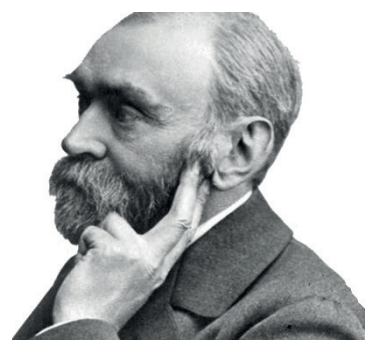


# NOBEL DAY FESTIVITIES 2018

10-YEAR ANNIVERSARY

ÖREBRO UNIVERSITY

10 DECEMBER 2018



Traditionally on 10 December, the anniversary of Alfred Nobel's death, the Nobel Prize in Physiology or Medicine, is awarded.

Organised and hosted by:  
School of Medical Sciences and School of Health Sciences  
acknowledge this day by organizing  
their own research activities and festivities.

## BOOK OF ABSTRACTS

Schools of Medical Sciences and  
School of Health Sciences  
Örebro University, Örebro, Sweden  
10 December 2018

Editors: Programme Committee  
Professors: Nikolaos Venizelos, Allan Sirsjö,  
Elisabeth Ericsson, Magnus Johansson,  
Hans Hjelmqvist, Johan Jendle, Mats Eriksson,  
Mats G Karlsson, Margareta Möller.



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## Preface

The "Nobel Day Festivities" were established 2009 by Biomedicine, Department of Clinical Medicine, Schools of Medical Sciences and Health Sciences at Örebro University, and is organized traditionally every year in order to notice the anniversary of Alfred Nobel's death (10th of December) with scientific activities including poster presentations and selected oral presentations by doctoral students, postdocs/researchers and medical students, which are documented in this "Book of abstracts". Nobel day's activities are open and scheduled so that all students and personnel can attend the scientific activities.

We warmly welcome you to enjoy all the good science that will be presented at Nobel Day Festivities, Örebro University 2018.

### *The Committee*

Editors: Programme Committee

Professors: Nikolaos Venizelos, Allan Sirsjö, Elisabeth Ericsson, Magnus Johansson, Hans Hjelmqvist, Johan Jendle, Mats Eriksson, Mats G Karlsson, Margareta Möller.



## Smoking in pregnant women diagnosed with ADHD – A nationwide population-based study

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**Objective:** Attention-deficit/hyperactivity disorder (ADHD) is associated with an increased risk for smoking, younger age at smoking initiation and more difficulties with smoking cessation compared to non-ADHD individuals. However, less is known about smoking in pregnant women diagnosed with ADHD.

**Methods:** Women giving birth to their first child between 2000 and 2013 in Sweden (n = 622,037) were identified of which, 1.2% (n = 7,444) were diagnosed with ADHD. Information on smoking at three different time points was collected during pregnancy.

**Results:** ADHD was associated with an increased risk of smoking prior to pregnancy, adjusted risk ratio (adjRR) (95% confidence interval) 2.11 (2.05-2.16), early in pregnancy, 2.97 (2.85-3.09), and late in pregnancy, 3.31 (3.14- 3.47). Women with ADHD were less likely to cease smoking during pregnancy, compared to women without ADHD (adjRR for continuing to smoke from prior to early in pregnancy: 1.55 (1.50-1.60), and from early to late in pregnancy: 1.17 (1.14-1.21). Pregnant women with a sibling diagnosed with ADHD had a twofold increased risk of smoking prior to and during pregnancy, compared to women without a sibling with ADHD.

**Conclusions:** Women with ADHD are considerably more likely to smoke throughout pregnancy and are less likely to cease smoking. Women with ADHD in their fertile or pre-fertile years, should be targets for smoking prevention and smoking cessation programs to ensure better mother and child outcomes. Family history of ADHD rather than ADHD status itself could be used by clinicians to identify women in need of support with smoking cessation prior/during pregnancy.

## Complex Psychiatric Symptomatology emerging into Neuromyelitis Optica Spectrum Disorder with Increased Aquaporin-4 Microparticles in Cerebrospinal Fluid: A Case Report

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**Background:** Neuromyelitis optica spectrum disorders are severe autoimmune inflammatory diseases of the central nervous system associated with the presence of immunoglobulin G antibodies against the water channel protein aquaporin 4. During exacerbation, specific aquaporin 4 immunoglobulin G may be produced intratechally. We measured extracellular aquaporin-4 microparticles in the cerebrospinal fluid of a patient who later developed the usual symptoms and signs of neuromyelitis optica spectrum disorder.

**Case presentation:** A 17-year-old girl developed acute onset motor and vocal tics and difficulties in walking, peripheral numbness, muscle pain and bilateral headache following a strep infection. At age 22 she had a multitude of symptoms. Over the years she fulfilled the diagnostic criteria for anorexia nervosa, depression, sleep disorder, obsessive compulsive disorder, generalized anxiety disorder, panic disorder, agoraphobia, social anxiety disorder, development coordination disorder, attention deficit disorder, hypomania, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections, conversion disorder, psychosis and schizotypal personality syndrome. At age 24 she was found to have elevated titres of aquaporin 4 antibodies in serum, suggestive of a probable neuromyelitis optica. Visual impairment and swollen optical nerves were verified by Magnetic resonance imaging. Rapid symptom relief was obtained after treatment with the immunomodulatory drug rituximab (anti-CD20 antibodies). We found a significant increase of extracellular microparticles of aquaporin 4 in cerebrospinal fluid two years prior the full clinical development of neuromyelitis optica.

**Interpretation:** Microparticles of aquaporin 4 represent subcellular arrangements, which may influence the pathogenesis of Neuromyelitis optica spectrum disorder and may serve as biomarkers for the underlying cellular disturbances. The increase of aquaporin-4 microparticles in cerebrospinal fluid may be used for early diagnostic purposes, for prevention and for evaluation of effective treatment, long-term follow-up studies and elucidating the pathophysiology in neuromyelitis optica spectrum disorders.

## Impaired ambulatory function, or orofacial function increase the risk for obstructive airway symptoms in children and young people with cerebral palsy

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**Objective:** Cerebral palsy (CP) is characterized by impaired muscle control that can result in difficulties with orofacial functions (eating, controlling saliva, and co-ordination of breathing and swallowing) and gross motor function (sitting, standing, and walking). Impaired muscle control is often combined with impaired airway protective responses making individuals with CP vulnerable to respiratory illness. The aim of this study was to investigate the prevalence of and identify risk markers for treatment-requiring obstructive airway symptoms in children and young people with CP.

**Methods:** This study was conducted on a geographically defined population aged between 5 and 22 years diagnosed with CP. An interview based on three instruments and was accomplished by 129 out of 132 eligible individuals and/or their parents. Respiratory symptoms indicative of upper airway obstruction (wheezing or whistling in the chest) and nasal airway obstruction (sneezing, or a runny, or a blocked nose when not having a cold), were registered according the International Study of Asthma and Allergy in Children (ISAAC) protocol. Orofacial dysfunction was assessed according to the Nordic Orofacial Test – Screening (NOT-S) 'chewing and swallowing' and 'saliva control' domains. Gross motor function was classified according to Gross Motor Function Classification System (GMFCS) five-level system. In short, level I walk stairs without use of handrail, level II walk without walking aids but need to use handrail, level III walk with handheld mobility device, level IV use wheelchair, and level V transported in wheelchair.

Odds ratios (OR) were calculated to explore the relationship between treatment-requiring obstructive airway symptoms (yes/no) and each variable potentially associated.

**Results:** The prevalence of obstructive airways symptoms treated with medication and/or Positive Expiratory Pressure (PEP) was 21.7%. The prevalence of respiratory treatment and treatment types was highest among non-ambulant individuals in need of sitting support (GMFCS level V) and lowest among ambulant individuals (GMFCS I).

The largest risk marker for treatment-requiring obstructive airway symptoms was having all nutrition by gastrostomy tube (OR=40.0). Moreover, gastrostomy tube in use, difficulty with consistencies, long meals, cough during meals, and loss of saliva were all significantly associated (OR=3.5–21.1). Severe (GMFCS level V) gross motor impairment (OR=28.8), dyskinetic CP (OR=8.5), and a body-weight below the 5th percentile (OR=3.1) were also associated while sex and age were not.

**Conclusion:** Risk markers for treatment-requiring obstructive airway symptoms among children and young people with cerebral palsy were having severe motor impairment, having nutrition by gastrostomy, or having dyskinetic type of cerebral palsy.

## Differential virulence of *Neisseria meningitidis* serogroups W and Y in transgenic mice

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**Objective:** *Neisseria meningitidis* serogroups W and Y are the most common serogroups causing invasive meningococcal disease in Sweden. The aim of this study was to investigate the increased incidence of serogroup W and Y, which seems to be associated with different clinical forms and severity of disease.

**Methods:** Thirteen serogroup W and eight serogroup Y isolates were included. Intraperitoneal infections were followed for 24 hours in transgenic BALB/c mice expressing human transferrin. Blood was drawn to determine CFU/ml and amount of KC, a pro-inflammatory cytokine. Induction of apoptosis in the human epithelial cell line Hec-1-B and the recruitment of immune cells after infection in a mouse was investigated by FACS.

**Results:** Large differences in infection were found between serogroups; mice infected with serogroup W isolates had higher CFU/ml and KC in the blood, compared to serogroup Y. A higher induction of apoptosis was detected *ex vivo* following serogroup W infections compared to serogroup Y infections. For serogroup W a recruitment and apoptosis of neutrophils and monocytes/macrophages was detected following infection *in vivo*.

**Conclusions:** The results show that serogroup W had higher invasiveness *in vivo* in transgenic mice than serogroup Y. We propose that the increased apoptosis of neutrophils and monocytes/macrophages in serogroup W allows these isolates to escape the immune system and cross the mucosal epithelial barrier into the blood stream. However, our data did not allow an explanation for the high incidence of serogroup Y in Sweden. This increase might be due to other factors than an increased virulence.



## Peritoneal bridging versus fascia closure of the defect in Intraperitoneal Onlay Mesh Repair (IPOM). A randomised controlled trial

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**Background:** Laparoscopic ventral hernia repair (LVHR) was first described in 1992 and has since then become a routine procedure. Simple Intraperitoneal Onlay Mesh (IPOM) Repair and IPOM with fascia closure prior to mesh placement (IPOM-plus) are the two main methods employed for laparoscopic ventral hernia repair (LVHR). Although IPOM-plus results in less post-operative seroma complications than simple IPOM, it results in more post-operative pain. As an alternative, the hernia sac may be used for peritoneal bridging between the mesh and the abdominal wall. The aim of this randomised controlled trial was to test whether IPOM with peritoneal bridging causes less postoperative complications and earlier recovery than IPOM-plus.

**Method:** The study was conducted as randomized double blind with 50 patients, randomised to IPOM-plus or IPOM with peritoneal bridging. The primary outcome measure was post-operative seroma, and secondary outcome measure were post-operative pain and mobilization. The patients were followed-up after one week, one month, and will be followed-up for further 6 months and one year in this ongoing study. The seroma formation will be radiologically assessed at one-year follow-up.

