Norsk Epidemiologi

Norwegian Journal of Epidemiology

Årgang 28, supplement 1, november 2018

Utgitt av Norsk forening for epidemiologi

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ISSN 0803-4206
Opplag: 150
Trykk: NTNU Grafisk senter
Layout og typografi: Redaktøren

Tidsskriftet er åpent tilgjengelig online:
www.www.ntnu.no/ojs/index.php/norepid
Også via Directory of Open Access Journals (www.doaj.org)

Utgis vanligvis med to regulære temanummer pr. år. I tillegg kommer supplement med sammendrag fra Norsk forening for epidemiologis årlige konferanse.

DEN 25. NORSKE EPIDEMIOLOGIKONFERANSEN

TRONDHEIM,

14.–15. NOVEMBER 2018

The 25th Norwegian Conference on Epidemiology
Trondheim, November 14–15, 2018

We would like to welcome you to Trondheim and the 25th conference of the Norwegian Epidemiological Association (NOFE). We are pleased that EPINOR again will hold their annual meeting in conjunction with the NOFE Annual Conference, and that several EPINOR members will participate at the conference and present their studies. We hope that the cooperation between NOFE and EPINOR will continue, and that EPINOR members will continue to enjoy participation in NOFE also after completing their PhD.

Understanding causality is an underlying goal of epidemiological research. As the counterfactual model suggests, causality is not directly observable. Still, several methods have been developed to approach the question of causality, each of these methods having their strengths and limitations. Ultimately aiming at improving population health, researchers need to revisit the topic of causal inference again and again. We have therefore chosen *Causality – a never-ending story* as the topic of this year's conference.

We are pleased to welcome our three distinguished keynote speakers. Dr Janet Rich-Edwards will set the scene at the beginning of the conference with her talk about cause and consequence. Dr George Davey Smith will introduce us to Mendelian randomization, an increasingly popular method in epidemiological research, and Dr Jon Michael Gran will inform us about the use of multi-state models in registry studies.

The winners of the Publication of the year award and the the Honorary membership award will be announced on Wednesday from 13.00. Furthermore, the 2018 NOFE Annual Meeting will be held on Wednesday at 16.30 at the conference hotel, Radisson Blu Royal Garden.

The conference dinner will take place at the conference hotel.

We thank the Department of Public Health and Nursing, NTNU, for their financial support to the conference.

Welcome to Trondheim and NOFE 2018!

The NOFE Steering Committee
and
The organizing committee for the NOFE 2018 Conference

Gunnhild Åberge Vie
Linda Ernstsen
Signe Opdahl
Johan Håkon Bjørngaard
Tom Ivar Lund Nilsen (EPINOR)
Eivind Schjelderup Skarpsno (EPINOR)
NTNU, Norwegian University of Science and Technology

The 25th Norwegian Conference on Epidemiology

Trondheim, November 14–15, 2018

Programme Overview

Wednesday, November 14th

09:00	**Registration**, Radisson Blu Royal Garden Hotel
10:00	**Welcome and opening**: NOFE leader Linda Ernstsen
10:10	**Invited speaker: Janet Rich-Edwards, Radcliff institute/ Harvard T.H. Chan School of Public Health, Boston** *"Cause and Consequence: What Really Matters in Public Health?"* Chair: Bjørn Olav Åsvold
11:00	**Oral presentations of submitted abstracts – 1:** *Pregnancy A1-A3* *Obesity B1-B4* *Mental health C1-C4*
12:00	**Lunch**
13:00	**Publication of the year award and Honorary membership award**
13:45	**Oral presentations of submitted abstracts – 2:** *Cancer A4-A9* *Cardiovascular disease B5-B9* *Diabetes C5-C8*
15:00	**Coffee break** with refreshments
15:30	**Oral presentations of submitted abstracts – 3:** *Lifestyle A10-A12* *Various topics 1 B10-B12* *Various topics 2 C9-C11*
16:15	**Coffee break**
16:30-17:30	**NOFE annual meeting**
19:30	**Conference dinner**, Radisson Blu Royal Garden Hotel

