# Abstract samling

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# EXERCISE AND CARDIAC FUNCTION BY TISSUE DOPPLER ECHOCARDIOGRAPHY: THE COPENHAGEN CITY HEART STUDY

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**Background**

TDI (Tissue Doppler Imaging) is a sensitive marker of myocardial dysfunction and mortality in heart disease and in the general population. Regular physical activity is associated with risk reduction in coronary heart disease and mortality. There is a need for studies to clarify whether exercise has beneficial effects on cardiac function. The aim of this study was to test the hypothesis that regular physical exercise is associated with better cardiac function measured by TDI in the general population.

**Methods**

Within a large prospective community-based population study, 2,053 persons were examined by conventional echocardiography and TDI. Peak systolic (s´), early diastolic (e´) and late diastolic

(a´) velocities were measured by colour TDI. Longitudinal displacement (LD) was calculated from the velocity curve during ejection. Statistical tests were performed by linear univariate and multivariable regression analyses, in relation to age groups (<50years, 50-65 years, >65 years) and physical activity level: I (inactivity), II (light activity), III (moderate activity) and IV (high-level activity). These levels were graded from the physical activity questionnaire, which contained information about activity level at work and in leisure time.

**Results**

Participants aged<50 years had a significantly higher level of e´ and LD in the most active group: e´=11.0 (± standard deviation, SD=2.0), $p<0.001$; LD=12.8 (SD=2.1), $p<0.003$. This pattern remained significant after adjusting for sex, hypertension, diabetes, and ischaemic heart disease and after Bonferroni correction. Both e´ and LD were strongly correlated to age, thus being significantly different in the three age groups regardless of the activity level. This correlation remained highly significant after adjustments for potential confounders ($p<0.001$). For e´, there was significant interaction between age and activity level ($p<0.001$), which supports the findings of better cardiac function with increasing activity in the young age group.

**Conclusion**

In the general population, the association between increasing level of exercise and better cardiac function was found only in the youngest age group ( <50 years old). Among the elder age groups, higher level of activity was not correlated to better cardiac function.

# HUMAN PAPILLOMAVIRUS INFECTION – A POSSIBLE CAUSE OF SPONTANEOUS ABORTION AND SPONTANEOUS PRETERM DELIVERY

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**Background**
30% of pregnancies end with a spontaneous abortion, while 7% of deliveries are preterm. Recently, an association between Human Papillomavirus (HPV) infection and spontaneous abortion/ spontaneous preterm delivery was suggested. Reported HPV prevalence in pregnant women is varying and a reliable conclusion is difficult. Here, we investigate HPV infection in placental material of a Danish study cohort.

**Methods**
Placental material was analyzed for HPV infection by nested PCR in the following four study groups: on-term delivery (n=103), spontaneous preterm delivery (n=68), elective abortion (n=54), and spontaneous abortion (n=46). Patient data was recorded including age, BMI, smoking, ethnicity, previous pregnancy outcomes, HPV-related incidences, and HPV vaccination.

Patient data and HPV status were compared between study groups to identify possible association between HPV infection and adverse pregnancy outcome.

**Results**
HPV prevalence in placental material from on-term and spontaneous preterm deliveries is 8.7% and 8.8%. HPV is detected in 10.9% of spontaneous abortions and in 20.4% of elective abortions. The four groups were similar in respect to age, BMI and ethnicity, with most patients being of European origin. Previous HPV-related disease history shows no apparent differences between groups, and HPV vaccination coverage varies from 44% to 62%.

**Conclusions**
Overall our results indicate that women with adverse pregnancy outcomes do not carry a higher HPV burden than women with normal/elective pregnancy outcomes. We therefore conclude that HPV infections are not likely to constitute a risk factor for spontaneous preterm labor or spontaneous abortions in the Danish population.

# APPLICATION OF VENOUS TO ARTERIAL CONVERSION (V-TAC) SOFTWARE IN THE EMERGENCY MEDICINE CONTEXT

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**Background**

v-TAC is a software able to convert peripheral venous acid-base and blood gas values to theirs arterial equivalents. Furthermore, a v-TAC sample provides immediately others useful venous parameters, such as lactate and electrolytes, without arterialization. This study evaluates v-TAC's clinical application in the emergency medicine context.