**Results:** The incidence of post-operative seroma was 3/25 in the IPOM-plus group and 0/25 in the IPOM with peritoneal bridging group at one month of follow-up ( $p=0.074$ ). The mean VAS score was  $6.4\pm 1.1$  vs  $2.0\pm 1.2$  ( $p<0.05$ ) for IPOM-plus and IPOM with peritoneal bridging respectively at one week follow-up.

**Conclusion:** IPOM with peritoneal bridging results in less post-operative seroma formation, less post-operative pain, and earlier recovery than IPOM-plus, but larger studies are required to confirm this finding.

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## Central and peripheral blood pressure and the association with BMI in young adults – the Lifestyle, Biomarkers, and Atherosclerosis Study

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**Objective:** Obesity has nearly tripled worldwide during the last four decades, especially in young adults, and is of growing concern since it is a risk factor for cardiovascular disease (CVD) and several other non-communicable diseases. We explored how body mass index (BMI) are associated with central and peripheral systolic blood pressure (SBP) in a population of healthy, young women and men, from the Swedish Lifestyle, Biomarkers, and Atherosclerosis (LBA) Study.

**Methods:** The 834 individuals were self-reported healthy, non-smoking, age 18-25 years. Brachial blood pressure (peripheral blood pressure) was measured with an oscillometric, non-invasive blood pressure method using a digital automated device (GE Healthcare, Dinamap V100, Buckinghamshire, UK). Carotid blood pressure (central blood pressure) was measured with applanation tonometry over the right common carotid artery (AtCor Medical Pty Ltd, SphygmoCor, Sydney, Australia). BMI (kg/m<sup>2</sup>) was calculated and categorized into underweight (<18.50), normal (18.50-24.99), overweight (≥ 25.00), or obese (≥ 30) according to classification by World Health Organization.

**Results:** The women with overweight and obesity had significantly higher central and peripheral SBP than the under- and normal weight women, P<0.001. The overweight men had significantly higher central and peripheral SBP than the normal weight men, P<0.01. The men with overweight and obesity had also significantly higher peripheral SBP than the underweight men, P<0.01.

**Conclusions:** The positive association between central and peripheral SBP and BMI is observed already in young adults. BMI is a very simple but useful CVD risk indicator, significantly related to both central and peripheral blood pressure.

## **Self-rated joint hypermobility: The five-part questionnaire evaluated in a Swedish non-clinical adult population.**

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**Objectives:** The aim of this study was to test validity and reliability of the five-part questionnaire on hypermobility (5PQ) translated into Swedish on a non-clinical adult population.

**Methods:** A structured procedure was used for the translation of the 5PQ into Swedish. The Beighton Score was used as reference standard for generalised joint hypermobility. Test-retest reliability was tested in a separate group who filled in the questionnaire twice with a ten-week interval. Participants consisted of a convenience sample recruited in Stockholm, Sweden (2017).

**Results:** A total of 328 subjects were included in the study, 297 subjects in the validity group and 31 subjects in the reliability group. When evaluated against a Beighton Score including historical hypermobility, cut-off  $\geq 5/9$ , the Swedish 5PQ attained a sensitivity of 78%, a specificity of 73% and an area under the curve of 0.81. The Swedish 5PQ showed substantial to almost perfect test-retest reliability.

**Conclusions:** The Swedish 5PQ is a valid and reliable instrument to screen for or identify generalised joint hypermobility.

**Beneficial bacteria that affect Toll-like receptors in the gut immune system: the case of PSA on *Bacteroides fragilis* and transcription profile of developmentally-regulated genes**

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Abstract not available  
Only Poster

## IL-6 signaling regulates production of IL-8 in human vascular endothelial cells

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**Objective:** IL-6 exerts its biological function via two distinct pathways, namely the anti-inflammatory or classic pathway and the pro-inflammatory or trans-signaling pathway. Here, we present a regulatory role for IL-6 trans-signaling on IL-8 expression and we aim at elucidating the underlying mechanism for these observations.

**Methods:** Human umbilical vein endothelial cells were seeded at a density of 60-300x10<sup>3</sup> cells/well in 24 or 6-well plates with complete endothelial medium overnight. Subsequently, the medium was replaced with antibiotic-free medium and the cells were stimulated with different stimuli prior to incubation with IL-6 and soluble IL-6 receptor for up to 48hs. Secreted IL-8 in supernatant was measured using ELISA and the gene expression was measured with qRT-PCR.

**Results:** Our results show that IL-6 trans-signaling, but not classic signaling, significantly downregulates basal expression of IL-8 in vascular endothelial cells in a dose- and time-dependent manner. Likewise, activation of TGF- $\beta$  signaling pathway was also observed to downregulate IL-8 expression. However, the effect of TGF- $\beta$  was significantly smaller. On the other hand, stimulation with IL-17A, LPS and TNF- $\alpha$  were found to induce expression and secretion of IL-8, suggesting a pro-inflammatory role for IL-8. Induced IL-8 expression by these stimuli were slightly reduced by incubation with IL-6 and its soluble receptor. This downregulation seems to be mediated via Janus Kinase pathway as inhibition of this pathway with JAK inhibitors restores IL-8 level.

**Conclusions:** Taken together, our data suggest that IL-6 trans - but not classic signaling regulates basal, and to a certain extent induced, IL-8 production in human vascular endothelial cells.

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**Title of presentation: Treatment for upper limb malformation in different areas of the world**

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**Objective:** Children with upper limb malformation present with deficiencies in many ways<sup>1</sup> and the treatment may vary greatly around the world<sup>2</sup>. Handsmart is a volunteer organization with the mission to support and empower people world-wide who are engaged in this field of rehabilitation. The aim was to gather information from different areas of the world and share this on the [www.handsmartgroup.org](http://www.handsmartgroup.org) web-place.

**Method:** A web-based survey was used to gather data. The survey was shared on the Handsmart website, through providers and members using snowball sampling.

**Results:** Sixty-eight respondents from 18 countries representing Oceania, Asia, Europe, and North America with 35 occupational therapists, 6 physiotherapists, 23 prosthetists, and four other health care professionals participated. Only five of these countries do not have governmental funding for the provision of care for people with upper limb loss. Intervention is guided by the presentation of the limb. Not all respondents reported that they fit body-powered prostheses for children. In some clinics (12 of 68 respondents), no treatment other than functional prostheses is provided for the children. Overuse or repetitive strain injuries are common with this population, especially as children age into adolescence and adulthood. Many people stated they would like to see clear treatment guidelines used by multi-disciplinary teams to fit children. Recommendations should include follow-up practices.

**Conclusion:** Children are treated differently in various parts of the world based on their level of limb loss, different funding, family support, and therapy resources. Further studies should encompass a representative sample of children's clinics.

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## Protein interactions in the NLRP3 inflammasome

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**Objective:** Inflammasomes are an important part of the inflammatory response, responding to a plethora of stimuli by activating pro-inflammatory cytokines and promoting inflammation. While several distinct inflammasomes have been identified, one of the most extensively studied is the NLRP3 inflammasome. Malfunctions in, or dysregulation of, the NLRP3 inflammasome can lead to chronic inflammation and disease with potentially devastating effects to the body. Although much is known about NLRP3 inflammasome activation and output, there are many unanswered questions regarding its composition and structure, and next to no knowledge exists about if and how various stimuli or mutations affect the structure and composition of the inflammasome. The objective of this project is thus to develop methods for analysis of inflammasome composition and examine if/how it is affected by different stimuli and genetic variation. Experimental data and previously published results will be compiled and utilized in computer modelling and simulations to either verify existing hypotheses, or be used to create a new or improved model with the purpose of explaining individual variations in the inflammatory response.

**Methods:** NLRP3 inflammasome formation will be stimulated in the human THP-1 cell line, extracted and purified using immunoprecipitation or other comparable method. Existing protocols using Lipid- based Protein Immobilization technology will be modified and/or optimized for use with soluble protein complexes, promoting immobilization of inflammasome complexes that will allow precise, sequential digestion. Obtained peptides will be analyzed by mass spectrometry. Controlled digestion will hopefully yield structural and compositional information usable in the generation of computer models of inflammasome structure and function.

**Results:** The project is still in an early phase and results are pending. Expression of NLRP3 protein has been verified in unstimulated and stimulated THP-1 cells by Western blot. A lysis method that is both Lipid-based Protein Immobilization technology and mass spectrometry compatible has been successfully developed. Evaluation of cytosolic protein immobilization in the LPI™ flow-cell is underway, while results regarding detection of NLRP3 inflammasome components by mass spectrometry are pending.

The expectation is that changes, if any, in inflammasome structure or composition which are dependent on variations in stimulus or genetics will be detectable, and that this information can be incorporated into a computer model that links inflammasome composition and structure to function.

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## The mucosal transcriptomic host response to faecal microbiota transfer in irritable bowel syndrome

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**Introduction:** Faecal microbiota transfer (FMT) consists of the introduction of a new microbiota into the intestine of a patient with the aim to restore a disturbed gut microbiota. Studies have shown that FMT reduces inflammation in ulcerative colitis, and improves insulin sensitivity in metabolomic syndrome (1). However, the colonic mucosal host response to FMT by gene expression has, to the best of our knowledge, not yet been studied.

**Aims and Methods:** The aim of the study was to investigate the IBS patients' colonic mucosal response to the administration of allogenic (from a donor) or autologous (own) faecal material into the colon. In a recently conducted randomised, double-blinded placebo-controlled clinical trial, 16 IBS patients were treated with FMT by colonoscopy after bowel cleansing. RNA was isolated from colonic biopsies, collected by sigmoidoscopy, at baseline, 2 weeks and 8 weeks after FMT in the group that received allogenic faecal material as well as in the group that received autologous faecal material. Whole genome microarray (Genechip Human Gene 2.1 ST, Affymetrix) was used to analyse gene expression. Pathway analysis was performed by Gene Set Enrichment Analysis.

**Results:** Pathway analysis of the gene expression data showed that in patients treated with allogenic faecal material, significantly upregulated pathways consisted mainly of immune response-related pathways such as "Allograft rejection" and "Intestinal immune network for IgA production". On the contrary, in the patients receiving autologous faecal material, pathways involving immune response-related processes, such as "Primary immunodeficiency" were significantly downregulated.

**Conclusion:** This study shows that the host mucosa responds to FMT by up- and downregulating gene expression pathways involved in immunological processes. The upregulated immune-related pathways in the allogenic FMT and downregulated immune-related pathways in the autologous FMT group indicate that the host reacts to the newly introduced, foreign microbiota in a different way than to the bowel cleansing and re-introduction of the own microbiota. Further analysis need to be performed in order to identify which molecular interaction networks are involved, and if these gene expression results are transferable to protein level.

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**Saffron, naked ladies and bear's garlic:  
a suicide attempt inspiring explorations into toxicology, botany and linguistics**

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**Background:** Considerable uncertainty prevails regarding the presumed toxicity imposed by excessive intake of the traditional spice saffron. Nonetheless, saffron has been documented as an effective antidepressant agent (1).

**Case report:** A case of severe depression is described, involving intoxication with a high dose of saffron, taken with suicidal intent. To the patient's disappointment, no symptoms of toxicity emerged. Five days later, the author examined the patient clinically in order to characterise signs of assumed toxicity. Findings were insubstantial, thereby questioning the alleged harmfulness of saffron. Subsequently, the patient was successfully treated with electroconvulsive therapy (ECT).

