

Discussion

Total WBC not correlating with solar variability is plausible, since leukocyte abnormalities would be clinically expected for acute infections and other conditions, which would unlikely be seen in the non-hospitalized study cohort.

In differential WBCs, significant correlations were observed for monocytes and lymphocytes. The most substantial correlations were found for monocytes, where elevated monocytes could be interpreted as an indicator of chronic inflammatory states. Therefore, periods of high cosmic ray- and low geomagnetic intensity could imply an inflammatory response in certain subjects, as described in magnetobiological studies about changes in the human pro-inflammatory system related to artificial VLF electromagnetic fields (Hosseinabadi et al., 2019): The authors compared blood samples of exposed employees of a power plant to an unexposed group and found the mean level of IL-1β and IL-6, WBC and lymphocyte percentage significantly increased in the exposed group. An elevated lymphocyte count, as observed in present study as well, could be interpreted as a pro-inflammatory response, similar like in a viral infection.

Considering time-lags, short-term increases in solar activity suggest an activation of the lymphocyte system after 1-2 days. In a second step, monocyte increase after 6 days suggests a broader inflammatory response. Clinical studies found - within the various leukocytes - monocyte count to be an independent predictor of CVD risk (Chung et al., 2019). Therefore, present results support other heliobiological studies on CVD as summarized in a recent review (Zenchenko & Breus, 2021): Increases in CVD hospitalization with

several days of time-lag after geomagnetic disturbances were described by the authors, which could be caused by pro-inflammatory changes with similar time-lags as seen in present study. Furthermore, heliobiological studies looking at comparable periods of high cosmic ray- and low geomagnetic intensity found increases in CVD and stroke in Azerbaijan hospital statistics, e.g. (Eliyahu Stoupel et al., 2006; E. Stoupel, Babayev, Abramson, & Sulkes, 2013).

The subgroup analysis suggested that changes in differential WBC mostly affect younger age groups and male subjects with a lower KSK score. Previous heliobiological studies rarely compared different age groups, genders or other demographic parameters. Still, one study conducted on an elderly Israeli population found, that specifically male subjects below 65 years experienced higher rates of strokes and paroxysmal atrial fibrillation during periods of very low geomagnetic activity (E. Stoupel, Martfel, & Rotenberg, 1994). In present study`s results, the most affected age group 1 was in a similar age range of 49-62 years, and the male gender was comparably more affected, as well.

Lipid panel

LDL and Total Cholesterol

Total Cholesterol, as well as LDL-Cholesterol and its related parameters SD-LDL and Friedewald-LDL showed a significant correlation with geomagnetic indices after a time-lag of 6 days (Fig. 13f/ Appendix B). In contrast, HDL-Cholesterol did not show comparable behavior, indicating Total Cholesterol correlation to be associated predominantly with an increase of constituent LDL-Cholesterol. Applying Bonferroni correction for LDL/ AP-Index correlation at a 6-day time-lag, its significance decreased from 4.5 σ to 3.5 σ.

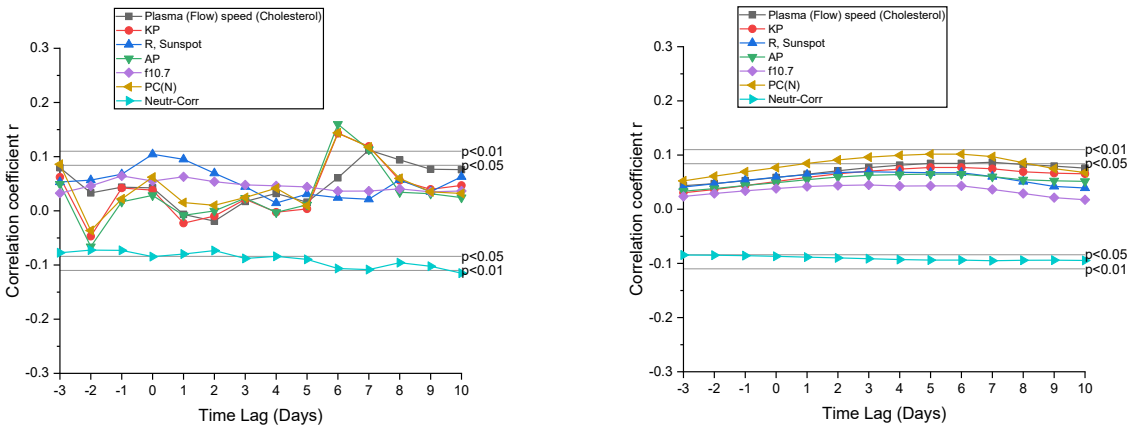

Figure 13: Cholesterol (mmol/l) correlation time-lag analysis (left: unsmoothed, right: smoothed with 25 days window)

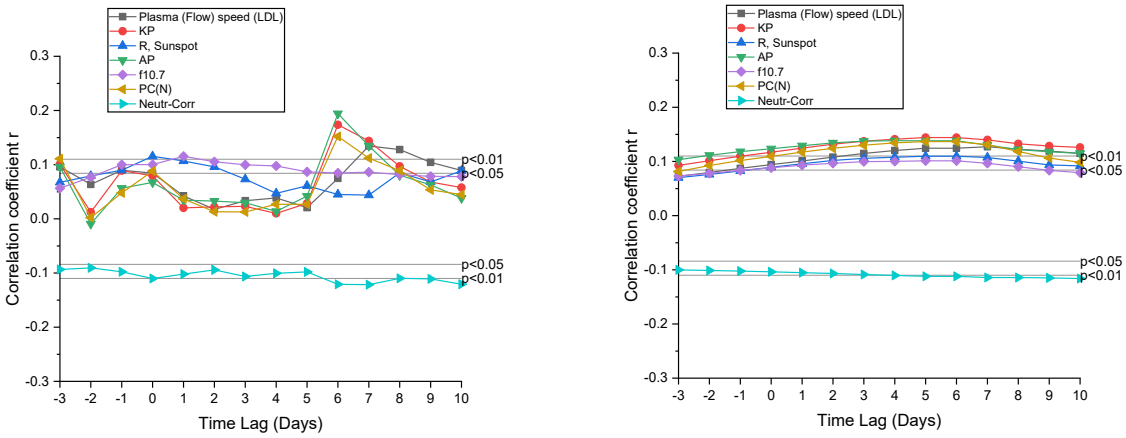

Figure 14: LDL-Cholesterol (mmol/l) correlation time-lag analysis (left: unsmoothed, right: smoothed with 25 days window)

Applying data smoothing, correlations with geomagnetic parameters flattened for LDL- and Total Cholesterol with a shallow maximum at a comparable time-lag (Fig. 13f) and a broad 3σ-level anticorrelation for LDL-Cholesterol with Neutron Count became evident.

Since lipid parameters showed significant correlation peaks exclusively at specific time-lags of 6 days, false results due to sampling problems were ruled out by analyzing Fourier transformations of frequency spectra from all geospace- and medical data sets. No data sets did show specific power density peaks at 6-day- or other time-lags within the study window, therefore results could be assumed to be nondependent of data sampling issues.

Apolipoproteins

Apolipoprotein parameters correlated significant and broad in time domain with F10.7, specifically they anticorrelated with Apo A1 and positively correlated with Apo B (Fig. 15f). Furthermore, Apo B showed a peak with geomagnetic indices after 6 days comparable to the behavior of LDL-Cholesterol - though less expressed. Applying Bonferroni correction for the Apo B / F10.7 correlation, its significance decreased from 3.5 σ to 2.5 σ.

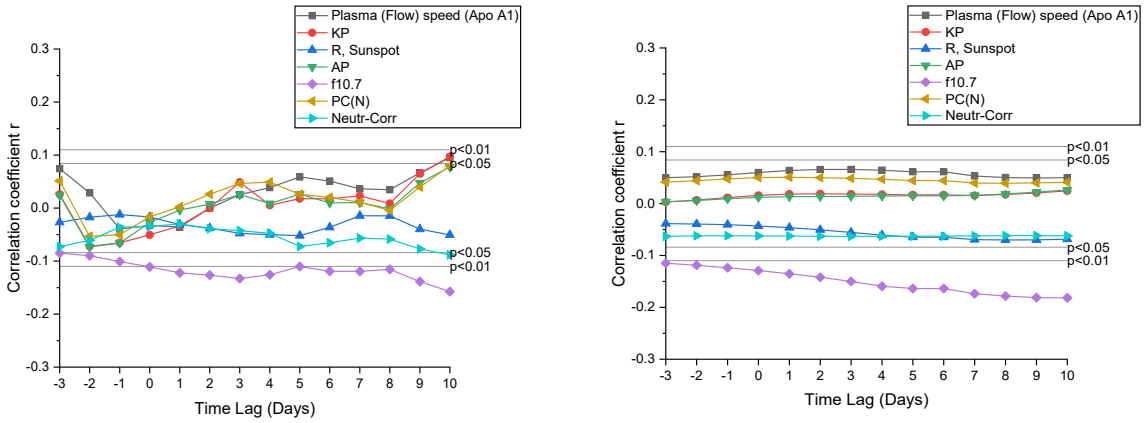

Figure 15: Apo A1 [g/l] correlation time-lag analysis (left: unsmoothed, right: smoothed with 25 days window)

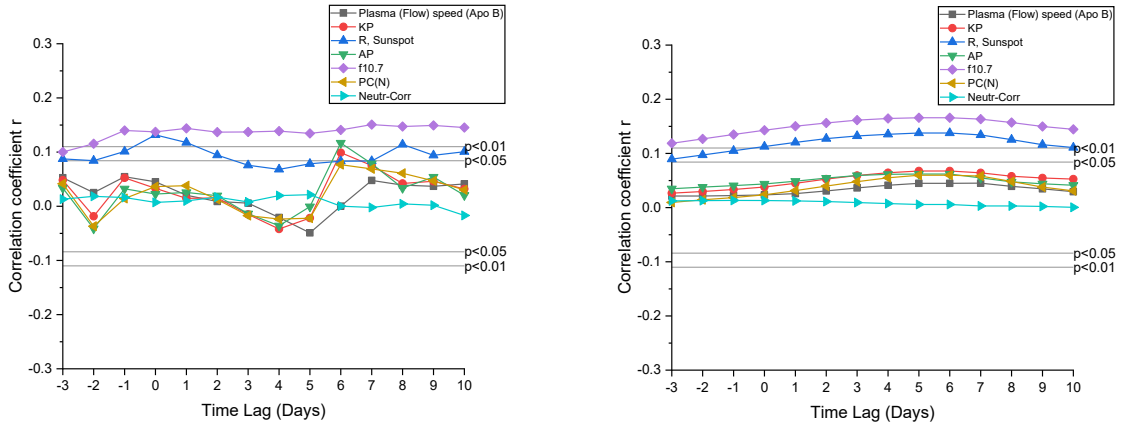

Figure 16: Apo B [g/l] correlation time-lag analysis (left: unsmoothed, right: smoothed with 25 days window)

Applying smoothing, a peak became visible for the Apo B / F10.7 correlation at 5 - 6 days – at a similar time-lag as for the geomagnetic index correlations in the unsmoothed data. Further, geomagnetic index correlations vanished after smoothing. Additionally, F10.7 correlation coefficients reached considerably higher values, corresponding to a significance of 3.5 σ, after applying Bonferroni correction. Sunspot Number became clearly correlated with Apo B at comparable time-lags as in the F10.7 correlation.

Medical Subgroups

The lipid panel showed significant correlations with geomagnetic indices and F10.7. Geomagnetic correlations appeared at a specific time-lag of 6 days, whereas F10.7 correlations were broad in the time domain. For this reason, lipid parameter medical subgroups were analyzed with a 6-day time-lag.

Total- and LDL- Cholesterol showed significant correlations only in the oldest age group (Appendix C). In health score groups, a similar result as for monocytes was observed: Significant correlations were only found in the low KSK-, respectively in the high

PSK-division. The difference between both KSK groups was considerably higher ($\Delta \sigma \leq 2$), compared to both PSK groups ($\Delta \sigma \leq 0.5$). Comparing genders, the male subgroup was clearly more affected than the female one ($\Delta \sigma \leq 2.5$) - similar as in monocyte results. Looking at specific pathologies, *hypertension* group maintained significant correlations yet with decreased p-values compared to the full sample ($\Delta \sigma \leq 3.5$) - comparable to WBC results. Correlations of the *stroke* / *myocardial infarction* group became more significant compared to the full sample ($\Delta \sigma \leq 1$) for Total Cholesterol.

For apolipoproteins, in health score groups significant correlations could only be observed in the low KSK division (Appendix C): P-values for all geospace parameters clearly increased in this division ($\Delta \sigma \leq 2$). No clear trends were evident for age groups and genders. Looking at pathologies, *hypertension* group correlations became more significant compared to the full sample ($\Delta \sigma \leq 0.5$ for F10.7). Other pathology groups did not show significant correlations.

Discussion

The analysis of apolipoproteins revealed a cardiovascular risk factor (Apo B / Apo A1 - ratio) to be increased during extended periods of high solar activity, respectively increased values of F10.7 and Sunspot Number. The increase in significance to 3.5 σ after smoothing (Bonferroni corrected) and the long-term character were evident. Increased CVD risk factors during long-term periods of high solar activity could explain hospital studies of CVD, MI, Ischemic Heart Disease and Acute Coronary Syndrome from North America, Europe, Russia and Israel, which found correlations for these pathologies with periods of increased solar and geomagnetic activity (Cornélissen et al., 2002; Eliahu Stoupel et al., 1995).

