

ANNUAL REPORT 2017

CENTER FOR CLINICAL EPIDEMIOLOGY

Center for Clinical Epidemiology
Research Unit for Clinical Epidemiology
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OUH
Odense
University Hospital

Region of
Southern Denmark


UNIVERSITY OF SOUTHERN DENMARK

WELCOME

We welcome everybody with an interest in clinical epidemiology and data analysis and we ask anyone with a project, advisory task or research project, in the need of assistance within clinical epidemiology and data analysis, to contact us: Bente Mertz Nørgård – bente.noergaard@rsyd.dk, Susanne Møllerstrøm – susanne.moellerstroem@rsyd.dk.

The vision of Center for Clinical Epidemiology is to be known and respected for projects and research within clinical epidemiology at an international level and to provide expert knowledge within a wide range of diseases and clinical epidemiological methods to solve issues regarding the prognosis for patients. We want the staff at the Center for Clinical Epidemiology to be desirable collaborators in local, regional, national, and international projects and research activities.

Our mission is to ensure correct diagnosis and treatment of patients through research results and thereby to ensure that all clinical decisions in the treatment processes are evidence based. We want to focus especially on research findings that can be applied and implemented in the daily clinical practice.

Center for Clinical Epidemiology handles the following activities:

1. Special projects and consultancy services within clinical epidemiology and data analysis
2. Clinical epidemiological research and academic work

Apart from the above activities, the center houses and supports tasks for the RKKP (the regional clinical quality program - the Danish Clinical Registries).

In 2017 we published 33 peer reviewed articles in international medical journals. In 2017 we have brought external fundraising into a special focus of interest and we will continue this focus in the following years.

Bente Mertz Nørgård

Professor and head of Center for Clinical Epidemiology and the Research Unit of Clinical Epidemiology

