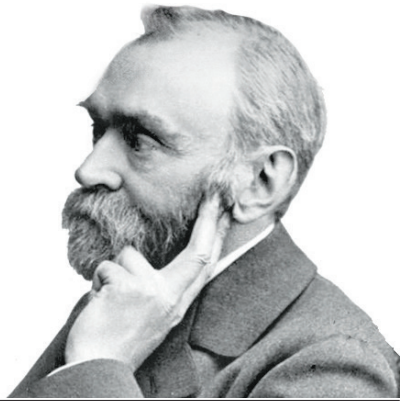
ÖREBRO UNIVERSITY'S
NOBEL DAY FESTIVITIES



BOOK OF ABSTRACTS

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Preface

The ”Nobel Day Festivities” were established 2009 by researchers within Biomedicine, Department of Clinical Medicine (now School of Health Sciences and School of Medical Sciences) at Örebro University.

Every year, the Nobel Prize in Physiology or Medicine is awarded on the 10th of December, the anniversary of Alfred Nobel's death. The School of Health Sciences and the School of Medical Sciences at Örebro University traditionally honor this day by organizing research activities and festivities. This year the festivities will take place on the 9th of December and has been switched to a virtual meeting due to the Covid-19 pandemic.

The day includes scientific activities that are open for all, such as lectures, poster presentations and selected oral presentations by doctoral students, postdocs and specially invited students. All poster presentations are documented in this Book of abstracts.

We warmly welcome you to enjoy the research that will be presented at Nobel Day Festivities 2020.

The Committee:

Editors: Programme Committee
Simon Athlin, Åsa Berglind, Karuna Dahlberg, Camilla Ehnfors, Daniel Eklund, Johanna Hulldin, Caroline Larsson, Cecilia Pettersson.

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Brachytherapy, deeper and faster than ever before

Christoffer Andersén 1), Tobias Rydén 2), Per Thunberg 1), Jakob Heydorn Lagerlöf 1,3)

1) Department of Medical Physics, Faculty of Medicine and Health, Örebro University, Örebro, Sweden
2) Department of Medical Physics and Biomedical Engineering, Sahlgrenska University Hospital, Gothenburg, Sweden
3) Department of Medical Physics, Karlstad Central Hospital, Karlstad, Sweden

Background/Aim: Brachytherapy is a radiation therapy treatment where a radioactive source is inserted through hollow needles into or near the tumor. The digitisation time for a prostate brachytherapy treatment is around 10 min which artificial intelligence could reduce to matter of seconds.

The aims of this study were to develop a 3D U-net CNN algorithm for finding needles in TRUS image volumes and to evaluate its performance in relation to manual digitisation.

Method: Transrectal ultrasound (TRUS) image volumes from 1102 treatments were used to create a clinical ground truth (CGT) including 24422 individual needles that had been manually digitised by medical physicists during brachytherapy procedures. A 3D CNN U-net with 128x128x128 TRUS image volumes as input was trained using 17215 needle examples. Predictions of voxels constituting a needle were combined to yield a 3D linear function describing the localisation of each needle in a TRUS volume. Manual and AI digitisations were compared in terms of the root-mean-square distance (RMSD) along each needle, expressed as median and interquartile range (IQR). The method was evaluated on a dataset including 7207 needle examples. A subgroup of the evaluation data set (n=188) was created, where the needles were digitised once more by a medical physicist (G1) trained in brachytherapy. The digitisation procedure was timed.

Result: The RMSD between the AI and CGT was 0.55 (IQR: 0.35-0.86) mm. In the smaller subset, the RMSD between AI and CGT was similar (0.52 [IQR: 0.33-0.79] mm) but significantly smaller ($p<0.001$) than the difference of 0.75 (IQR: 0.49-1.20) mm between AI and G1. The difference between CGT and G1 was 0.80 (IQR: 0.48-1.18) mm, implying that the AI performed as well as the CGT in relation to G1. The mean time needed for human digitisation was 10 min 11 sec, while the time needed for the AI was negligible.

Conclusion: A 3D CNN can be trained to identify needles in TRUS images. The performance of the network was similar to that of a medical physicist trained in brachytherapy. Incorporating a CNN for needle identification can shorten brachytherapy treatment procedures substantially.

POSTER 2

The effectiveness of the Standardized Course of Care – Identification of colorectal cancer in the Region Örebro County, Sweden

Emilia Andersson 1), Nils Nyhlin 2), Michiel van Nieuwenhoven 2)

1) School of Medical Sciences, Örebro University, Örebro, Sweden
2) University hospital Örebro, Division of Gastroenterology, Örebro, Sweden

Background/Aim: To shorten time to diagnosis of suspected colorectal cancer (CRC) in Sweden, a standardized course of care (SCC) was introduced in 2016. However, the effects of the SCC are still uncertain, and CRC is also found in patients undergoing a routine colonoscopy. The aim of this study was to identify all CRC-cases in the Region Örebro County and to investigate via which diagnostic pathway they were diagnosed. Furthermore, to investigate the reasons for and possible effect of not being included in the SCC-CRC for cases found via colonoscopy.

Method: Review of medical records of patients with CRC referred to the clinic of surgery in the Region Örebro County in 2016-2018 (n=459).

