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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 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!

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Molecular autopsy - solving sudden cardiac death with new technology

Emma Adolfsson^{1,2)}, Alvida Qvick^{1,2)}, Daniel Kling³⁾, Henrik Green³⁾, Cecilia Gunnarsson⁴⁾, Jon Jonasson²⁾, Anna Green²⁾

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

2) Department of Laboratory Medicine, clinical pathology and genetics, Örebro University Hospital, Sweden

3) Department of Forensic Genetics and Forensic Toxicology, National Board of Forensic Medicine, Linköping, Sweden

4) Department of Clinical Genetics and Department of Biomedical and Clinical Sciences, Centre for Rare Diseases in South East Region of Sweden, Linköping University, Linköping, Sweden

Background/Objective: Sudden cardiac death (SCD) is a tragic and traumatic event often associated with hereditary genetic disease. In such cases sequencing of stored formalin fixed paraffin embedded tissue (FFPE) is often crucial in trying to find a causal genetic variant. This study was designed to compare two massive parallel sequencing assays for differences in sensitivity and precision regarding variants related to SCD in FFPE material and to evaluate the performance in a clinical setting.

Method: From eight cases of SCD where DNA from blood had been sequenced using HaloPlex, corresponding FFPE samples were collected six years later. DNA from FFPE samples were amplified using HaloPlex HS, sequenced on MiSeq as well as amplified using modified Twist with Unique Molecular Identifiers, and sequenced on NextSeq. In both approaches read coverage, uniformity and variant detection were compared using genomic DNA isolated from blood and corresponding FFPE tissue, respectively.

Result: In terms of coverage uniformity, Twist performed better than HaloPlex HS for FFPE samples. Despite higher overall coverage amplicon-based HaloPlex technologies, both for blood and FFPE tissue, suffered from design and/or performance issues resulting in genes lacking complete coverage. Although Twist had considerably lower overall mean coverage, high uniformity resulted in equal or higher fraction of genes covered at $\geq 20X$. By comparing variants found in the matched samples in a predefined cardiodiagnostic gene panel, HaloPlex HS for FFPE material resulted in high sensitivity, 98.0% (96.6–100%), and high precision, 99.9% (99.5–100%) for moderately fragmented samples, but suffered from reduced sensitivity (74.2–91.1%) in more severely fragmented samples due to lack of coverage. Twist had high sensitivity, 97.8% (96.8–98.7%) and high precision, 99.9% (range 99.3–100%) in all analyzed samples, including the severely fragmented samples.

The Twist technology was applied to a consecutive cohort of 20 SCD cases with the aim to identify causative variants. Of the 20 FFPE cases analyzed, a pathogenic causative variant was detected in two cases. In six cases variant(s) of uncertain significance were detected. Three cases remained negative after sequencing. In nine cases analysis failed due to too poor sample quality.

Conclusion: With Twist NGS technology, severly damaged DNA can be sequenced. By using modern genetic approaches for molecular autopsies, many more victims of SCD has the chance of getting a molecular diagnosis.

A clinical study of neurocognitive functions of post COVID-19 patients

T. Castilla¹⁾, K. Borg²⁾, A. Meehan³⁾, H. Hjelmqvist^{1,4)}, Y. Freund Levi^{1,3,5)}

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

2) Department of Clinical Sciences, Division of Rehabilitation Medicine, Karolinska Institutet, Danderyd University Hospital, Stockholm 3) Department of Geriatrics, Faculty of Medicine and Health, Örebro University Hospital 4) Department of Anesthesiology and Intensive Care, Örebro University Hospital 5) Center for Alzheimer Research, Division of Clinical Geriatrics, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Stockholm

Background/Objective: Some patients that have endured COVID -19, will develop post acute sequel of COVID-19 (PASC) and develop residual symptoms such as fatigue, headache, cognitive decline, depressive symptoms, anxiety and PTSD. Cognitive symptoms include memory deficit, concentration difficulties, impaired attention as well as impairments in executive and visuospatial functions. The neurological complications include ischemic stroke, acute necrotizing encephalopathies and micro thrombosis. PURPOSE: To gain a deeper understanding of the underlying neurological mechanisms of PASC, identify risk factors, objectively assess patient's cognitive and psychological state using a digital platform for cognitive testing (Mindmore) and psychiatric enquirers in correlation to diagnostic and prognostic markers in blood, cerebrospinal fluid and brain MRI. The aim is to aid the healthcare community – such as policy makers, physiotherapy, occupational therapists, counsellors and dieticians - in the long term to establish specific rehabilitation profiles so that PASC patients may recover faster and return to their work.

Method:

- Follow 100 patients 6, 12 and 24 months after COVID-19 infection.
- Investigate what long-term psychiatric, psychological and neurocognitive effects PASC patients experience in their everyday life using Mindmore (neuropsychological testing kit), and psychiatric questioners.
- Evaluate how patients with PASC are affected in terms of health-related quality of life, activity limitations, incapacity to work, and the time it takes to return to work.
- Identify potential predictors of impaired outcomes, defined as changes in biomarkers in plasma and cerebrospinal fluid in patients with PASC.
- Detect neuroradiological changes on MRI in patients with PASC over time in correlation to their psychological and cognitive function.
- Investigate possible connections between ApoE4 and PASC.

Result: Inclusion will take place early spring of 2022.

Conclusion: N/A

References: Lopez-Leon S et al. More than 50 Long-term effects of COVID-19: a systematic review and meta-analysis. medRxiv [Preprint]. 2021 Jan 30:2021.01.27.21250617. doi: 10.1101/2021.01.27.21250617. Taquet M et al. 6-month neurological and psychiatric outcomes in 236 379 survivors of COVID-19: a retrospective cohort study using electronic health records. Lancet Psychiatry. 2021 May;8(5):416-427. doi: 10.1016/S2215-0366(21)00084-5.