**Methods**

Between January and February 2016, all patients admitted through Hjoerring Hospital's emergency department were subjected to routine peripheral venous blood (PVB) sampling. Additionally, a separate PVB sample was analyzed using v- TAC. The population was divided in 2 groups based on clinical indication for arterial blood gas (ABG) sampling (group A, n= 119 ,with indication; group B, n=454, without indication). Every clinical journal was rewied, in order to study v-TAC's clinical usefulness in both groups. Patients were then stratified according to triage. The potential correlation between patient's triage and lactacte's measurement was statistically analyzed.

**Results**

After exclusion of 82 patients due to missing data, 573 patients were studied. In group A, 45,38% (54/119) of v-TACs appeared to be clinically useful; in group B this percentage was 15,64% (71/454). Furthermore, progressively increasing mean values of lactates were observed from green to red triage groups, with a statistically significant difference.

**Conclusions**

v-TAC is a low cost, painless blood sampling, whose results are immediately available. v-TAC can, in most cases, substitute ABG test. Paricularly interesting is the result obtained in group B: v-TAC appears to provide supplemental clinical informations and could therefore be added to routine PVB sampling among patients with no indication for ABG.

# THERAPEUTIC DRUG QUANTIFICATION USING TARGETED MASS SPECTROMETRY

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**Background**

Rheumatic diseases involve auto-immune, and inflammatory diseases, in which the inflammatory activity degrades cartilage, and eventually destroys the joints. We have, since 2009, systematically reduced treatment frequency and dosage using empirical clinical data and patient outcome. Previous, determination of the optimal treatment dosage and frequency for biological drugs was based on clinical symptoms and patient questionnaire feedback, with no truly objective biochemical evaluations. Hence, we seek to quantify the biological drug concentrations in the patients to establish a more objective dosing strategy. Previous studies have utilized immuno-based assays, which are sensitive, but limited to availability of good antibodies. These assays also require high volumes of sample, and are not readily multiplexed. In this study, we developed a parallel reaction monitoring (PRM) based method on four selected biological drugs on a QExactive HF.

**Methods**
A standard method for ELISA preparation was optimized and scaled down for nUPLC-MS/MS. Four biological drugs and serum samples from patients were immunoprecipitated, and characterized on a Q Exactive high field mass spectrometer. Based on the results, a target list of proteotypic peptides and a spectral database was constructed, and used to establish a PRM method in Skyline, which was utilized to reanalyze the samples.

**Results**
We have successfully established a method able to quantify three of the four biological drugs. Interestingly, we show that the PRM method from one commonly administered biological drug, infliximab, also works on the biosimilar version of infliximab with no modifications made to the method used above.

**Conclusion**
We have established the foundation for accurately determining the concentration of several biological drugs routinely used in clinical settings. The methods can provide objective measurements to help establish the correct treatment dosage and frequency.

# INTERRATER RELIABILITY OF THE VOLUME VISCOSITY SWALLOW TEST IN ACUTELY ADMITTED OLDER MEDICAL PATIENTS

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**Background**

Oropharyngeal dysphagia (OD) affects 51% of institutionalized older persons. OD is related to age and frailty and its complications include pneumonia, malnutrition, dehydration, social isolation, and death. In spite that screening for OD internationally is recommended, elderly patients are currently not systematically screened for OD in Denmark. OD can be diagnosed by various subjectively interpretable signs and may fluctuate over time. The Volume Viscosity Swallow Test (V-VST) has high sensitivity for detecting OD based on seven signs of impaired safety or efficiency while swallowing liquid in different viscosity and volume, but the reliability of the test is only investigated in a Spanish sample, wherein the prevalence of OD was rather high. Therefore the reliability of the V-VST among geriatric and medical patients at four Danish hospitals was investigated.

**Methods**

Following the protocol of FIMM (Patijn j & Remvig L 2007), this study was preceded by a training phase and an overall agreement phase before a study phase. In the training phase, the assessors completed the V-VST together. Any doubts or disagreement about the test approach and results were discussed between the assessors and the researchers (authors DM, KS, SW) until consensus was reach. In the overall agreement phase the assessors, following the criteria of the study phase, completed the V-VST independently and an 80% overall agreement of the presence or absence of OD was required before proceeding. In the study phase, patients were consecutively admitted from the four hospitals. The interrater reliability was completed within one hour. Presence of OD was calculated by the kappa-coefficient of agreement and whether OD was diagnosed due to impaired safety or efficiency. Percentage agreement was calculated for the specific sign at a specific viscosity and volume.