Result: In CRC-cases found through colonoscopy (n=347), 37.5% were diagnosed via routine waiting list and 62.5% within the SCC-CRC. No difference in tumor stage or tumor grade was found between the two groups. The non-SCC-CRC showed a longer time to diagnosis than the SCC-CRC group (21.5 days, IQR 7-43 vs. 13 days, IQR 8-17 ($p<.001$), respectively).

Non-rectal cancer was more common in the non-SCC-CRC group (81.5% vs. 57.6%, $p<.001$). The non-SCC-CRC group had lower median Hb-value (106, IQR 87-129 vs. 117, IQR 101-136, $p=.001$). 85% of the non-SCC-CRC group was found to meet one or more SCC-CRC referral criteria, with bleeding anemia being the dominant criterion to meet.

Conclusion: The SCC-CRC reduced the interval from referral to diagnosis but did not appear to improve prognostic outcomes for CRC-patients. Our results may warrant further evaluation of the benefits of the SCC-CRC.

Activation of MYC signaling in platelets from patients with myeloproliferative neoplasms with accentuation in myelofibrosis – a proteomics study

Simon Golowin 1), Maria Åström 1), Dirk Repsilber 1)

1) School of Medical Sciences, Örebro University, Örebro, Sweden

Background/Aim: The Philadelphia chromosome negative (BCR-ABL-) myeloproliferative neoplasms (MPNs) are hematological diseases arising from clonal hematopoietic stem cells. The most common BCR-ABL- MPNs are Polycythemia vera (PV), Essential thrombocythemia (ET) and Primary myelofibrosis (PMF). The transcriptome of platelets in MPNs has recently been investigated, but we are unaware of corresponding proteomic studies.

To investigate if the proteome of platelets from MPN patients is dysregulated compared to healthy controls and explore possible differences between MPN subtypes.

Method: 17 MPN patients (5 ET, 6 PV, 6 Myelofibrosis (MF)) and 11 healthy controls (C) participated. Platelets were isolated and lysed for quantitative mass spectrometry. Differences in protein levels between groups were expressed with fold changes (FC), false discovery rates (FDR, q-values) and p-values. The datasets were analyzed by Inguenity Pathway Analysis (IPA) and selected proteins were further analyzed for gene ontology enrichments.

Result: Totally 2915 proteins were successfully identified and quantitated in both patients and controls. Dysregulated protein numbers (with FC > ±1.2) in MPN vs C were 291 with $q<0.05$, 448 with $p<0.05$. XBP1, MYC, ELL2, ERN1 and NFE2L2 were predicted to be the top activated upstream regulators based on 96 downstream proteins with q and/or $p<0.05$. MYC contributed with the largest number of dysregulated downstream proteins (n = 48) and MF generally showed the largest dysregulations.

Conclusion: The proteome of platelets from MPN patients was significantly dysregulated compared to healthy controls. MYC signaling was activated in the platelet proteome of all MPN subtypes, with accentuation in MF.

Role of RSAD2 in vascular cells and its relevance for atherosclerosis

Assim Hayderi 1), Liza U Ljungberg 1), Allan Sirsjö 1)

1) Cardiovascular Research Center, School of Medical Sciences, Örebro University Sweden

Background/Aim: Vascular cells and leukocytes play an important role in several stages of atherosclerosis. Activated vascular cells secrete chemokines that facilitate the migration of specific leukocytes. The secreted chemokine profile in turn is governed by the stimulus that activates these cells. In response to viral antigens, vascular cells secrete interferons, which induce the expression of interferon stimulated genes (ISGs), including RSAD2.

RSAD2 was discovered in 2001 as an antiviral protein with a low basal expression in all cells. Its expression is strongly induced by viruses, both via interferon stimulation and directly by the virus, independent of interferons. Olofsson and colleagues reported RSAD2 in endothelium of carotid plaques but not healthy renal arteries. Immunostaining of carotid plaques from our lab indicates RSAD2 to be expressed not only in endothelial but also macrophages and SMCs, which raises the questions of what its role in these cells is and whether it contributes to atherosclerosis.

Method: To investigate the possible role of RSAD2 in vascular cells, we used the siRNA approach to silence RSAD2 in SMCs prior to stimulation with interferon gamma and analysis of secreted proteins.

Result: Among the roughly 200 secreted proteins, CCL3, CXCL9, CXCL10 and CXCL11 were reduced by RSAD2 knockdown. The reduction in CXC-motif chemokines but not CCL3 was confirmed by qRT-PCR and ELISA.

Conclusion: RSAD2 regulates the expression of CXC-motif chemokines, which upon interaction with CXCR3 and CCR5 are believed to be important for chemotaxis of activated T lymphocytes. Thus studying the mechanism by which RSAD2 regulates the expression of these specific set of chemokines and whether a reduction in the levels of these chemokines by RSAD2 knockdown affects the recruitment of leukocytes in vitro may give us important information about its role in atherosclerosis.

References: Olofsson, P. S., Jatta, K., Wagsater, D., Gredmark, S., Hedin, U., Paulsson-Berne, G., ... & Sirsjo, A. (2005). The antiviral cytomegalovirus inducible gene 5/viperin is expressed in atherosclerosis and regulated by proinflammatory agents. *Arteriosclerosis, thrombosis, and vascular biology*, *25*(7), e113-e116.