For cholesterols, the increase of the cardiovascular risk factors LDL- and Total Cholesterol 6 days after geomagnetic disturbances could explain cardiovascular pathologies observed a few days after geomagnetic disruptions. The most substantial correlations were found for LDL-Cholesterol (3.5 σ, Bonferroni corrected). The specific delay of 6 days could be caused by cascaded metabolic processes in the body. On the other side, it could also be related to the dynamics of a geomagnetic storm (GMS): Analyzing atmospheric resonance frequencies during GMS, studies pointed out implications of Pc1 pulsations during GMS recovery phases after 3–5 days and correlated them with CVD and MI in hospital cases from Moscow and Bulgaria (Kleimenova, Kozyreva, Breus, & Rapoport, 2007). Since geomagnetic parameters in this study did not differentiate between specific pulsations, further research in this field would be required. Similar to LDL-Cholesterol, Apo B also showed a specific response to geomagnetic indices after 6 days, which persisted after smoothing for the Apo B / F10.7 correlation. Taking into account that F10.7 data was not correlated with the geomagnetic parameters related to GMS, this finding for Apo B would rather support a cascaded metabolic cause for observed time-lag behavior.

In subgroup analysis, short-term responses to geomagnetic disturbances were more expressed in older age groups and men, specifically for Total Cholesterol. Long-term correlations of Apo B / Apo A1 with solar activity factors did not depend on age or gender. All lipid correlations were significantly more expressed in participants with a lower KSK-score - comparable to WBC results. Considering that both increased risk-associated lipids and increased monocyte / lymphocyte counts can have a worsening impact on cardiovascular health, their comparable subgroup results support a general conclusion: For male subjects within the lower KSK-Score groups and within age group 1– especially if suffering from hypertension - a negative health impact from space-weather events would be more likely expected.

Inflammation parameters

CRP correlations were not significant (Appendix C), yet the cytokines IL-6 and TNF-a showed correlations on 3σ-level.

Cytokines

IL-6 showed most significant correlations with Neutron Count at a 0-day time-lag for unsmoothed data (Fig. 17). TNF-a showed a comparable anticorrelation with Sunspot Number (Fig. 18). Applying Bonferroni correction, both correlations became unsignificant (0.5σ).

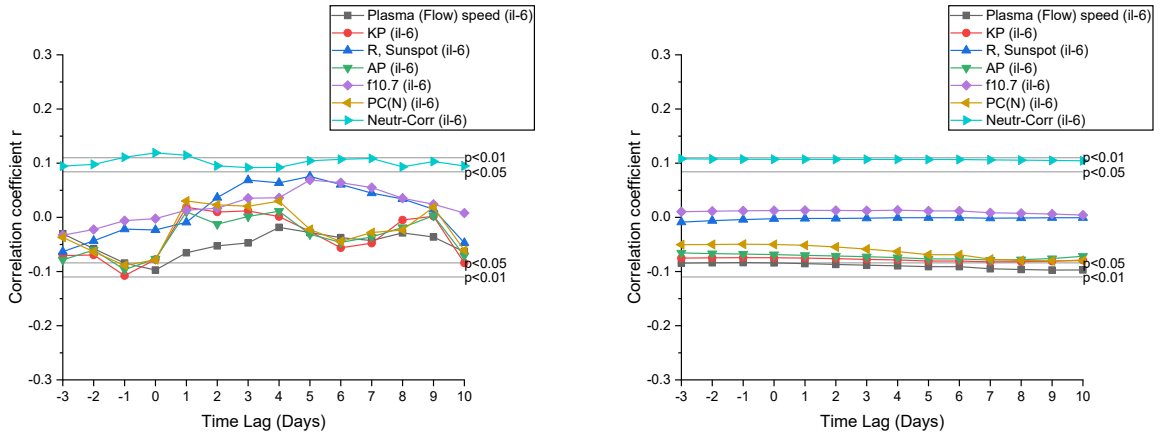

Figure 17: IL-6 (pg/ml) correlation time-lag analysis (left: unsmoothed, right: smoothed with 25 days window)

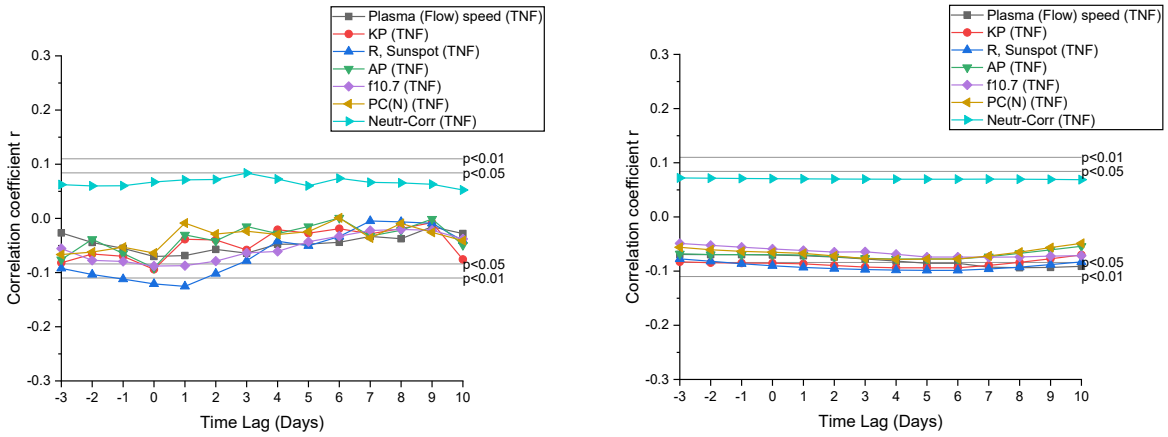

Figure 18: TNF-a (pg/mL) correlation time-lag analysis (left: unsmoothed, right: smoothed with 25 days window)

Medical Subgroups

Subgroups were analyzed at a 0-day time-lag. The initially significant correlations were not broadly confirmed in the subgroups (Appendix C): For health scores, only the

lower KSK group showed a 3σ-correlation (TNF-a/ Sunspot Number). In age groups, only the youngest division showed 3σ-correlations (IL-6/ Neutron Count).

Discussion

Since CRP is an unspecific marker commonly used to detect acute infection or sepsis, it would not be expected finding elevated CRP values in the non-hospitalized subjects of the study cohort.

The anticorrelation of TNF-a with Sunspot Number could imply a decrease during events with higher solar activity, which appeared to be valid especially on shorter time-scales. The broad correlation of IL-6 with Neutron Count - evident after smoothing - could imply a response during extended periods of high cosmic ray intensity. Together with WBC results, this could indicate an increase in inflammation during these periods. The anti-correlation of TNF-a with Sunspot Number would confirm this tendency, since periods of high solar activity correlate with lower cosmic ray intensity. Inflammation parameter correlations became unsignificant after Bonferroni correction, however it should be noted that Bonferroni correction can be over-conservative.

In subgroup analysis, only limited significant results were observed, however they agreed with previous findings in differential WBC: Correlations showed higher significance for the lower KSK group regarding periods of lower solar activity and higher cosmic ray intensity. For IL-6, the age group 1 was the only age group to show significant results. In summary, for both cytokines younger age groups with lower physical health scores appeared to be more affected by solar factors – a similar result as in WBC analysis.

Coagulation parameters

Coagulation parameters did not show significant correlations. Correlation coefficients of INR - a standard clinical coagulation test - were continuously below the P=0.05 line (Fig. 19). Similar results were observed for Platelet Count and MPV (Appendix B). For this reason, no further analysis was conducted on coagulation parameters.

The absence of correlations could be interpreted either as the parameters being not specific enough, or included geospace parameters not affecting coagulation behavior of the blood.

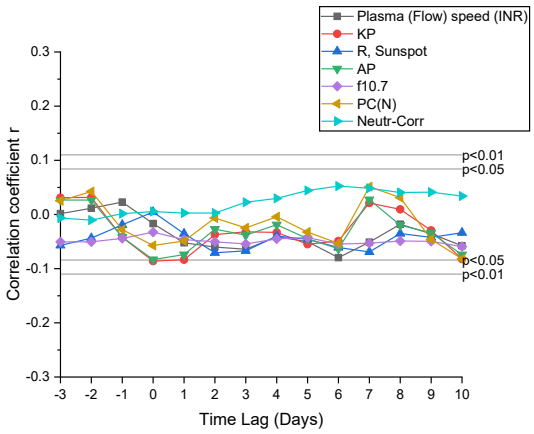

Figure 19: INR correlations time-lag analysis

Clinical Routine Parameters

Liver and kidney function

GOT and GPT values were broadly correlated with Neutron Count (Fig. 20f), whereas GGT did not show well-expressed correlations (Appendix B). Applying data smoothing, correlations of GOT and GPT with Neutron Count broadened further and became more significant – similar for geomagnetic indices at larger time-lags. Applying Bonferroni correction (GOT/ Neutron Count; 1-day time-lag), significance decreased from 3 σ to 1.5 σ. Creatinine showed a significant correlation with AP-Index after 6 days and only in the raw data (Fig. 22).

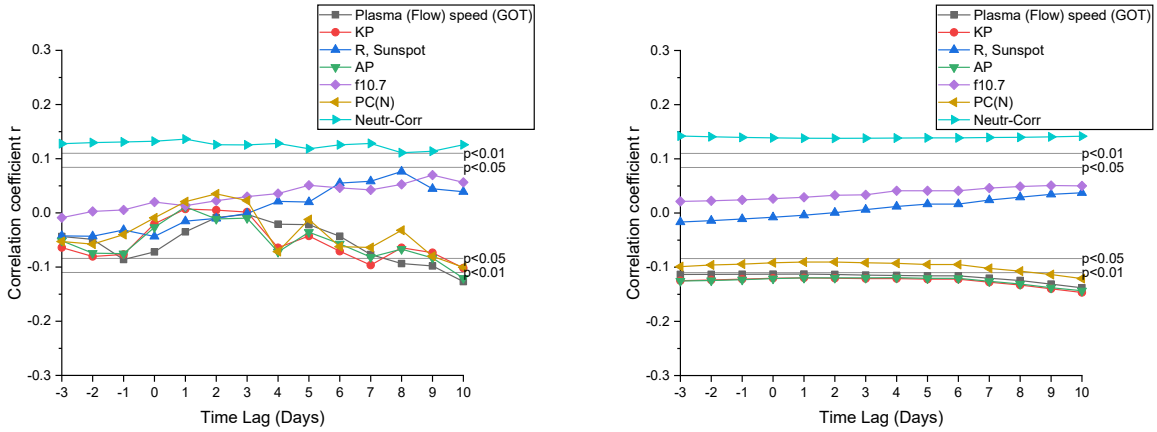

Figure 20: GOT [ukat/l) correlation time-lag analysis (left: unsmoothed, right: smoothed with 25 days window)

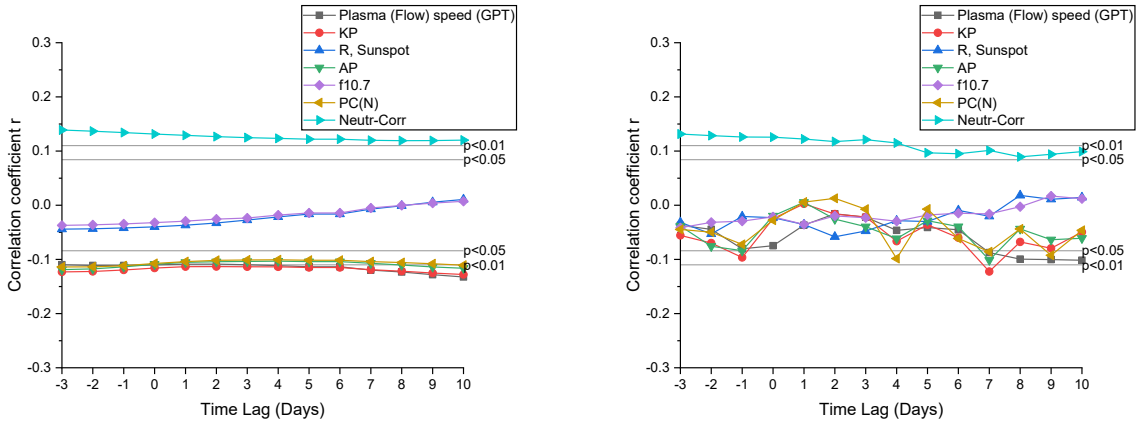

Figure 21: GPT [ukat/l] correlation time-lag analysis (left: unsmoothed, right: smoothed with 25 days window)

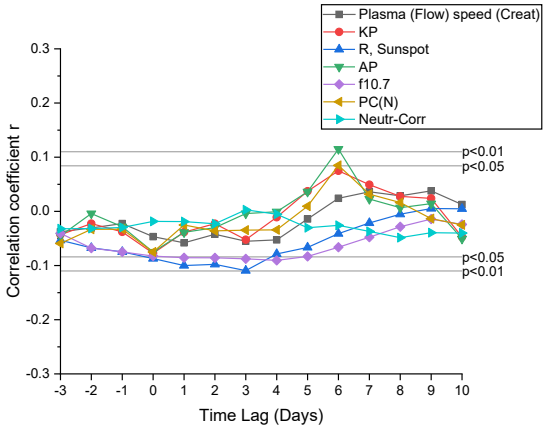

Figure 22: Creatinine [umol/l] correlations time-lag analysis

Glycemic parameters

Glucose correlations were significant (Appendix B), but much less expressed as for the highly significant HgA1c correlation with Neutron Count and geomagnetic parameters (Fig. 23). HgA1c correlations were broad in the time-domain and the most significant ones for the entire study (8 σ). Since previous results for total hemoglobin showed correlations with Neutron Count, absolute HgA1c values should be treated with caution. However, relative HgA1c (%) values are not affected by hemoglobin baseline fluctuations and showed similar significant correlations.