**Results and conclusion**

This will be presented at ESSD2016 in Milan.

# MAPPING OF HPV-33 ALTERNATIVE SPLICING IN VULVAR CANCER, AND IDENTIFICATION OF POSSIBLE DEPENDENT HOST SPLICING FACTORS

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**Background**

Vulvar Squamous Cell Carcinoma (VSCC) is a rare malignancy resulting in approximately 100 new cases per year in Denmark. The basaloid and warty squamous carcinoma, a histological subtype of VSCC, is reported to be associated with human papillomavirus (HPV). HPV is a small DNA virus and its life cycle is known to be dependent on host epithelial differentiation. Due to limited genome size and a requirement to tightly control a specific orchestrated expression pattern of early and late genes, the virus is dependent on alternative splicing executed by the host splicing machinery. 150 VIN and VSCC patients were previously screened for HPV infection. 56% of patients were tested HPV positive and HPV-33 accounted for 19%, being the second most frequently detected HPV-type after HPV-16. Opposite to HPV-16, HPV-33 is not included in the HPV vaccines. Although the alternative splicing pattern of HPV-16 and its regulation is well known, limited knowledge about HPV-33 splicing exists. This study aims to map the alternative splice sites for HPV-33 and to identify possible host splicing factors.

**Methods**

Using PCR and DNA sequence analysis, transcripts from 13 FFPE samples will be analyzed to identify splice sites. In addition, cell line experiments will be carried out to identify host splicing factors, that may influence HPV-33 splicing.

**Results and conclusion**

This study will describe HPV-33 splice sites and possible host splicing factors. Results will be presented later.

# THE HUMAN GUT MICROBIOME AND ITS ROLE IN CHILDHOOD DEVELOPMENT

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**Background**

More than 1000 bacterial species reside in the human gut, constituting, together with viruses and fungi, the "gut microbiome". The function is still not well known, however studies suggests a role in supporting the immune system and ensuring intestinal homeostasis. Imbalances in the gut microbiome (dysbiosis) have been linked to a large number of different diseases and dysfunctions including diabetes, obesity, and asthma. More recently, studies have supported bi-directional interactions between the human brain and the gut microbiome. This "gut-brain axis" may impact human behavior and conditions such as depression, anxiety, and autism. Based on newly emerging data on the interplay between gut bacteria and brain function, we hypothesize that specific microbiota profiles in infants and children, may be involved in delayed psychomotor development. In addition, to elucidate how gut microbiome can affect the local neural functions, we wish to investigate the association between the gut microbiome composition and functional constipation.

**Methods**

For this purpose, we will collect fecal samples from 100 children with delayed psychomotor development as well as 100 children with functional constipation, and compare the microbiome of these participants with a non-affected age-matched control group. Total DNA will be extracted from the fecal samples, and following 16s RNA gene sequencing, the microbiome profiles of the children will be compared.

**Results and conclusion**

This study will describe microbiota compositions associated with the two patients groups and are expected to provide an understanding of potential associations between specific bacteria or bacteria populations and psychomotor development or constipation in children.

# IS OBESITY ASSOCIATED WITH INCONTINENCE AND NOCTURIA IN 6-YEAR OLD CHILDREN? A CROSS-SECTIONAL INTERVIEW-BASED STUDY OF 4013 DANISH CHILDREN AT SCHOOL ENTRANCE

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**Background**

Enuresis and daytime urinary incontinence (DUI) are common disorders in young children. Simultaneous overweight and obesity is increasingly common among children. A possible association between obesity and child incontinence has been suggested. The aim of this study was to determine the prevalence of incontinence in children at school entrance and to elucidate if overweight was related to fecal incontinence (FI), DUI, enuresis or nocturia.

**Methods**

Questionnaires were completed by trained school nurses, interviewing children and parents during the first school year. The questionnaire included information on age, height, weight, BMI and four questions on incontinence and nocturia.