Attitudes towards family involvement in care in Cardiothoracic surgical departments in Sweden - A Mixed-Methods study

Drakenberg. A¹⁾, Ericsson. E¹⁾, Ågren. S³⁾, Arvidsson-Lindvall. M-L⁴⁾, Sundqvist. A-S⁴⁾

 School of Health Sciences, Örebro University, Örebro, Sweden
Department of Cardiothoracic and Vascular Surgery, Örebro University Hospital, Örebro, Sweden, 3) Department of Medical and Health Sciences, Linköping University, Sweden, Department of Cardiothoracic Surgery, Department of Medical and Health Sciences, Linköping University, Linköping, Sweden, 4) University Health Care Research Center, Faculty of Medicine and Health, Örebro University, Sweden.

Background/Objective: Family involvement in care enhances patient care quality (1), patient safety (2), and family health (3). Professionals' attitudes toward families influence the way families are cared for and involved in patient care (3). It is therefore of importance to describe attitudes among health care professionals toward family involvement in care. The aim of this study was to describe the attitudes of cardio-thoracic nurses, -surgeons, and –anesthesiologists towards family involvement in care.

Method: A mixed-method convergent parallel design (4) was used combining and contrasting results from qualitative interviews with twenty physicians, and quantitative and qualitative data from the questionnaire Families Importance in Nursing Care-Nurses Attitudes (FINC-NA) answered by 306 nurses. Nurses were recruited to the cross-sectional part of the study from all eight cardiothoracic centers in Sweden between April-November 2020. Physicians were recruited simultaneously to the qualitative interview section of the study from three cardiothoracic centers in Sweden. Qualitative and qualitative data were analyzed separately and thereafter integrated.

Result: The analysis is ongoing. Preliminary results will be presented during the poster presentation on Nobel day.

Conclusion: Preliminary results will be discussed concerning attitudes, ethics, and interprofessional teamwork during the poster presentation on Nobel day.

References: 1 Leino-Kilpi H, Gröndahl W, Katajisto J, Nurminen M, Suhonen R. Participation of family members and quality of patient care - the perspective of adult surgical patients. J Clin Nurs. 2016 Aug;25(15-16):2242-50.

2 Park M, Giap TT. Patient and family engagement as a potential approach for improving patient safety: A systematic review. J Adv Nurs. 2020 Jan;76(1):62-80. 3 Wright LM, Bell JM. Beliefs and illness: a model for healing. [Calgary]: 4th Floor Press; 2009.

4 Creswell JW, Plano Clark VL. Designing and conducting mixed methods research. 2. ed. Los Angeles: SAGE Publications; 2011.

Implication of lower genetic predisposition in twins developing Crohn's disease later in life

Fart. F^{1} , Amcoff. K^{1} , Bergemalm. D^{1} , Andersson. E^{1} , Lindqvist. C.M.¹, Halfvarson. $J^{1,2)\dagger}$, Schoultz. $I^{1)\dagger}$

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

2) Department of Gastroenterology, Faculty of medicine and Health, Örebro University, Sweden

t= Equally shared supervision

Background/Objective: Serological markers have been used to differentiate Crohn's disease (CD) from ulcerative colitis (UC), and to characterize underlying disease processes. Current serological markers towards microbial antigens, including Escherichia coli outer membrane porin C (anti-OmpC), CBir1flagellin (anti-CBir1), Pseudomonas fluorescens-related protein (anti-I2) and anti-Saccharomyces cerevisiae antibody (ASCA), have been associated with a severe course of CD, with increased risk of complicated disease behavior and surgery. Intriguingly, increased levels serological antibodies to microbial antigens have also been seen in healthy first-degree relatives of patients with CD. Historically, late-onset CD has been regarded as a less aggressive phenotype and associated with lower levels of these serological antibodies. Whether these observations indicate that the adaptive immune response varies with the age at CD diagnosis or if they are explained by differences in clinical phenotypes across agegroups are largely unknown. Studies of twin pairs discordant for CD may be help in this respect since the healthy sibling are exposed to shared genetic and environmental risk factors. Hence, this paper aim to disentangle the relative contribution of genetic and environmental factors regarding serological markers towards anti-I2, anti-OmpC, anti-CBir1 and ASCA regarding age at diagnosis in CD.

Method: 49 discordant, same-sex twin pairs were studied, whereof one twin had CD and one twin was IBD healthy. This cohort have previously been studied regarding concordance between the twins' levels of ASCA, anti-OmpC, anti-Cbir1 and anti-I2. Inflammatory markers, calprotectin and genetic data regarding four single-nucleotide polymorphisms that has previously been connected to risk factors of CD were studied.

Result: Anti-OmpC and anti-CBir1 in the healthy twin sibling were inversely correlated to age at diagnosis of their CD-afflicted twin sibling (p=0.019 and p=0.003 respectively). When stratifying, this was only found in the monozygotic twin pair, where also anti-I2 (p=0.004) was found to be inversely correlated to age at diagnosis. No correlation was seen between age at diagnosis to local or systematic inflammation. No associations between the serological markers and genetical risk score was found. However, few discordant twins above 40 years were available in this analysis (dizygotic twins n=2, monozygotic twins n=6).

Conclusion: There seems to be a lower adaptive immune response towards microbial antigens in healthy twin siblings that correlate to a higher age at diagnosis of their CD-afflicted twin. This was seen especially in the monozygotic pairs, indicating that the genetic predisposition might be lower for those receiving their diagnosis later in life, however this must be further validated in a larger and older cohort.