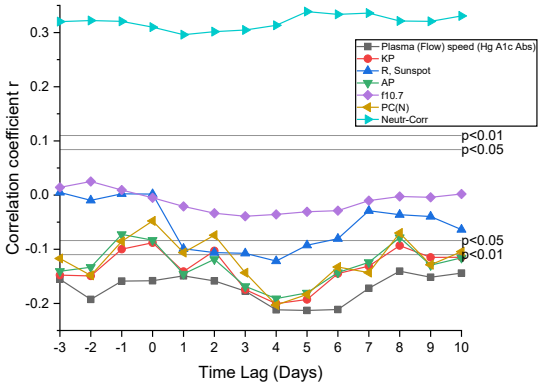

Figure 23: Hemoglobine A1c [g/dl] correlations time-lag analysis

Applying smoothing, HgAlc (%) correlations with Neutron Count and geomagnetic parameters flattened and their significance increased (Fig. 24): Geomagnetic parameters showed a shallow minimum at 2–3-day time-lags, corresponding to 5.5 σ significance after Bonferroni correction.

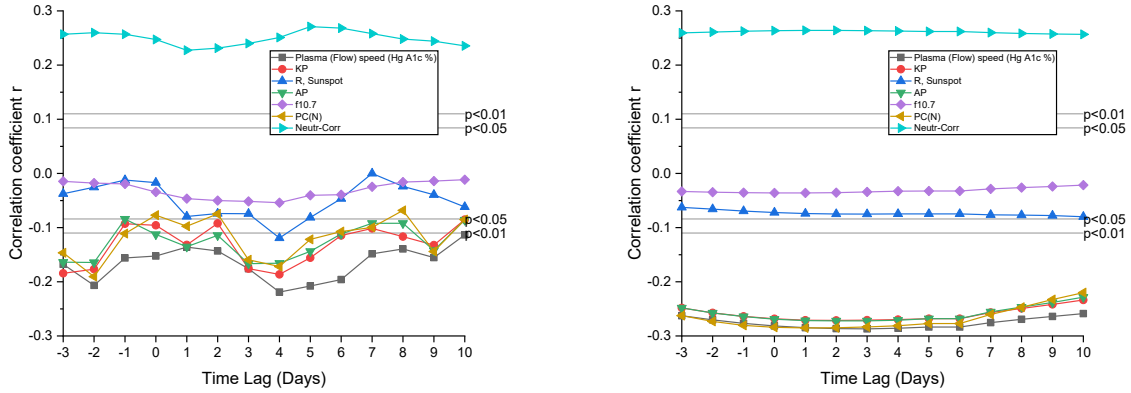

Figure 24: HgA1c (%) correlation time-lag analysis (left: unsmoothed, right: smoothed with 25 days window)

B-type natriuretic peptide

B-type Natriuretic Peptide (pNTroBNP) showed no significant correlations in raw and smoothed data, except for the Kp-Index at a 3-day time-lag (Fig. 25), which was invalidated by Bonferroni correction.

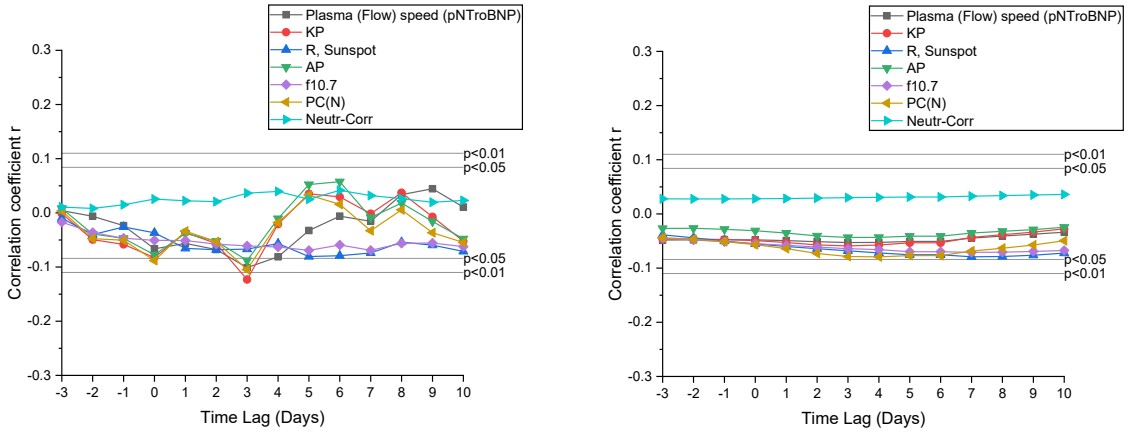

Figure 25: pNTroBNP [pg/ml] correlation time-lag analysis (left: unsmoothed, right: smoothed with 25 days window)

Medical Subgroups

Analyzing HgA1c (%) correlations in subgroups with a time-lag of 6 days, age group 1 showed generally higher significance than in the full sample (Appendix C), while for age group 3 significance decreased substantially. Differences between age groups were large ($\Delta \sigma \leq 3$). For genders, p-values were comparable except for Neutron Count correlation becoming more significant for females ($\Delta \sigma = 2$). In both health score groups, lower score groups' correlations were more significant, while largest differences could be observed between both KSK divisions ($\Delta \sigma \leq 2.5$). Pathology subgroups maintained initial

significance, whereas lower p-values were observed for *hypertension* group compared to the other groups ($\Delta \sigma \leq 2.5$).

Discussion

Periods of high cosmic ray levels and calm geomagnetic conditions appeared to affect liver function, mediated by increased GOT- and GPT levels. This would add another possible impact, beside previous results for inflammation factors in these periods. However, liver function may also be affected secondarily by initial inflammatory changes - particularly since its correlations were less significant.

In terms of glycemic parameters, the long-term indicator HgA1c showed highly significant correlations (5.5 σ, Bonferroni corrected). HgA1c correlations were broad in the time domain, which is plausible due to the HgA1c clinical nature with 8-12 weeks of latency. Blood glucose levels depend on the recent diet of the participant and the time of sample collection; therefore, it is plausible that they did not show clear trends. The subgroup analysis for HgA1c showed similar results as for WBC- and inflammation parameters, especially for age groups and KSK-score.

Studies have shown, that inflammation and hyperglycemia negatively affect cardiovascular factors like blood pressure in their response to geomagnetic activity (Vencloviene, Babarskiene, & Kiznys, 2017): The authors found cardiovascular variables from diabetes- and metabolic syndrome-patients in Lithuania to be adversely affected by increased geomagnetic activity. In hospital admissions for acute coronary syndrome, a stronger negative impact on these patients could be seen. Interpreting present HgA1c results as a tendency towards hyperglycemia – another cardiovascular risk factor – they support previous results of increased differential WBC- and inflammation parameters during periods of high cosmic ray- and low geomagnetic activity.

For the peptide pNTroBNP, which is primarily released in acute complications of the heart, it would be unexpected to find higher levels in the not hospitalized participants of the study cohort. pNTroBNP would require further studies to be associated with publications, e.g. about cardiologic incidents in relation to GMS storms (Kiznys et al., 2020; Shaposhnikov, Revich, Gurfinkel, & Naumova, 2014).

Heart Rate Variability

For HRV parameters, significant correlations were found for the low frequency (LF) and high frequency (HF) components with geomagnetic parameters at a time-lag of 3-4 days (Fig. 26 f). Applying smoothing, correlations disappeared, indicating shorter timescale characteristics. Applying Bonferroni correction (HF / AP-Index) significance decreased from 4.5σ to 3.5σ.

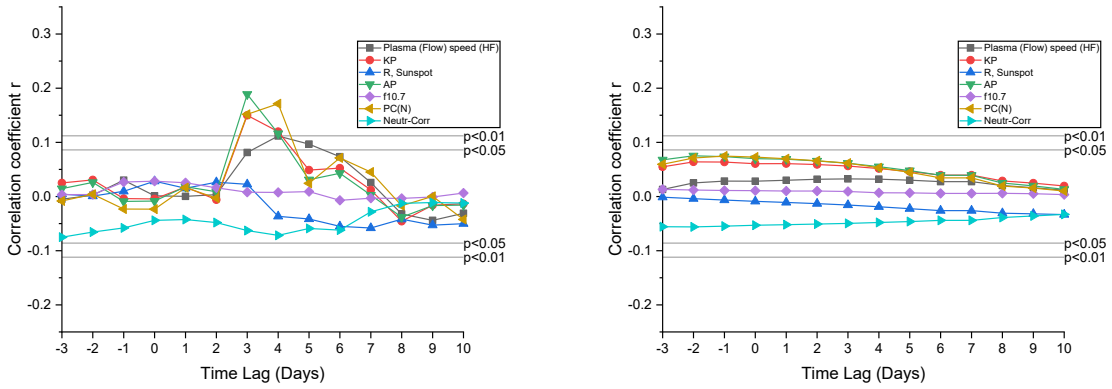

Figure 26: HRV HF-Component correlation time-lag analysis (left: unsmoothed, right: smoothed with 25 days window

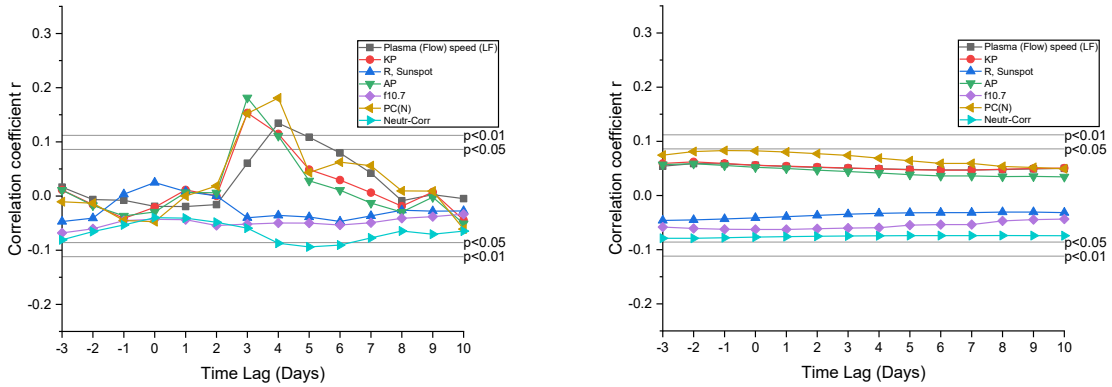

Figure 27: HRV LF-Component correlation time-lag analysis (left: unsmoothed, right: smoothed with 25 days window)

At a similar time-lag of 3-4 days, correlations were found for the Very Low Frequency (VLF) component and the Standard Deviation of Normal-to-Normal Intervals (SDNN) with geomagnetic parameters (Fig. 28 f) – though less expressed.