Altered serum protein levels in inflammatory bowel disease: A baseline, cross-sectional comparison between patients with inflammatory bowel disease, symptomatic and healthy controls

William Kalina 1), Jonas Halfvarson 1,2)

1) School of Medical Sciences, Örebro University, Örebro, Sweden
2) Department of Gastroenterology, Faculty of Medicine and Health, Örebro University, Örebro, Sweden

Background/Aim: Inflammatory bowel disease (IBD) is characterised by chronic inflammation in the gastrointestinal tract and a heterogenous disease course. Establishing diagnosis and prognostic stratification is a continuous challenge, and there is a need for novel biomarkers to aid clinical decision making. Within an inception cohort consisting of treatment-naïve patients, we aimed to identify serum proteins associated with IBD by the Proximity Extension Assay (PEA) method and explore their diagnostic and prognostic properties.

Method: Prospective, multi-centre case-control study of patients with incident IBD, symptomatic controls and healthy controls. Disease course events were captured by journal review. Minimum follow-up was 2 years. Levels of clinical markers (C-reactive protein, f-Calprotectin, albumin) and relative abundance of 184 serum proteins was determined at baseline, assessed by univariate analysis with false discovery rate. Individual diagnostic and prognostic performance was assessed by probability of superiority.

Result: 227 patients with incident IBD (95 Crohn's disease, 132 ulcerous colitis), 107 symptomatic- and 48 healthy controls were included. 26 proteins were differentially regulated between IBD patients and healthy controls; diagnostic capability of top performers was equal to that of clinical markers. 13 proteins were differentially regulated between IBD and symptomatic controls; none equalled f-Calprotectin in diagnostic capability. IL-6, IL-24 were up-regulated in IBD patients with poor disease course.

Conclusion: We go beyond the previous literature and identify several serum proteins as significantly differentially regulated at baseline comparing treatment-naive incident IBD patients to controls and, to a lesser extent, along future disease course. We propose several candidates in the serum proteome for multivariate analysis and evaluation of combined diagnostic performance.

Validation of the Brief ICF core set for hearing loss

Elin Karlsson 1,2,3), Elina Mäki-Torkko 1,2,4) Stephen Widén 1,2,3), Johanna Gustafsson 1,2,3), Vinaya Manchaiah 5), Faheema Mahomed- Asmail 6), De Wet Swanepoel 6), Krishna Yerraguntla 7), Sarah Granberg 1,2,3)

1) Audiological Research Centre, Örebro University Hospital, Sweden
2) School of Health Sciences, Örebro University, Sweden, 3) Swedish Institute of Disability Research (SIDR), 4) School of Medical Sciences, Örebro University, Sweden, 5) Department of Speech and Hearing Sciences, Lamar University, Beaumont, TX, USA, 6) Department of Speech-Language Pathology and Audiology, University of Pretoria, 7) Department of Speech and Hearing, Manipal College of Health Professions, Manipal, India

Background/Aim: The international classification of functioning disability and health (ICF) is a classification with a bio-psycho-social approach to functioning and disability and health. To make the classification more easy to use, ICF core sets for specific health conditions are developed. The ICF core sets for hearing loss was developed in 2012 but are not yet validated, which is the final step when developing core sets. The aim of the study is to test the psychometric aspects content validity and construct validity of the Brief ICF core set for hearing loss.

Method: The study is a qantitative international validations study. Adults (≥ 18 years) with verified hearing loss were recruited from clinical populations in India, South Africa, Sweden and US. Structured interviews were performed using the Brief ICF core set and the participants rated their functioning according to ICF-standard 0-5, (zero meaning no problem). Descriptive statistics and explorative factor analysis was used.

Result: The result of the explorative factor analysis shows a five factor structure, explaining 67.13 of the variance. Only one category, d820 school education, did not fit the model. Cronbach's alpha was 0.98. The category d820 school education was not relvenat for 95.6 percent, followed by remunitive empolyment (60.7%), sensations associated with hearing and vestibular function (34.8%), products and technology for communication (27.1%) and community life (19.2%). All respons options (0-5) were used for all categories, except from d820 school education. For most categories, there are no differences in the ratings of functioning or disability between the people with hearing loss regarding the variables degree of hearing loss, sex or age.

Conclusion: The categories of the Brief ICF core set seem to be valid internationally. The category d820 school education is a bit problematic. Thus, we suggest the use of a higher level ICF definition instead, in order to broaden the definition to include higher education. This study contributes to the validation of ICF core sets for hearing loss and confirms the content and construct validity. The core set is valid to use in hearing rehabilitation and research. Further validation studies of the comprehensive core set and in other contexts are still needed.

Prevalence, diagnoses and rehabilitation services related to severe dual sensory loss (DSL) in older persons: a cross-sectional study based on medical records

Elin Lundin 1), Stephen E. Widén 1), Moa Wahlqvist 1), Agneta Anderzén-Carlsson 2), Sarah Granberg 1)

1) School of Health Sciences, Örebro University, Örebro, Sweden and Swedish Institute for Disability Research

2) University Health Care Research Centre and Swedish Institute for Disability Research, Örebro University, Örebro, Sweden

Background/Aim: Worldwide, in the nearest decades, individuals aged 65 years or older will increase substantially. With increasing age, the risk of developing concurring hearing- and vision loss, defined as dual sensory loss (DSL) increases. No consensus of how to define DSL exists, this means that it is difficult to compare the prevalence of DSL between studies. Few studies have described which diagnoses are involved in DSL, and about rehabilitation services for older person with DSL. Therefore, the aim was to estimate the prevalence of severe DSL among older adults. The aim was further to identify the diagnoses involved in severe DSL, and to identify rehabilitation services in which the participants have been involved in.