Thursday, November 15th

09:00	**Invited speaker: George Davey Smith, MRC Integrative Epidemiology Unit, University of Bristol** *"Mendelian randomization and the potential of genetics to inform causality"* Chair: Johan Håkon Bjørngaard
10:00	**Poster viewing** and coffee break *Posters P1-P8*
10:45	**Oral presentations of submitted abstracts – 4:** *Causal inference A13-A17*
12:00	**Lunch**
13:00	**Invited speaker: Jon Michael Gran, Oslo Centre for Biostatistics & Epidemiology/ University of Oslo** *"Causal inference in multi-state models with application to population-wide registry studies"* Chair: Gunnhild Åberge Vie
14:00	**Coffee break** with refreshments
14:15	**Oral presentations of submitted abstracts – 5:** *Cardiovascular disease A18-A20* *Methods B12-B14*
15:00	**Closing of the conference**

The 25th Norwegian Conference on Epidemiology

Trondheim, November 14–15, 2018

Scientific Programme for Parallel Sessions

Oral presentations of submitted abstracts – 1

Olav Trygvasson II/III			
Time	**No.**	**Pregnancy**	**Presenters**
11:00	A1	Estimated risk of miscarriages in Norwegian health registries according to pregnancy history	Magnus, Maria C
11:15	A2	Time trends in placental pregnancy complications after assisted reproduction in the Nordic countries	Petersen, Sindre H
11:30	A3	Placental weight and birthweight; the relations with number of daily cigarettes and smoking cessation in pregnancy. A population study	Bjelland, EK

Sverresborg			
Time	**No.**	**Obesity**	**Presenters**
11:00	B1	Energy and macronutrient intake and associations with body mass index and fat mass index: The seventh Tromsø Study 2015-16	Lundblad, Marie W
11:15	B2	Quantifying the impact of genes on BMI during the obesity epidemic	Brandkvist, Maria B
11:30	B3	Associations of fathers and their offsprings weight gain with non-allergic asthma	Lønneboth, M
11:45	B4	Associations between parental polygenic obesity risk and offspring's weight at birth, early and late adolescence – The HUNT Study, Norway	Næss, Marit

Munkholmen/ Kristiansten			
Time	**No.**	**Mental health**	**Presenters**
11:00	C1	Survival and years of life lost in various aetiologies of dementia, mild cognitive impairment (MCI) and subjective cognitive decline (SCD) in Norway	Strand, Bjørn Heine
11:15	C2	Prenatal exposure to benzodiazepines and z-hypnotics and child behavior problems at 5 years	Sundbakk, Lena M
11:30	C3	Psychiatric comorbidity and genetic correlations provide new insights into differences between attention-deficit/hyperactivity disorder and autism spectrum disorder	Solberg, Berit S
11:45	C4	Neighborhood built environment influence on activity participation and mental health in childhood and adolescence: a systematic review	Aamodt, Geir

Oral presentations of submitted abstracts – 2

Olav Trygvasson II/III			
Time	**No.**	**Cancer**	**Presenters**
13:45	A4	Breast cancer women lack normal immune response after full-term pregnancies	Lund, Eiliv
14:00	A5	Carcinogenic and chemopreventive effects of prescription drugs: A register-based screening approach	Andreassen, Bettina K
14:15	A6	Recent increase in incidence of cervical precancerous lesions in Norway: nationwide study from 1992 to 2016	Orumaa, Madleen
14:30	A7	Prospective association between sedentary lifestyle and incidence of lung cancer in Norwegian adults: the HUNT study	Jiang, Lin
14:45	A8	Menopausal hormone therapy and breast cancer risk: effect modification by body mass through life	Sandvei, Marie S
15:00	A9	Lifetime indoor tanning and risk of cutaneous squamous cell carcinoma	Lergenmuller, Simon