**Review of relevant literature:** Almost no reports exist of toxicity attributed to common saffron (*Crocus sativum* L.) (2). In contrast, numerous severe intoxications, including lethal multi-organ failure with shock, have repeatedly been caused by meadow saffron (*Colchicum autumnale* L.). This plant is not related to the *Crocus* genus, but has somewhat similar flowers, known as **naked ladies**. Notably, it contains high concentrations of the alkaloid colchicine, a potent inhibitor of microtubule formation and mitosis. Carefully dosed, colchicine may be used to treat familial Mediterranean fever and gouty arthritis; however, the therapeutic index is dangerously narrow. Thus, a meal including leaves of meadow saffron is likely to be fatal. The customary reason for such hazardous meals is that the foliage of *Colchicum autumnale* strikingly resembles **ramson** (*Allium ursinum* L.); also known as **bear's garlic**, a delicious nutrient popular among cognisant chefs.

**Conclusion:** The fortunately miscalculated self-harm of the patient contrasts with the fatally ignorant feeding of other cases. Behind lies linguistic and botanic confusion regarding three somewhat similar plants. Saffron, *Crocus sativum*, seems innocuous and probably has anti-depressant properties. Naked lady, *Colchicum autumnale*, however, is deadly poisonous, while bear's garlic, *Allium ursinum*, is a culinary asset.

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## Increased gene expression and protein levels of inflammatory cytokines in patients with severe mental illness

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**Background:** Research indicates inflammatory processes involvement in the pathophysiology of psychiatric diseases. Abnormalities in cytokine levels have been reported, but studies on gene- and protein expression are scarce. Psychiatric diagnostics is a contentious area; possibly severity rather than specific symptomatology could define psychiatric subgroups. Our aim was to investigate inflammatory perturbations in severe psychiatric disorders by studying both gene expression and cytokines associated with the NLRP3 inflammasome, with a trans-diagnostic approach.

**Methods:** This study includes 40 severely ill psychiatric patients with obsessive-compulsive disorder, schizophrenia spectrum disorder, autism spectrum disorder and/or non-suicidal self-injury disorder. Forty healthy subjects, matched for age, gender and ethnicity, were controls. Gene expressions of inflammatory-related genes were analyzed using real-time qPCR. From plasma, protein levels were measured using electrochemiluminescence ELISA technology.

**Results:** We found increase in patients' gene expression compared to controls in the genes, *CASP1* ( $p = 0.0005$ ), *NLRP3* ( $p = 0.0426$ ), *PYCARD* ( $p = 0.0484$ ), *IL1B* ( $p = 0.0014$ ) and *IL-1RN* ( $p = 0.0013$ ). However, *IL18* levels did not differ. For more general markers of inflammation, *TNF* ( $p = 0.0308$ ) was significantly increased compared to controls, but not *IL6* and *IL10*.

Cytokine levels for the IL-1 family showed significant higher levels for IL1Ra ( $p < 0.0001$ ) and IL-18 ( $p = 0.0005$ ) in patients compared to controls, but not for the IL-1 $\beta$  levels. Patients had also higher levels of the cytokines TNF ( $p = 0.0001$ ) and IL-6 ( $p < 0.0001$ ), but not IL-8.

### Conclusion

The data indicate that individuals with severe psychiatric disorders have increased inflammatory activity irrespective of diagnostic categories.

## Integrated analysis reveals reciprocal immune response signaling between bone marrow multipotent stromal cells and hematopoiesis at the transcriptional but not at the protein level in myelofibrosis

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**Purpose:** Signaling pathways in response to crosstalk between hematopoiesis and bone marrow multipotent stromal cells (BMSC) in Philadelphia chromosome negative myeloproliferative neoplasms (MPN) have been insufficiently explored. Therefore, a whole genome microarray screening on cultured BMSC from fibrotic and non-fibrotic MPN subtypes was performed., quantitative proteomics was also performed on BMSC from patients with primary/secondary myelofibrosis. The results were compared with official MPN datasets from GEO2 for an integrated understanding.

**Methods:** BMSC from trephine biopsies were cultured, characterized, and analyzed by global gene expression microarray and/or proteomics (in passages 4-8). Dysregulated genes with absolute fold change (FC) >2 and uncorrected  $P < 0.05$  from comparisons of 9 PMF/MF (grade 2-3/3 fibrosis) and 6 non-fibrotic MPN (grade 0-1/3 fibrosis) patients respectively against 8 healthy controls, and from other MPN transcriptomic datasets from the GEO2 repository, were subjected to Ingenuity Pathway Analysis (IPA). Comparisons included the proteomics results from quantitative mass spectrometry of BMSC from 5 PMF/MF patients and 5 healthy controls (absolute FC >1.2,  $P < 0.05$ ).

**Results:** In the new PMF/MF BMSC transcriptomic dataset, the 7 most significant canonical pathways from IPA with absolute z-score >2 all showed suppressed inflammation/immune response signaling. Interferon signaling (suppressed) was the top significant pathway. Comparison with the other PMF BMSC transcriptomic dataset GSE44426 revealed several gene expressions and pathways of inhibited inflammation/immune response in common, contrasting to activated inflammation/immune response signaling in datasets of PMF CD34+ cells (GSE53482), granulocytes (GSE54646) and megakaryocytes (GSE53482). As upstream regulators, interferons and TNF were predicted to be inhibited in the PMF/MF BMSC datasets, but activated in the hematopoietic datasets. However, in the proteomic analysis of myelofibrosis BMSC, interferon signaling was clearly activated, thus reciprocal to the transcriptomic BMSC results. Upregulation of the interferon-induced proteins IFI44L and ISG15 in PMF/MF BMSC was validated by Western blot.

**Conclusions:** The cultured PMF/MF BMSC exhibited suppressed immune response signaling at the transcriptomic level, but opposite regulation at the protein level. Including the dataset comparisons showing reciprocal transcriptomic signaling between BMSC and hematopoiesis, the findings indicate a “sense and switch” reaction at the mRNA level in BMSC to activated inflammation/immune response signaling. Further investigations of multiple cell types and with co-culturing techniques are necessary for unraveling the roles of interferons and other regulators in MPN pathogenesis, as well as in efforts to find novel treatment options.

## Reinvestigation of a proportion of HPV-negative tumors in a Swedish cohort of cervical cancer

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**Objective:** Despite the common perception that HPV is a requirement for the development of Cervical cancer (CC), in many studies a considerable number of CC test HPV-negative. Presently, many countries are shifting to HPV primary CC screening and it is of importance to increase the knowledge about the group of CC that test HPV-negative. The aim of this study was to reinvestigate a proportion of cervical tumors with a negative or invalid test result in a Swedish cohort (n=209) of patient samples previously analyzed for detection of HPV where 14 % of the tumors initially were found to be HPV negative.

**Methods:** All tumors with a HPV negative or invalid result from genotyping with Anyplex<sup>TM</sup> II HPV28 (Seegene), a real time PCR method targeting the viral L1 gene, were included (n=37). Second approach included an in house real time PCR protocol instead targeting the viral oncogenes E6 or E7. Samples with HPV negative results with both methods were assessed by pathologist and tumors with lacking amount and quality were excluded. Remaining HPV-negative samples were investigated with immunohistochemistry.

**Results/Conclusion:** The HPV negativity proportion could after reinvestigation be reduced by half. Part of the HPV negative cases show strong/diffuse p16 immunoreactivity, indicating a lower actual negativity rate than the presented of 7 %. Confirmed HPV negativity was significantly associated with worse prognosis, high patient age, longer sample storage time and AC histology. The prognosis difference between HPV positive and negative CC seems to depend on histology rather than HPV status.

**A novel purine analogue bearing nitrate ester inhibits platelet functions by decreasing ROCK activity**

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**Abstract not available**  
**Only Poster**

## The potential of osteopontin to predict recurrence of hormone receptor positive breast cancer

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**Introduction:** Tumor expression of hormone receptors are analyzed in order to identify patients likely to benefit from endocrine therapy. More than one third of the patients still experience recurrence, which highlights the need for additional predictive biomarkers. The glyco-phosphoprotein osteopontin (OPN), encoded by the SPP1 gene, has previously shown association with poor prognosis, but to date, few studies regarding the predictive value of OPN have been made.

**Aim:** To evaluate the potential of OPN as a discriminator of recurrence and non-recurrence of hormone receptor positive breast cancer by analyzing gene- as well as protein expression of C- and N-terminal OPN (OPN-C and OPN-N, respectively).

**Material and methods:** We evaluated expression of OPN-C and OPN-N by immunohistochemistry (n=116) and SPP1 gene expression by quantitative polymerase chain reaction (n=100), in recurrent and non-recurrent hormone receptor positive and tamoxifen treated breast cancer patients, diagnosed at Department of Oncology, Örebro University Hospital, Sweden between 2000 and 2010.

**Results:** We found an increased risk of recurrence with OR=2.50 per one-unit of SPP1 expression ( $p = 0.006$ ), strengthened by multivariate regression analysis adjusting for tumor grade, HER 2-status and other treatments (OR=3.62, 95 % CI 1.45-9.07,  $p = 0.006$ ). However, protein expressions did not associate to risk of recurrence and were not correlated to SPP1-expression.

**Conclusion:** Primary tumor SPP1 gene expression seems to be associated with risk of recurrence of hormone receptor positive breast cancer, while the protein expression seems to be of less influence according to our methods of detection.

## Individual variations in platelet reactivity towards ADP, epinephrine, collagen and nitric oxide, and the association to arterial function in young, healthy adults.

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**Introduction:** Platelet aggregation and secretion can be induced by a large number of endogenous activators, such as collagen, adenosine diphosphate (ADP) and epinephrine. Conversely, the blood vessel endothelium constitutively release platelet inhibitors including nitric oxide (NO) and prostacyclin. NO and prostacyclin are also well-known vasodilators and contribute to alterations in local blood flow and systemic blood pressure.

**Materials and Methods:** In this study we investigated individual variations in platelet reactivity and arterial functions including blood pressure and flow-mediated vasodilation (FMD) in 43 young, healthy individuals participating in the Lifestyle, Biomarkers and Atherosclerosis (LBA) study.

Platelet aggregation and dense granule secretion were measured simultaneously by light transmission and luminescence. FMD was measured with ultrasound.

**Results:** The platelet function assay showed inter-individual differences in platelet reactivity. Specifically, a sub-group of individuals had platelets with an increased response to low concentrations of ADP and epinephrine, but not collagen. When the NO-donor S-nitroso-N-acetyl-DL-penicillamine (SNAP) was combined with high doses of these platelet activators, the results indicated for sub-groups of NO-sensitive and NO-insensitive platelets. The individuals with NO-sensitive platelets in response to SNAP in combination with collagen had a higher capacity of FMD of the arteria brachialis.

**Conclusions:** Platelet reactivity towards ADP, epinephrine and NO differs between young, healthy individuals. Some individuals have a more effective response towards NO, both in the aspect of platelet inhibition *ex vivo*, as well as vasodilation *in vivo*.



## Eye gaze technology to gain access to cognitive processes in individuals with profound intellectual and physical disabilities

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**Objective:** Individuals with profound intellectual and physical disabilities (PIPD) often cannot speak for themselves and do things for themselves. Their level of cognitive abilities is unclear. Eye gaze technology has the potential to gain access to cognitive processes and eventually enable communication among these individuals<sup>1</sup>.