Method: A cross-sectional study design was applied. Primary source were medical records. The participants were aged ≥65 years, resided in two counties in Sweden and fulfilled objective standardized measurements for severe DSL. 1257 individuals fulfilled the criteria for severe HL (pure tone average [PTA4] for the frequencies 0.5, 1, 2, and 4 kHz, ≥70 dB HL in the better ear) and out of those, 101 individuals also fulfilled the criteria for VL (visual acuity ≤0.3 for distance in the best eye with best correction).

Result: In the two counties, the prevalence of severe DSL was 0.08%. Within the group (n=101), 71% were aged ≥85 years and no statistical significant differences between women and men were found. In a subset of the sample (n=21), the primary diagnoses for VL were cataract and/or age-related macular degeneration (AMD) in combination with sensorineural HL. The rehabilitation services were focusing mainly on different devices and interventions to facilitate activities of daily living.

Conclusion: Despite difficulties to compare the prevalence between studies, this study confirmed previous results, indicating that the prevalence of severe DSL increases with age and that sensorineural HL coexist with AMD, cataract and glaucoma. In the subset of the sample, the identified rehabilitation services focused mainly on either the person's HL or VL, not on DSL as a complex health condition.

Risk of extrahepatic cancer in a nationwide cohort of HCV infected persons treated with direct acting antivirals

Charlotte Lybeck 1)*, Daniel Bruce 2), Scott M Montgomery 3,4,5), Soo Aleman 6,7)†, Ann-Sofi Duberg 1)†

1) Department of Infectious Diseases, Faculty of Medicine and Health, School of Medical Sciences, Örebro University, Örebro, Sweden.
2) Scandinavian Development Services, Stockholm, Sweden.
3) Clinical Epidemiology and Biostatistics, School of Medical Sciences, Örebro University, Örebro, Sweden.
4) Clinical Epidemiology Division, Karolinska Institutet, Stockholm, Sweden.
5) Department of Epidemiology and Public Health, University College London, London, UK.
6) Department of Infectious Diseases, Karolinska Institutet, Stockholm, Sweden.
7) Department of Gastroenterology and Hepatology, Karolinska Institutet, Stockholm, Sweden.
† Equally shared last authorship.

Background/Aim: Recent data have indicated an increased risk for extrahepatic cancer (EHC) in the era of direct acting antivirals (DAAs) against HCV. We therefore aimed to assess the risk of EHC following DAA treatment compared with the risk in interferon (IFN)-treated and untreated persons with HCV, and with a matched general population cohort without HCV.

Method: This is a nationwide cohort study with prospectively collected data for 19,685 persons with HCV, 4,013 DAA-treated, 3,071 IFN-treated and 12,601 untreated, from 2008-2016. The general population cohort consisted of 35,650, 28,905 and 117,900 individuals matched to the DAA-group, IFN-group and untreated group, respectively. Follow-up time was maximum three years. The risk for EHC was compared between the groups using Cox regression analyses, with adjustment for age and Charlson Comorbidity Index (CCI).

Result: In total 341 EHCs were identified, 84, 43 and 214 EHC in the DAA-, IFN- and untreated group, respectively. The EHC risk in DAA-treated compared with IFN-treated was doubled, but when adjusted for age and CCI the HR was 1.07 (95% CI 0.74-1.56). Compared with general population, the HR of EHC for the DAA-group was 1.45 (CI 1.13-1.86), with the difference remaining statistically significant after adjusting for CCI.

Conclusion: We found no increased risk for EHC associated with DAA-therapy when adjusted for age and CCI. An increased risk of EHC in DAA-treated compared with general population was though seen, and attention should be paid to this risk in the aging population with a history of HCV infection.

Carbohydrate restriction following strenuous glycogen-depleting exercise does not potentiate the acute molecular response associated with mitochondrial biogenesis in human skeletal muscle

Catarina Ramos 1), Arthur J. Cheng 2,3), Sigitas Kamandulis 4), Andrejus Subocius 4,5,6), Marius Brazaitis 4), *Tomas Venckunas 4), *Thomas Chaillou 1)

1) School of Health Sciences, Örebro University, Örebro, Sweden, 2) Department of Physiology and Pharmacology, Karolinska Institutet, 171 77 Stockholm, Sweden, 3) Muscle Health Research Centre, School of Kinesiology and Health Sciences, Faculty of Health, York University, M3J 1P3 Toronto, Canada, 4) Sports Science and Innovation Institute, Lithuanian Sports University, 44221 Kaunas, Lithuania, 5) Department of Surgery, Kaunas Clinical Hospital, 47144 Kaunas, Lithuania, 6) Clinic of Surgery, Republican Hospital of Kaunas, 45130 Kaunas, Lithuania

Background/Aim: Carbohydrate (CHO) restriction could be a potent metabolic regulator of endurance exercise-induced muscle adaptations. Here, we determined whether post-exercise CHO restriction following strenuous exercise combining continuous cycling exercise (CCE) and sprint interval exercise could affect the gene expression related to mitochondrial biogenesis and oxidative metabolism in human skeletal muscle.