Sverresborg			
Time	**No.**	**Cardiovascular disease**	**Presenters**
13:45	B5	Predictors for stroke mortality. A comparison of the Oslo-study 1972/73 and the Oslo II-study in 2000	Håheim, Lise Lund
14:00	B6	Gender contrasts in adverse effect of diabetes on the risk of incident myocardial infarction. The Tromsø study 1979-2012	Albrektsen, Grethe
14:15	B7	Time trends in stroke incidence rates in Norway 2001-2014: Analyses from the CVDNOR project	Ariansen, Inger
14:30	B8	Concurrent changes in body weight and physical activity in relation to all-cause and cardiovascular mortality: the HUNT Study	Nordstoga, Anne Lovise and Zotcheva Ekaterina
14:45	B9	Folate related birth defects and future maternal cardiovascular mortality	Klungsøyr K

Munkholmen/ Kristiansten			
Time	**No.**	**Diabetes**	**Presenters**
13:45	C5	The validity of FINDRISC as a prediction tool for diabetes in a contemporary Norwegian population. A 10-year follow-up of the HUNT Study	Jølle, Anne
14:00	C6	Trends in diabetes prevalence. The Tromsø Study 1994-2016.	Hopstock, Laila A
14:15	C7	Childhood-onset Type 1 diabetes in Norway 1989-2014: individual level analysis of socioeconomic factors	Ruiz, Paz LD
14:30	C8	Maternal and Newborn Vitamin D-Binding Protein, Vitamin D levels, Vitamin D Receptor genotype, and Childhood Type 1 Diabetes	Stene, Lars C

Oral presentations of submitted abstracts – 3

Olav Trygvasson II/III			
Time	**No.**	**Lifestyle**	**Presenters**
15:30	A10	Is paternal alcohol intake suitable as an IV for offspring alcohol intake?	Degerud, Eirik
15:45	A11	Higher levels of estimated cardiorespiratory fitness is associated with reduced risk of atrial fibrillation: The HUNT study	Garnvik, Lars E
16:00	A12	Associations of changes in cardiorespiratory fitness and depressive symptoms with white matter hyperintensities: the HUNT Study	Zotcheva, Ekaterina

Sverresborg			
Time	**No.**	**Various topics 1**	**Presenters**
15:30	B10	Health impact of air pollution in early life – A Nordic collaboration (NordicWelfAir)	Oftedal, Bente
15:45	B11	The association of osteoporosis with mortality in a COPD cohort. The HUNT Study, Norway	Vikjord, Sigrid Anna
16:00	B12	Comparison of pre- and post-bronchodilator lung function as predictors of mortality: the Nord-Trøndelag Health Study (HUNT)	Bhatta, Laxmi

Munkholmen/ Kristiansten			
Time	**No.**	**Various topics 2**	**Presenters**
15:30	C9	Improvement in work ability, psychological distress and pain sites in relation to low back pain prognosis: A longitudinal observational study in primary care	Nordstoga, Anne Lovise
15:45	C10	Contact with primary health care physicians prior to a severe emergency hospitalization	Skarshaug, Lena J
16:00	C11	Hordaland County Public Health Survey 2018 – some results	Nilsen, Thomas S

Oral presentations of submitted abstracts – 4

Olav Trygvasson II/III			
Time	**No.**	**Causal inference**	**Presenters**
10:45	A13	Estimation of causal effects using the co-twin regression model	Magnusson, Karin
11:00	A14	Causal inference in continuous time: an example on prostate cancer therapy	Ryalen, Pål C
11:15	A15	Prolonged length of emergency department stay and risk of death within 30 days – an instrumental variable analysis	Asheim, Andreas
11:30	A16	Evidence of a causal relationship between body mass index and psoriasis: a Mendelian Randomization study	Åsvold, Bjørn Olav
11:45	A17	Causal association of lipid fractions with estimated glomerular filtration rate. A multivariable Mendelian randomization analysis of the HUNT Study, Norway	Rasheed, Humaira

Oral presentations of submitted abstracts – 5

Olav Trygvasson II/III			
Time	**No.**	**Cardiovascular disease**	**Presenters**
14:15	A18	Cardiovascular disease after hypertensive disorders of pregnancy: the role of conventional cardiovascular risk factors. The HUNT Study in Norway	Haug, Eirin B
14:30	A19	Evaluation of the NORRISK2 model for cardiovascular risk prediction in South-Asians living in Norway	Rabanal, Kjersti S
14:45	A20	Asthma, asthma control and risk of acute myocardial infarction: results from the Nord-Trøndelag Health Study (HUNT)	Cepelis, Aivaras