**Results**

4013 questionnaires were collected. Complete interview results were obtained from 3869 children. 96% of children in the cohort participated in the study. Mean age; boys 6.48±0.40 years and girls 6.40±0.37 years. Mean BMI boys and girls was 15.88±1.67 and 15.86±1.81 respectively. 5.6% of boys were obese, 16,6% overweight and 6.0% of girls were obese,16,3% overweight. Boys were significantly older, taller, and heavier than the girls. Overall 11.2% had FI, 22.2% had daytime wetting, 17.1% had enuresis and 31.6% had nocturia at least once during the past month. FI, enuresis and nocturia were significantly more common in boys than in girls. Obesity (BMI SDS>2) and overweight (BMI 1-2) was related to fecal incontinence ($p<0.05$). No statistically significant associations was observed between BMI and DUI, enuresis or nocturia, respectively.

**Conclusion**

The frequency of FI is higher among children at school entrance with overweight/obesity compared to normal weight children. At this age where urinary incontinence is more prevalent and obesity more rare we cannot conclude that enuresis or nocturia is associated with obesity. An association might become evident in older age groups when prevalence of obesity increases.

# EFFEKTEN AF HIGH INTENSITY INTERVAL TRAINING (HIIT) OG MODERAT TRÆNING I BEHANDLINGEN AF SVÆRT OVERVÆGTIGE BØRN OG UNGE. ET RANDOMISERET KONTROLLERET STUDIE

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**Baggrund**
Overvægt og fedme er i dag blevet en folkesygdom med alvorlige følgesygdomme og konsekvenser. Blandt børn og unge ses hyppigheden af overvægt og fedme at stige, med en aktuel prævalens på 20-25% i Nordjylland, defineret ud fra WHO´s kriterier. Mere viden på området samt bedre og mere effektive behandlingsmodaliteter er nødvendig for at kunne hjælpe den voksende gruppe af svært overvægtige børn og unge.

**Metoder**
Med dette studie ønsker vi at undersøge om 12 ugers HIIT træning versus moderat træning, i tillæg til den aktuelle behandling med TCOCT-protokollen (Holbækmodellen) i ambulant regi, ænder på vægttab, aktivitetsniveau (målt med sensewear), kondital samt 24-timers blodtryk hos svært overvægtige børn og unge, både på kort sigt og efter 1 års follow-up. Tredive børn og unge, alder 8-16 år, henvist til Videnscenter for Børn og Unge med Overvægt

(VIBUO), måles på ovennævnte parametre og randomiseres herefter til HIIT eller moderat træning, 2 gange om ugen i 12 uger. Målinger gentages efter 6 og 12 ugers behandling og træning, og igen ved 1-års follow-up. Børnene bliver i hele forløbet fulgt i VIBUO.

**Præliminære resultater og konklusion**

Efter træning 2 gange om ugen i 12 uger, i kombination med ambulant behandling efter TCOCT protokol, ses HIIT træning at have mest gavnlige effekt på fald i BMI. For begge grupper ses forbedring i døgnblodtryksprofiler, kondital, biokemi og sensewearprofiler. Der gøres follow-up ultimo 2016, med endelige resultater.

# GEOGRAPHIC VARIATION IN MORTALITY RATES OF ACUTE MYOCARDIAL INFARCTION – REGISTRATION PRACTICE, DISEASE OR HEALTH BEHAVIOR DRIVEN?

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**Background**
Pronounced Inter-regional variation in mortality rates of Acute Myocardial Infarction (AMI) has been well documented. National registers are used for the monitoring of mortality rates. Obtaining reliable results hinges upon the quality of death certification which highly depends on the individual physicians' notification. Previously it has been established that AMI is stated far too often. The purpose of this study was to examine if the pronounced inter-regional variation in mortality rates of AMI is affected by coding practice.

**Methods**
A prospective historical cohort study, based on Danish nationwide administrative registers, has been performed. Individual-based comparison of death certificates with patient records and dispensed medicine were used to categorize citizens, who died from

AMI during 2002-2014, in three diagnostic categories (Definite AMI, Conceivable AMI and Uncertain AMI). Age-standardized rates were used to describe time-trends in mortality among regions. Predictors related to being classified in the group of Uncertain AMI were assessed by logistic regression analysis, adjusted for patient-related factors.