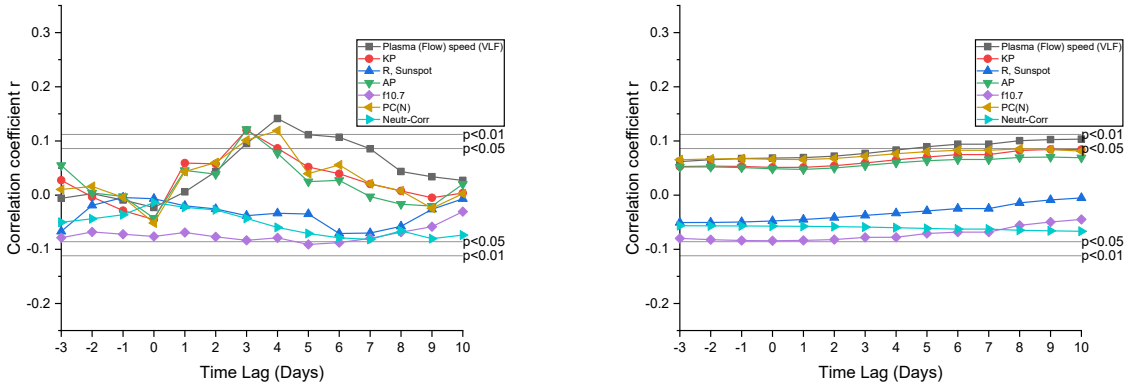

Figure 28: HRV VLF-Component correlation time-lag analysis (left: unsmoothed, right: smoothed with 25 days window)

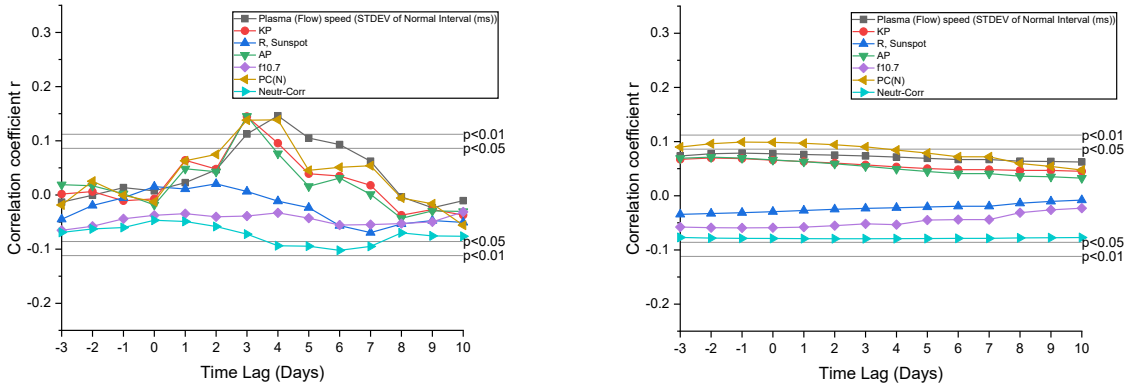

Figure 29: HRV Standard Deviation of Normal-to-Normal Intervals (SDNN) (ms) correlation time-lag analysis (left: unsmoothed, right: smoothed with 25 days window

In summary, 3 - 4 days after geomagnetic disturbances a general power intensification in all frequency bands (VLF, LF, HF) could be observed. This could be interpreted as a positive health response after space-weather events; however, the interpretation would not be clear together with previous results, e.g. for lipid parameters. By inversion the finding could also be regarded as a decrease in total HRV power for periods of low geomagnetic activity. Studies have shown, that reduced HRV can be associated with subclinical inflammation in middle-aged and elderly subjects (Sajadieh et al., 2004). Furthermore, higher levels of inflammation factors and greater insulin resistance were associated with lower HRV in older individuals (Stein et al., 2008). Therefore, a decrease of total HRV power in periods of low geomagnetic activity would be in accordance with previous results for inflammation- and glycemic parameters. Noteworthy, the HRV response-time at 3 - 4 days was quicker compared to HgA1c and monocytes, which responded at 4 - 6-day time-lags.

Interpreting SDNN correlations, a decrease of this measure can be associated with aging, CVD and higher morbidity (Kleiger, Miller, Bigger, & Moss, 1987). Therefore, the decrease of both total HRV power and SDNN with geomagnetic activity may be interpreted as an increase of cardiovascular risk factors and a decrease in ANS regulation properties during periods of low geomagnetic activity. SDNN is not a direct indicator of arrhythmia, since it is calculated from Normal-to-Normal intervals, not accounting for abnormal beats, e.g. as in atrial fibrillation. However, it could reveal a tendency towards arrhythmia, which has been investigated in heliobiological studies: (E Stoupel & Shimshoni, 1991) observed that the number of supraventricular extrasystoles and ventricular extrasystoles increased for lower levels of geomagnetic activity. Furthermore, (E. Stoupel et al., 1994) found periods of low geomagnetic activity to be associated with a higher frequency in cases of atrial fibrillation. Conversely, in present dataset periods of low geomagnetic activity correspond to lower SDNN readings, respectively a tendency towards a more regular heartrate.

HRV parameters were derived from 15-minutes ECG assessments of the participants, therefore it is important to consider that HRV naturally undergoes extensive changes both as a function of participant's age and during the circadian rhythm. Previous heliobiological studies analyzed longer periods of ECG measurements in order to obtain HRV parameters, for instance 72-hour consecutive recordings corrected for circadian rhythms (Alabdulgader et al., 2018). Beside the short time period of HRV data collection, another limitation in present data was the missing information about exact ECG measurement timepoints.

Solar Phase Dependance

Reviewing the results of this study, primarily geomagnetic indices and cosmic rays showed significant correlations, whereas solar activity factors correlations were comparably less expressed. In the larger context of a 11-year SC, both intensity and variability of solar activity factors are at their lowest during the minimum period. Since the study time period laid in the minimum of SC 23 and 24, correlations with solar factors may have been less represented compared to other factors like cosmic rays, which are generally at their highest during a solar minimum.

In order to estimate implications of the restriction to a solar minimum period, solar activity correlations were further analyzed. Since Apolipoproteins and lymphocytes showed the most significant correlations with solar activity parameters (F10.7), they were chosen for the solar phase analysis. Analyzing Apo B/ F10.7 correlation raw data, data appeared concentrated in a bulk group characterized by F10.7 values below 75 solar flux units (Fig. 30).

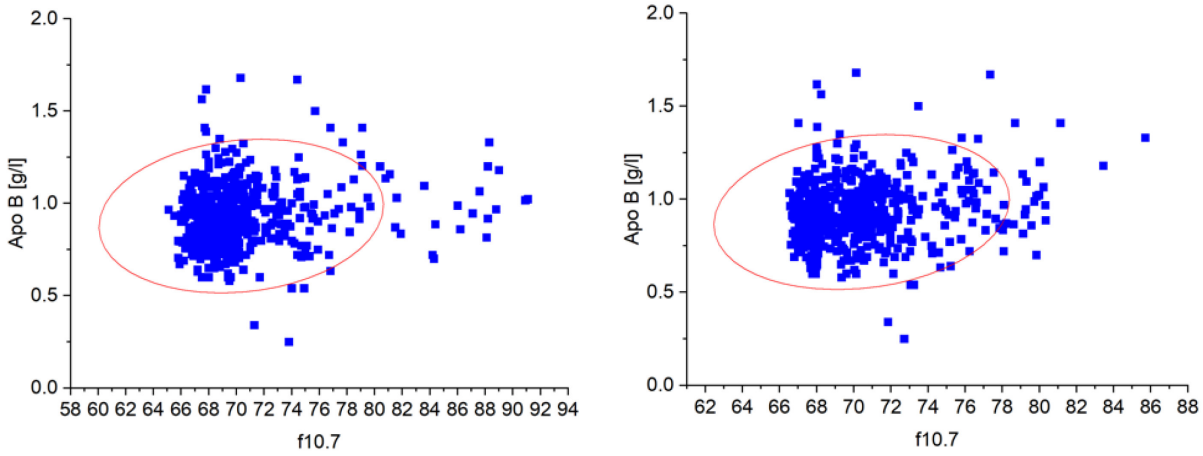

Figure 30: Apo B data with a 6-day time-lag compared against corresponding F10.7 values. Raw data (left) and smoothed data for a 25-days window (right), with 95% confidence ellipses (red).

In the geospace dataset, F10.7 values below 75 primarily corresponded to a range between April 2008 and September 2009 (Fig. 31). Treating this range as space data sub-window A with low F10.7 values, correlation coefficients for lymphocytes and Apo B were calculated.

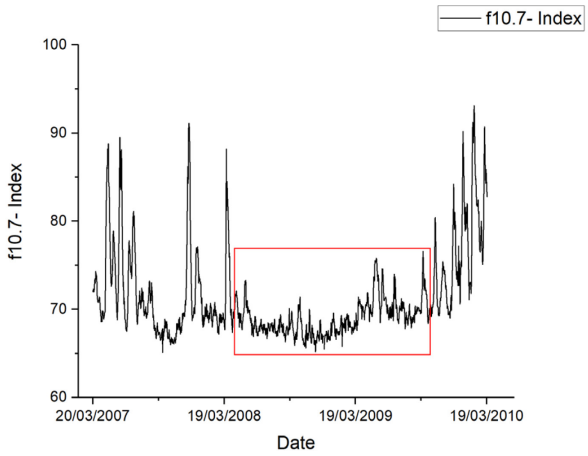

Figure 31: F10.7 readings for the study time period. The range between April 2008 and September 2009 was analysed as a low solar activity subwindow.

In the full data set, lymphocyte correlation coefficients had a distinctive peak at a 5-day time-lag, whereas Apo B showed a broader distribution. Comparing correlation coefficients from subwindow A and the full data set, coefficients were significantly lower in subwindow A (Tab. 5).

Table 5: Correlation coefficients for a low solar activity Subwindow A (unsmoothed data), in comparison with results of the full sample.

Correlation	Time lag (days)	R (Dataset)	R (Subwindow A)
Apo B / F10.7 flux	0	0.14	0.06
	5	0.13	0.09
Lymphocytes Abs. / F10.7 flux	0	0.08	0.02
	5	0.14	-0.01

In a further step, data outside the range April 2008 - September 2009 were analyzed in a subwindow B, corresponding to increased solar activity, elevated geomagnetic parameters and lower cosmic ray intensity (Tab. 6). Correlation coefficients in subwindow B showed increased significance for both medical parameters (Tab. 7). For lymphocyte correlations, the Pearson coefficient increased from originally R=0.14 to R=0.28 for subwindow B. Further, it decreased to zero for subwindow A (R=-0.01), corresponding to $\Delta \sigma = 4.5$ between both subwindows.

Table 6: Geospace data characteristics for both subwindows. Subwindow A: sample size: 539 geospace data points, 302 medical data points. Subwindow B: sample size: 557 geospace data points, 243 medical data points.

	Subwindow A		**Subwindow B**	
	Mean	Stdv	Mean	Stdv
Plasma (Flow) Speed	395.3	87.8	427.9	109.6
KP	11.1	7.6	13.7	9.79
R, Sunspot	2.9	6.0	11.9	14.5
AP	5.0	4.1	6.6	6.0
f10.7	69.0	1.9	73.3	5.9
PC (N)	0.7	0.5	0.8	0.6
Neutron Count	6737.9	74.8	6687.7	83.2

Table 7: Correlation coefficients for a high solar activity Subwindow B (unsmoothed data), in comparison with results of the full sample.

Correlation	Time lag (days)	R (full data)	R (Subwindow B)
Apo B / F10.7 flux	0	0.14	0.20
	5	0.13	0.18
Lymphocytes Abs. / F10.7 flux	0	0.08	0.19
	5	0.14	0.28

In conclusion, results depended strongly on solar cycle phases: More significant long-term solar activity correlations were observed during an active period of the sun. For this reason, results from this study are strictly applicable to solar minimum periods. Considering predictions for a grand solar minimum in near future (Zharkova et al., 2015), a lower solar activity may be observed throughout coming solar cycles. In this context, present results could become specifically relevant in near future.

5. Conclusions

The analysis revealed significant correlations between medical measurements obtained from the CARLA study cohort and geospace parameters during the observation period in the solar minimum between SC 23 and SC 24. Most significant correlations were found for geomagnetic indices and the parameter Neutron Count. Geomagnetic indices quantify the intensity of space-weather events and they correlated with blood parameters after introducing a time-lag of 4 - 6 days. Neutron Count represents Galactic Cosmic Ray intensity and during solar minima – as in this study period - lower solar activity allows for more cosmic rays to reach Earth's magnetosphere. Medical parameter correlations with Neutron Count were less dependent on the introduced time-lags, indicating long-term effects. Third-most significant correlations were found for Solar Radio Flux (F10.7). F10.7 correlations showed less time-lag dependence, similar as for Neutron Count. However, solar phase subwindow analysis showed that the comparably less expressed results for F10.7 could be related to the specific examination period within a solar minimum.

Hematologic-, Inflammatory- and Metabolic Biomarkers

Neutron Count correlations were particularly evident for several differential leucocytes and the parameter Glycated Hemoglobin A1c (HgA1c) quantifying long-term blood sugar levels. Anticorrelations of HgA1c with geomagnetic parameters were the most significant ones in the entire study (5.5 σ, Bonferroni corrected), becoming particularly evident on longer timescales, as geospace data smoothing analysis showed. Comparable long-term correlations with periods of low geomagnetic activity and high cosmic ray intensity were observed for lymphocyte- / monocyte counts; liver enzymes GOT and GPT; hemoglobin; and for cytokines IL-6 and TNF-a, though less expressed.

These combined results were interpreted as a physiological reaction characterized by increased inflammation and hyperglycemia – though implications of hemoglobin- and liver enzymes correlations were uncertain. Since inflammation can be associated with atherosclerosis, CVD and other age-related diseases (Sujarwoto & Tampubolon, 2015), present results could explain increased cases in CVD and stroke found in other studies for comparable geomagnetic periods (Eliyahu Stoupel et al., 2006; E. Stoupel et al., 2013). Increased monocyte count itself can not only be regarded an inflammation indicator, but also an independent predictor of CVD risk (Chung et al., 2019). Further, the highly significant correlations with HgA1c could explain studies, which found a stronger negative impact on hyperglycemic diabetes patients for cardiovascular variables affected by geomagnetic activity (Vencloviene et al., 2017).

The analysis did not reveal significant correlations in red blood cell parameters, except for hemoglobin levels being slightly decreased and RDW elevated for periods of low cosmic ray- and high geomagnetic activity. Since a wide spectrum of red blood cell parameters was analyzed, the impact of geomagnetic disturbances on the hematological system can be considered neglectable.

Lipids

The lipid panel analysis revealed remarkable correlations, which followed geomagnetic disturbances with a time-lag of 6 days. Specifically, Total- and LDL-Cholesterol - lipid parameters associated with cardiovascular risk - were affected. The observed time-lag behavior corresponded well with hospital statistics studies on CVD and stroke, as summarized in a recent review (Zenchenko & Breus, 2021): The authors concluded an increase in cardiovascular risk and morbidity during geomagnetic storm (GMS) days with a delay of up to 4 days from the GMS onset. The time-lag in cholesterols may be related to metabolic processes; further it could be related to GMS dynamics, since geomagnetic

Pc1 pulsations - found during GMS recovery phase after 3–5 days – were associated with increased cases of CVD and MI (Kleimenova et al., 2007).