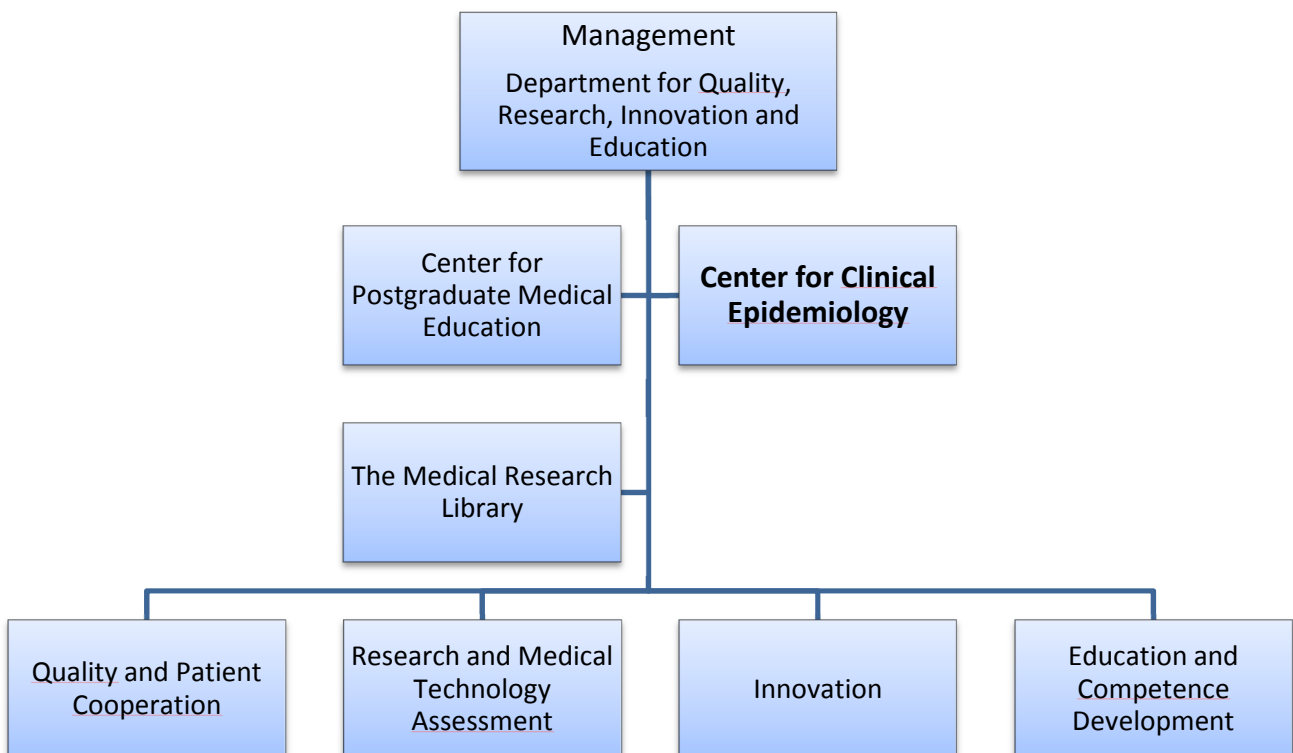
ORGANIZATION

On 1 May 2017 Center for Clinical Epidemiology celebrated its 10th anniversary. The center is affiliated with the Department of Quality, Research, Innovation and Education, Odense University Hospital, as an independent unit and all research activities from the research unit refer to the Department of Clinical Research, University of Southern Denmark.

An executive coordinating group is associated with the Center for Clinical Epidemiology with representatives from the management in the Region of Southern Denmark (chief of staff), the University of Southern Denmark (head of the Department of Clinical Research), and Odense University Hospital (chief of staff).

An overview of the staff at the Center for Clinical Epidemiology is available at our web-site: www.ouh.dk/cke

Quality, Research, Innovation and Education



WORKING RELATIONS

The employees at the Center for Clinical Epidemiology have been members of a variety of project groups in 2017: steering groups of clinical databases, technician groups regarding transfer of quality data, project groups at the Danish Board of Health and the Danish Regions.

Activities within the following special projects and consultancy tasks in particular have occupied the center's resources in 2017 (the following is not a complete list of consultancy functions):

Center for Clinical Epidemiology has provided the RKKP with a number of consultancy services in 2017. The support has been given within the area of clinical epidemiology, data management, and biostatistical analyses to a number of national clinical databases. CKE will also provide RKKP with consultancy services in 2018.

The cooperation with Emergency Medicine, Odense University Hospital, concerning the daily operation of "The emergency cohort of Southern Denmark" has been ongoing for several years. The database comprises data on all patients admitted via the Emergency Medicine Units in the Region of Southern Denmark, and the project is based on a cooperation with Professor Annmarie Lassen, established in 2012.

Many staff members in the Center for Clinical Epidemiology handled consultancy tasks for a number of external parties locally, regionally and nationally, all within clinical epidemiology and analysis. For instance:

A consultancy agreement on a project on antibiotic use, with the Focused Research Unit in Emergency Medicine, Institute of Regional Health Research, University of Southern Denmark, was inaugurated in 2017. Six months of data from all acutely admitted patients will be collected, followed by six months of implementing an

antibiotic stewardship program, and finalized by another six months of data collection from all acutely admitted patients. Data comprising variables of microbiology, antibiotics, and clinics will be compiled and analyzed by our employees.

A consultancy agreement with the Research Unit of General Practice has been ongoing in 2017 and we have, within this agreement, supported the Research Unit of General Practice with different biostatistical analyses in 2017.

A consultancy agreement with the Department of Infectious Diseases, Odense University Hospital, was established in 2017. The agreement involves statistical, epidemiological, and data management support to different infectious disease projects, e.g. tuberculosis in HIV patients in Ghana, hepatitis C in drug users, and sepsis biomarkers, to name a few. The collaboration will continue in 2018.