Munkholmen/ Kristiansten			
Time	**No.**	**Methods**	**Presenters**
14:15	B13	Incorporating genome-wide methylation and genotype data to elucidate how region-wise methylation level might influence allele-defined relative risks	Romanowska, Julia
14:30	B14	Evaluation of methods for analysis of 2x2 contingency tables	Lydersen, Stian
14:45	B15	A systematic approach to assess ethical issues in stem cell researc	Håheim, Lise Lund

Poster presentations of submitted abstracts

Olav Trygvasson II/III			
Time	**No.**		**Presenters**
10:00	P1	Coffee consumption and overall and cause-specific mortality – the Norwegian Women and Cancer Study (NOWAC)	Lukic, Marko
10:00	P2	Sport participation among adolescents and its association with mental health in different age-groups: The Young-HUNT Study	Guddal, MH
10:00	P3	Transcriptional profiles of whole blood from women with ovarian cancer. A prospective nested case-control study from the NOWAC Post-genome Cohort	Jareid, Mie
10:00	P4	The "Healthy Soldier Effect": The role of self-selection and lifestyle factors	Strand, Leif Åge
10:00	P5	The Norwegian Armed Forces Health Registry and data from medical screening for service suitability	Fadum, Elin Anita
10:00	P6	Relative mortality of Norwegian military veterans of foreign missions	Rudvin, Inger
10:00	P7	Tinnitus and chronic pain: The Tromsø Study	Ausland, Jannike H-L
10:00	P8	Reproductive factors and risk of melanoma: a population-based cohort study	Støer, Nathalie C

A1

Estimated risk of miscarriages in Norwegian health registries according to pregnancy history

Maria C. Magnus[1,2,3], Allen J. Wilcox[4], Nils-Halvdan Morken[5], Siri E. Håberg[1]

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2) MRC Integrative Epidemiology Unit, University of Bristol, Bristol, United Kingdom
3) Department of Population Health Sciences, Bristol Medical School, Bristol, United Kingdom
4) National Institute of Environmental Health Sciences, National Institutes of Health, Durham, North Carolina, United States
5) Department of Clinical Science, Medical Faculty, University of Bergen, Bergen, Norway

Introduction: Few previous population-based studies have prospectively studied determinants of miscarriage.

Aims: To examine how the risk of miscarriage varies according to pregnancy history.

Methods: We identified the total number of pregnancies in Norway between 2009 and 2013 using information from the Medical Birth Registry of Norway, the Norwegian Patient Registry and the abortion registry. We used log-binomial regression to evaluate the risk of miscarriage according to the outcome of previous pregnancies while adjusting for mother's age.

Results: There were 420,129 pregnancies during the study period. Mothers were an average of 30 years at the time of delivery (SD 5 years). When we accounted for induced abortions, the overall risk of miscarriage was 12.7%. We observed a strong recurrence risk of miscarriage, with adjusted relative risks (aRRs) of 1.54 (95% CI: 1.48, 1.60) after one, 2.21 (95% CI: 2.03, 2.41) after two and 3.97 (95% CI: 3.29, 4.78) after three miscarriages when compared to women without a previous registered pregnancy. The risk of miscarriage was also increased if the previous live birth resulted in a baby that was preterm (aRR 1.23; 95% CI: 1.15, 1.31), small-for-gestational-age (aRR 1.07; 95% CI: 1.01, 1.13), large-for-gestational-age (aRR 1.06; 1.00, 1.12), or if the previous live birth was complicated by gestational diabetes (aRR 1.20; 1.05, 1.37). There was no strong evidence of an increased risk if the baby had a congenital malformation, or if the previous pregnancy was complicated by pre-eclampsia.

Conclusions: This is the first population-based study in Norway to estimate the risk of miscarriage. Our findings indicate a strong recurrence risk of miscarriage, and an increased risk with previous preterm birth, small-for-gestational-age, large-for-gestational-age or gestational diabetes.