Apolipoproteins showed long-term correlations with the solar activity index F10.7: Broad positive correlations with Apo B and anti-correlations with Apo A1 suggested an increase of the Apo B/ Apo A1 ratio for periods of increased F10.7. Since the Apo B/ Apo A1 ratio is a well-studied cardiovascular risk factor (Lima, Carvalho, & Sousa, 2007), this result supports other heliobiological studies: Cases of CVD, MI, Ischemic Heart Disease and acute coronary syndrome were found to be correlated with long-term periods of increased solar activity (Cornélissen et al., 2002; Eliahu Stoupel et al., 1995). It is remarkable, that the F10.7 correlation was clearly evident in present study`s dataset, though obtained in a solar minimum period with reduced solar activity.

Coagulation

For the analyzed coagulation parameters, no significant correlations were observed. Although previous heliobiological studies did not examine clinical coagulation factors, physiological studies on geomagnetic disturbances and capillary blood flow in CVD patients suggested corresponding changes in blood chemistry (Gurfinkel, Lyubimov, & Oraevskii, 1995). The association of most heliobiological pathologies with blood circulation would also suggest observable changes in coagulation factors.

Since present analysis of the coagulation parameters INR, PLT and MPV did not support this hypothesis, it would be advisable to analyze a wider range of parameters in future studies - similar as in magnetobiological VLF-field studies about thrombogenic effects on mice (Gorczynska, 1986; Vallejo et al., 2019; Vallejo, Torre, Sanz, & Picazo, 2003).

Heart Rate Variability

For HRV parameters, a general increase in absolute power across all frequency bands and in SSDN was observed for increased geomagnetic indices at a time-lag of 3 - 4 days. By inversion, this could was interpreted as a decrease of these HRV measures for periods of low geomagnetic activity. A decrease in total HRV power was associated with subclinical inflammation (Sajadieh et al., 2004), with higher levels of inflammation factors and greater insulin resistance in older individuals (Stein et al., 2008). Similarly, decreased SDNN was associated with CVD, aging, and higher morbidity (Kleiger et al., 1987). Accordingly, the observed decrease of total HRV power and SSDN for periods of low geomagnetic activity was in agreement with present study`s results for inflammation- and glycemic parameters. Noteworthy, HRV correlations response-time was 1 -2 days shorter compared to these blood parameters, suggesting the autonomic nervous system responding faster to solar variability as compared to changes in clinical chemistry.

Medical subgroups

In the medical subgroup analysis, male participants showed more significant correlations than females, especially for parameters associated with CVD risk in white blood cells and lipids. In age divisions, the youngest age group (49 - 62 years) showed the most prominent correlations, specifically for leucocyte- and glycemic parameters. These results compared well to a study, which found hospital incidences of stroke and CVD to be correlated with low geomagnetic activity - particularly for male subjects below an age of 65 years (E. Stoupel et al., 1994).

Comparing health score groups, the lower physical health score (KSK) group showed clearly more significant results. Furthermore, the higher psychological health score (PSK) group showed less significant results than its counterpart, though differences were

smaller than within KSK groups. Since previous heliobiological studies did not analyze health scores yet, these results could not be compared to the literature at this timepoint.

For pathology subgroups, participants with high blood pressure showed more expressed correlations, followed by participants with a history of stroke or MI. The depression group did not show clear results, possibly related to its small sample size.

General considerations

Present study was based on a specific demographic group of the older population with an average age of 67 years. The majority of cited reference studies - which were in good agreement with present study`s results - investigated pathologies, which primarily affect the elderly population, e.g. cardiac death rates. Noteworthy, a small number of heliobiological studies was conducted on younger participants and showed different results as compared to present study: E.g., a long-term HRV study found a positive correlation for HRV Total Power with cosmic rays (Alabdulgader et al., 2018); another study found an anticorrelation between CRP blood levels and cosmic rays (Elyiahu Stoupel, Abramson, Israelevich, Sulkes, & Harell, 2007). For this reason, present study results must be strictly attributed to the demographic group of the elderly population from a northern geographic region.

Present work can be considered as a pilot study for heliobiological effects on clinical blood parameters, substituting further physiological mechanisms to explain previous phenomelogic heliobiological studies. The field of physiological heliobiology requires additional studies to understand effects on human health. Further implications regarding subject`s age, geographic location, timescales and other geospace- and meteorological factors still need to be analyzed.

Funding: This research received no external funding

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Geospace Data was obtained from NASA/Goddard Space Flight Centre Space Physics Data Facility as part of the Omni 2 data set (https://spdf.gsfc.nasa.gov/pub/data/omni/low_res_omni/omni_01_av.dat), except for Neutron Count Rate, which was obtained from Finland's University of Oulu's Sodankyla Geophysical Observatory (https://cosmicrays.oulu.fi).

Acknowledgments: The author would like to express his sincere gratitude to Dr. Alexander Kluttig (Institut für Medizinische Epidemiologie, Biometrie und Informatik; Martin-Luther-Universität Halle-Wittenberg) for kindly providing the medical dataset from the CARLA study. Further, he extends heartfelt thanks to Dr. Rollin McCarty (The HeartMath Institute), Prof. Alfonsas Vainoras (Cardiology Institute; Lithuanian University of Health Sciences) and Prof. Abdullah Alabdulgader (Prince Sultan Cardiac Center KSA) for their valuable support and consultation throughout the project.

Conflicts of Interest: The author declares no conflict of interest.

List of Abbreviations

ANS	Autonomic Nervous System
Apo A1	Apolipoprotein A1
Apo B	Apolipoprotein B
CARLA	Cardiovascular Disease, Living and Ageing in Halle Study *(Hassan et al., 2022)*
CES-D	Centre for Epidemiologic Studies Depression Scale
CME	Coronal Mass Ejection
CRP	C-Reactive Protein
CVD	Cardiovascular Disease
ECG	Electrocardiography
EEG	Electroencalography
F10.7	Solar Radio Flux
GGT	Gamma-Glutamyltransferase
GMS	Geomagnetic Storm
GOT	Aspartate Transaminase
GPT	Alanine Transaminase
GSM	Grand Solar Minimum
HbA1c	Glycated Hemoglobin A1c
HCT	Hematocrit
HDL	High-Density Lipoprotein Cholesterol
HF	HRV High Frequency Power
HRV	Heart Rate Variability
Il-6	Interleukin-6
INR	International Normalized Ratio
KSK	Physical Health Score KSK-12
LDL	Low-Density Lipoprotein Cholesterol
LF	HRV Low Frequency Power
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MI	Myocardial Infarction
MPV	Mean Platelet Volume
PLT	Platelets Count
pNTroBNP	B-Type Natriuretic Peptide
PSK	Mental Health Score PSK-12
RBC	Red Blood Cell Count
RDW	Red Blood Cell Distribution Width
SC	Schwabe Solar Cycle
SR	Schumann Resonances
STDV	Standard Deviation
TNF-a	Tumor-Necrosis-Factor Alpha
TSI	Total Solar Irradiance
VLF	Very Low Frequency
WBC	White Blood Cell Count

Appendix

Appendix A (Materials and Methods - Correlation analysis)

Inter-correlations of geospace parameters

To evaluate interdependence of geospace parameters, internal correlation coefficients were calculated (Tab. 8)

Table 8: Geospace parameter internal Pearson correlations coefficients

		Plasma speed	**KP-Index**	**AP-Index**	**PC(N) - Index**	**f10.7-Index**	**Neutron Count rate**	**Sunspot-Number**
Geomagnetic parameters	Plasma speed	-	0.75	0.67	0.65	-0.07	-0.58	-0.04
	KP-Index	0.75	-	0.95	0.89	-0.01	-0.47	0.03
	AP-Index	0.67	0.95	-	0.88	0.00	-0.43	0.05
	PC(N) - Index	0.65	0.89	0.88	-	0.01	-0.39	0.05
Solar- / Cosmic parameters	f10.7- Index	-0.07	-0.01	0.00	0.01	-	0.06	0.82
	Neutron Count rate	-0.58	-0.47	-0.43	-0.39	0.06	-	-0.02
	Sunspot-Number	-0.04	0.03	0.05	0.05	0.82	-0.02	-

Geospace data smoothing

The smoothing process of geospace data is illustrated for the parameter Plasma (Flow) Speed, which measures the average particle speed in the solar wind approaching earth. For this highly fluctuative parameter smoothing was applied on different timescales to evaluate its long-term trends. For the polynomial Savitzky–Golay filter data peaks on small timescales were well reproduced even with a large sampling window of 50 days. The Adjacent Weighted Average algorithm was less sophisticated in capturing steep fluctuations on small time scales (Fig. 32), especially with increasing sampling windows.

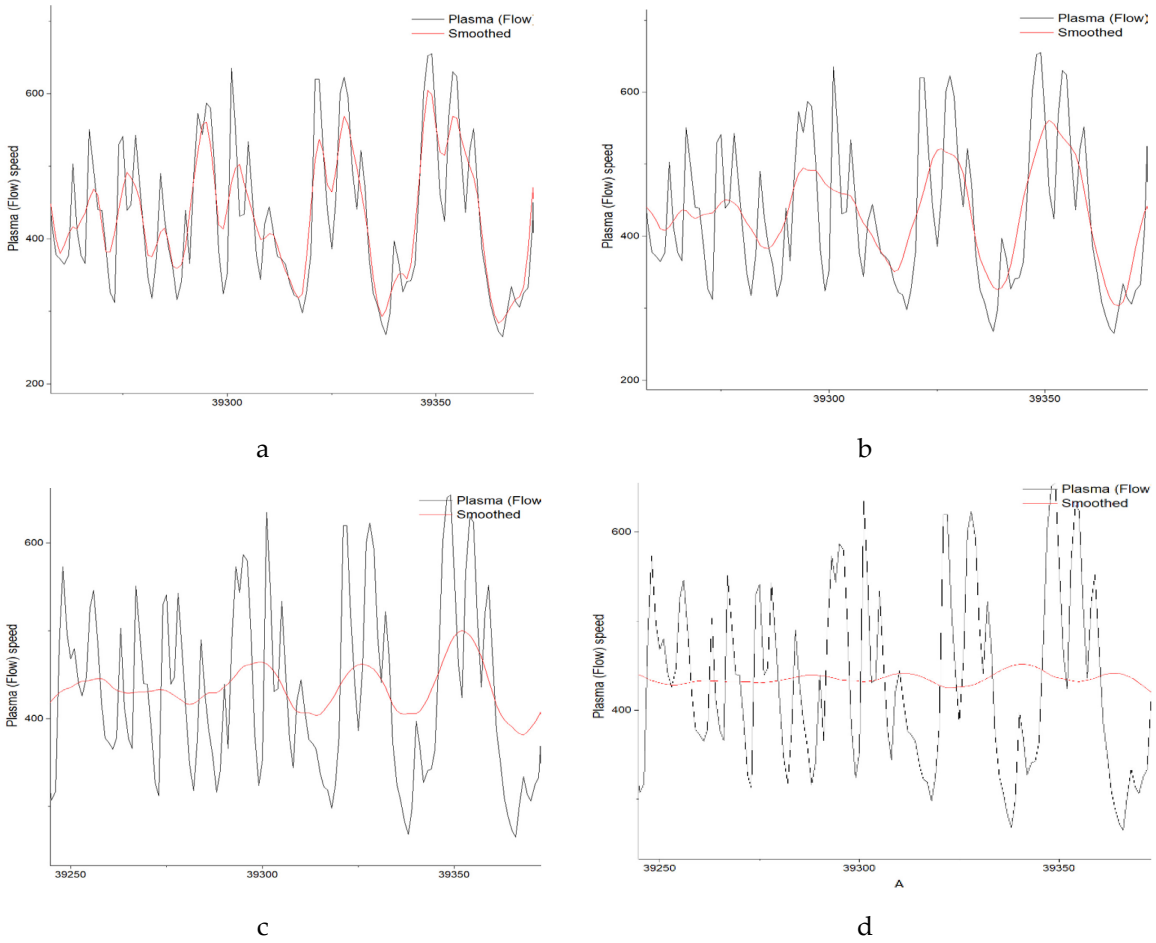

Figure 32: Geospace data smoothing process for plasma flow: Adjacent Weighted Average method. Raw data (black) and Adjacent Weighted Average result (red) illustrated with increasing smoothing windows of 5, 10, 25 and 50 days (a-d) for a range of 100 days.

Comparing results of both smoothing methods on the entire study period, it could be seen that the averaging method generally produced a smoother signal both for a 25-day and 50-day window size (Fig. 33).