Method: In a randomized cross-over design, 8 recreationally active males performed two cycling exercise sessions separated by 4 weeks. Each session consisted of 60-min CCE and six 30-s all-out sprints, which was followed by ingestion of either a CHO or placebo beverage in the post-exercise recovery period. Muscle glycogen concentration and the mRNA levels of several genes related to mitochondrial biogenesis and oxidative metabolism were determined before, immediately after, and at 3 h after exercise.

Result: Compared to pre-exercise, strenuous cycling led to a severe muscle glycogen depletion (> 90%) and induced a massive increase in PGC1A and PDK4 mRNA levels (~ 20 fold and ~ 10 fold, respectively) during the acute recovery period in both trials. The abundance of the other transcripts was not changed or was only moderately increased during this period. CHO restriction during the 3-h post-exercise period blunted muscle glycogen resynthesis but did not increase the mRNA levels of genes associated with muscle adaptation to endurance exercise, as compared with abundant post-exercise CHO consumption.

Conclusion: CHO restriction after a glycogen-depleting and metabolically-demanding cycling session is not effective for increasing the acute mRNA levels of genes involved in mitochondrial biogenesis and oxidative metabolism in human skeletal muscle.

INTRA-INDIVIDUAL VARIABILITY IN INTESTINAL PERMEABILITY IN IBS-D PATIENTS

M. Fernanda Roca Rubio 1), Richard A. Forsgård 1), Julia Rode 1), Robert J. Brummer 1), Julia König 1)

1) Nutrition-Gut-Brain Interactions Research Centre, School of Medical Sciences, Örebro University, Örebro, Sweden

Background/Aim: Increased intestinal permeability has been associated with several diseases and disorders including irritable bowel syndrome (IBS), a common gastrointestinal disorder defined by abdominal pain and altered bowel habits. IBS is further divided into three subtypes based on stool consistency: diarrhoea-predominant (IBS-D), constipation-predominant or a mix of those. About 40% of the patients with IBS-D have been shown to have an increased intestinal permeability. However, it is not known how this varies over time within the same patient. Therefore, we aimed to investigate the intra-individual variation in intestinal permeability in IBS-D patients.

Method: A total of 29 IBS-D patients (12 males, 17 females; age 37±12 years) underwent two visits three weeks apart. Intestinal permeability was assessed by a multi-sugar urinary recovery test. Lactulose/rhamnose ratio in 0-5h urine measured small intestinal permeability. Sucralose/erythritol in 5-24h urine indicated colonic permeability. Blood and saliva were also collected for the analysis of biomarkers relating to intestinal permeability, stress and inflammation. In addition, the study subjects were asked to fill out questionnaires about their gastrointestinal symptoms and quality of life. Awakening cortisol response was computed as an area under the curve. The intra-individual coefficient of variation (CV) was used as a measure of variability. Data are reported as the mean percentage CV.

Result: The average intra-individual variation in small intestinal permeability was 25.8%. Colonic permeability showed a variation of 18.8%. The awakening cortisol response had a CV of 15%. Intra-individual variation on intestinal fatty acid-binding protein was 26.4%. Lipopolysaccharide binding protein had a variation of 11.5%. Variation of C-reactive protein was 44.7%. All questionnaire data is currently being analyzed.

Conclusion: These preliminary data show that there appears to be intra-individual variations in intestinal permeability measurements, which should be taken into account when designing permeability assays. Whether this variability concerns specifically IBS-D patients or if it is also present in a healthy cohort should be evaluated in future studies.

In-depth characterisation of healthy subjects to reveal biosignatures related to serotonergic stimulation

Julia Rode 1), Julia König 1), Rebecca Wall 1), Ashley N Hutchinson 1), M Fernanda Roca Rubio 1), Robert Jan Brummer 1)

1) School of Medical Sciences, Örebro University, Örebro, Sweden

Background/Aim: Serotonin is one of the key neurotransmitters of the gut-brain axis, acting both in the enteric as well as the central nervous system. Alterations of the serotonin signalling system are known to play a role in the development of gastrointestinal and psychological symptoms in disorders such as irritable bowel syndrome (IBS). In order to better understand the pathophysiological changes of the serotonergic system in IBS, we are currently performing a study to examine the response of subjects with, and without, IBS to serotonergic stimulation. As part of this study, we included healthy subjects and carefully characterised them at baseline.

Method: 20 healthy subjects (aged 18-65 years, male and female) were included in the study and the results of 13 of those have been used for an interim analysis. Subjects' general health, quality of life, gastrointestinal and psychological symptoms have been assessed by validated questionnaires, among other baseline parameters. Subsequently, subjects' brain response to different task was assessed in different serotonergic states.

Result: Quality of life was with 84.8 ± 9.9% generally high. Similar results were found for IBS-related quality of life with 95.4 ± 3.2 %. Gastrointestinal health was in general good. Subjects reported only minor gastrointestinal symptoms (assessed by gastrointestinal symptom rating scale for IBS) with a total score of 16.7 ± 5.5 (minimum possible score: 13, maximum: 91). Ratings on symptom subscores were low with a small in-between subject variation only. The visceral sensitivity index was good with 88.8 ± 2.2 (best possible score: 90). Psychological health was also good. Subjects reported low stress levels with 9.5 ± 5.1 (assessed by perceived stress scale, cut-off < 14). Anxiety and depression ratings were low. Subjects had a total score of 5.0 ± 4.0 on the Hospital Anxiety and Depression Scale with 3.9 ± 3.5 on the anxiety subscore and 1.1 ± 1.0 on the depression subscore, respectively (cut-off < 8 for each of the two subscores). Similarly, subjects rated low on the Montgomery Åsberg Depression Rating Scale (3.6 ± 2.7, cut-off < 13). Results for the State-Trait Anxiety Inventory were 29.8 ± 8.9 and 29.7 ± 7.8 for subscale Y1 and Y2, respectively (minimum possible score: 20, maximum: 80, for each subscore).