**Method:** Six individuals with PIPD were given multiple sessions of eye gaze training (9-36 sessions) between February 17 to October 18. They used a screen eye-tracker (Tobii pc eye-mini) to control the objects on the screen. An eye-gaze training program with different levels of activities was used to teach *cause and effect, give appropriate response, explore the whole screen, target specific objects, choosing objects AND turn taking*. Eye-tracking data was video-recorded by Tobii gaze viewer program. The software shows heat maps and gaze plots of the areas the user has viewed on the screen. The heat map and gaze plot are superimposed over the image that the client was viewing at the time. The heat map shows what areas of the screen the user was looking at and the gaze plot shows the order of the user's gaze.

**Result:** Five out of six individuals understood *cause and effect* (>7 times). Five of them were able to *give appropriate response, explore the whole screen, target specific objects and turn-taking* (2-7 times). Only 3 of them were able to *choose between objects* (2-5 times).

**Conclusion:** Training with multiple sessions to learn to use eye gaze is necessary to gain access to cognitive processes among Individuals with PIPD.

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## Identifying compensatory movement patterns in upper extremities in prosthesis users during activity performance

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**Objective:** Low dexterity of conventional two-function (open, close) myoelectric hand prosthesis with no wrist movement often leads to compensatory shoulder and elbow movements, e.g. shoulder abduction and elbow flexion. Compensatory movements may lead to musculoskeletal pain<sup>1</sup>. It is thus important to measure objectively the amount of compensatory movements and initiate treatment to prevent overuse pain.

**Method:** Twenty-seven users of conventional myoelectric hand prosthesis performed the activity “packing a suitcase” as part of the Assessment of capacity for myoelectric control (ACMC)<sup>2</sup> at the Limb Deficiency and Arm Prosthesis Centre at Örebro University Hospital. The performances were recorded and analyzed with Dartfish motion capture video analysis software. This was used to track and measure the maximum angles for shoulder abduction and elbow flexion at the non-prosthetic and prosthetic sides during the activity performance. Two independent raters used Dartfish to analyze 10 videos and intra-class coefficient was used to calculate Inter-rater reliability. The ability to control the myoelectric prosthetic hand was assessed by the ACMC.

**Results:** The within-individual differences for shoulder abduction ranged from 2° to 52° and for elbow flexion from 1° to 66°. Prosthesis users with low ability to control the prosthetic hand (ACMC < 0) showed a significant angle difference between the elbows but no significant angle difference between the shoulders (p<0.05). Inter-rater reliability was excellent (ICC 0.9).

**Conclusion:** Measurement of compensatory movements can help to identify amputees with frequent compensatory movements. Higher ability to control the prosthetic hand may reduce compensatory movements of the elbow in prostheses users.

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## Severe sepsis and septic shock: a meta-regression analysis of the mortality 1991-2013

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**Background:** Epidemiologic data have reported an increased incidence and declining mortality rate in sepsis. However, confounding effects due to differences in disease classification and underlying severity might have contributed to these trends. To assess if a declining mortality rate over time could be supported by data derived from high-quality prospective studies, a meta-analysis was performed, using data from randomised controlled trials (RCTs) on sepsis. The primary aim of this study was to assess whether the mortality in sepsis trials has changed over time. The secondary aim was to investigate how many of the included trials that could show efficacy of the studied intervention regarding 28-day mortality.

**Methods:** We searched PubMed for RCTs enrolling patients with severe sepsis and septic shock published between the years 2002 and 2016. The included trials were assessed for quality and sorted after date of first inclusion. The meta-analysis was performed to synthesise data from individual sepsis trials.

**Results:** Of 418 eligible articles, 44 RCTs on sepsis trials were included in the final analysis, enrolling 13,315 patients in the usual care arm. The included studies enrolled patients between the years 1991 and 2013. In this time-period the mortality decreased by 0.42% annually ( $p=0.0422$ ), showing a total decline by 9.24%. Of the included trials, only 4 showed any efficacy in regards of mortality.

**Conclusion:** This study suggests that there is a declining trend in mortality in patients with severe sepsis and septic shock and that the number of new treatment options are limited.

Prospero registration number: CRD42018091100

**Keywords:** Severe sepsis, septic shock, mortality, randomised controlled trial, meta-analysis

## The effect of biases in Svebar- a new system for antibiotic resistance surveillance".

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**Introduction:** Antibiotic resistance is a constantly increasing threat to modern medicine and well-functioning surveillance systems are therefore important. Svebar is a Swedish national IT-system, with the purpose to improve national and local antibiotic resistance surveillance. Data, on all bacterial findings and antibiotic resistance, are on a daily basis transferred from local laboratories in Sweden to Svebar. However, there are several potential biases that may influence the interpretation of surveillance data.

**Aim:** To investigate the ability of Svebar to describe the current resistance levels for selected bacterial species, and thereby highlight potential biases in the system.

**Material and methods:** Data was retrieved from the Svebar database for 2017. The bacterial species chosen were *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Klebsiella variicola*, *Pasteurella multocida* and *Pasteurella canis*. Nine laboratories were included and antibiotics were selected based on nationally accepted guidelines. The effects of potential biases on resistance levels were evaluated and analysed.

**Results:** Resistance levels were lower in *K. variicola* than in *K. pneumoniae* for all antibiotics, resulting in overestimation in *K. variicola* resistance when these, as most laboratories did, were reported together. Further, laboratories testing <50% of their isolates often yielded significant higher resistance levels than those testing >90% for a specific antibiotic.

**Conclusion:** This study found several biases potentially affecting the national resistance data. In attempt to avoid these biases we suggest reporting of *Klebsiella* as subspecies, a minimum limit of 90% tested isolates towards an antibiotic when including laboratories in national data and a warning flag highlighting when a laboratory has few isolates.

**Modified lipoproteins in periodontitis - a link to cardiovascular disease?**

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**Objective:** There is a strong association between periodontal disease and atherosclerotic cardiovascular disorders. A key event in the development of atherosclerosis is accumulation of modified lipoproteins within the arterial wall. We hypothesize that patients with periodontitis have an altered lipoprotein profile towards an atherogenic form. Therefore, this study aims at identifying modifications of plasma lipoproteins in periodontitis.

**Methods:** Lipoproteins from ten female patients with periodontitis and gender and age matched healthy controls were isolated by density/gradient-ultracentrifugation. Proteins were separated by two-dimensional gel-electrophoresis and identified by map-matching or by nano-liquid chromatography followed by mass spectrometry. ApoA-I methionine oxidation, Oxyblot and total antioxidant capacity were assessed.

**Results:** Reduced levels of apoJ, phospholipid transfer protein, apoF, complement C3, paraoxonase 3 and increased levels of alpha-1-antichymotrypsin, apoA-II, apoC-III were found in HDL from the patients. In LDL/VLDL, the levels of apoL-1 and platelet-activating factor acetylhydrolase as well as apo-B fragments were increased. Methionine oxidation of apoA-I was increased in HDL, corresponding to periodontal parameters, and decreased in LDL/VLDL. Alpha-1 antitrypsin and alpha-2-HS glycoprotein were oxidised in LDL/VLDL and total antioxidant capacity was increased in the patient group.

**Conclusions:** Patients with periodontitis have an altered plasma lipoprotein profile, defined by altered protein levels as well as posttranslational and other structural modifications towards an atherogenic form, which supports a role of modified plasma lipoproteins as central factors in the link between periodontal and cardiovascular disease.

## **Different inflammasome triggers results in diverse net outcomes of inflammasome activation**

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Inflammation is an essential process for eradication of pathogenic invasions, regulation of the immunological response and tissue repair with the NLRP3 inflammasome as one of the key mediators. The NLRP3 inflammasome can be activated by a broad range of PAMPs and DAMPs. Though molecular pathways leading to assembly of the inflammasome have been extensively studied, less is known about the role of the inflammasome in directing subsequent inflammatory responses in relation to the initial stimulus. The aim of the study was to investigate the outcome of inflammasome activation by three well-known inflammasome triggers with respect to production of IL-1 family cytokines and cell death.

The extracellular concentrations of IL-1 $\beta$  and IL-18 depend on the NLRP3 inflammasome after stimulation with ATP, chitosan and SiO<sub>2</sub>. However, the cytokine concentration, especially IL-18, is sensitive to the LPS concentration as a high dose of LPS appear to saturate the system. The different triggers generate distinct quotes between IL-18 and IL-1 $\beta$ , which are 1:6, 1:4 and 1:13 for ATP, chitosan and SiO<sub>2</sub>, respectively.

IL-1 $\beta$  release is commonly used in the literature as a generic readout for NLRP3 inflammasome activation in cellular systems. However, we found that the resulting net outcome of inflammasome activation, measured in this study as released IL-1 $\beta$  and IL-18, relies heavily on the trigger used. Hence, it could be necessary revisit how we interpret the outcome of inflammasome activation and fore most we need to quantify the whole aspect of inflammasome functionality to draw conclusions on the involvement of inflammasome activity.

## High Frequency of Labral Pathology in Symptomatic Borderline Dysplasia. A Prospective Magnetic Resonance Arthrography Study of 99 Patients

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Labral pathology is seen in both dysplastic and borderline dysplastic hips. Periacetabular osteotomy (PAO) is the treatment of choice for dysplasia. However, some authors have suggested that borderline dysplastic hips with concurrent labral pathology should be treated arthroscopically. The purpose of this study was to investigate the frequency of labral pathology between dysplastic and borderline dysplastic hips, whether center-edge (CE) angle is associated with labral pathology, and finally if pain and labral pathology are associated.

99 symptomatic patients (104 hips) scheduled for PAO were examined. Five patients were excluded due to complaints from multiple joints and 4 failed to show at 2-year follow-up. 5 patients did not fill out questionnaires pre-operatively. Hips were characterized as dysplastic (CE angle  $<20^{\circ}$ ) and borderline dysplastic (CE angle  $20^{\circ} \leq 25^{\circ}$ ). A Magnetic Resonance Arthrography was performed labral pathology was classified according to the Czerny classification. Association with the CE angle, the acetabular index and preoperative WOMAC pain score was tested by multiple linear regression.

There was no significant difference in frequency of labral pathology when comparing the two groups. Across the cohort, 86 of 99 patients had labral pathology. The CE angle was associated with increasing severity of labral pathology whereas the AI angle and preoperative pain were not associated with labral pathology.

Decreased lateral coverage adversely loads the labrum, predisposing it to tears. We advocate reorienting the biomechanical forces through PAO, not arthroscopic treatment. Level of pain was not associated with labral pathology, suggesting that labral pathology may not alone explain the dysplastic pain complex.

## Have the pregnancy outcomes in women with type 1 diabetes improved in Sweden?

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**Introduction:** There have been improvements in obstetric surveillance and diabetes monitoring for women with type 1 diabetes (T1DM). Yet, the goal of normalizing pregnancy outcomes in the diabetes population, according to the St Vincent Declaration, remains difficult to achieve.

**Objective:** To investigate the trends in maternal and perinatal outcomes in T1DM pregnancies, in Sweden during 1998 to 2012. Have we reached the goal of St Vincent declaration?

**Methods:** This population based cohort study included all singleton births recorded in Medical Birth Registry (MBR), in Sweden between 1998 and 2012. Poisson regression analysis was used to calculate incidence trends. Stratification analysis was done to analyse the effects of possible confounders.