A2

Time trends in placental pregnancy complications after assisted reproduction in the Nordic countries

Sindre Hoff Petersen[1], Bjørn Olav Åsvold[1,2], Anna Karina Aaris Henningsen[3], Mika Gissler[4], Ulla-Britt Wennerholm[5], Christina Bergh[5], Liv Bente Romundstad[1,6,7], Aila Tiitinen[8], Steen Christian Rasmussen[9], Max Petzold[10], Anja Pinborg[11], Signe Opdahl[1]

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11) Department of Obstetrics and Gynecology, Hvidovre Hospital, Institute of Clinical Medicine, Copenhagen University Hospital, Copenhagen, Denmark

Introduction: Use of assisted reproductive technology (ART) is increasing worldwide and ART conception currently comprises 3-5% of birth cohorts in the Nordic countries. The risk of placental complications is higher after ART compared to spontaneously conceived (SC) pregnancies. Whether the excess risk of placental complications in ART pregnancies has remained stable over time, is unknown.

Aims: To investigate whether trends in occurrence of pregnancy complications (hypertensive disorders in pregnancy [HDP], placental abruption and placenta previa) differ for ART compared to SC pregnancies during three decades of ART treatment in the Nordic countries.

Methods: In a population-based cohort study, with data from national health registries in Denmark, Finland, Norway and Sweden, we included 6,049,581 pregnancies resulting in delivery between 1988 and 2015. Among these, 135,722 were ART pregnancies. We used logistic regression with post-estimation to estimate absolute risks and risk differences (RDs) for each complication. We repeated analyses for singleton and twin pregnancies, separately.

Results: The risks of each placental complication were consistently higher in ART compared to SC pregnancies across the study period, with the exception of HDP in twin pregnancies, where risks were similar. Risk of HDP increased over time in twin pregnancies for both conception methods (RD 1.6 percentage points [*pp*] per 5 years, 95% confidence interval [CI] 1.17 to 2.01 for ART and 0.6 *pp,* 95% CI 0.43 to 0.74 for SC). No clear trends were found for HDP in singletons pregnancies. Risk of placental abruption decreased over time in all groups (RD -0.13 *pp,* 95% CI -0.17 to -0.09 and -0.05 *pp,* 95% CI -0.05 to -0.04 for ART and SC, respectively, for singletons and multiple pregnancies combined). The risk of placenta previa increased over time among ART singletons (RD 0.2 *pp,* 95% CI 0.12 to 0.26) and twins (RD 0.25 *pp,* 95% CI 0.11 to 0.40), but remained stable in SC pregnancies.

Conclusions: The risk of placental complications following ART conception is higher than for SC pregnancies. For HDP and placental abruption, ART pregnancies follow the same trends as the background population, whereas for placenta previa, risk has increased over time in ART pregnancies.

A3

Placental weight and birthweight; the relations with number of daily cigarettes and smoking cessation in pregnancy. A population study*

Larsen S[1,2], Haavaldsen C[1], **Bjelland EK**[1,3], Dypvik J[1,2], Jukic AM[4], Eskild A[1,2]

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2) Institute of Clinical Medicine, Campus Ahus, University of Oslo, Lørenskog, Norway
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4) Yale School of Public Health, Yale University, New Haven, USA

Introduction: Growth of the fetus depends on a well-functioning placenta, and birthweight and placental weight are highly correlated in normal pregnancies. Women who smoke in pregnancy give birth to infants with lower birthweight than non-smokers, but the relation with the placental weight remains unclear. Also, knowledge about the dose–relationships and the effects of smoking cessation in pregnancy is limited.

Aims: We studied associations of number of daily cigarettes in the 1st trimester with placental weight and birthweight in women who smoked throughout pregnancy, and in women who stopped smoking after the 1st trimester.

Methods: We included all women with delivery of a singleton in Norway during 1999-2014 (N = 698 891), by using data from the Medical Birth Registry of Norway. We assessed dose-response associations by applying linear regression with restricted cubic splines.