Conclusion: Healthy subjects included in the study showed a good general health, high quality of life and low gastrointestinal and psychological symptoms as expected and can therefore be regarded as an adequate reference group.

The Desire to Move to a Nursing Home: Experiences of People Ageing in Place

Lisa Spang 1), Liselotte Hermansson 1,2), Marie Holmefur 1) Kajsa Lidström Holmqvist 2)

1) School of Health Sciences, Örebro University, Örebro, Sweden
2) University Health Care Research Center, Faculty of Medicine and Health, Örebro University, Sweden

Background/Aim: To age and remain living in ordinary housing is called aging in place (1). To support aging in place in Sweden, older people can receive home health care and apply for home-based care for assistance with self care and services such as Meals on Wheels or response alarm. Despite this support, the municipalities receive applications to nursing homes on a daily basis, which indicates that aging in place does not fill everyone's needs. The aim of this study was to describe the daily life experiences that influence people who age in place to apply to a nursing home.

Method: This study has a descriptive design. Face to face interviews were conducted with older people with declining physical health who had a granted application for a place in a nursing home and were waiting for a placement. Interviews were analyzed by qualitative content analysis according to Elo and Kyngäs (2).

Result: One main category emerged - "To maintain control of my life". It was characterized by a feeling of decreasing level of independence which led to experiences of lack of social context or being in a state of dependence where someone else controlled decisions of their lives. The participants had reached a point where they strongly felt that something has to be done to change their situation. This was usually associated with a critical event such as a hospitalization or after been informed of a cancer diagnosis. These experiences are described by three generic categories with seven subcategories. The generic categories are "A state of dependence", "The opportunity to belong to a context" and "Reaching a turning point".

Conclusion: The findings show that a feeling of lost control due to perceived dependence, falling health or critical everyday life events may lead to a nursing home application. Therefore, in order to enhance aging in place it is important to enable older people to be socially involved, get support to stay as independent as possible in their daily activities and to handle critical events such as hospitalization.

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Roles of ESCRT proteins during intracellular flavivirus infection

Pham-Tue-Hung Tran 1), Magnus Johansson 1), Wessam Melik 1)

1) School of Medical Sciences, Örebro University, Örebro, Sweden

Background/Aim: The genus Flavivirus (family Flaviviridae) consists of important zoonotic viruses including mosquito-borne West Nile virus, Zika virus, Dengue virus, and tick-borne flaviviruses.

The Endosomal sorting complex required for transport (ESCRT) machinery play essential roles in multivesicular body biogenesis, in which the endosome membrane was invaginated to form vesicles inside its body. In addition, the machinery is also responsible for other functions such as the membrane abscission step in cytokinesis, generation of autophagosome, and especially budding of most membrane enveloped viruses (1). In this project, we aim to study roles of ESCRT proteins at stages during host cell infection by flaviviruses and to characterize the modes of interactions between ESCRT proteins and flaviviral proteins.

Method: We used siRNA to knock down TSG101, ALIX, CHMP4A in A549 cells and infected these cells with flaviviruses. Cells were lyzed by repeatedly fast freezing in liquid nitrogen and thawing cycles to release intracellular viral particles. Infectious viral particles from cell culture supernatants and cell lysates and were measured by plague assay or immuno focus assay. Viral gene copy numbers were measured by qPCR. We generated stable cell lines expressing flaviviral reporter replicons to study viral replication during ESCRT depletion. We used electron microscopy to capture images of changes during ESCRT protein-depleted conditions. In addition, we used CoIP and IF microscopy to study virus-host cell protein-protein interactions.

Result: We found that the ESCRT III CHMP4A is essential for flavivirus replication, while ESCRT I TSG101 acts during viral budding. These ESCRT proteins interact with the flavivral NS3 protein and E protein.

Conclusion: In this study, we showed multifunctions of ESCRT proteins in many stages of flavivirus infection cycle. The knowledge about host cell proteins and virus proteins interactions reveal new anti-flavivial targets for future drug development.

References: (1) Hurley, J.H., *The ESCRT complexes.* Crit Rev Biochem Mol Biol, 2010. **45**(6): p. 463-87.

Regulation of cytokines in endotoxin-tolerant human monocytes ex vivo

Kristine Midtbö* 1,2), Kedeye Tuerxun* 1,2), Eva Särndahl 1,2), Alexander Persson 1,2), Robert Kruse 1,2), Daniel Eklund 1,2)

1) School of Medical Sciences, Örebro University, Örebro, Sweden
2) Inflammatory Response and Infection Susceptibility Centre (iRiSC), Faculty of Medicine and Health, Örebro University, Örebro, Sweden.
*Contributed equally

Background/Aim: Myeloid-derived suppressor cells (MDSCs) are immunosuppressive cells that arise and expand during highly inflammatory conditions, demonstrate a negative immuno-regulatory activity. MDSCs were considered involved in the pathology of certain diseases, such as cancer and sepsis. By using endotoxin-tolerance as a model of sepsis-induced MDSC-like cells, the aim of this study was to identify novel markers of MDSC activity.