The first national study of genomic epidemiology of Neisseria gonorrhoeae isolates in Sweden, 2016

Ronza Hadad^{1),} Daniel Golparian¹⁾, Inga Velicko²⁾, Ylva Lindroth³⁾, Anna-Karin Ohlsson⁴⁾, Eva-Lena Ericson⁴⁾, Lars Engstrand⁵⁾, Hans Fredlund¹⁾, Magnus Unemo¹⁾

1) WHO Collaborating Centre for Gonorrhoea and other STIs, Dept Lab Med, Faculty of Medicine and Health, Örebro University, Örebro, Sweden

2) Public Health Agency of Sweden, Solna, Sweden

3) Dept of Lab Med, Med Microbiol, Lund University, Skåne LabMed, Lund, Sweden

4) Dept of Clin Microbiol, Karolinska University Hospital, Huddinge, Sweden

5) Center for Translational Microbiome Research, CTMR, Dept of Microbiol, Tumor and Cell Biology (MTC), Karolinska Institutet, SciLife Lab, Solna, Sweden

Background/Objective: The increasing transmission and antimicrobial resistance (AMR) in *Neisseria gonorrhoeae* is both a national and global health concern. The number of reported cases of gonorrhoea in Sweden continuously increased from an incidence of 7.8 per 100 000 inhabitants in 2009 to 31.4 in 2019. No national molecular epidemiological study investigating the population of *N. gonorrhoeae* circulating in Sweden has been performed in the last two decades. Our aim was to examine the antimicrobial resistance (AMR) and genome-based epidemiology, in conjunction to patient epidemiological data, of all gonococcal isolates (n=1279; one isolate per case) from gonorrhoea cases in Sweden during 2016.

Method: AMR testing was performed using Etest, and MICs were interpreted using current clinical resistance breakpoints from EUCAST. All isolates were whole genome sequenced using Illumina HiSeq X platform. Patient epidemiological data was obtained from the Public Health Agency of Sweden.

Result: The gonorrhoea patients consisted of 252 (19.7%) women and 1027 men (80.3%). The medium age of the women was 27.4 years and of the men 32.1 years. Regarding sexual orientation, 619 (48.4%) reported homosexual, 605 (47.3%) heterosexual, 31 (2.4%) bisexual, and 24 (1.9%) did not report. Most prevalent countries of infection were Sweden (n=875, 68.4%), followed by Thailand (n=70, 5.5%) and Germany (n=32, 2.5%).

Overall, the phenotypic AMR was as follows: ceftriaxone and spectinomycin (0%), cefixime (1.7%), azithromycin (1.3%) and ciprofloxacin (51.1%).

The phylogenomic analysis revealed two main lineages (A and B) with lineage A divided into two main sublineages (A1 and A2). Resistance and decreased susceptibility to ESCs and azithromycin and associated AMR determinants were predominantly found in sublineage A2.

Conclusion: AMR in *N. gonorrhoeae* in Sweden remains low, in particular to ceftriaxone and azithromycin that is recommended internationally for dual therapy. Continuous surveillance of the spread and evolution of *N. gonorrhoeae*, including phenotypic AMR testing and WGS, is essential for enhanced knowledge regarding the dynamic evolution of *N. gonorrhoeae* and gonorrhoea epidemiology.

Alteration of laminin genes by cytokines and endothelial cell response to laminin-332

Assim Hayderi¹⁾, Mulugeta Zegeye¹⁾, Ashok Kumawat¹⁾, Allan Sirsjö¹⁾, Liza Ljungberg¹⁾

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

Background/Objective: Laminins are structural components of the basement membrane. In mammals, the twelve laminin genes are believed to encode 16 laminin isoforms, which are expressed in a tissue-specific manner. The two major isoforms associated with vascular endothelial cells are the alpha four and alpha five-containing isoforms. However, during inflammatory diseases, including atherosclerosis, the expression of the laminin genes is altered (1). Here, we aimed to study the effect of inflammatory cytokines on the expression of laminin genes and characterise the response of endothelial cells to laminin-332.

Method: Endothelial cells were treated with TNF-alpha, interferon-gamma and IL-6 for different time points and the laminin genes were analysed with qRT-PCR. Endothelial cells were then cultured on laminin-332, laminin-511-or uncoated plastic ware and the supernatant was analysed for inflammatory cytokines and chemokines and used in trans-well system for evaluating the migration of primary monocytes.

Result: While the expression of the majority of the laminin genes in endothelial cells was affected by the inflammatory cytokines, LAMB3 and LAMC2, which together with LAMA3 encode laminin-332, were drastically affected by TNF-alpha, IFN-gamma and IL-6 trans-signalling. Both of these genes are upregulated in atherosclerotic lesions and correlate with TNF-alpha. Endothelial cells cultured on laminin-332 demonstrated elevated expression and secretion of ICAM-1, VCAM-1 and pro-inflammatory chemokines. These cells tend to also express lower levels of endothelial-specific tight junction protein, claudin-5. Supernatant from cells cultured on laminin-332 attracts more monocytes in comparison to supernatant from cells cultured on plastic ware or laminin-511.

Conclusion: We demonstrate that TNF-alpha induces the expression of epithelialspecific LAMB3 and LAMC2 genes in endothelial cells. These genes are up-regulated in human atherosclerostic lesions and correlate with TNF-alpha. Endothelial cells cultured on laminin-332 are more inflammatory in nature.

References: 1. Rauch, U. et al. Laminin isoforms in atherosclerotic arteries from mice and man. 711–724 (2011).

Regulation of CXCR3 ligands by RSAD2 in interferon-stimulated vascular cells and its effect on monocyte migration in vitro

Assim Hayderi^{1,2)}, Ashok Kumawat^{1,2)}, Mats Dreifaldt^{1,3)}, Allan Sirsjö^{1,2)}, Liza Ljungberg^{1,2)}

- 1) School of Medical Sciences, Örebro University, Örebro, Sweden
- 2) Cardiovascular Research Centre
- 3) Örebro University Hospital

Background/Objective: Atherosclerosis which can partially be treated with lipid lowering statins still remains the main cause of cardiovascular mortalities. An antiviral protein (RSAD2) that has demonstrated expression in endothelial cells of human carotid lesions (1) could prove a valuable mediator of inflammatory activity. Moreover, it was found to regulate lipid metabolism (2) and dendritic cell maturation (3), two processes involved in the development of atherosclerosis. Taking these findings into account, we aimed to characterise the function of RSAD2 in interferon-stimulated human vascular cells to better understand its potential as a therapeutic target for inflammation in atherosclerosis.