**Results:** The cohort consisted of 1,020,246 singleton births, and 6,393 (0.6 %) of these women had T1DM. In the T1DM cohort, the trends in caesarean section increased by 0.9 % per year ( $p = 0.032$ ), large-for-gestational-age (LGA) infants increased by 1.1 % per year ( $p = 0.009$ ), and small-for-gestational-age infants decreased by 4.4 % per year ( $p < 0.001$ ). However, in the background population the trends in LGA infants decreased by 1.4 % per year ( $p < 0.001$ ) and of SGA infants increased by 0.7 % per year ( $p < 0.001$ ). Parity seemed to affect the incidence for T1DM mothers, for LGA infants.

**Conclusion:** Despite improved obstetrical surveillance and diabetes monitoring among women with T1DM, the rates of LGA infants have increased over the studied 15 years in Sweden. Conversely, in the general population the rates of LGA infants decreased. We are far from reaching the goal of St Vincent declaration. Further research is needed to find targets for improvement in preconceptional and obstetrical care in Sweden.

**Keywords:** *Trends, Pregnancy, Type 1 Diabetes, Outcomes, Medical birth registry*



## Validity of the 36-item version of WHODAS 2.0 in a Swedish speaking general population

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**Objective:** The objective was to evaluate scaling properties, internal consistency, concurrent validity, and construct validity of the self-administered, 36-item Swedish version of the World Health Organization Disability Assessment Schedule 2.0 in general population.

**Methods:** By a cross-sectional survey design a random sample of adults in a Swedish region were invited by regular mail. Statistical analysis including Cronbach's alpha for internal consistency, Pearson's correlation between WHODAS 2.0 and RAND-36 for concurrent validity were performed. For construct validity known group validity by Mann-Whitney U test and 1-way ANOVA, item-scale convergent and discriminant validity and Confirmatory Factor Analysis of the proposed second order factor structure model was analyzed.

**Results:** With a response rate of 43 percent, 3482 adults participated in this study. The result showed acceptable scaling properties and good internal consistency. Concurrent validity was in line with previous studies and in expected direction. Small differences in disability between genders was observed and a significant increase in disability was reported with older age. Item-scale convergent validity was satisfactory and discriminant validity was acceptable for all domains except Self-care, Getting along and Participation. Data showed a mild support for the factor structure.

**Conclusions:** The self-administered Swedish, 36-item version of WHODAS 2.0 is comparable to other language version of WHODAS 2.0<sup>1</sup>. Validity, reliability and responsiveness of the Swedish versions of WHODAS 2.0 in different patient populations remains to be evaluated.

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## Novel purine analogues as IL-1 $\beta$ inhibitors targeting vascular inflammation

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**Objective:** Inflammation is an important factor in promoting atherosclerosis. From the recent study, Canakinumab Antiinflammatory Thrombosis Outcome Study (CANTOS) it is evident that reducing inflammation in the absence of concomitant lipid lowering reduces the rate of cardiovascular events<sup>1</sup>. Considering the profound role of IL-1 $\beta$  in promoting inflammation, IL-1 $\beta$  has gained attention as a possible therapeutic target. Novel purine analogues were synthesized to impart protective effect by inhibiting inflammation in the vessel wall. The aim of the present study is to study the possible impact of novel purine analogues on the IL-1 $\beta$  secretion in vascular cells.

**Methods:** Human aortic smooth muscle cells were incubated with or without purine analogues in the presence or absence of LPS followed by evaluation of the expression and release of IL-1 $\beta$  and additional target genes. Furthermore, purine analogues were examined for their anti-inflammatory effect in an ex-vivo model using human atherosclerotic plaque.

**Results:** Preliminary data shows that purine analogues MK118, MK176, MK177, MK175 and MK169 are effective in inhibiting IL-1 $\beta$  release in the presence of inflammatory stimuli, LPS. In addition, MK118 also reduces the IL-1 $\beta$  levels in ex vivo experiments.

**Conclusions:** We found that several of the novel purine analogues are effective in IL-1 $\beta$  inhibition in vascular cells. Our data indicate that it is necessary to study the detailed mechanism by which purine analogues inhibit the IL-1 $\beta$  secretion in vascular cells.

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## Validation of Eosinophilic Esophagitis (EoE) in Sweden

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**Background:** Eosinophilic esophagitis (EoE) is a clinicopathological diagnosis based on both histopathologic features and clinical symptoms.

**Aim:** This study aimed to validate the diagnosis in Swedish biopsy registers against patient charts. To calculate the positive predictive value (PPV) for EoE in patients with a histopathology record indicating eosinophilia in the esophagus; and to review symptoms and treatment of patients with EoE in Sweden.

**Methods:** We randomly selected 165 patients from 5 Swedish healthcare regions with a histopathology diagnosis of EoE. Out of 84 received patient charts, 73 (87%) had sufficient information and were included. Confidence intervals were calculated using Wilson Score Interval.

**Results:** Out of the 73 patients with available data, 67 had EoE, corresponding to a PPV of 92%.

**Conclusion:** Histopathology reports indicating eosinophilic inflammation in the esophagus can be used to identify patients with EoE.

**Body fat percentage is more strongly associated with biomarkers of low-grade inflammation than traditional cardiometabolic risk factors in healthy young adults - The Lifestyle, Biomarkers and Atherosclerosis Study**

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Abstract not available  
Only Poster

## The effects of adolescent depression on earnings in adulthood

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**Background:** The estimated cumulative probability of depression rising from around 5% in early adolescence to 20% in late adolescence. Adolescent depression is associated with subsequent role impairment and future societal costs. Earnings is a major marker of labor market achievement that depression in adolescence can affect with both direct effects and indirect effects by pathways of human capital factors such as education, work experience and occupation choice.

**Aims:** Our aims was to investigate (i) adult earnings of males and females with a history of persistent depressive disorder, major depressive disorder, subthreshold depression, and no depression in adolescence; and (ii) how major psychiatric comorbidities affect the association of adolescent depression and adult earnings.

**Method:** This study was based on Uppsala Longitudinal Adolescent Depression study (ULADS), initiated in Uppsala, Sweden, in 1991. The study population was all first-year students in upper secondary school (16–17 years old). We have combined comprehensive diagnostic interviews conducted in adolescence with yearly register-based data up to approximately age 40. Details on earnings was obtained for each year for the period 1993 to 2015 from the Longitudinal Integration Database for Health Insurance and Labour Market Studies (LISA). We have adjusted our results for parental socioeconomic status and comorbidity in adolescence.

**Results:** A total of 539 individuals (78.8% females) were included in the analyses. We found that earnings in adulthood for both females and males were affected by adolescent depression. Persistent depressive disorder in adolescence had a significantly robust impact on earnings in adulthood. Even after adjustments for psychiatric comorbidity such as childhood or adolescent anxiety and childhood disruptive behavioral disorders these relative differences for earnings were sustained. Disruptive behavioral disorder had a negative effect on earnings for females independent of depression subgroup.

**Conclusion:** Increased understanding of labor market outcomes in depressed adolescents can guide interventions to strengthen the human capital. Our findings demonstrate the importance of differentiating between diagnostic subgroups of adolescent depression in studying earnings in adulthood. The duration of the adolescent depressive episode proved to be decisive for adult earnings in both males and females, this underscores the importance of early treatment and indicated preventive interventions.

## **Pre-analytical aspects of extracted circulating cell-free DNA: impact of storage conditions and exposure to freeze-thawing**

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**Introduction:** Cell free DNA (cfDNA) has quickly ascended as a promising alternative for diagnosing and monitoring patients on treatment. Methods used for the analysis of cfDNA require immense sensitivity due to its low abundance. We therefore sought to investigate how different storage conditions and exposure to freeze-thawing would affect extracted cfDNA.

**Methods:** cfDNA was extracted from plasma from 30 healthy individuals. Eluates were pooled and stored in aliquots at either -80°C, -20°C, +4°C or at room temperature (RT) with measurements made at extraction day (day 0) and after 1, 4, 7, 30 and 90 days. A portion of the original pool was exposed to 10 freeze-thaw cycles at extraction day. Analysis was performed using TapeStation and qPCR. The experiment was repeated using TapeStation technology. Data from qPCR contained concentration of fragments of 41, 129 and 305 base pairs in length, calculated from a standard curve, and TapeStation was manually analyzed for the same fragments. DNA quality was assessed as fragments of 129 base pairs divided by 41 base pairs length.

**Results:** Exposure to 10 freeze-thawing cycles did not result in degradation of cfDNA ( $p > 0.05$ ).

A significant decrease in concentration was found at 30 days for -20°C and +4°C (only TapeStation) ( $p < 0.05$ ) accompanied by a trend towards degradation at 90 days, although not significant ( $p > 0.05$ ).

**Conclusion:** For cfDNA to be standardized and validated as a clinical biomarker, both analytical as well as pre-analytical procedures need to be thoroughly investigated. Our data indicate that cfDNA is stable once extracted.

## The effect of dehydration on intestinal permeability

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**Background:** Dehydration can affect individuals of all ages. Studies concerning the effect of dehydration on intestinal permeability have mostly been performed under exercise-related conditions. However, it is unknown if the increased intestinal permeability after exercise is an effect of dehydration or of other mechanisms related to exercise.

**Aim:** To explore the effect of dehydration at rest on the intestinal barrier function.

**Methods:** Twenty healthy volunteers (10 males and 10 females) were recruited and underwent three conditions: (1) Dehydration by heat (sauna, loss of 3% body weight), (2) no intervention (negative control), (3) administration of indomethacin (positive control). The order of the test conditions was random and separated by two wash-out periods of minimum five days. Small intestinal permeability was assessed in each condition, using the ratio of urinary lactulose to urinary L-rhamnose (L/R ratio) after oral administration of those sugars. Blood, saliva and faeces were collected for the analysis of other permeability or intestinal damage related biomarkers, including plasma intestinal fatty acid binding protein (i-FABP). The non-parametric Wilcoxon signed-ranked paired test at  $\alpha = 0.05$  with a Bonferroni correction was used to detect significant differences between negative control and dehydration as well as between negative and positive control.

**Results:** Indomethacin treatment significantly increased plasma i-FABP from a median of 295.0 (interquartile range 188.1 - 436.9) to a median of 577.9 (443.1 - 729.9,  $p < 0.0001$ ). Dehydration did not significantly affect i-FABP (median of 358.2, 254.7-634.6,  $p = 0.294$ ). Urinary L/R ratio and other biomarkers of intestinal barrier function are currently being analysed.

**Conclusions:** Further analyses have to be performed before proper conclusions can be drawn. However, this preliminary data shows that dehydration may not affect intestinal barrier function.

## **A study tool using functional magnetic resonance imaging (fMRI) to assess how modification of the gut microbiota can affect the gut-brain axis**

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**Background:** The gut microbiota consists of a huge bacterial community that usually colonizes the host's intestine in peaceful symbiosis. Modification of the gut microbiota could occur naturally or could be introduced actively by e.g. dietary intervention such as probiotics. The gut microbiota and its modifications do not only have local effects on the gut, but also systemic effects, for example via the gut-brain axis.

**Aim:** To establish a non-invasive tool (i.e. fMRI paradigm) to investigate the effect of modifications of the gut microbiota on the gut-brain axis, using functional magnetic resonance imaging (fMRI).