Results: In total, 12.6% smoked daily in the 1st trimester, and 3.7% stopped daily smoking. In women who smoked throughout pregnancy, placental weight and birthweight decreased by number of cigarettes; however, above 11-12 cigarettes we estimated no further decrease (*P* for non-linearity < 0.001). Maximum decrease in placental weight in smokers compared to non-smokers was 18.2 grams [95% confidence interval (CI): 16.6 to 19.7] and for birthweight the maximum decrease was 261.9 grams (95% CI: 256.1 to 267.7). In women who stopped smoking, placental weight was higher than in non-smokers and increased by number of cigarettes to a maximum of 16.2 grams (95% CI: 9.9 to 22.6). Birthweight was similar in women who stopped smoking and non-smokers, and we found no change by number of cigarettes (*P* for non-linearity < 0.001).

Conclusions: In women who smoked throughout pregnancy, placental weight and birthweight decreased non-linearly by number of cigarettes in the 1st trimester. In women who stopped smoking, placental weight was higher than in non-smokers and increased linearly by number of cigarettes. Birthweight was almost similar to that of non-smokers.

***Reference:**

Sandra Larsen, Camilla Haavaldsen, Elisabeth Krefting Bjelland, Johanne Dypvik, Anne Marie Jukic, Anne Eskild; Placental weight and birthweight; the relations with number of daily cigarettes and smoking cessation in pregnancy. A population study. *Int J Epidemiol* 2018, https://doi.org/10.1093/ije/dyy110

A4

Breast cancer women lack normal immune response after full-term pregnancies

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Introduction: There is a large body of evidence demonstrating long-lasting protective effect of each full-term pregnancy (FTP) on the development of breast cancer, a phenomenon that could be related to both hormonal and immunological changes during pregnancies.

Aim: In this work, we studied the pregnancy-associated differences in peripheral blood gene expression profiles between healthy women and women diagnosed with breast cancer in a prospective design.

Methods: Using an integrated systems epidemiology approach, we modelled breast cancer incidence as a function of parity in the Norwegian Women and Cancer (NOWAC) cohort (165 000 women), and then tested the resulting mathematical model using gene expression profiles in blood in a nested case-control study (460 invasive case-control pairs) of women from the NOWAC postgenome cohort. Lastly, we undertook a gene set enrichment analysis for immunological gene sets.

Results: A linear trend fitted the dataset precisely showing an 8% decrease in risk for each FTP, independent of stratification on other risk factors and lasting for decades after a woman's last FTP. Women with six children demonstrated 48% reduction of the breast cancer incidence compared to nulliparous. When we looked at gene expression, we found that 756 genes showed linear trends in cancer-free controls (FDR 5%), but this was not the case for any of the genes in breast cancer cases. Gene set enrichment analysis of immunologic gene sets (C7 collection in Molecular Signatures Database) revealed 215 significantly enriched human gene sets (FDR 5%).

Conclusions: We found marked differences in gene expression and in enrichment profiles of immunologic gene sets between breast cancer cases and healthy controls suggesting an important protective effect of the immune system on breast cancer risk.

A5

Carcinogenic and chemopreventive effects of prescription drugs: A register-based screening approach

Bettina Kulle Andreassen[1], Nathalie Støer[1], Giske Ursin[1], Hege Thoresen[2], Karen Boldingh Debernard[3], Øystein Karlstad[4], Kari Furu[4], Anton Pottegård[5], Søren Friis[6]

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Introduction: Surveillance of unintended effects of pharmaceuticals (pharmacovigilance or drug safety) is an important task, as knowledge of rare or late side effects is limited at the time of the introduction of new medications into the market. Side effects of drugs may involve increased or decreased risk of cancer, but these typically appear after a long induction period. The long latency of cancer development together with low incidences of many cancer types limit the usefulness of traditional pharmacovigilance strategies, primarily based on spontaneous reporting of adverse events, to identify associations between drug use and cancer risk. Post-marketing observational pharmacoepidemiological studies are therefore crucial in the evaluation of drug-cancer associations.