Method: Human carotid plaques were stained for RSAD2 by immunohistochemistry to evaluate its expression in diseased vessels. Since RSAD2 is not basally expressed in human vascular cells, we stimulated vascular cells with interferon gamma right after transfection with scramble or anti-RSAD2 siRNAs to induce RSAD2. The secretion of approximately 200 proteins were evaluated in the supernatant of these cells by Olink proteomics. ELISA, qRT-PCR and patient mRNA data from the biobank collection of carotid plaque samples from hypertensive patients undergoing endarterectomy surgery at the university hospital of Lyon were used to further confirm these findings.

Result: We demonstrate that RSAD2 expression is not restricted to endothelial cells in human carotid plaques. Carotid plaque macrophages and smooth muscle cells also express RSAD2. Silencing RSAD2 in interferon gamma-stimulated human aortic smooth muscle and endothelial cells caused a reduction in the levels of CXCL10 and CXCL11, and CXCL9 and CXCL11, respectively. CXCL10 and CXCL11, but not CXCL9, mRNAs are significantly highly expressed in diseased carotid vessels and correlate with RSAD2 in both diseased and healthy vessels. Furthermore, supernatant from RSAD2 knockdown aortic smooth muscle cells attracts fewer monocytes as compared to supernatant from control knockdown aortic smooth muscle cells *in vitro*.

Conclusion: RSAD2 regulates the expression of CXCR3 ligands in interferonstimulated vascular cells. Supernatant from RSAD2 knockdown cells attract fewer monocytes. In summary, these observation support the utility of RSAD2 as a therapeutic target of inflammatory activity in the development of atherosclerosis.

References:

- 1. Olofsson P.S et al., 2005. ATVB, 25(7), e113-e116.
- 2. Eom J et al., 2019. PNAS, 116(35), 17419-17428.
- 3. Jang J et al., 2018. Cell death & disease, 9(8), 1-11.

Learning in the operating room; from student nurse anesthetists' and supervisors' perspective. An integrative review

Jakob Hedlund^{1,3)}, Karin Blomberg¹⁾, Hans Hjelmqvist^{2,3)}, Maria Jaensson^{1,3)}

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

2) School of Medical sciences, Örebro University, Örebro, Sweden

3) Department of Anesthesia and Intensive Care, Örebro University Hospital, Örebro, Sweden

Background/Objective: In Sweden there is a major shortage for specialist nurses (1). Eduction to become a nurse anesthetist involves theory and practice. During clinical placement, students perform anesthesia under supervision. The objective for this study was to describe enhancing and limiting factors on learning during clinical placement in the operating room for student nurse anesthetists', from a students' and supervisors' perspective.

Method: An integrative review with an inductive analysis was conducted. Searches were performed in four databases; Medline, Cinahl, PsycInfo and ERIC.

Result: In the preliminary result, 58 references are included. Two categories and six subcategories emerged. The first category "context associated aspects on learning", includes three subcategories: "learning in the operating room", "didactic and pedagogic approach before clinical practice" and "didactic and pedagogic approach during clinical practice". The second category "relationship that impacts learning", includes three subcategories: "the operating room team", "the student nurse anesthetist" and "the supervisor".

Conclusion: The student nurse anesthetists' trajectory through the clinical placement starts before entering the operating room. Student learning can be reinforced or hindered by didactic and pedagogical approaches as well as relational aspects both before and during clinical placement.

References:

1. Universitetskanslersämbetet (Swedish Higher Education Authority). (10 oktober 2021). *Specialistsjuksköterskeexamen, samtliga inriktningar*. <u>https://www.uka.se/</u>statistik--analys/analys-och-uppfoljning/prognoser-for-behovet-av-hogskoleutbildade/ halso--och-sjukvard-samt-social-omsorg/specialistsjukskoterskeexamen-samtligainriktningar.htmltsjuksköterskeexamen, Samtliga inriktningar | UKÄ - granskar, analyserar och utvecklar högskolor och universitet (uka.se)

Dance and yoga reduced functional abdominal pain in young girls: A randomized controlled trial

S Högström^{1,2)*}, A Philipson^{1,2)*}, L Ekstav³⁾, M Eriksson¹⁾, U L. Fagerberg⁴⁾, E Falk²⁾, M Möller²⁾, E Sandberg²⁾, S Särnblad^{3,5)}, A Duberg²⁾

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

2) University Health Care Research Center, Faculty of Medicine and Health, Örebro University, Örebro, Sweden, 3) Department of Pediatrics, Faculty of Medicine and Health, Örebro University, Örebro, Sweden, 4) Department of Pediatrics, Center for Clinical Research, Västmanland Hospital, Västerås, Uppsala University, Sweden, 5) School of Medical Sciences, Örebro University, Örebro, Sweden

* = Equally shared authorship

Background/Objective: Functional abdominal pain disorders (FAPDs) (Hyams et al., 2016) affect 13.5% of school-aged children worldwide with a higer prevalence among girls (Korterink et al., 2015). FAPDs include Irritable Bowel Syndrome (IBS), functional dyspepsia, abdominal migraine and functional abdominal pain (FAP) – not otherwise specified, (Hyams et al., 2016). The aim with this study was to compare the effects of an 8-month dance/yoga intervention with standard health care on maximum abdominal pain among 9- to 13-year-old girls with FAPDs.

Method: This study was a prospective randomised controlled trial including 121 girls, with IBS and/or FAP, recruited from outpatient clinics as well as the general public. The intervention group participated in dance and yoga twice weekly for 8 months, controls received standard care. Abdominal pain, as scored on the Faces Pain Scale–Revised (Hicks et al., 2001), was recorded in a pain diary. A linear mixed model was used to estimate the outcomes and effect sizes.

Result: Dance and yoga were superior to standard healthcare alone, with a medium to high between-group effect size (0.67) and significantly greater pain reduction (b = -1.29, p = 0.002) at the end of the intervention.

Conclusion: This study shows that a non-pharmacological intervention including combined dance and yoga, can be an effective complement to standard health care, for 9- to 13-year old girls with FAPDs.