**Method:** Subjects were exposed to a dietary intervention such as probiotic administration. To assess the effect of this dietary intervention on brain function, subjects underwent a functional magnetic resonance imaging of the brain while performing an emotional attention task. Using this paradigm and advanced post-imaging processing, the activity of a resting brain and an emotionally challenged brain was measured and compared.

**Results:** Our group confirms that this emotional attention task fMRI paradigm is able to reveal and identify brain areas specifically activated by this task.

**Conclusion:** This fMRI paradigm may offer a highly sensitive and non-invasive method to assess the effect and Mode-of-Action of dietary intervention on the gut-brain axis in general and brain function specifically as a major step towards inventing dietary modifications to improve mental health.

## Overview of Nesbit Procedures in Patients with Peyronie's Disease at Örebro University Hospital

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**Introduction:** Peyronie's disease (PD) is a condition where a fibrotic plaque is formed in the penis causing penile deviation. Penetrative intercourse might become impossible and is an indication for surgery. The Nesbit procedure, a surgical method for deviation correction, has little risk of serious complications. There is however, risk of post-operative erectile dysfunction (ED). The disease is rare but more common among individuals with diabetes.

**Aim:** Primary aim is to chart the recovery rate and satisfaction rate in patients with PD corrected by Nesbit procedure at USÖ<sup>1</sup>. Secondary aim is to chart post-operative complications.

**Method:** This was a retrospective descriptive study where patients with PD who underwent surgery ad modum Nesbit at USÖ between 2008-2017, were included (n=77). They were followed up 2-3 months post-operatively. Recovery criteria were ability for penetrative intercourse after surgery. Information about recovery, complications and satisfaction were gathered from medical records.

**Results:** Post-operative ability for penetrative intercourse rate was 87.0 %. Of all the patients 72.7 % were satisfied with the post-operative results. The most common complication was local pain (22.1 %), 14.3 % experienced post-operative ED and 10.4 % were re-operated. Total complication rate and post-operative ED rate were not higher regarding diabetes and older age ( $P > 0.05$ ).

**Conclusions:** Recovery rate and satisfaction rate were good. Post-operative ED rate was in line with other studies. Neither older age nor diabetes was associated with higher complication/post-operative ED rate. Better consistent follow-up is desirable and further studies are needed.

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## Long-term results of silicone oil tamponade in severe retinal detachment surgery

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**Introduction:** Retinal detachment is a sight-threatening condition in need of advanced surgical intervention. In severe retinal detachment, when there is an element of proliferative vitreoretinopathy (PVR), retinal surgery with silicone oil tamponade is used due to its' retinal stabilizing properties and ability to be used as long-term tamponade.

**Objective:** The objective/aim was to make an analysis of the patients operated for complex retinal detachment with the use of silicone oil tamponade, and to evaluate the long-term results of these surgeries.

**Method:** This was a descriptive, retrospective case study which analyzed 42 patients operated in 2014 for severe retinal detachment. Their medical records were audited to collect all the data needed for the study. Groups of primary retinal detachment and retinal re-detachment were compared to find differences and prognostic factors.

**Results:** Among the 18 patients who had primary retinal detachment, 78% had improved vision, 11% had impaired vision and 11% had unchanged vision after retinal surgery with silicone oil tamponade. Of the 24 patients with retinal re-detachment, 29% had improved vision, 50% had impaired vision and 8% had unchanged vision. The group of retinal re-detachment had significantly poorer results, more retinal surgeries, more had the silicone oil left in situ and they had a longer follow-up time.

**Conclusion:** Retinal surgery with the use of silicone oil tamponade often improves the visual acuity. Retinal re-detachment shows a poorer prognosis than primary retinal detachment even though they receive the same treatment.

**Effect of pro-inflammatory cytokines on intestinal commensal *Escherichia coli*, ATCC® 8739™.**

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Co-supervisor: Isak Demirel, PhD

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**Introduction:** The precise pathogenesis of IBD and IBS is still unclear. An accepted hypothesis is the development of an aberrant immune response towards the gut microbiota. The effect of inflammatory markers characteristic of these diseases on the gut microbiota is not known.

**Aim:** The aim of this study was primarily to analyse the growth of a commensal *E. coli* when exposed to pro-inflammatory cytokines. The secondary aim was to study the effect that these pro-inflammatory cytokines had on bacterial gene expression.

**Materials and method:**

A commensal *Escherichia coli*, ATCC® 8739™, was exposed to the cytokines TNF- $\alpha$ , IFN- $\gamma$ , IL-1 $\beta$ , IL-6 and IL-8 in two different concentrations (0.5ng/ml and 10ng/ml) and its' ability to grow was measured. Real-time qPCR was performed to analyze the gene expression.

**Results:**

In the presence of all cytokines at 0.5ng/ml *E. coli* had a slight tendency to decrease in growth. Although only IFN- $\gamma$  0.5ng/ml was significantly lower compared to the control, IL-6 and IL-1 $\beta$  at 22-24 hours, respectively. With the 10ng/ml concentration, the growth in IL-1 $\beta$  was significantly inhibited compared to IL-6(8-24h), TNF- $\alpha$  (10-14h) and IFN- $\gamma$  (12-18h) but not compared to the control. The qPCR results showed that the cytokines do appear to affect the expression of the genes *flu*, *fimH*, *pgi*, *ppsA* and *frdA*.

**Conclusion:**

The growth and expression of certain genes of a commensal *E. coli* seem to be affected by exposure to certain pro-inflammatory cytokines. Further studies are necessary to uncover the connections between inflammatory process and the microbiota of the gastrointestinal tract.

## Parent's role in decision and treatment of children with congenital limb reduction deficiency

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**Objective:** Parents of children with congenital limb reduction deficiency are facing many decisions related to their child during the child's first years, e.g. when, or if to start, and to choose from different interventions. Usually the interventions concern surgical and/or prosthetic treatment options. A family-centred approach indicates the importance of providers to understand family belief systems with respect to the involvement of family members and is, thus, important to implement in childcare. The aim of this study was to describe parent's experiences of their role in decision-making and treatment for children with congenital limb reduction deficiency.

**Method:** A descriptive, qualitative design was used. Semi-structured interviews were conducted with 17 parents of children with upper and/or lower limb reduction deficiency, including mothers (n=12) and fathers. Mean age of their child was 5.9 years. Data was analysed using qualitative content analysis with inductive approach.

**Results:** The results show that parental role in making decisions included: awareness of being a decision-maker in this context, and experiences of the role to make the best decisions for another person's future as self-evident but maybe not wanted. The parental roles in treatment processes included: being a collaborator within the family and between health care providers and family; being a constant supporter for challenges in everyday life; and handling a variety of needs based on psychosocial issues.

**Conclusion:** We conclude that the results contribute to new knowledge and understanding of parents' as decision makers and may improve family-centred health service and enhance the care for children with congenital limb reduction deficiency.

**Impaired quality of life after radioiodine therapy compared with anti-thyroid drugs or surgical treatment for Graves' hyperthyroidism. A long-term follow-up with ThyPRO and SF-36**

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**Background:** Hyperthyroidism is known to have a significant impact on the quality of life(QoL) at least in the short term. This study assesses QoL in patients at 6-10 years after treatment for Graves' disease(GD) with radioiodine(RAI) to those treated with thyroidectomy or antithyroid drugs(ATD) as assessed with both a thyroid-specific(ThyPRO) and general QoL(SF-36) surveys.

**Methods:** We evaluated 1186 GD patients in a subcohort from an incidence study 2003-2005 which had been treated according to routine-clinical practice at seven participating centers. Scores from ThyPRO were compared with scores from a matched general population sample (n=712), using multiple linear regression adjusting for age and gender as well as multiple testing. Treatment related QoL outcome was adjustment for the number of treatments received, sex, age and co-morbidity.

**Results:** Regardless of treatment modality, patients with GD had worse thyroid-related QoL 6-10 years after diagnosis compared with the general population. Patients treated with RAI had worse thyroid-related and general QoL than patients treated with ATD or thyroidectomy on the majority of QoL-scales. Sensitivity analyses supported the relative negative comparative effects of RAI treatment on QoL in patients with hyperthyroidism.

**Conclusions:** Graves' disease is associated with a lower QoL many years after treatment compared to the general population. RAI may worsen the QoL in GD patients compared to ATD or thyroidectomy. The way RAI may adversely affect QoL is unknown, but since the results may be important for future considerations regarding treatment options for GD they need to be substantiated in further studies.

## Treatment Outcome 6-10 years after diagnosis of Hyperthyroidism in 2916 patients – a longitudinal evaluation of a Swedish incidence cohort

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**Background:** Treatment of Graves' disease (GD) and toxic nodular goiter (TNG) has the objectives to cure hyperthyroidism, prevent recurrent disease and preserve thyroid function. Treatment efficacies and long-term outcomes of antithyroid drugs (ATD), radioactive iodine (RAI) or surgery varies in the literature. We report the outcome over a 6 to 10-year period.

**Methods:** A prospective incidence-cohort of *de novo* diagnosed GD and TNG patients (n=2916) from 2003-05, were invited to a follow-up 6-10 years after diagnosis. Questionnaires were sent to 2430 patients regarding treatments, demographic data, comorbidities, and more. Patients were treated according to clinical routine.

**Results:** 1186(83.3%) had GD and 237(16.7%) had TNG.

In GD patients, 351(45.3%), 264(81.5%), and 52(96.3%) were cured by ATD, RAI or surgery respectively as first line treatment. Of those, 77.0%, 15.4%, and 3.8% respectively were without levothyroxine supplementation at follow-up at  $8 \pm 0.9$  years. At follow-up, 278(23%) of GD patients had been operated.

In TNG patients, RAI cured 88.6% and surgery 92.9%.

The proportion that did not feel fully recovered at follow-up was 25.3% of GD and 18.1% of the TNG patients.

**Conclusion:** Overall, treatment of hyperthyroidism results in preserved thyroid function only in 35.3% and 44.7% of GD and TNG cases, respectively.

As many as 23.4% of the GD patients end up with surgery although only 4.6% choose it from the beginning. The high number of patients who do not feel recovered 6-10 years after hyperthyroidism in GD and TNG is a reminder of the chronic nature of hyperthyroidism.

## Etiology of CNS Infections in Nepal Using the FilmArray Meningitis/Encephalitis Panel

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**Objective:** The etiology of infections of the central nervous system (CNS) in Nepal often goes unrecognized. The aim of this study was to investigate the microbial etiology of CNS infections at a hospital in Nepal.

**Methods:** Cerebrospinal fluid (CSF) was collected, from 176 consecutive patients presenting at United Mission Hospital in Tansen, Nepal, with symptoms of possible CNS infection. Patient data was registered and analysis of blood cells in CSF was performed at the hospital. Multiplexed PCR was performed targeting six bacteria, seven viruses and two fungi (FilmArray ME panel, BioFire, BioMerieux).

**Results:** 67 percent of the patients had taken antibiotics before lumbar puncture, mainly oral cephalosporins. 88 percent had CSF white cell count  $>3/\mu\text{L}$  suggesting CNS infection. *H. influenzae* was found in 10 samples, *S. pneumoniae* in 13, and *N. meningitidis* in one sample. *Cryptococcus neoformans/gatti* was found in four samples. The viruses detected included enterovirus (n=8), varicella zoster virus (n=5), herpes simplex virus 1 (n=3) and human herpes virus 6 (n=3). Fifty-nine percent of the samples were negative.