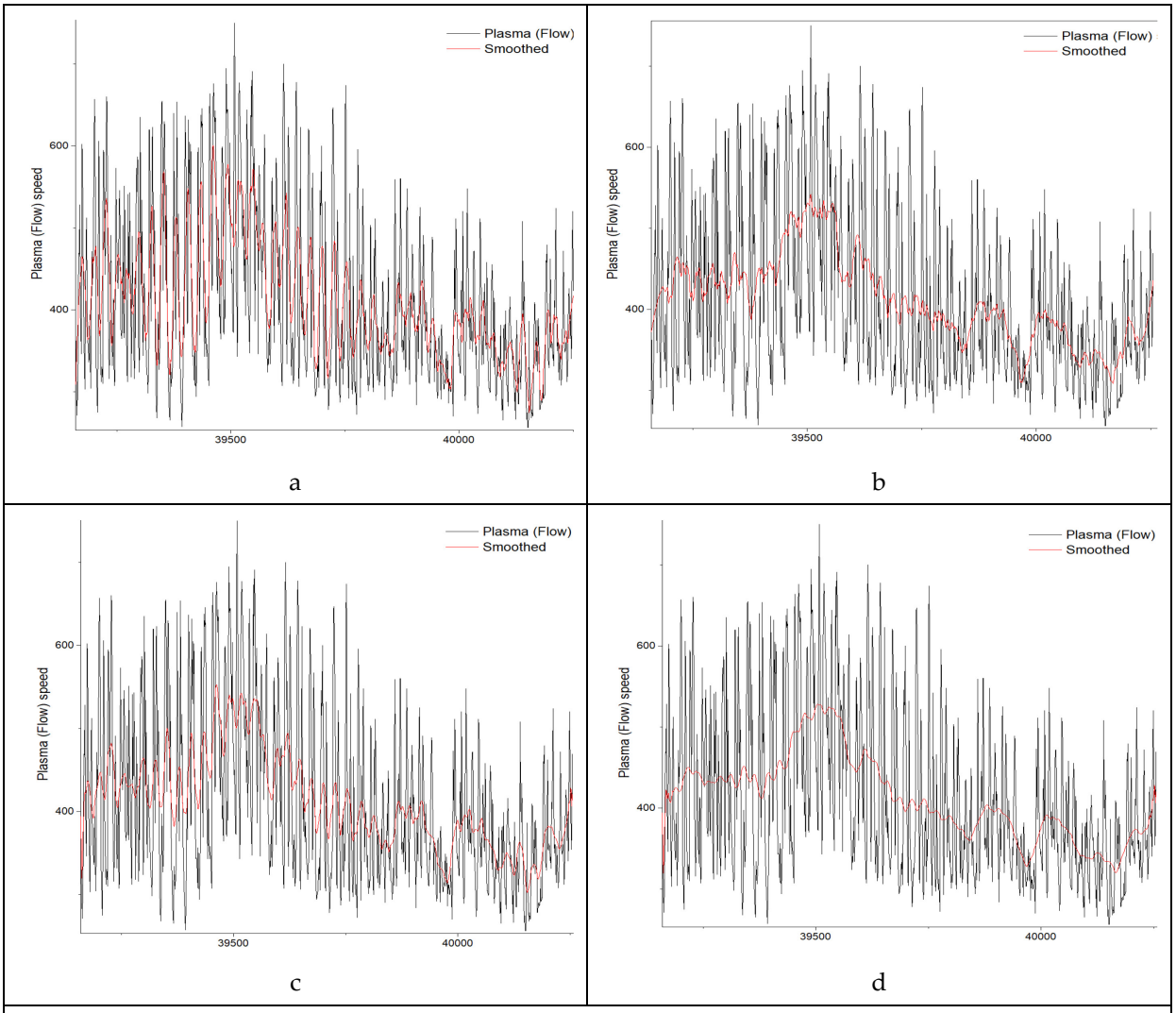

Figure 33: Smoothing methods compared on the entire study period. Smoothed signal (red) for 25 days- (left) and 50 days (right) window sizes, for Savitzky–Golay filter (a,b) and Adjacent Weighted Average algorithm (c,d)

Subgroups

Male Subgroup

Table 9: Characteristics of male subgroup (N=790, N*=442)

Data	Mean	Standard Deviation	Minimum	Maximum
Age	67.8	10.0	49.9	87.2
KSK12 - score	44.7	9.8	16.3	63.9
PSK12 - score	50.6	10.5	5.2	68.3
CES-D Depression Score	8.7	7.3	0.0	42.0

Female Subgroup

Table 10: Characteristics of female subgroup (N=646, N*=399)

Data	Mean	Standard Deviation	Minimum	Maximum
Age	66.7	9.3	50.0	87.2
KSK12 - score	43.3	10.0	17.2	67.1
PSK12 - score	47.9	12.2	3.6	66.3
CES-D Depression Score	11.4	9.1	0.0	54.0

Age Group 1 (Age: 49 - 62 years)

Table 11: Characteristics of age group 1 (N=513, N*=331)

Data	Mean	Standard Deviation	Minimum	Maximum
Age	56.8	3.4	49.9	63.0
KSK12 - score	46.6	9.7	16.3	67.1
PSK12 - score	49.0	11.8	9.8	67.4
CES-D Depression Score	10.5	9.4	0.0	54.0

Age Group 2 (Age: 63 - 75 years)

Table 12: Characteristics of age group 2 (N=599, N*=383)

Data	Mean	Standard Deviation	Minimum	Maximum
Age	68.9	3.5	63.0	76.0
KSK12 - score	44.8	9.2	17.2	61.9
PSK12 - score	50.8	10.3	3.6	66.6
CES-D Depression Score	8.9	7.1	0.0	41.0

Age Group 3 (Age: 76 - 87 years)

Table 13: Characteristics of age group 3 (N=324, N*=259)

Data	Mean	Standard Deviation	Minimum	Maximum
Age	81.0	3.0	76.0	87.2
KSK12 - score	38.5	9.4	18.7	57.6
PSK12 - score	47.3	12.2	5.2	68.3
CES-D Depression Score	10.8	8.1	0.0	46.0

Appendix B (Time-lag correlation analysis)

Supplementary time-lag graphs of blood parameters and HRV measurements are included below.