References: Hicks, C. L., von Baeyer, C. L., Spafford, P. A., van Korlaar, I., & Goodenough, B. (2001). The Faces Pain Scale-Revised: toward a common metric in pediatric pain measurement. *Pain*, 93, 173-183. <u>http://doi.org/10.1016/s0304-3959(01)</u> 00314-1

Hyams, J. S., Di Lorenzo, C., Saps, M., Shulman, R. J., Staiano, A., & van Tilburg, M. (2016). Functional Disorders: Children and Adolescents. *Gastroenterology*. <u>http://doi.org/10.1053/j.gastro.2016.02.015</u>

Korterink, J. J., Diederen, K., Benninga, M. A., & Tabbers, M. M. (2015). Epidemiology of Pediatric Functional Abdominal Pain Disorders: A Meta-Analysis. *PloS One*, 10, e0126982. <u>http://doi.org/10.1371/journal.pone.0126982</u>

Quality of care from the patients' perspective – a phenomenographic approach within the oncology out-patient setting

Jeanette Kittang^{1,2)}, Emma Ohlsson-Nevo^{1,3)}, Agneta Schröder^{1,3)}

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

2) Department of Oncology, Faculty of Medicine and Health, Örebro University, Örebro, Sweden.3) University Health Care Research Center, Faculty of Medicine and Health, Örebro University, Örebro, Sweden.

Background/Objective: Quality of care is a multidimensional concept which lacks a clear, accepted definition regarding oncological care. The tradition within health care has been that professionals dictate what quality of care is, but studies have shown that health care staff and patients don't share the same view upon what is important in health care. In spite of increasing medical advances and more people being offered cancer treatment, there are only a few studies examining how the patients perceive the quality of care within the oncology out-patient setting.

The aim of the study is to explore how oncology patients perceive quality of care in the oncology out-patient setting.

Method: Using a phenomenographic research approach and a purposive sampling method, semi-structured interviews were conducted with adult patients receiving oncological treatment in out-patient settings. Time and place for the interviews were initially to be decided by the patient, but due to pandemic restrictions a majority of the planned physical interviews were instead conducted over the phone or by video call; 8 physical, 7 telephone, 5 video call. The same interview guide, consisting of 6 questions, was used irrespective of interview form. Verbatim transcripts were analysed using Martons' Phenomenographic approach in four steps.

Result: Twenty adult patients, age 25-84, from four different hospitals participated in the study. Results are preliminary, but indicates an outcome space with four descriptive categories, at the moment named; Atmosphere, Structure, Autonomy and Professionalism.

Conclusion: Patients within the oncology out-patient setting perceive quality of care as something good, normative and how care should be like. They report feeling safe, being seen and receiving the proper treatment as important features of quality of care.

Surgical-site infection after hip fracture surgery; preoperative fullbody disinfection compared to local disinfection of the surgical-site

Noelle Probert^{1,2)}, Åsa G Andersson³⁾, Anders Magnuson⁴⁾, Elin Kjellberg⁵⁾, Per Wretenberg⁶⁾

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

2) Centre of Clinical Research, Region Värmland, Sweden

3) Department of Geriatrics, Faculty of Medicine and Health, Örebro University, Örebro, Sweden4) Clinical Epidemiology and Biostatistics, School of Medical Sciences, Örebro University,Örebro, Sweden

5) Department of infectious diseases, Central Hospital of Kristianstad, Kristianstad, Sweden6) Department of Orthopaedics, Faculty of Medicine and Health, Örebro University, Örebro, Sweden

Background/Objective: Swedish national guidelines recommend full-body disinfection (FBD) with 4% chlorhexidine before hip fracture surgery to prevent surgical-site infection (SSI) (1) despite little evidence. Our objective was to compare preoperative FBD with local disinfection (LD) of the surgical site regarding SSI incidence.

Method: In this Population-based observational cohort-study we included all patients with hip fracture, diagnosed with ICD-10 codes S72.0, S72.1 or S72.2, operated at Karlskoga hospital in Sweden, January 1st, 2018 (n = 237) to December 31st, 2019 (n = 259). Patients in 2018 were prepared with FBD and patients in 2019 with LD. Primary outcome was SSI and secondary outcome was SSI/death. We adjusted for potential confounders with logistic regression. The adjusted analysis was performed in two models to enable assessment of smoking and surgeon experience that lacked SSI/ death outcome. In the first model these variables were not adjusted for, and the second model was restricted to non-smokers for the SSI/death-outcome and non-smokers operated by a senior surgeon for the SSI-outcome.

Result: There were 16 (6.8%) cases of SSI 2018 and 8 (3.1%) cases 2019. FBD (2018) compared to LD (2019) presented adjusted OR of 1.9 (95%CI 0.8-4.9, P=0.16) respectively 2.0 (95%CI 0.8-5.1, P=0.14) in the first and second model of the logistic regression. In addition, 40 (16.9%) patients 2018 and 29 (11.2%) patients 2019 had the combined outcome of SSI/death, adjusted OR 1.6 (95% CI 0.9-2.8, P=0.08) respectively 1.7 (95% CI 0.8-2.9, P=0.06).

Conclusion: We found a non-significant increased risk of SSI 2018 (FBD) compared to 2019 (LD) after adjustment. The study has limitations and randomized control-trials are needed. Nonetheless, results suggest that LD is not inferior to FBD regarding SSI prevention, meaning patients could potentially be spared significant levels of pain.

Work loss in patients with celiac disease: a population-based longitudinal study

Soran R Bozorg¹⁾, Jonas Söderling²⁾, Åsa H Everhov²⁾, Benjamin Lebwohl³⁾, Peter HR Green³⁾, Martin Neovius²⁾, Jonas F Ludvigsson^{4)†}, Karl Mårild^{5)†}

 School of Medical Sciences, Örebro University, Örebro, Sweden
Clinical Epidemiology Division, Department of Medicine, Karolinska Institutet, Sweden
Celiac Disease Center, Department of Medicine, Columbia University Medical Centre, Columbia University, New York, USA
Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm Sweden; School of Medical Sciences, Örebro University, Örebro, Sweden
Department of Pediatrics, Institute of Clinical Sciences, Sahlgrenska Academy, Gothenburg,

Sweden

t= Equally shared supervision

Background/Objective: Celiac disease (CD) is an immune-mediated disease triggered by gluten intake and affects around 1% of the population worldwide (1). Although patients with CD have an increased use of healthcare (2), data on work disability remains scarce. In this study, our aim was to estimate work loss in patients with CD, including its temporal relationship to diagnosis.