We have an advisory cooperation with Rygcenter Middelfart (Research Department Spine Centre of Southern Denmark, Hospital Lillebaelt, Middelfart) on two main projects:

- Incidence and regional variation of Morbus Bechterew and Spondyloarthritis from 2000-2013: A nationwide cohort study. The aim of the study is to describe the incidence of ankylosing spondylitis and spondyloarthritis in the Danish population from 2000-2013, for the whole nation and for each of the five regions to evaluate if there is a trend over time explained by use of magnetic resonance imaging.
- Prognostic factors of the patients' course when referred to the Spine Centre of Southern Denmark for decision support (Prognostiske faktorer for forløb for patienter henvist til Rygcenter Syddanmark til brug i beslutningsstøtteredskab). The aim of this project is to describe a course of disease and the effect of prognostic factors in the process. Based on the identified prognostic models algorithms are set up to develop individually adapted decision support tools.

Regarding all working partners related to research projects please see the chapter "Research activities".

RESEARCH ACTIVITIES

The Research Unit of Clinical Epidemiology was established in 2009 with the purpose of handling all research and academic activities in the center. The unit is academically affiliated with the Department of Clinical Research at the University of Southern Denmark.

Several of the employees at the Center for Clinical Epidemiology have a formal academic employment at the Department of Clinical Research. We have a clinical professorship which is also linked to the daily management at the center, and academic affiliations (lecturer/adjunct) of two biostatisticians and two clinical epidemiologists.

The professor of the department is also nominated as Senior Epidemiologist at the Brigham and Women's Hospital, Boston, and lecturer, part-time, at Harvard Medical School.

The Research Unit of Clinical Epidemiology has affiliated an adjunct professor in clinical epidemiology (Sonia Friedman, MD, Visiting Professor Harvard Medical School and Brigham and Women's Hospital, Boston). Sonia Friedman is an expert within chronic inflammatory bowel disease and reproduction issues. At the same time Sonia Friedman is an associated professor at Harvard University, Boston.

In 2017 we have also affiliated Pedro Manuel Sarmiento Rodrigues Póvoa, Unidade de Cuidados Intensivos Polivalente, MD, Hospital de São Francisco Xavier, Lisbon, as an adjunct professor. Pedro Póvoa is an expert researcher within areas related to intensive care and patients suffering from sepsis. Pedro Póvoa has especially focused on the importance of C-reactive protein of which daily records exceed a single count in monitoring the patient's condition.

The employees at Center for Clinical Epidemiology conduct their own initiated research projects in collaboration with domestic and foreign researchers. Our research is mainly

within the following areas (for the specific publications please refer to the last chapter 'Publications'):

Cancer

Acute medicine and intensive care

Sepsis

Bowel diseases and chronic inflammatory bowel disease

Human reproduction

Chronic diseases

Obstetrics

Gynecology

Psychiatrics

Geriatrics

Social medicine

PHD-STUDENTS

Phd-students supervised by Center for Clinical Epidemiology staff members, 2017

- Line Riis Jølving: Morbidity in children born to women with chronic disease. Ongoing
- Heidi Kammerlander: Biologic therapy during pregnancy in inflammatory bowel disease – clinical epidemiologic aspects focusing on use, treatment regimes, disease activity and safety during pregnancy. Ongoing
- Majken Munk Brønserud: Patientrapporteret livskvalitet hos lungecancer patienter – Anvendelse af patientrapporterede oplysninger (PRO) som kvalitetsindikator (Patient reported quality of life in patients with lung cancer – Applied patient reported information as a quality indicator). Ongoing
- Ken Lund: Disease control in pediatric and adolescent patients with inflammatory bowel disease: aspects of Anti-TNF- α and physical activity. Protocol accepted November 2017, project to start January 2018

ACADEMIC ASSESSMENT

In 2017 the staff at the Center for Clinical Epidemiology has

- worked as reviewers for scientific journals
- evaluated research protocols for local, national, and international scientific foundations
- participated in scientific congresses
- given scientific oral presentations
- undertaken assessments of PhD protocols and dissertations for the Faculty of Health Sciences at the University of Southern Denmark and other universities in Denmark

TEACHING

The staff at the center has trained, supervised, and examined a large number of bachelor students and master's thesis students at the Faculty of Health Sciences at University of Southern Denmark.