Method: Primary monocytes were isolated from blood collected from anonymous healthy donors. Cells were then cultured and stimulated with 10ng/ml LPS to induce MDSC-like cells. After the second chanllenge with LPS, the supernatants were collected. A panel of 181 inflammatory markers were screened using proximity extension assay (PEA) and 16 of which were further validated by an electrochemiluminescence assy. Gene expression of five candidate transcription factors tracked from the validated markers using software application IPA (ingenuity pathway analysis) were analyzed by real-time PCR.

Result: A cytokine profile of 12 markers in total was discovered, including unique response markers of naïve monocytes (CXCL-10, IL-12p40 and CCL2) and MDSC-like cells (HGF and CXCL5), and shared response markers in both phenotypes (TNF, IL-10, CCL8, CCL4, TGF-alpha, CXCL6 and IL1alpha). Transcription factor EPAS1 was downregulated, while SPI1was upregulated in MDSC-like cells.

Conclusion: The study identified unique markers of MDSC-like cells activity after threat recognition (LPS response) and two potential transcription factors with differential expression in naïve and MDSC-like cells. The present study may contribute to the development of novel early phase markers for MDSCs activity in sepsis. Moreover, the ex vivo MDSC-like cell model established here can be used as an approach to further study the role of MDSCs in inflammation.

Developing a quantitative technique for detection of low levels of TBE virus in ticks and milk

Amélie Wallenhammar 1), Anita Koskela von Sydow 1,2), Naveed Asghar 1), Magnus Johansson 1)

1) School of Medical Sciences, Örebro University, Örebro, Sweden
2) Department of Laboratory Medicine, Örebro University Hospital, Sweden

Background/Aim: Tick distribution in Sweden has increased in recent years, with the prevalence of ticks predicted to spread towards the northern parts of the country, thus increasing the risk of tick-borne zoonoses in new regions. Tick-borne encephalitis (TBE) is the most significant viral tick-borne zoonotic disease in Europe. The disease is caused by TBE virus (TBEV) infection which often leads to severe encephalitis and myelitis in humans. Quantitative PCR (qPCR) has become the gold standard for TBEV detection, however its sensitivity has been questioned for detecting extremely low levels of TBEV. The droplet digital polymerase chain reaction (ddPCR) is a novel technology that provides absolute and direct quantification of target DNA. ddPCR have shown to yield more accurate results than qPCR and may thereby provide a more precise and reliable method for low-level quantification (1). The aim of this study is to develop a ddPCR assay for the detection of TBEV in ticks and milk samples.

Method: Ticks were homogenized followed by RNA extraction. Single-stranded cDNA was synthesized from total RNA using specific primers for TBEV. The ddPCR reaction mixtures were emulsified with droplet generator oil and loaded to a QX200 Droplet generator (Bio-Rad) for generation of droplets. The droplets were then transferred to a PCR plate and standard PCR was performed. After PCR, the droplets were analysed by the QX200 Droplet Reader (Bio-Rad). Absolute quantification and data analysis were then performed using QuantaSoft software (Bio-Rad), designed to quantify the concentration of the target and give the results in copies/ul of input sample.

Result: The optimal annealing temperature were optimized by testing a range of 55-65°C, above and below the Tm for the primers. The optimal annealing temperature were decided to 55 °C, where the largest fluorescence amplitude differences were seen between positive and negative droplets. Two positive TBEV samples were ten-fold diluted in serial between 100 ng and 0.001 ng, to estimate limit of detection. TBEV detection and viral load will be analysed in the samples.

Conclusion: The ddPCR is a method to provide a more precise and reliable method for low-level quantification of TBE virus in ticks and milk. Method optimization have been done to obtain a reliable method for sample screening.

References: (1) Hindson et al. High-throughput droplet digital PCR system for absolute quantitation of DNA copy number. *Anal Chem.* 2011;83:8604–10.

Improved time management skills after the intervention Let's Get Organized are maintained over time

Maria Wingren 1), Kajsa Lidström-Holmqvist 2), Afsaneh Hayat Roshanai 3), Patrik Arvidsson 4), Gunnel Janeslätt 3), Suzanne White 5), Marie Holmefur 1)

1) School of Health Sciences, Faculty of Medicine and Health, Örebro University, Örebro, Sweden, 2) University Health Care Research Center, Faculty of Medicine and Health, Örebro University, Örebro, Sweden, 3) Department of Public Health and Caring Sciences, Uppsala University, Uppsala, Sweden, 4) Centre for Research and Development, Region Gävleborg/ Uppsala University, Gävle, Sweden, 5) State University of New York, Downstate Medical Center, Brooklyn, New York, United States

Background/Aim: Time management skills are essential to maintain work and family life. People with impaired executive functioning often experience persistent difficulties with managing time and organizing daily life, consequently there is a need to establish interventions with sustainable results.Aim: The aim of this study was to evaluate the long-term results of the intervention Let's Get Organized (LGO-S) for people with attention deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD) or mental disorders 12 months after the intervention.