Method: We identified 16,005 working-age patients with prevalent CD, and 4,936 incident working-age patients diagnosed in 2008-2015 through biopsy reports from Sweden's 28 pathology departments. CD was defined by presence of villus atrophy (Marsh 3) on biopsy (gold standard). Each patient was compared to up to 5 matched general-population comparators. Using nationwide social insurance registers, we retrieved prospectively-recorded data on compensation for sick leave and disability.

Result: In 2015, patients with prevalent CD had a mean of 42.5 (95%CI: 40.9-44.1) lost work days as compared with 28.6 (27.9-29.2) in the general-population comparators, corresponding to a relative difference of 49%. Among incident patients, the annual mean difference between patients and comparators was 8.0 (5.4-10.6) lost work days 5 years before CD diagnosis, which grew to 13.7 (9.1-18.3) days 5 years after diagnosis. In addition to the continuously increasing mean difference in lost work days over time, there was also a transient increase in work loss in patients with CD during the year of diagnosis (mean difference: 15.6 days, 95%CI: 13.1-18.0).

Conclusion: Patients with CD miss more work days than comparators before their diagnosis, and this loss increases and persists after diagnosis despite presumed installation of treatment with gluten-free diet.

References:

1.Singh P, Arora A, Strand TA, Leffler DA, Catassi C, Green PH, et al. Global Prevalence of Celiac Disease: Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol. 2018;16(6):823-36 e2.

2. Mårild K, Söderling J, Bozorg SR, Everhov Å H, Lebwohl B, Green PHR, et al. Costs and Use of Health Care in Patients With Celiac Disease: A Population-Based Longitudinal Study. Am J Gastroenterol. 2020;115(8):1253-63.

The taste of chocolate

Julia Rode¹⁾, Johan Swahn²⁾, Per Thunberg^{1,3)}, Åsa Öström²⁾

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

2) School of Hospitality, Culinary Arts and Meal Science, Örebro University, Örebro, Sweden

3) Department of Medical Physics, Örebro University, Örebro, Sweden

Background/Objective: Likewise other stimuli, gustatory (taste) stimuli are processed in the brain. By the development of a (chocolate) tasting paradigm, we aim to enhance the paradigm toolbox currently available at the recently established Center for Experimental and Biomedical Imaging in Örebro (CEBIO).

Method: To assess the taste of chocolate on brain level, 5 healthy, adult subjects (3 male/ 2 female) underwent functional magnetic resonance imaging (fMRI) using a GE Signa Premier 3T with a 48 channel head coil. An initial 5-minutes structural scan (T1-weighted, voxel size 1x1x1 mm) was followed by three 1-minute functional scans (voxel size 2x2x2 mm, temporal resolution 2 s, interleaved acquisition). During the functional scan, subjects were instructed to focus on a fixation cross displayed on a screen for 25 s (denoted as rest condition), followed by a 5 s period when the subjects were ask to place a chocolate bit on their tongue (instruction "eat chocolate" displayed on screen). During the last 30 s of the scan, the subjects left the chocolate bit on their tongue while focusing a fixation cross (denoted as chocolate condition). Subjects were allowed to rinse their mouth between the three runs of the chocolate tasting paradigm. The contrast chocolate>rest was analysed for effects on brain activity on individual and group level using SPM12; and for functional connectivity changes on individual and group level using seed-to-voxel and ROI-to-ROI analyses in CONN.

Result: The pilot experiments revealed that it is possible to perform a tasting experiment in our setting. Nevertheless, the results indicated that the taste stimulus administration needs to be performed with high caution to avoidance of head movements or magnetic field disturbances by e.g. extensive arm movement. Quality control parameters suggested that those caution measures were violated during the exam of one subject, which led to exclusion of this subject's data from analyses. The results from the remaining four subjects showed similar brain activity on individual level (p-FWE<0.05) despite some heterogeneity, with one subject showing considerably more activation than the other three subjects. Group level analysis indicated activation (p-uncorrected<0.001, extent threshold 35) in the central operculum, anterior and posterior insular in both hemispheres, all of which might be involved in taste. Functional connectivity changes (cluster-size threshold p-FDR<0.05) have been observed between opercular regions and brain regions of motor and somatosensory cortices, sense of touch and limbic system.

Conclusion: This paradigm may offer the possibility to assess how gustatory stimuli are presented on brain level. We were able to show brain activity and functional connectivity changes even in a small sample size of four subjects, which might indicate robustness of the developed paradigm. In the near future we aim to combine gustatory stimuli with others, such as visual or auditory stimuli.

Individuals with eosinophilic esophagitis are at greater risk of later psychiatric disorder

Lovisa Röjler¹⁾, John J Garber²⁾, Agnieszka Butwicka³⁾, Bjorn Roelstraete³⁾, Jonas F Ludvigsson^{1,3,4,5)}

 School of Medical Sciences, Örebro University, Örebro, Sweden
Gastrointestinal Unit, Massachusetts General Hospital, Harvard Medical School, Boston MA, USA, 3) Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden, 4) Division of Epidemiology and Public Health, School of Medicine, University of Nottingham, Clinical Sciences Building 2, City Hospital, Nottingham, UK,
Celiac Disease Center, Department of Medicine, Columbia University College of Physicians and Surgeons, New York, New York, USA

Background/Objective: Several gastrointestinal and allergic diseases have been linked to psychiatric disease, but there is limited data on psychiatric disease in eosinophilic esophagitis (EoE). Our aim is to study the association between EoE and later psychiatric disorders.