The staff at the center has acted as external examiners at other academic institutions (Aarhus University and Copenhagen University).

The staff has taught 'Introduction to epidemiology and register based research in Denmark' at the pre-PhD course at University of Southern Denmark.

FUNDINGS

PI (USD 339,991, approx. DKK 2,209,942 for a period of three years). In 2015-2017 the research unit was awarded a three-year grant from the CCFA (Crohn's & Colitis Foundation of America) for special research projects concerning patients with chronic inflammatory bowel diseases. These projects are carried out in collaboration with researchers from Brigham and Women's Hospital and Harvard Medical School, Boston.

PI (DKK 545,000). Disease control in pediatric and adolescent patients with inflammatory bowel disease: aspects of anti-TNF- α therapy and physical activity, from the research foundation in the Region of Southern Denmark. Granted to cover one year's salary for a PhD student.

PI (DKK 300,000). Disease control in pediatric and adolescent patients with inflammatory bowel disease: aspects of anti-TNF- α therapy and physical activity, from the research foundation in the Region of Southern Denmark. Granted to cover running costs in a PhD project.

PI (USD 8,300, DKK 55,000). Is chronic inflammatory bowel disease provoked by anti-TNF therapy? Granted from Brigham and Women's Hospital (Joshua Korzenik, MD), Boston, Massachusetts 02115. Granted to cover biostatistical analyses.

PI (DKK 200,000). Is chronic inflammatory bowel disease provoked by anti-TNF therapy? Granted from the Odense University Hospital Research Foundation. Granted to cover biostatistical analyses. PI (DKK 100,000). Biliary cancer: diagnosis, etiological factors, treatment, and prognostic factors. Granted from the Danish Colon Cancer Group (DCCG).

PI (DKK 260,000). The efficacy of assisted reproductive technology treatment in women with rheumatoid arthritis and epilepsy. Granted from the Odense University Hospital Research Foundation to cover biostatistical analyses.

Co-PI (DKK 255,000). Mental health related disorders in patients with back pain.
Granted from the Odense University Hospital Research Foundation to cover
biostatistical analyses.

PUBLICATIONS

Scientific publications

In 2017, 33 papers were published in peer-reviewed journals. Please refer to our website <http://info.ouh.dk/wm354812> or the list below.

2017

1. Wehberg S, Guldberg R, Gradel KO, Kesmodel US, Munk L, Andersson CB, Jølvig LR, Nielsen J, Nørgård BM. Risk factors and between-hospital variation of caesarean section in Denmark: a cohort study. *BMJ Open* 2017
2. Krogh Rasmussen B, Hansen S, Laursen RJ, Kosteljanetz M, Schultz H, Nørgård BM, Guldberg R, Gradel KO. Epidemiology of glioma: clinical characteristics, symptoms, and predictors of glioma patients grade I-IV in the Danish Neuro-Oncology Registry. *J Neurooncol* 2017;135:571-579
3. Winter RW, Larsen MD, Magnussen B, Friedman S, Kammerlander H, Nørgård BM. Birth outcomes after preconception paternal exposure to methotrexate: A nationwide cohort study. *Reproductive Toxicology* 2017;74:219-223
4. Larsen MD, Friedman S, Magnussen B, Nørgård BM. Birth outcome of children fathered by men treated with systemic corticosteroids during the conception period – A cohort study. *Basic Clin Pharmacol Toxicol*, 2017 Aug 14. Doi: 10.1111/bcpt.12857
5. Soelberg K, Jarius S, Skejoe H, Engberg H, Mehlsen JJ, Nilsson AC, Madsen JS, Reindl M, Wildemann B, Grauslund J, Kyvik KO, Smith TJ, Lillevang ST, Paul F, Weinshenker BG, Asgari N. A population-based prospective study of optic neuritis. *Mult Scler* 2017
6. Kammerlander H, Nielsen J, Kjeldsen J, Knudsen T, Gradel KO, Friedman S, Nørgård BM. Fecal calprotectin during pregnancy in women with moderate-

severe inflammatory bowel disease. Accepted for publication in *Inflamm Bowel Dis*