Method: The study was a 12-month follow-up of a pretest-posttest intervention study. Participants in this study were recruited from the sample participating in the earlier study of Holmefur et al. (1). Time management, organization and planning and regulation of emotions were measured with Assessment of Time Management Skills (ATMS-S), executive functioning was measured with Weekly Calendar Planning Activity (WCPA-SE), and satisfaction with daily occupations was measured with the Satisfaction with Daily Occupations instrument (SDO-13).

Result: The 38 participants in the long-term follow-up maintained their improved results in time management, organization and planning and regulation of emotions 12 months after the intervention, as well as their satisfaction with daily occupations and global satisfaction.

Conclusion: Participation in the LGO-S intervention can improve and maintain time management, organization and planning, regulations of emotions and satisfaction with daily occupations in the long term.

References: (1) Holmefur M, Lidström-Holmqvist K, Roshanay AH, et al. Pilot Study of Let's Get Organized: A Group Intervention for Improving Time Management. Am J Occup Ther. 2019;73(5):7305205020.

IL-6 as a mediator of the association between traditional risk factors and future Myocardial Infarction: A nested case-control study

Mulugeta M Zegeye 1), Jonas SO Andersson 2), Patrik Wennberg 3), Dirk Repsilber 1), Allan Sirsjö 1), Liza U Ljungberg 1).

1) School of Medical Sciences, Örebro University, Örebro, Sweden
2) Department of Public Health and Clinical Medicine, Skellefteå Research Unit, Umeå University, 931 86 Skellefteå, Sweden
3) Department of Public Health and Clinical Medicine, Family Medicine, Umeå University, Sweden

Background/Aim: Studies elucidating the importance of IL-6 trans-signaling to risk of future MI are scarce. Additionally, whether elevation in IL-6 explains part of the association between traditional risk factors and future MI has not been explored.

Method: We conducted a nested case-control study including a total of 584 participants (292 cases and 292 controls) from VIP and MONICA cohorts. At baseline, plasma cholesterol levels were measured, and clinical characteristics of participants were collected. In this study, we measured the plasma concentrations of IL-6, sIL-6R and sgp130. To estimate extent of IL-6 trans-signaling, we estimated plasma concentrations of a novel biomarker, the IL-6 binary complex.

Result: We found that IL-6 binary complex concentration was significantly elevated in participants who experienced MI compared to those who did not. Univariate analyses showed that a 2-fold increase in IL-6 binary complex was associated with 2.45 times higher risk of future MI (95%CI RR=1.65-3.66, p<0.001). ROC analyses revealed that the predictive performance of IL-6 binary complex concentration (AUC=0.614) was equivalent to that of plasma IL-6 concentration (AUC=0.603). Further, using Process mediation analyses, we found statistically significant indirect effect of smoking and hypertension to future MI that is mediated through increased IL-6 binary complex or plasma IL-6.

Conclusion: Both IL-6 binary complex and IL-6 concentrations were significantly associated to future MI with equivalent performances in prediction. Our data additionally imply that both the elevated plasma IL-6, and the IL-6 binary complex concentration could partly explain the increased risk of MI in smokers and hypertensive participants.

Physical Training for Patients with Depression and Anxiety – a Randomized Controlled Study

Qiwei Zhai 1,2), Assar Horn 2), Ann-Charlotte Fridenberger 2), Elisabet Lager 2), Jonas Persson 3), Scott Montgomery 1), Yvonne Freund 1,2)

1) School of Medical Sciences, Örebro University, Örebro, Sweden
2) Department of Psychiatry, Örebro University Hospital, Örebro, Sweden
3) School of Law, Psychology and Social Work, Örebro University, Örebro, Sweden

Background/Aim: Pharmaceutical treatment and psychotherapy constitute the most common treatment methods for depression and anxiety, major alternatives in treatment of depression and anxiety. Physical training has been shown to have comparable effect to cognitive behavioral therapy in treatment of mild to moderate depression and anxiety. Physically active individuals also have lower risks to develop depression and physical activity can also reduce relapse in depression.

The aim of this randomized controlled study (RCT) is to evaluate if and how physical activity can affect mental health, by examining biomarkers in blood and the gut and cognitive functions of patients with depression and anxiety as an add-on to standard psychiatric treatment.

Hopefully, this can lead to new treatment strategies for patients with depression and anxiety. The project aims to be holistic in its approach, combining the defining clinical psychiatric symptoms in patients who have both depression and anxiety with the finding and evaluation of new biomarkers from blood and gut to improve cognitive functions.

Method: 102 patients are randomized to two groups and undergo 12 weeks intervention in addition to standard outpatient treatment. The first group will participate in physical training three times per week and the other group will have relaxation therapy once a week. Activity intensity will be measured before and at the last week of intervention. Blood and faeces sample collection, symptom grading by clinician and with self-rating scales and cognitive screening will be performed at baseline, at week 12 and at one year of follow-up. The cognitive screenings are performed digitally in cooperation with Mindmore.

Result: The results will be published in scientific articles and presented in congresses.

Conclusion: The RCT is currently recruiting patients within Region Örebro and the Dep of Psychiatry.

References: Cooney GM et al. Exercise for depression. *Cochrane Database Syst Rev.* 2013 Mammen G et al. Physical Activity and the Prevention of Depression: A Systematic Review of Prospective Studies. *Am J Prev Med.* 2013;45(5):649–57.