Red blood cells, hemoglobin, and hematocrit

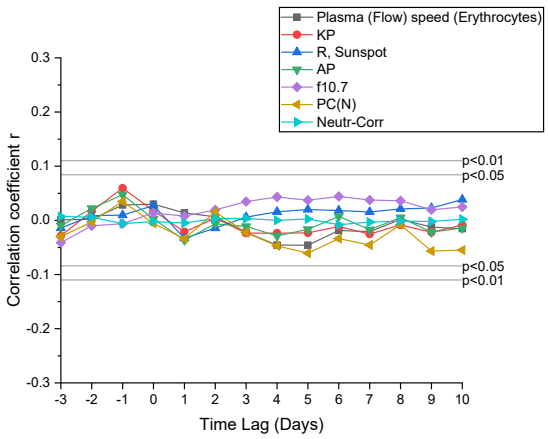

Figure 34: Erythrocytes (RBC) [exp 12/l] correlations time-lag analysis

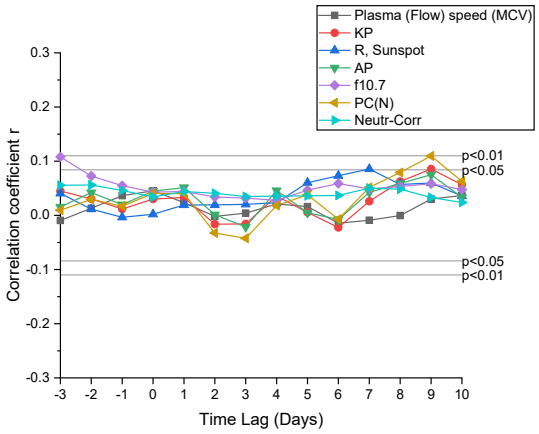

Figure 35: MCV correlations time-lag analysis

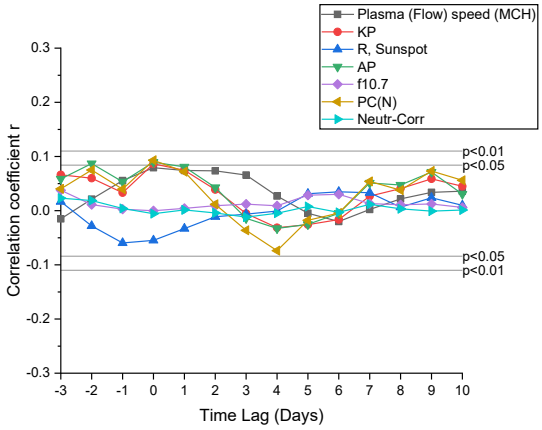

Figure 36: MCH correlations time-lag analysis

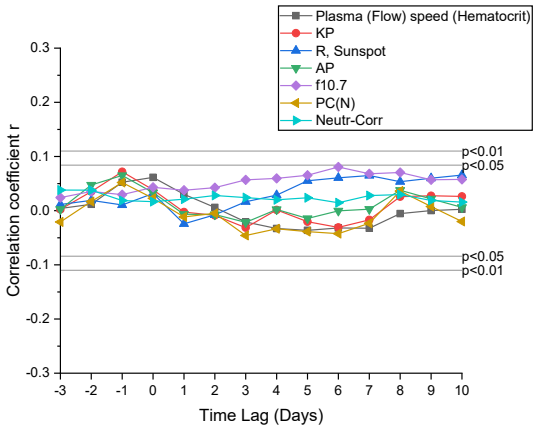

Figure 37: Hematocrit correlations time-lag analysis

White blood cells

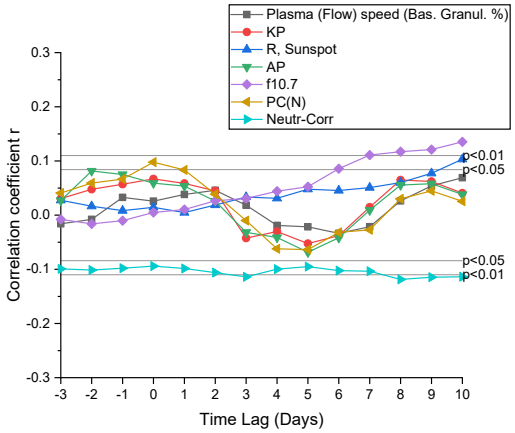

Figure 38: Basophile Granulocytes % correlations time-lag analysis

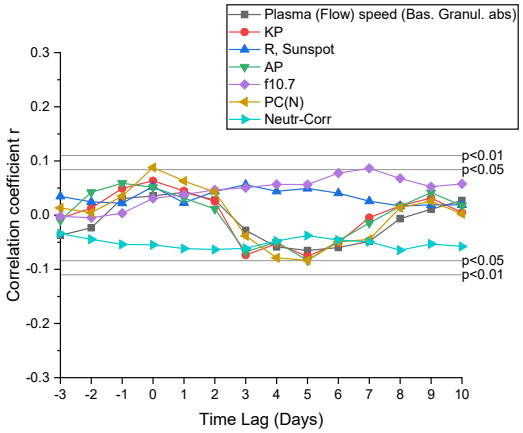

Figure 39: Basophile Granulocytes [exp 9/l] correlations time-lag analysis

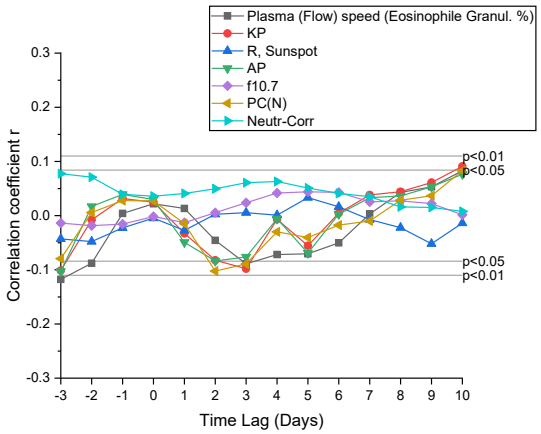

Figure 40: Eosinophile Granulocytes [%] correlations time-lag analysis

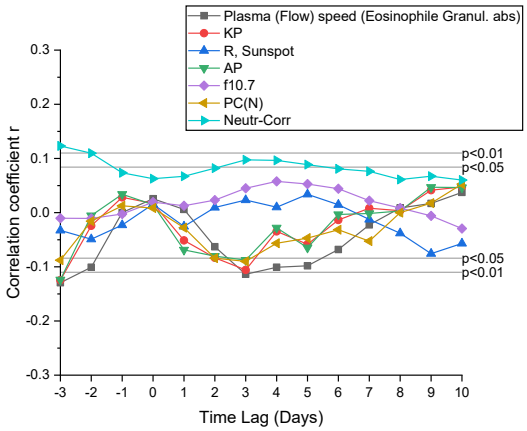

Figure 41: Eosinophile Granulocytes [exp 9/l] correlations time-lag analysis

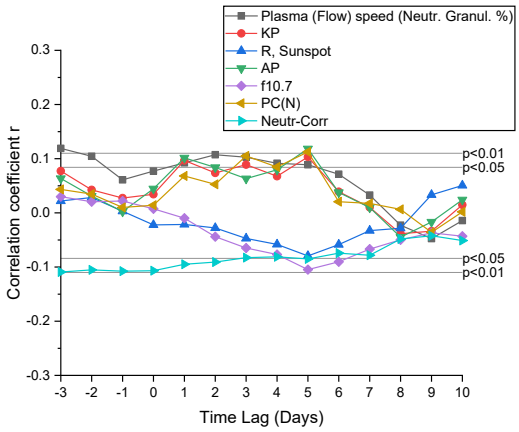

Figure 42: Neutrophile Granulocytes [%] correlations time-lag analysis

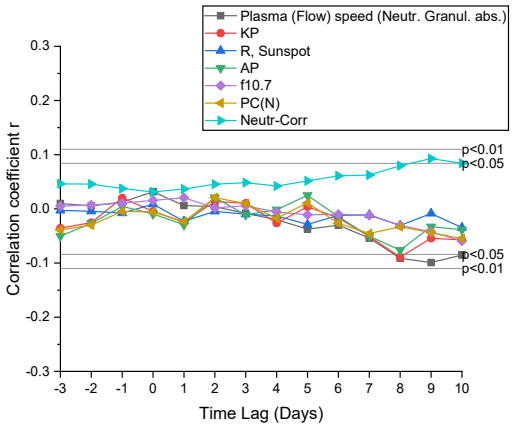

Figure 43: Neutrophile Granulocytes [exp9/l] correlations time-lag analysis

Lipid panel

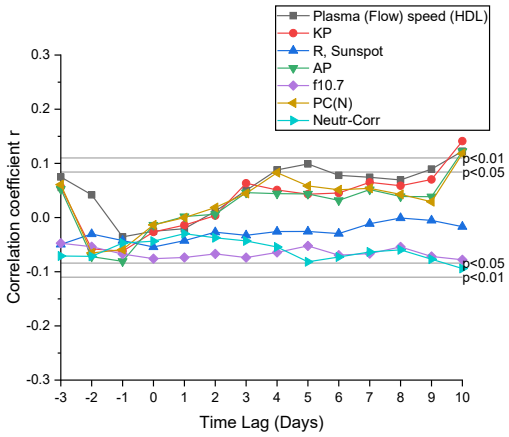

Figure 44: HDL-Cholesterol [mmol/l] correlations time-lag analysis

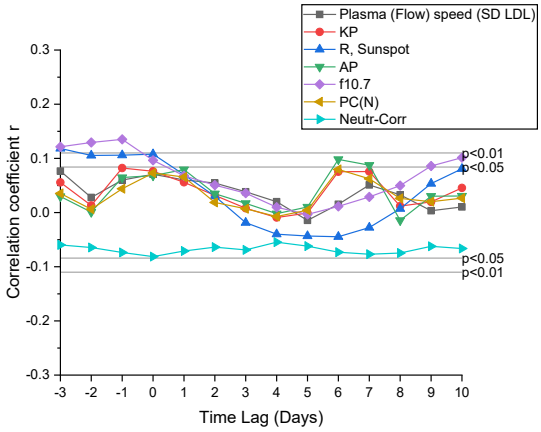

Figure 45: Small dense LDL (Denka Saike) [mmol/l] correlations time-lag analysis

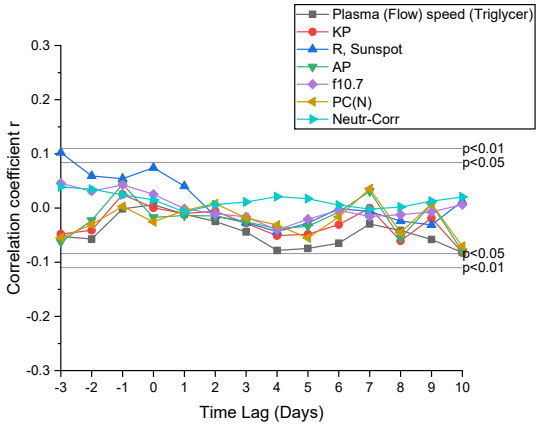

Figure 46: Triglyceride [mmol/l] correlations time-lag analysis

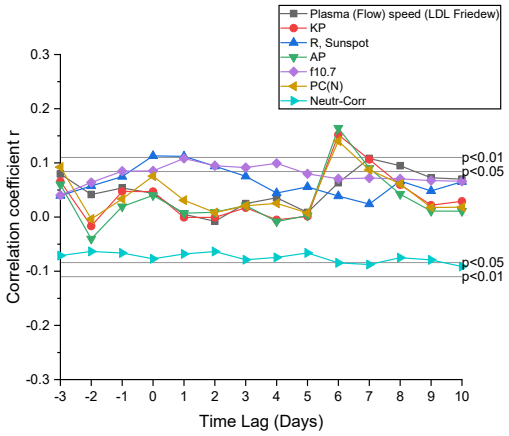

Figure 47: LDL-Cholesterol (Friedewald) [mmol/l] correlations time-lag analysis

Inflammation parameters

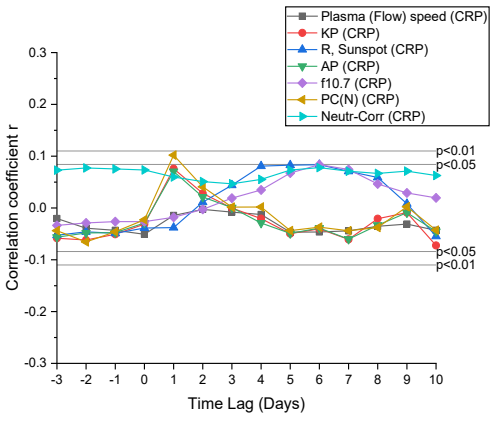

Figure 48: CRP [mg/l] correlations time-lag analysis

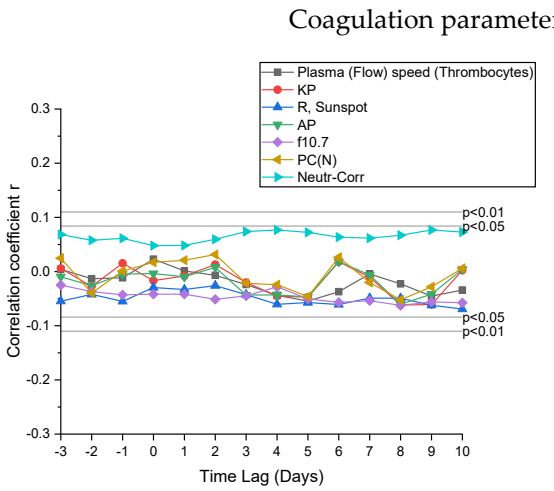

Figure 49: Thrombocytes (PLT) [exp 9 /l] correlations time-lag analysis

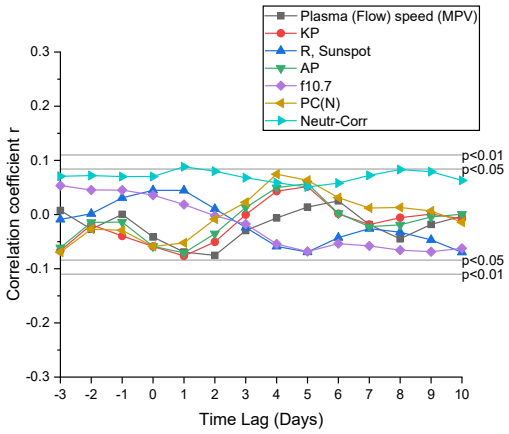

Figure 50: MPV correlations time-lag analysis

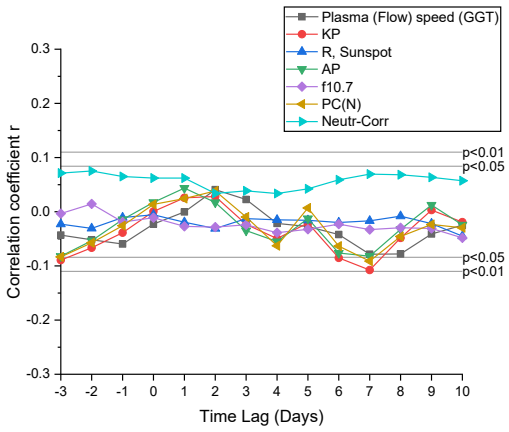

Figure 51: GGT [ukat/l] correlations time-lag analysis

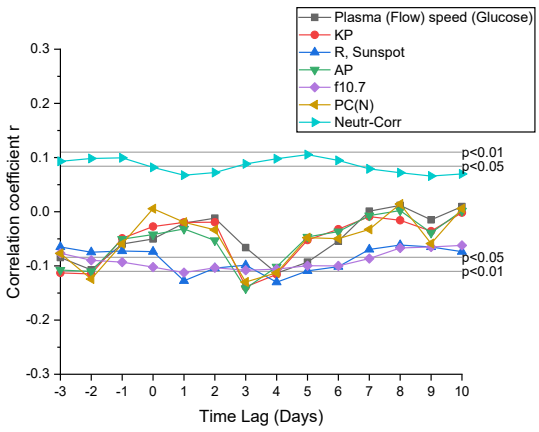

Figure 52: Glucose [mmol/l] correlations time-lag analysis

Heart Rate Variability (HRV)

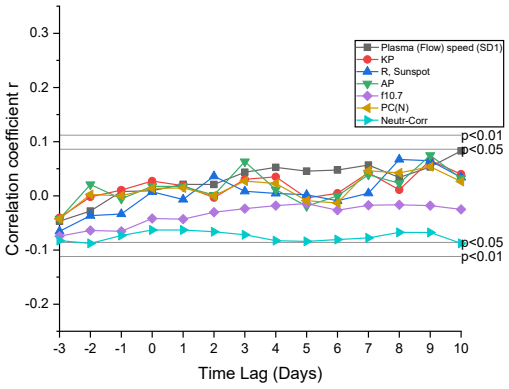

Figure 53: SD1 correlations time-lag analysis

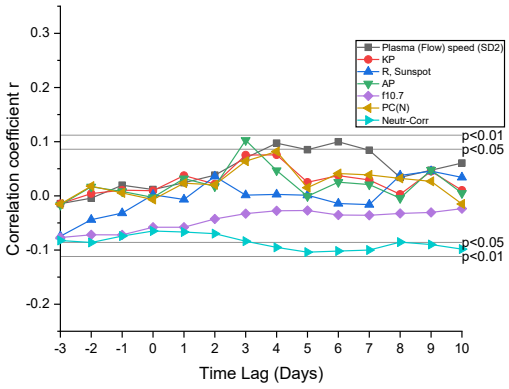

Figure 54: SD2 correlations time-lag analysis

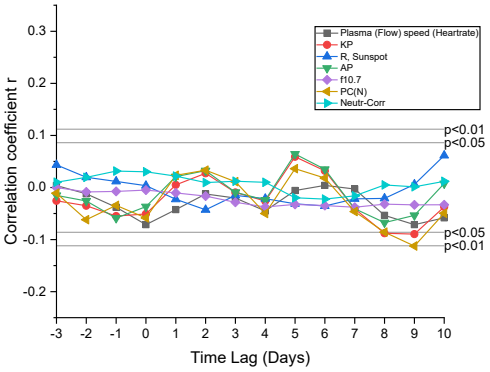

Figure 55: Heartrate (ECG) correlations time-lag analysis

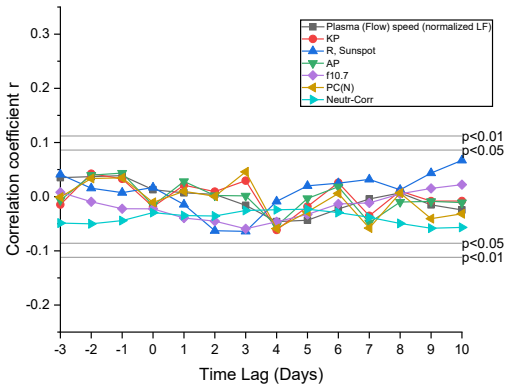

Figure 56: Normalized LF correlations time-lag analysis

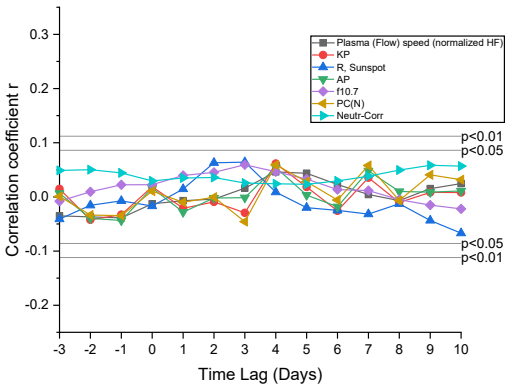

Figure 57: Normalized HF correlations time-lag analysis

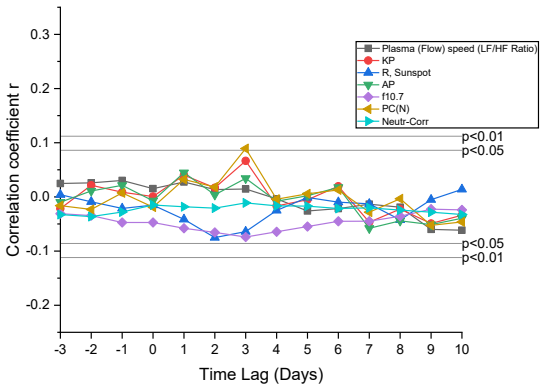

Figure 58: LF/HF Ratio correlations time-lag analysis

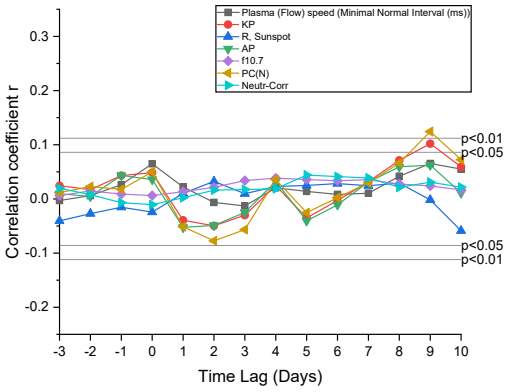

Figure 59: Minimal Normal Interval (ms) correlations time-lag analysis

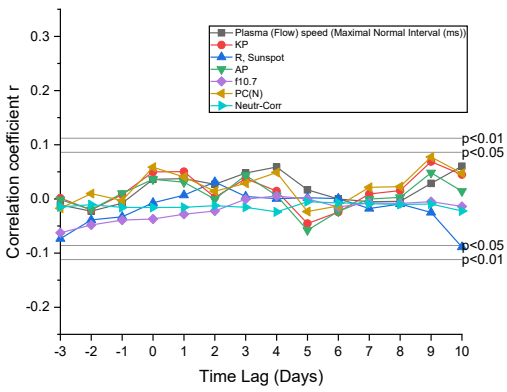

Figure 60: Maximal Normal Interval (ms) correlations time-lag analysis

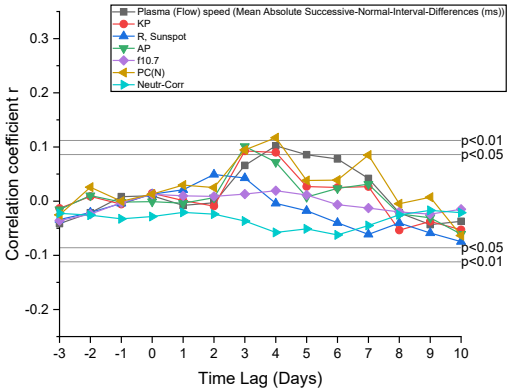

Figure 61: Mean Absolute Successive-Normal-Interval-Differences (ms) correlations time-lag analysis