Method: Population-based nationwide cohort study. Individuals with EoE diagnosed 1989-2016 in Sweden (n=1437) were identified through the ESPRESSO histopathology cohort that represents all gastrointestinal biopsy reports in Sweden's 28 pathology departments. EoE individuals were matched with up to five reference individuals on sex, age, county, and calendar year (n=6346). Cox proportional hazard modeling estimated adjusted hazard ratios (aHRs). In a secondary analysis we compared EoE individuals with their siblings to adjust for intrafamilial confounding.

Result: Median age at EoE diagnosis was 39 years, and 76% of the enrolled EoE individuals were male. During a median follow-up of 3 years, 94 EoE individuals (17.66/1000 person-years) developed a psychiatric disorder compared with 258 (10.57/1000 person-years) reference individuals, corresponding to aHR of 1.72 (95% CI=1.35-2.17). The increased risk was seen in the first five years of follow-up, but not thereafter. The highest relative risks were seen in individuals diagnosed with EoE in childhood. Compared with siblings, individuals with EoE were at an almost twofold increased risk of psychiatric disease (aHR=1.85, 95%CI=1.25-2.74). EoE was linked to mood disorders, anxiety, eating disorders, and attention-deficit hyperactivity disorder. No EoE individual attempted suicide.

Conclusion: Individuals with EoE are at greater risk of psychiatric disease than their siblings and the general population. This risk needs to be considered in clinical care to detect, prevent, and treat comorbidity.

Roles of ESCRT proteins (ALIX and CHIMP4A) and their interplay with ISG15 during tick-borne flavivirus infection

Hung Tran¹⁾, Abhilash I. Chiramel²⁾, Magnus Johansson¹⁾, Wessam Melik¹⁾

 School of Medical Sciences, Örebro University, Örebro, Sweden
Innate Immunity and Pathogenesis Section, Laboratory of Virology, Rocky Mountain Laboratories (RML), National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), Hamilton, MT 59840, USA

Background/Objective: Flaviviruses, usually transmitted to humans via mosquito or tick bites, often lead to infections that cause severe diseases such as encephalitis or hemorrhagic fever. You might mean this: During infection, virus replication and assembly, whose cellular sites are relatively close, are controlled by virus proteins and a diverse range of host proteins. By siRNA-mediated gene silencing, we show that ALIX and CHMP4A, two members of the host endosomal sorting complex required for transport (ESCRT) protein machinery, are required for flavivirus infection.

Method: In this study, we generated cell lines expressing subgenomic replicons and virus-like particles to study ESCRT protein roles as specific stages of the virus cellular life cycle. We also employed molecular cloning, biochemical methodology and high-resolution microscopy to characterize the roles of ESCRT proteins and ISG15.

Result: In this study, we demonstrate specific roles for ALIX and CHMP4A in viral replication and assembly, respectively. We show that the ESCRT proteins are recruited by a putative specific late (L) domain motif LYXLA within the NS3 protein of tickborne flaviviruses. Furthermore, to counteract the recruitment of ESCRT proteins, the host cells may elicit defense mechanisms. We found that ectopic expression of the interferon-stimulated gene 15 (ISG15) or the E3 ISG15-protein ligase (HERC5) reduced virus replication by suppressing the positive effects of ALIX and CHMP4A.

Conclusion: Collectively, these results have provided new insights into flavivirus-host cell interactions that function as checkpoints, including the NS3 and the ESCRT proteins, the ISG15, and the ESCRT protein, at essential stages of the virus life cycle.

The Swedish Standardized Course of Care – colorectal cancer prevalence and predictive values of revised entry criteria

Linnea Uebel¹⁾, Michiel van Nieuwenhoven²⁾, Nils Nyhlin²⁾

School of Medical Sciences, Örebro University, Örebro, Sweden
University hospital Örebro, Division of Gastroenterology, Örebro.

Background/Objective: The Swedish Standardized Course of Care for colorectal cancer (SCC-CRC) is a fast-track pathway for patients with symptoms suggestive of cancer. A revised version was implemented in 2019, aiming to prove its efficacy. The aim of this study was to evaluate the revised entry criteria for SCC-CRC in terms of prevalence of colorectal cancer (CRC) in referrals to the hospitals in Region Örebro County. Also, to investigate the positive predictive values (PPVs) and odds ratios (ORs) for the revised entry criteria with respect to CRC and identify possible future criteria.

Method: Review of medical records and SCC-CRC referrals, including all patients accepted for SCC-CRC colonoscopy in Region Örebro County in 2019 and 2020 (n=1268).

Result: CRC yield was 17.5%. Highest predictive values and significant risk increase was seen for abnormal radiology (PPV 31.7%, OR 2.7 (95% CI 1.9-3.8), p <0.001), abnormal rectal examination (PPV 27.0%, OR 2.0 (95% CI 1.4-2.9), p <0.001) and anaemia (PPV 21.5%, OR 1.5 (95% CI 1.1-2.0), p 0.012). PPV and OR for the suggested combination of symptoms according to the new entry criteria was low and statistically insignificant; however other combinations such as anaemia plus abdominal pain performed better (PPV 39.1%, OR 3.3 (95% CI 1.9-5.5), p-value <0.001). Adding a positive faecal (f)-Hb to any of the SCC-CRC increased the PPV and OR. Negative predictive value of f-Hb was 96.3%.

Conclusion: CRC prevalence was slightly higher than before the revision, although the PPVs remain roughly the same. The combinations of symptoms incorporated in the new criteria showed no statistical significance. Other symptoms such as abdominal pain should be considered as well. Faecal-Hb testing should be added to the SCC-CRC criteria to increase diagnostic efficacy.