**Conclusion:** By using the FilmArray multiplex PCR panel we detected important pathogens known to cause CNS infections. A relatively large proportion of the samples were tested negative for the pathogens included in the PCR assay. This finding indicates that CNS infections in the area often are caused by other important pathogens such as other viruses or mycobacteria. Interestingly a majority of the patients had taken broad-spectrum antibiotics before arrival to hospital, which highlights the urgent need for improved routine diagnostics.

## The effects of butyrate on induced hyperpermeability and tight junction-related gene expression in human colonic mucosa

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The intestinal permeability is an indicator of intestinal barrier function and an increased permeability has been associated with several diseases such as irritable bowel syndrome (IBS), inflammatory bowel diseases (IBD), coeliac disease and type 2 diabetes. Strengthening the barrier function and keeping the intestinal permeability at a normal level could therefore be beneficial for prevention or treatment of these diseases. Butyrate, a short-chain-fatty acid produced by specific members of the intestinal microbiota, has previously been shown to reduce permeability and strengthen the barrier function in cell culture experiments and animal models. However, data from clinical experiments is very scarce.

In this study, butyrate's effect on mast cell-induced hyperpermeability in human colonic biopsies was tested in an *ex vivo* setting. For this, mucosal biopsies from the sigmoid colon of 16 healthy volunteers were pre-incubated with 5 or 25 mM butyrate in Ussing chambers. The mast-cell degranulator compound 48/80 (C48/80) was used to induce tissue hyperpermeability. The transepithelial electrical resistance (TER) as well as the paracellular and transcellular permeability were measured after 0 and 60 minutes. After the Ussing experiment, RNA was isolated from biopsies of 9 participants and the gene expression of Claudin 1, 2 and 7, Occludin and NF $\kappa$ B-inhibitor  $\alpha$  was assessed via reverse transcription real-time PCR.

Biopsies stimulated with C48/80 together with 25 mM butyrate showed an increased intestinal permeability on the paracellular pathway and a decreased Claudin 1 expression rate compared to the stimulation with C48/80 alone. Butyrate at 5 mM concentration did not significantly affect the intestinal permeability or gene expression.

These results contrast previous data from cell culture and animal experiments that have shown a positive effect of butyrate on barrier function, and remain to be studied in more detail.



## Clinical outcomes in patients with bipolar disorder before and after single therapy or combination treatment with Clozapine and Lithium

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**Background:** Bipolar disorder, with its manic and depressive periods, is a chronic and often life threatening ailment. Worldwide 60 million people are estimated to be affected by the disease (1). During the last decades Lithium as a therapeutic agent has successfully been used to treat acute manic episodes. Clozapine, a second-generation anti-psychotic agent, similar to lithium has unique anti-impulsive and anti-suicidal effects. These two agents have been studied in relation to suicidality and aggression, but their mechanism of action is not known. It is not known either, whether the two agents act through the same or different pathways and whether they have additive or synergistic effects (2).

**Method:** Our group investigated the clinical outcome in seven patients (hospitalization, compulsory treatment, self-injury, suicide attempts, permission for home visit, and need for somatic care and side) before and after single therapy or combination treatment with Clozapine and Lithium. Four patients were initially treated with Clozapine for four weeks before Lithium was added

**Results:** Clozapine compared to baseline showed significant reductions in compulsory treatment and self-injury, with a significant increase in permissions for home visits. Combined treatment with clozapine and lithium was even more effective compared to clozapine alone. Compared to baseline, combination treatment with clozapine and lithium reduced compulsory treatment (-69%; p=0,01), watch (-70%; p=0,001), self-injury (-76%; p=0,0001), suicide attempts (-83%; p=0,012), need for somatic care due to self-injury (-78%; p=0,0004) and increased permission for home visit (+95%; p=0,001).

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## Loneliness and inflammatory changes at older ages: English Longitudinal Study of Ageing

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**Background:** Loneliness has been associated with adverse health outcomes including inflammatory age-related diseases such as those of the cardiovascular system. The inflammatory mechanisms linking loneliness with somatic disease are incompletely understood.

**Objective:** We investigated whether loneliness is related to changes in high-sensitivity C-reactive protein (hs-CRP), fibrinogen and haemoglobin.

**Methods:** The English Longitudinal Study of Ageing was used, with 3,239 participants (numbers vary slightly by outcome) with complete biological and questionnaire/interview data from 2008/9 and 2012/2013. The association of *change* in loneliness with *change* in biomarkers was assessed using linear regression conditional change models, with adjustment for potential confounding factors.

**Results:** In men, changes in experiencing loneliness were associated with changes in biomarkers for inflammation and other systemic characteristics linked with disease risk. Onset of loneliness was associated with a statistically significant increase in hs-CRP level, with  $\beta$  coefficients (and 95% CI) of 0.36 (0.09 to 0.62) and with an increase in plasma fibrinogen (0.18 (0.04 to 0.31)) and a decrease in haemoglobin levels (-0.43 (-0.72 to -0.14)), not explained by the onset of diagnosed diseases. Among women, becoming lonely was only associated with lower haemoglobin level (-0.17 (-0.32 to -0.01)).

**Conclusions:** Men may be more susceptible to loneliness-associated disease risks signalled by systemic inflammation, although both men and women may be at increased risk of anaemia. Combined social and targeted medical interventions may be required to reduce the health risks associated with loneliness.

## Clinical effectiveness of golimumab: interim analysis of the GO-SWIBREG study

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**Objective:** Clinical trials may not reflect clinical practice. Therefore, we aimed to assess the effectiveness of golimumab in a real world cohort.

**Methods:** This is a prospective, observational, multi-centre cohort study. Eligible patients had moderate-to-severe disease activity ulcerative colitis, defined as a Mayo endoscopic subscore  $\geq 2$ . Clinical characteristics, treatment, disease activity and quality of life measures were recorded at baseline and prospectively, using an electronic Case Record Form, integrated with the Swedish National Quality Registry for IBD (SWIBREG). Primary objective was clinical effectiveness at 12 weeks and 52 weeks, i.e. clinical response (defined as a decrease in Mayo score by  $\geq 3$  points or 30% from baseline) and remission (defined as a score of  $\leq 2$  with no individual subscores  $> 1$ ). Data from the 12 week induction part are presented.

**Results:** At study entry, 24/50 (48%) were on concomitant treatment with immunomodulators, 16/50 (32%) on oral corticosteroids and 27/50 (54%) on 5-ASA. In total, 35/50 (70%) had previously been exposed to at least one TNF-antagonist. At 12 weeks, 37/50 (74%) were still on treatment with golimumab. Of the patients continuing golimumab until week 12, 8 (22%) were in clinical remission and 13 (35%) had a clinical response. The median Mayo score decreased from 7 (6-10) at baseline to 5 (1-8) at 12 weeks ( $p < 0.01$ ). Consistently, median faecal calprotectin decreased from 710 (275-1850)  $\mu\text{g/g}$  to 390 (45-870)  $\mu\text{g/g}$  ( $p = 0.02$ ). Quality of life improved in golimumab treated patients, with a significant reduction of the overall short health scale (SHS) score ( $p = 0.04$ ).

**Conclusions:** This cohort of golimumab treated patients represents a treatment-refractory group. Improvements in disease activity and quality of life can be achieved already at 12 weeks.

The study was financially supported by MSD.

## Designing a new training method for patients with advanced hand prostheses

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**Objective:** New prosthetic hands with advanced technology making it possible to perform many different grasps and positions are now available on the market. This new advanced technology is also difficult for users to control, and studies have shown that the new hand functions are not used to the extent expected (1).

When introducing a new prosthetic hand with questionable merits, the reasons for these results need to be considered. In light of our experience from fittings in Örebro, we decided that the training programs for the new hand models were not comprehensive enough, and there was a need for the development of a new method for training.

**Methods:** We performed a review of existing training programs for advanced hand prostheses, combined with clinical experiences and the treatment philosophy with early fitting and regular follow up used in Örebro.

**Results:** The new training method follows a structured program based on 14 steps described in Skills Index Ranking Scale Adult (SIRS Adult). The SIRS Adult comprise integration, control training and activity performance. The ADL's are chosen individually through a Canadian Occupational Performance Measure interview. Further, regular support and feedback from an occupational therapist is important. The capacity to use different grasps and integrating the new prosthesis when performing ADL are evaluated through the Assessment of Capacity for Myoelectric Control (2).

**Conclusions:** The method has now been used on patients with good results and can be applied upon prescription of any advanced multifunctional prosthetic hand to enhance the functional use of the hands.

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## Expression of neuronal markers in human carotid atherosclerotic plaques in the Biobank of Karolinska Endarterectomies (BiKE) cohort

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**Objective:** Neuro-immune regulation have been under study in relation to many inflammatory diseases, and some interventions have seen its way to clinical trials, but little is known about the role of neural signaling in regulation of atherosclerosis. The aim is to investigate the mRNA and protein expression levels of a defined set of neural markers in carotid atherosclerotic plaques taken from BiKE, and localize the selected targets to defined plaque regions and major cell types using target-specific antibodies.

**Methods:** Bioinformatic tools like R program was used to analyze pre-generated microarray data from the BiKE plaques to obtain potential candidates. Immunofluorescence and immunohistochemistry to be used to confirm the expression of the selected targets on the protein level and to localize them into specific plaque regions and cell types.

**Results:** A group of neuronal receptors and proteins (HTR2B, CHRNA1, GRIA1, GRIA2, NEFH, DLG4) was differentially expressed in carotid plaques compared to control (p-value=0.0001; fold- change range from 1.48 to 5.58). Antibodies were provided by Human Protein Atlas and were tested for their specificity and proper concentration on human tonsil sections.

**Conclusions:** Gene expression data analysis gives supported evidence that some neuronal genes are differentially expressed in carotid plaques compared to normal arteries. Also, antibodies for the selected targets were titrated and evaluated on human tonsil tissue using Immunofluorescence. Experiments are currently ongoing to characterize the protein expression of the selected markers and their localization in the plaque.

## Elucidating the impact of IL-6 trans-signaling in the Endothelial to Mesenchymal transition (EndMT) and Osteogenic differentiation

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**Objective:** Endothelial dysfunction, which plays a pivotal role in the development of atherosclerosis, is caused by chronic inflammatory damage to the vessel wall. It involves sustained activation of endothelial cells (ECs) by inflammatory cytokines which then leads to endothelial to mesenchymal transition (EndMT), a process of phenotypic and functional switch of ECs into Mesenchymal Stem Cells (MSCs). The pleiotropic cytokine IL-6 plays a central role in inflammation and it has previously been associated with the initiation and progression of atherosclerosis. In addition, IL-6 has been shown to favor Osteoblastic differentiation of bone marrow derived MSCs. In this study, we aim to shed light on the role of IL-6 in EndMT progression and Osteogenic differentiation of vascular ECs.

**Methods:** We treated HUVECs with IL-6 and sIL-6R and analyzed gene expression using qPCR and protein release using Proximity Extension Assay (Olink<sup>®</sup>, Sweden).