7. Jølving LR, Nielsen J, Kesmodel US, Nielsen RG, Beck-Nielsen SS, Nørgård BM. Children born by women with rheumatoid arthritis have increased susceptibility for selected chronic diseases – a nationwide cohort study. Accepted for publication in *Arthritis Care & Research* 2017
8. Bengtsson J, Thygesen PS, Kaerlev L, Knudsen LE, Bonde JP. Potential exposure to endocrine disrupting chemicals and selected adverse pregnancy outcomes: a follow-up study of pregnant women referred for occupational counselling. *J Occup Med Toxicol* 2017
9. Grynderup MB, Nabe-Nielsen K, Lange T, Conway PM, Bonde JP, Garde AH, Gullander M, Kaerlev L, Persson R, Rugulies R, Vammen MA, Høgh A, Hansen ÅM. The association between workplace bullying, salivary cortisol, and long-term sickness absence: a longitudinal study. *BMC Public Health* 2017
10. Rasmussen BK, Hansen S, Laursen RJ, Kosteljanetz M, Schultz H, Nørgård BM, Guldborg R, Gradel KO. Epidemiology of glioma: clinical characteristics, symptoms, and predictors of glioma patients grade I-IV in the Danish Neuro-Oncology Registry. *Neurooncol* 2017
11. Halling ML, Kjeldsen J, Knudsen T, Nielsen J, Koch-Hansen L. Patients with inflammatory bowel disease have increased risk of autoimmune and inflammatory diseases. *World J Gastroenterol* 2017, September 7; 23(33): 6137-6146
12. Friedman S, Larsen PV, Fedder J, Nørgård BM. The reduced chance of a live birth in women with IBD receiving assisted reproduction is due to a failure to achieve a clinical pregnancy. *Gut* 2017;66:556-558
13. Friedman S, Larsen PV, Fedder J, Nørgård BM. The efficacy of assisted reproduction in women with inflammatory bowel disease and the impact of surgery. *Inflamm Bowel Dis* 2017;23:208-217

14. Mikkelsen S, Forman JL, Fink S, Vammen MA, Thomsen JF, Grynderup MB, Hansen ÅM, Kaerlev L, Kolstad HA, Rugulies R, Bonde JP. Prolonged perceived stress and saliva cortisol in a large cohort of Danish public service employees: cross-sectional and longitudinal associations, *Int Arch Occup Environ Health* 2017, 11 July
15. Nabe-Nielsen K, Grynderup MB, Conway PM, Clausen T, Bonde JP, Garde AH, Hogh A, Kaerlev L, Török E, Hansen ÅM. The role of psychological stress reactions in the longitudinal relation between work place bullying and turnover. *J Occup Environ Med* 2017;59:665-672
16. Hansen MF, Lose G, Kesmodel US, Gradel KO. A national population-based cohort study of urethral injection therapy for female stress and mixed urinary incontinence: the Danish Urogynaecological Database. 2007-2011. *Int Urogynecol J* 2017;28:1309-1317
17. Rasmussen AH, Wehberg S, Fenger-Groen J, Christensen HT. Retrospective evaluation of a national guideline to prevent neonatal hypoglycemia. *Pediatr Neonatal* 2017, Jan 24
18. Gradel KO, Jensen US, Schönheyder HC, Østergaard C, Knudsen JD, Wehberg S, Søgaard M and for the Danish Collaborative Bacteraemia Network (DACOBAN). Impact of appropriate empirical antibiotic treatment on recurrence and mortality in patients with bacteraemia. *BMC Infectious Diseases* 2017;17:122
19. Jeppesen MM, Mogensen O, Hansen DG, Iachina M, Korsholm M, Jensen PT. Detection of recurrence in early stage endometrial cancer – the role of symptoms and routine follow-up. *Acta Oncol* 2017;56:262-269
20. Buttenschøn HN, Krogh J, Nielsen NM, Kærlev L, Nordentoft M, Mors O. Association analyses of depression and genes in the hypothalamus-pituitary-adrenal axis. *Acta Neuropsychiatr* 2017;29:59-64
21. De Silva PS, Hansen HH, Wehberg S, Friedman S, Nørgård BM. Ectopic pregnancy in women with inflammatory bowel disease – a 22 year nationwide

cohort study. Accepted for publication in Clinical Gastroenterol Hepatol June 2017