References: Kromodikoro I, van Nieuwenhoven M, Nyhlin N. The Swedish Standardized Course of Care: colorectal cancer prevalence and the predictive value of entry criteria. United Eur Gastroenterol J 2020 Vol 88S 144 - 887 736-37 A1199. Availble from: <u>https://www.nxtbook.com/ueg/UEG/Abstracts/index.php#/p/736</u>

In safe hands: a qualitative study on older patients' experiences of a tailored primary health care unit

Ulrika Westerling^{1,2)}, Mikko Hellgren²⁾, Liselotte Hermansson²⁾, Emma Nilsing Strid²⁾

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

Background/Objective:

Today's health care system faces challenges in meeting the needs of older people with multimorbidity. To better cope with these needs, tailored primary health care (PHC) with geriatric competence and person-centred care has been suggested. The aim of this study was to explore older patients' experiences of a tailored PHC unit.

Method:

This is a qualitative study using semi-structured individual interviews and qualitative content analysis. Nineteen patients were recruited from a tailored PHC unit for people aged 75 years or older in Örebro region in the middle of Sweden. The interview data were analysed using inductive category development.

Result:

In the analysis, the theme *In safe hands when in need of primary health care* emerged. The interviewees expressed a desire to participate in their own care. Easy access, enough consultation time and a calm environment, along with the PHC professionals' welcoming and attentive approach enhanced their feeling of being in safe hands. PHC professionals were perceived as having geriatric knowledge and taking responsibility for the care of older patients. Although the interviewees experienced that they received every attention for their health conditions, a need for a more preventive approach to care emerged.

Conclusion:

Older patients highly appreciated their tailored PHC and they emphasised that it was an improvement compared to ordinary PHC. This study provides valuable insights into older patients' experiences, which may be helpful in the ongoing process of improving care for older patients in PHC.

Development of novel antibacterial substances for efficient treatment of bacterial wound infections

Emanuel Wiman¹⁾, Hazem Khalaf^{1)†}, Torbjörn Bengtsson^{1)†}

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

†= Equally shared supervision

Background/Objective: Using *in silico* models, we have discovered and developed novel antibacterial substances, several of which are very potent *in vitro* and inhibit both gram-positive and gram-negative bacteria at micromolar concentrations. Work is currently ongoing to further develop and characterize these novel compounds, with regards to their effectiveness, safety, and interactions with both bacteria and human cells.

Method: To develop and characterize our novel substances, we use several different *in vitro* models, such as determination of MIC and MBC, checkerboard assays, cell culture models and ELISA, in combination with *ex vivo* and *in vivo* models.

Result: Of the several potent substances discovered, we have identified a leading substance on which to focus. MIC and MBC values for *S. aureus* and *E. coli* are at micromolar concentrations, and the substance does not appear to be cytotoxic to human keratinocytes. When combining the substance with several different antibiotics, we see a synergistic or additive effect. In addition, keratinocytes infected with *S. aureus* and treated with the substance are able to effectively combat the infection and remain viable for over 24 hours.

Conclusion: Our results indicate that our substance could be effective and safe to use as a topical treatment for infected wounds, either alone or in combination with low doses of antibiotics. We believe this could reduce the overall use of antibiotics and help combat the increasing prevalence of antibiotics-resistant bacteria. Further studies are required, such as *ex vivo* and *in vivo* models, as well as developing different formulations for topical administration.

Criminal Convictions in Males and Females Diagnosed with ADHD: A Population-Based Study

Anna-Karin Ångström¹⁾, Anneli Andersson¹⁾, Miguel Garcia-Argibay¹⁾, Laura Ghirardi²⁾, Catherine Tuvblad^{3,4)}, Henrik Larsson^{1,2)}

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

- 2) Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Sweden
- 3) School of Psychology, Law and Social Work, Örebro University, Sweden
- 4) Department of Psychology, University of Southern California, United States

Background/Objective: In general, individuals with Attention-Deficit/Hyperactivity Disorder (ADHD) has previously been shown to have an increased risk of arrests, convictions, incarcerations, and recidivism, compared to individuals without ADHD (1,2,3). However, less is known about the association between ADHD and criminal convictions in males and females separately.

Method: Individuals born between 1986 and 1997 were identified using Swedish national registers, and the final cohort consisted of n = 635,391 males and n = 600,548 females. Of which, a total of 5.1% of the males and 2.7% of the females had been diagnosed with ADHD.

Result: In males, ADHD was associated with an increased risk of being convicted of a violent crime, adjusted hazard ratio (adjHR) (95% confidence interval) 3.37 (3.26-3.50), and a non-violent crime 2.50 (2.42-2.53). In females, ADHD was associated with an increased risk of being convicted of a violent crime 4.28 (3.99-4.60), and a non-violent crime 2.52 (2.42-2.62).

Conclusion: After adjustments for year of birth, socioeconomic status (SES), and comorbid psychiatric disorders, both males and females diagnosed with ADHD had an substantial increased risk of being convicted of a violent and a non-violent crime, compared to males and females without ADHD. This highlights the importance of crime prevention strategies, and early intervention specifically targeted towards individuals diagnosed with ADHD.

References: 1. Lichtenstein, P., Halldner, L., Zetterqvist, J., Sjölander, A., Serlachius, E., Fazel, S., Långström, N., & Larsson, H. (2012). Medication for attention deficit-hyperactivity disorder and criminality. *The New England journal of medicine*, 367(21), 2006–2014. <u>https://doi.org/10.1056/NEJMoa1203241</u>

2. Mohr-Jensen, C., & Steinhausen, H. C. (2016). A meta-analysis and systematic review of the risks associated with childhood attention-deficit hyperactivity disorder on long-term outcome of arrests, convictions, and incarcerations. *Clinical psychology review*, 48, 32–42. <u>https://doi.org/10.1016/j.cpr.2016.05.002</u>

3. Mohr-Jensen, C., Müller Bisgaard, C., Boldsen, S. K., & Steinhausen, H. C. (2019). Attention-Deficit/Hyperactivity Disorder in Childhood and Adolescence and the Risk of Crime in Young Adulthood in a Danish Nationwide Study. *Journal of the American Academy of Child and Adolescent Psychiatry*, 58(4), 443–452. https://doi.org/10.1016/j.jaac.2018.11.016