**Result:** We found that IL-6 trans-signaling upregulates the release of proteins that participate in leukocyte adhesion and diapedesis (i.e. CCL2, CXCL1, CCL15, IL-1RT1), and proteins that are associated with vascular calcification (i.e. TR-AP, IL-18BP, OPG) from HUVECs. In subsequent experiments, we revealed that IL-6 trans-signaling downregulates EC markers such as PECAM-1 and Claudin-5 while upregulating MSC marker SOX2, and Osteogenic lineage markers RUNX2 and Col1A1. Our observations from Alizarin S and ALP activity staining also suggest that IL-6 trans- signaling in HUVECs increases mineralization and ALP enzyme activity respectively.

**Conclusion:** Collectively, our preliminary data suggests that IL-6 trans-signaling provokes pro- inflammatory pathways and favors EndMT progression and Osteoblastic lineage differentiation of human vascular ECs.

**Sex-related differences in management of COPD**

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**Objective:** Women with Chronic Obstructive Pulmonary Disease (COPD) have more symptoms, more exacerbations, lower health status scores, and more comorbidity. However, it is unclear whether management of COPD differs by sex. The aim of the study was to investigate differences by sex in the care of patients with COPD.

**Methods:** The population included 1329 primary and secondary care patients with a doctor's diagnosis of COPD in central Sweden. Data were obtained from patient questionnaires and included patient characteristics and data on achieved COPD care. Analyses included cross-tabulations, chi-squared test and multiple logistic regression using several measures in COPD management as dependent variables, female sex as independent variable, and with adjustment for age groups, previous exacerbations, COPD Assessment Test (CAT), level of dyspnea assessed by the modified Medical Research Council scale (mMRC), comorbid conditions, self-rated moderate/severe disease, level of education and body mass index (BMI).

**Results:** Women were more likely to receive triple therapy (OR 1.86 (95 % CI 1.38-2.51)), to have any maintenance treatment (OR 1.82 (95 % CI 1.31-2.55)), to be on sick leave (OR 2.16 (95 % CI 1.19-3.93)), to have received smoking cessation support (OR 1.80 (95 % CI 1.18-2.75)) and to have had pneumococcal vaccination (OR 1.82 (95 % CI 1.37-2.43)), all independently of age, severity of disease or other potential confounders.

**Conclusion:** Management of COPD differs by sex, with women being more actively managed than men. It is unclear whether this is due to patient- or care related factors.

# LATE ABSTRACTS





## The effect of acute malaria on the levels of auto-antibodies in the malaria endemic area of Kilifi, Kenya

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**Background:** Malaria is a life-threatening disease caused by *Plasmodium* parasites, transmitted to humans via infected *Anopheles* mosquitos. The disease is one of the biggest reasons for illness and death among children under 5 years in the world. Malarial infections have been reported to lead to a dysregulated immune response with overactive B cells, hypergammaglobulinemia and elevated levels of autoantibodies. However, the mechanism(s) by which these autoantibodies develop remain poorly understood.

**Objective:** To investigate the kinetics of autoantibodies in plasma from children in a malaria endemic area during an acute malarial episode and in convalescents.

**Method:** 49 children living in the malaria endemic area Junju, Kilifi, Kenya were visited by field workers once every week and bled at four different time points: Baseline, at first sign of acute malaria, after 4 weeks (C1) and after 24 weeks (C2). The plasma was analyzed for 7 different auto-antibodies, anti-Scl-70, anti-PCNA, anti-MPO, anti-SSA/Ro52, anti-SSA/Ro60, anti-RNP/Sm and anti-C1q, using a Luminex™ assay.

**Results:** Significantly reduced levels of autoantibodies in plasma ( $p < 0.05$ ) were found between the baseline sample and the C2 sample for all examined analytes. No significant differences were found between baseline and acute samples, or between baseline and C1 for all examined autoantibodies with one exception: Anti-C1q were significance could be found between the baseline sample and the C1 sample as well.

**Conclusion:** Children who have undergone an acute malarial infection have significantly decreased levels of seven different autoantibodies compared to baseline samples 24 weeks after infection.

**Key words:** Acute Malaria, Autoantibodies, Kinetics, Kenya, Luminex

## Frail Elderly Patients at the Emergency Department

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**Introduction:** The population ages and the amount of frail older patients increases. The definition of the term “frail” is under development and many screening tools are being created for use at the emergency department (ED), in order to identify this high-risk group. Several previous studies have used the age of 75 as an age – limit when screening for frailty.

**Aim:** To map the patients 65 years and older that visited the ED at Örebro University Hospital (USÖ) during year 2017 and compare age groups with each other in terms of factors that may indicate frailty to see if 75 is an accurate age- limit when screening for frailty.

**Material and methods:** This study was a retrospective observation study. Patients 65 years and older who sought care at the ED at USÖ during year 2017 were included. 417 patients were randomized to reviewing of their medical records.

**Results:** 29% of the visits during the year were made by patients aged over 65. The patients 75 years and older showed several factors that may indicate frailty to a significantly greater extent.

**Conclusion:** It seems that it could be possible to use the age of 75 as a set off age for frailty. Patients aged 75 and older showed several factors that may indicate frailty to a significant greater extent than the younger group. These findings may justify the use of 75 years as an age – limit at the ED if screening for frailty.

**Key words:** Frail, elderly, emergency department

## Helicopter transport – does it save time? A geospatial simulation study in the setting of South Africa

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**Introduction:** Helicopter transport can be expected to be faster as compared to ground ambulance transport. However, in South Africa, a ground ambulance is always dispatched first to the site of injury to clinically assess the patient and then, if needed, requests helicopter transport. Trauma patients are the most commonly transported by helicopter and are associated with time-sensitive conditions. There is to date no study of the impact of helicopter transport on prehospital time in South Africa.

**Aim:** To determine whether there is a time-benefit for primary emergency responses when helicopter emergency medical services (HEMS) is used compared to ground emergency medical services (GEMS).

**Methods:** This was a retrospective chart review of primary HEMS responses in Johannesburg, South Africa. Google Maps was used to simulate the fastest route and driving distance for the ground ambulance to arrive from site to hospital. This simulated drive time was then compared to the helicopter mission time from the patient report forms. To assess the potential time benefit for helicopter transport, we performed a paired T-test. To calculate a potential minimum driving distance at which helicopter transport provides a time benefit, a regression line for the time difference was calculated by using linear regression analysis.

**Results:** We analyzed 118 helicopter cases. Preliminary results show that the mean helicopter transport time was 58 minutes (95% CI 54-62). The mean simulated drive time was 40 minutes (95% CI 36-44). The performed paired T-test showed a significant ( $p < 0.05$ ) time deficit for helicopter transport compared to ground ambulance transport. The mean time deficit was -15 (95% CI -19-(-11)). The mean driving distance was 50 km (95% CI 44-57).

**Conclusion:** The results suggest that HEMS does not provide a time benefit when compared to GEMS. Further analysis will be performed to seek significant driving distances where a time benefit may be expected for HEMS.

**Key words:** Helicopter emergency medical services, helicopter transport, ground emergency medical services, time benefit, prehospital care.

## Immediate breast reconstruction after mastectomy at Örebro University Hospital

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**Introduction:** Immediate breast reconstruction (IBR) can be offered to breast cancer patients after mastectomy. A satisfactory breast symmetry has positive effects on psychosocial morbidity, quality of life and body image. The frequency of IBR varies a lot among different regions and is in Region Örebro County 4%, lower than the national target on 20%.

**Aim:** The main purpose of this study was to investigate how they work with IBR at Örebro University Hospital. By extension, the ambition is to offer IBR to more breast cancer patients.

**Material and methods:** This was a retrospective study of all women who underwent mastectomy at Örebro University Hospital in 2016. The casebooks were examined from frequency of IBR, discussion about IBR at multidisciplinary team conferences, patient's own opinion in IBR, presence of delayed reconstruction and presence of contraindications or other important factors for IBR.

**Results:** Five of the 103 women got IBR with expander implants in connection to mastectomy. Five of the women have discussed about IBR at multidisciplinary team conferences and seven had notes about their attitude to IBR. Ten women underwent delayed reconstruction during the follow-up, additional seven patients were waiting for reconstructive surgery. There were no significant differences in patient characteristics between the groups "mastectomy and IBR" and "mastectomy only". Examined factors were smoking, radiotherapy, BMI, age, comorbidity and distance to hospital.

**Conclusions:** Besides the five women who got immediate breast reconstruction during 2016, there were additionally 28 women without any contraindications for this surgery. This indicates that there is a considerable group that can become candidates for immediate breast reconstruction.

## The impact of obesity on outcome of delivery

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**Introduction:** Pre-pregnancy obesity was prevalent among 18% of women who delivered in Örebro in 2017. The rate has increased and previous international studies have identified obesity as a major cause for poor reproductive health among women.

**Aim:** To analyze the association between maternal pre-pregnancy BMI and major maternal obstetrical outcomes within the Örebro region.

**Material and methods:** This retrospective observational study collected data from 1<sup>st</sup> Jan. 2015 to 30<sup>th</sup> Jun. 2018 via the Swedish Pregnancy Register. All women delivered during the study period were eligible for inclusion. Exclusion criteria were multiple pregnancies, BMI <18.5 kg/m<sup>2</sup>, delivery by forceps, incomplete data and admission to antenatal care at  $\geq 17$  gestational weeks. Women were categorized into obese (BMI >30 kg/m<sup>2</sup>) or non-obese (BMI <29.9 kg/m<sup>2</sup>) and compared by several obstetrical outcomes.

**Results:** Of the 6846 included women, 17.8% were classified as obese. Obese women had several adverse maternal obstetrical outcomes. They had a significantly increased risk of undergoing induction of labor (OR 1.85), cesarean delivery (CD) (OR 1.46), emergency CD (OR 1.38), repeated CD (OR 1.45), having longer cesarean duration, higher total blood loss, higher fetal birthweight and poorer self-reported (ante-, intra- and postpartum) health.

**Conclusions:** Pre-pregnancy obesity, among women in the Örebro region, is associated with multiple adverse maternal outcomes during delivery and intervention before, during and after delivery should be further studied in order to minimize risk of complications in this risk group.

**Key words:** obesity, delivery, cesarean delivery, reproductive health, pregnancy

## Surgical site infections in hip fracture patients

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**Introduction:** Hip fractures affect 18 000 people every year in Sweden. It is a disease mainly affecting the elderly population with a high mortality rate. Due to the severe prognosis of hip fractures, several precautions are taken against complications. The aim of this study is to examine the most common surgical and medical complications after hip fracture surgery, focusing on surgical site infections. It will also compare the number of surgical site infections between patients that receives prosthesis and patients receiving osteosynthesis material.

**Method:** A retrospective observational study including all patients operated at Karlskoga hospital between January and August 2018. Data collected from medical records from the hospital and primary care facilities were reviewed six weeks postoperatively for complications and surgical site infections.

**Result:** In total, 53 patients (30 %) suffered a post-operative complication. Pressure ulcers was the most common complication and affected 13 % of the patients. Nine patients (5%) got a surgical site infection. Six of the infected patients were operated with prosthesis, two with osteosynthesis and one received a flail joint. There was a significantly higher frequency of surgical site infections in the prosthesis group.

**Conclusion:** Postoperative complications affected 30 % of the patients. In total, five percent of the patients developed a surgical site infection. Patients receiving a prosthesis after hip fracture surgery had a significant higher frequency of surgical site infections.