22. Werngreen Nielsen S, Møller Ljungdahl P, Nielsen J, Nørgård BM, Qvist N. Maternal use of selective serotonin reuptake inhibitors during pregnancy is associated with Hirschprung's disease in newborns – a nationwide cohort study. Orphanet Journal of Rare Diseases 2017;12:116
23. Illum NO, Gradel KO. Parents' assessments of disability in their children using World Health Organization international classification of functioning, disability and health, child and youth version joined body functions and activity codes related wot everyday life. Clinical Medicine Insights: Pediatrics Volume 2017;11:1-11
24. Kammerlander H, Nørgård BM, Friedman S, Kjeldsen J, Knudsen T, Nielsen J. Anti-TNF- α use during the third trimester of pregnancy in women with moderate-severe inflammatory bowel disease and the risk of preterm birth and low birthweight'. Inflamm Bowel Dis-D-17-00272R2, Jun 14 2017
25. Iachina M, Brønserud MM, Jakobsen E, Trosko O, Green A. History of depression in lung cancer patients: impact of delay. Clinical Oncology 2017:1-8
26. Iachina M, Jakobsen E, Kudsk Fallesen A, Green A. Transfer between hospitals as a predictor of delay in diagnosis and treatment of patients with non-small cell lung cancer – a register based cohort-study. BMC Health Services Research 2017;17:267
27. Vestergaard R, Kammerlander H, Brock B, Julsgaard M. Immunoglobulin and infliximab concentrations in dichoriionic twins exposed to infliximab in utero. J Crohns Colitis 2017 Mar 10. Doi: 10.1093/ecco-jcc/jjx034
28. Kammerlander H, Nielsen J, Kjeldsen J, Knudsen T, Friedman S, Nørgård B. The effect of disease activity on birth outcomes in a nationwide cohort of women with moderate to severe inflammatory bowel disease. Inflamm Bowel Dis 2017;23:1011-1018

29. Bengtsson J, Søgaard Thygesen P, Kaerlev L, Knudsen LE, Bonde JP. Potential exposure to endocrine disrupting chemicals and selected adverse pregnancy outcomes: a follow-up study of pregnant women referred for occupational counselling. *J Occupat Med and Toxicol* 2017;12:6
30. Blixt T, Gradel KO, Homann C, Seidelin JB, Schønning K, Lester A, Houlind J, Stangerup M, Gottlieb M, Knudsen JD. Asymptomatic carriers to nosocomial *clostridium difficile* infection: a cohort study of 4508 patients. *Gastroenterology* 2017;152:1031-1041
31. Friedman S, Larsen MD, Magnussen B, Jølving LR, de Silva P, Nørgård BM. Paternal use of azathioprine/6-mercaptopurine or methotrexate within 3 months before conception and long-term health outcomes in the offspring – a nationwide cohort study. *Reprod Toxicol* 2017;73:196-200
32. Jølving LR, Nielsen J, Beck-Nielsen SS, Nielsen RG, Friedman S, Kesmodel US, Nørgård BM. The Association Between Maternal Chronic Inflammatory Bowel Disease and Long-term Health Outcomes in Children-A Nationwide Cohort Study. *Inflamm Bowel Dis* 2017;23:1440-1446
33. Rasmussen BK, Hansen S, Laursen RJ, Kosteljanetz M, Schultz H, Nørgård BM, Guldborg R, Gradel KO. Epidemiology of glioma: clinical characteristics, symptoms, and predictors of glioma patients grade I–IV in the Danish Neuro-Oncology Registry. *J Neurooncol* 2017; DOI 10.1007/s11060-017-2607-5