Appendix C (Medical Subgroups)

Supplementary subgroups` analysis is included below

White blood cells

Table 14: Monocytes [%] medical subgroups' correlations significance compared. P-values with 3σ significance and above are highlighted

PARAMETER: MONOZYTES [%] TIMELAG (D): 6

SUBGROUP	Plasma speed	KP	AP	PC(N)	Neutron Count
COMPLETE	**1.76E-04**	1.02E-02	1.95E-02	3.57E-02	**1.05E-03**
AGEGROUP 1	6.92E-02	4.68E-01	5.87E-01	5.87E-01	4.55E-02
AGEGROUP 2	**1.68E-03**	1.72E-01	1.18E-01	2.41E-01	**8.36E-04**
AGEGROUP 3	1.08E-01	1.00E+00	5.37E-02	3.65E-02	5.22E-01
MALE	**6.20E-03**	1.42E-01	9.30E-02	1.42E-01	**3.18E-03**
FEMALE	**6.50E-04**	7.25E-02	1.11E-01	2.32E-01	4.59E-02
NO MEDICATION	**9.90E-03**	3.95E-01	6.27E-01	2.73E-01	**3.19E-04**
STROKE/MI	6.48E-02	2.50E-01	3.01E-01	8.19E-01	4.22E-01
HYPERTENSION	**6.70E-04**	4.20E-02	4.20E-02	1.76E-01	1.28E-02
KSK LOW	**7.79E-05**	**1.88E-03**	**1.88E-03**	2.30E-02	3.89E-02
KSK HIGH	1.66E-02	6.91E-01	6.91E-01	4.26E-01	**5.14E-03**
PSK LOW	2.43E-02	3.07E-01	2.20E-01	1.00E+00	1.53E-01
PSK HIGH	**1.15E-04**	1.54E-02	1.54E-02	**4.66E-03**	**2.62E-04**
DEPRESSION	3.88E-01	6.32E-01	7.02E-01	3.88E-01	9.24E-01

Table 15: Lymphocytes [%] medical subgroups' correlations significance compared. P-values with 3σ significance and above are highlighted

PARAMETER: LYMPHOZYTES [%] TIMELAG (D): 6

SUBGROUP	f10.7
COMPLETE	1.02E-02
AGEGROUP 1	2.76E-01
AGEGROUP 2	1.18E-01
AGEGROUP 3	**3.65E-03**
MALE	2.08E-01
FEMALE	2.80E-02
NO MEDICATION	1.00E+00
STROKE/MI	2.50E-01
HYPERTENSION	**3.24E-03**
KSK LOW	9.88E-
KSK HIGH	1.11E-01
PSK LOW	1.02E-01
PSK HIGH	3.14E-01
DEPRESSION	7.74E-01

Table 16: Lymphocytes [EXP 9/l] medical subgroups' correlations significance compared. P-values with 3σ significance and above are highlighted

PARAMETER: LYMPHOZYTES [EXP 9/L] TIMELAG (D): 6

SUBGROUP	Neutron Count
COMPLETE	1.95E-02
AGEGROUP 1	1.08E-02
AGEGROUP 2	7.86E-02
AGEGROUP 3	3.36E-01
MALE	3.56E-02
FEMALE	1.65E-02
NO MEDICATION	1.80E-01
STROKE/MI	8.19E-01
HYPERTENSION	**3.24E-03**
KSK LOW	9.88E-02
KSK HIGH	**5.14E-03**
PSK LOW	1.02E-01
PSK HIGH	8.41E-01
DEPRESSION	3.38E-01

Lipid panel

Table 17: Cholesterol medical subgroups' correlations significance compared. P-values with 3σ significance and above are highlighted

PARAMETER: CHOLESTEROL TIMELAG (D): 6

SUBGROUP	KP	AP	PC(N)
COMPLETE	**1.05E-03**	**1.76E-04**	**1.05E-03**
AGEGROUP 1	2.04E-01	6.92E-02	1.02E-01
AGEGROUP 2	2.41E-01	7.86E-02	1.18E-01
AGEGROUP 3	1.00E+00	1.57E-02	**3.65E-03**
MALE	**5.87E-02**	**1.16E-02**	1.42E-01
FEMALE	2.71E-01	2.71E-01	4.30E-02
NO MEDICATION	8.08E-01	2.23E-01	8.08E-01
STROKE/MI	**1.64E-04**	**9.86E-05**	**6.77E-04**
HYPERTENSION	1.28E-02	**6.61E-03**	1.28E-02
KSK LOW	**1.88E-03**	**9.07E-04**	**9.07E-04**
KSK HIGH	1.00E+00	4.26E-01	4.26E-01
PSK LOW	3.07E-01	2.20E-01	6.57E-02
PSK HIGH	4.38E-02	**8.65E-03**	1.54E-02
DEPRESSION	5.03E-01	9.24E-01	6.32E-01

Table 18: LDL-Cholesterol. medical subgroups' correlations significance compared. P-values with 3σ significance and above are highlighted

PARAMETER: LDL TIMELAG (D): 6

SUBGROUP	KP	AP	PC(N)
COMPLETE	**6.65E-05**	**7.96E-06**	**4.42E-04**
AGEGROUP 1	6.92E-02	1.80E-02	1.02E-01
AGEGROUP 2	7.86E-02	3.14E-02	1.18E-01
AGEGROUP 3	1.00E+00	**3.65E-03**	**1.21E-03**
MALE	**3.18E-03**	**3.31E-04**	5.87E-02
FEMALE	1.42E-01	1.42E-01	4.30E-02
NO MEDICATION	2.23E-01	3.75E-02	7.16E-01
STROKE/MI	**6.77E-04**	**4.29E-04**	**1.05E-03**
HYPERTENSION	**3.24E-03**	**1.51E-03**	2.38E-02
KSK LOW	**7.79E-05**	**7.79E-05**	**7.79E-05**
KSK HIGH	4.26E-01	1.11E-01	4.26E-01
PSK LOW	6.57E-02	2.43E-02	2.43E-02
PSK HIGH	**8.65E-03**	**1.20E-03**	**8.65E-03**
DEPRESSION	5.66E-01	7.02E-01	5.03E-01

Table 19: APO B medical subgroups' correlations significance compared. P-values with 3σ significance and above are highlighted

PARAMETER: TIMELAG (D):
APO B 6

SUBGROUP	KP	AP	f10.7
COMPLETE	1.95E-02	**5.03E-03**	**1.05E-03**
AGEGROUP 1	2.04E-01	6.92E-02	5.87E-01
AGEGROUP 2	5.58E-01	2.41E-01	7.86E-02
AGEGROUP 3	1.00E+00	1.49E-01	1.57E-02
MALE	2.08E-01	5.87E-02	5.87E-02
FEMALE	7.14E-01	7.14E-01	**5.65E-03**
NO MEDICA-TION	4.66E-01	1.13E-01	2.23E-01
STROKE/MI	1.06E-02	1.06E-02	4.91E-01
HYPERTEN-SION	1.14E-01	1.14E-01	**6.70E-04**
KSK LOW	**7.15E-03**	1.31E-02	**3.75E-03**
KSK HIGH	6.91E-01	5.51E-01	2.32E-01

Table 20: APO A1 medical subgroups' correlations significance compared. P-values with 3σ significance and above are highlighted

PARAMETER: APO A1 TIMELAG (DAYS): 6

SUBGROUP	R	f10.7
COMPLETE	3.51E-01	**5.03E-03**
AGEGROUP 1	8.56E-01	2.76E-01
AGEGROUP 2	3.29E-01	3.14E-02
AGEGROUP 3	1.49E-01	1.57E-02
MALE	6.75E-01	3.56E-02
FEMALE	1.00E+00	2.32E-01
NO MEDICATION	**3.19E-04**	2.23E-01
STROKE/MI	6.48E-02	8.36E-02
HYPERTENSION	1.14E-01	**6.70E-04**
KSK LOW	6.32E-02	**1.88E-03**
KSK HIGH	5.51E-01	1.63E-01
PSK LOW	5.40E-01	1.02E-01
PSK HIGH	8.41E-01	2.65E-02
DEPRESSION	5.66E-01	6.32E-01

PSK LOW	5.40E-01	3.07E-01	4.08E-02
PSK HIGH	1.59E-01	4.38E-02	6.97E-02
DEPRESSION	8.48E-01	9.24E-01	1.01E-01

Clinical Routine

Table 21: Hemoglobin A1C (%) medical subgroups' correlations significance compared. P-values with 3σ significance and above are highlighted

PARAMETER: TIMELAG (DAYS): 6

HEMOGLOBINE A1C [%]

SUBGROUP	Plasma speed	KP	AP	Neutron Count
COMPLETE	**4.03E-06**	**7.20E-03**	**8.87E-03**	**2.03E-10**
AGEGROUP 1	**1.73E-04**	6.12E-02	8.44E-02	**4.53E-08**
AGEGROUP 2	**3.47E-03**	7.21E-02	6.05E-02	**1.84E-05**
AGEGROUP 3	1.72E-02	1.00E+00	3.24E-02	2.13E-02
MALE	**4.77E-03**	8.90E-02	8.90E-02	**1.45E-03**
FEMALE	**7.49E-03**	1.74E-01	2.63E-01	**9.99E-07**
NO MEDICATION	1.02E-01	4.01E-01	3.07E-01	**8.55E-03**
STROKE/MI	2.55E-02	1.57E-01	1.53E-01	**2.41E-03**
HYPERTENSION	**6.15E-04**	9.47E-02	8.61E-02	**3.96E-08**
KSK LOW	**9.07E-07**	**3.75E-03**	**8.09E-03**	**7.21E-08**
KSK HIGH	2.97E-02	2.17E-01	1.96E-01	**1.93E-06**
PSK LOW	**1.09E-05**	**4.36E-03**	**8.71E-03**	**5.97E-07**
PSK HIGH	1.23E-02	2.95E-01	2.27E-01	**3.73E-06**
DEPRESSION	**1.44E-03**	1.31E-01	2.30E-01	**3.65E-03**

Inflammation parameters

Table 22: IL-6 medical subgroups' correlations significance compared. P-values with 3σ significance and above are highlighted

PARAMETER: IL-6 TIMELAG (D): 0

SUBGROUP	Neutron Count
COMPLETE	**5.03E-03**
AGEGROUP 1	**6.25E-03**
AGEGROUP 2	1.00E+00
AGEGROUP 3	3.36E-01
MALE	2.07E-02
FEMALE	9.81E-02
NO MEDICATION	1.13E-01
STROKE/MI	2.50E-01
HYPERTENSION	1.28E-02
KSK LOW	9.88E-02
KSK HIGH	1.00E+00
PSK LOW	4.08E-02
PSK HIGH	6.87E-01
DEPRESSION	1.49E-01

Table 23: TNF-a medical subgroups' correlations significance compared. P-values with 3σ significance and above are highlighted

PARAMETER: TNF-A TIMELAG (D): 0

SUBGROUP	R
COMPLETE	**5.03E-03**
AGEGROUP 1	5.87E-01
AGEGROUP 2	5.05E-02
AGEGROUP 3	1.08E-01
MALE	3.56E-02
FEMALE	9.81E-02
NO MEDICATION	5.43E-01
STROKE/MI	9.09E-01
HYPERTENSION	7.08E-02
KSK LOW	**7.15E-03**
KSK HIGH	8.42E-01
PSK LOW	1.40E-02
PSK HIGH	1.59E-01
DEPRESSION	6.66E-02

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