**Results**

Among 35.102 citizens, who died from AMI, 39.7% (13.939) classified as definite AMI, 24.7% (8.652) as conceivable AMI and 35.6% (12.511) as uncertain AMI. Mortality rates, stratified by the three diagnostic categories, differed considerably among regions. Odds-Ratios for regions varied from 0.78 (95%CI:0.70;0.86) to 1.54 (95%CI:1.24;1.63). The strongest predictors for being classified as Uncertain AMI were Region North and if death occurred at home.

**Conclusion**

These findings stress the importance of further validating the nationwide registers to tell whether and how they can be used to reflect "true" incidence and mortality rates prospectively.

# DELAYED DIAGNOSIS, PAIN AND LOSS OF FUNCTION ARE SOME OF THE CONSEQUENCES OF SPONTANEOUS FRACTURES IN PATIENTS WITH RHEUMATOID ARTHRITIS – A QUALITATIVE ANALYSIS OF PATIENTS´ EXPERIENCE

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**Background**
Spontaneous fractures in patients with rheumatoid arthritis (RA) have only occasionally been reported in the literature. However, rheumatologists at North Denmark Regional Hospital have noticed several cases where new onset knee or ankle pain was misdiagnosed as arthritis activity but was later shown to be spontaneous fractures. An x-ray examination did not reveal the fracture, but it was identified on an MRI examination. The fractures are at risk of being overlooked, and this fact may lead to a delay in diagnosis and a risk of ineffective treatment with e.g. steroid injections. The study was carried out in the Physio- and Occupational Therapist unit in Vendsyssel Hospital. The included patients were diagnosed with RA and spontaneous fractures. Fifteen patients, all women, were identified. Ten patients in the age of 57-88 years participated in the study.

They had an average disease duration of 14.2 years and a MRI was performed at a median of eight months.

**Methods**
The patients were divided into two age specific groups: 57-69 and 70-88 years. The focus groups data were subjected to thematic analysis to provide a sense of the important themes. Categorizing, coding and analysing the data from the focus groups identified the themes.

**Results**
All patients identified the missing diagnosis as a significant burden. The patients were experiencing pain, but did not receive a diagnosis or an explanation for their symptoms. "I've never been as happy as when I was told my leg was broken…" Most of the patients experienced more pain than usual for their RA: "You suddenly have a lot more pain, but you just don't know where it comes from". All patients noticed a significant loss of function before the diagnosis was made and during immobilisation: "I was so unhappy about not being able to do anything… even just getting up at night to go to the toilet...". When the patients were immobilised they were offered crutches, but they were not able to use standard crutches due to their RA: "I can't use crutches because I don't have enough strength to lift myself…"

**Conclusions**
Patients with RA with spontaneous fractures experience the delayed diagnosis as a burden, and it is stressful for them to wait for an explanation for their pain. Due to the patients missing ability to use crutches or use a wheelchair, it is important to find other aids that patients with RA and spontaneous fractures can use. When the patients were immobilised they experienced loss of function. This calls for the need to focus on the diagnosis and guidance of these patients in relation to daily activities and aids.

# COMPUTED TOMOGRAPHY COLONOGRAPHIC DIAGNOSIS MADE BY RADIOGRAPHER

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**Background**
Computed tomography colonography (CTC) is the primary radiological examination for detection of colorectal cancer and premalignant polyps. In march 2014 a national screening program for malignant colon decease was initiated in Denmark, which increased the number of CTC. The CTC is a complex technique that requires special training and experience of both the radiographers performing the colonography and the radiologists who interpret the results. The considerable number of CTC performed means that interpretation of the examinations is a time-consuming task for radiologists. This study aimed to evaluate the diagnostic performance of radiographers who received a training programme in colon diagnosing.

**Methods**
During the period from December, 2014 to May, 2015, 126 patients underwent CTC screening or diagnostics. The colon was interpreted by both a radiographer and an experienced radiologist. Subsequently, results were compared and consensus established.

**Results**
A total of 100 patients were included, six polyps (6 - 9 mm) one polyp (>=10mm), four cancer suspect areas and four second opinions. The result was nine true positives, three false positives, no false negatives and 84 true negatives corresponding to a negative predictive value of 1.000 and an accuracy of 0.969.

**Conclusion**
This study shows that radiographers can be a valuable contribution in the interpretation of CTC. Since the project was completed the two radiographers have participated in the daily routine and have teached new radiologists in both interpretating the CTC and softwere skills in Syngo Via Workplace.

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