Aims: The main aim of this study is to identify associations between the use of prescription drugs and the incidence of cancer of various types and at different sites. We will also develop a surveillance tool, which may in coming years be used for efficient periodic screening and identification of novel drug-cancer associations in the entire Norwegian population.

Methods: The main data sources in the proposed project will be the Norwegian Prescription Database and the Cancer Registry of Norway. The underlying statistical model will be based on a multiple nested case-control design using all adult (approximately 200,000, aged 18-85 years) incident cancer cases from 2007 through 2015 in Norway as cases. Ten cancer-free population controls will be individually matched to these cases with respect to birth year, gender, and index date (date of cancer diagnosis). The statistical analyses will be performed based on logistic regression models adjusted for comorbidity (National Patient Register), concomitant drug use, socioeconomic parameters (Statistics Norway) and reproduction data (Medical Birth Registry).

Results: As this project is work in progress, we will focus on the (statistical) methods used in this project. The results of this association study will be reported in a key paper. Follow-up analyses of certain promising results will be presented during the second phase of our project. Finally, we will focus on the external validation/ meta-analysis.

A6

Recent increase in incidence of cervical precancerous lesions in Norway: nationwide study from 1992 to 2016

Madleen Orumaa[1], Maarit K. Leinonen[1], Suzanne Campbell[1], Bjørn Møller[2], Tor Åge Myklebust[2,3], Mari Nygård[1]

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Introduction: In 2016 in Norway, cervical cancer was the 11th most common cancer among women overall and the 3rd most common among women aged 25-49 years. With cervical cancer screening, cancer can be avoided. During the last years, the Norwegian Cervical Cancer Screening Program Annual Reports have noted an increase in the incidence of cervical precancerous lesions.

Aims: We analysed patterns in the incidence of cervical intraepithelial neoplasia grades 2 and 3 (CIN2, CIN3) and adenocarcinoma in situ (AIS) by age and histology in 1992-2016 in Norway and described changes in screening tests.

Methods: Incident cases of CIN2, CIN3, AIS, and cervical cancer were identified in the Cancer Registry of Norway, as were all women with at least one screening test. The triannual percentage change statistic was used to assess point estimates and changes in age-specific and age-standardised incidence rates (IR).

Results: Women aged 25-29 years had the highest incidence of cervical precancerous lesions (CIN2: $192.9/10^5$, CIN3: $737.2/10^5$, AIS: $32.5/10^5$ in 2014-2016). The IR of CIN2 increased for all screening ages (25-69 years) from 16.1% to 27.2% per 3-year period. CIN3 incidence increased by 40.6% (95% confidence interval [CI] 14.0-73.4) between 2011-2013 and 2014-2016. A steep increase in AIS incidence was observed in all age groups up to 45-49 years (23.6% per 3-year period, 95% CI 12.7-35.6). Cancer incidence was stable or decreasing. Since 2006, the proportion of screening performed with liquid-based cytology (LBC) started to increase, escalating in 2010, and in 2016, 86% of all the screening tests performed in Norway were LBC.

Conclusions: Changes in screening tests and the histological verification of cervical precancerous lesions alone cannot explain the steady increase in incidence we observed over the 25-year study period, and increased exposure to human papillomavirus (HPV) likely plays a role. Age-appropriate treatment of screening-detected cervical precancerous lesions is needed for effective cervical cancer control while avoiding overtreatment and related health risks. In order to perform an appropriate harm-benefit evaluation of cervical cancer control efforts, detailed information on screening technology and background risks, including HPV vaccination status, is needed to create optimal public health policy.

A7

Prospective association between sedentary lifestyle and incidence of lung cancer in Norwegian adults: the HUNT study*

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Introduction: Lung cancer is one of the most common cancer types with low survival rate all over the world. Sedentary lifestyle in general describes a series of human behaviors requiring very low energy expenditure when awake and has been suggested to increase risk of several adverse health outcomes, including cancers. Prolonged sitting which is measured by total sitting time daily is a major sedentary behavior. People who are prolonged sitting and also leisurely inactive may reflect the group of people with the most sedentary lifestyle.

Aims: To investigate prospective associations of total sitting time and its combination with physical activity with incidence of lung cancer overall and histologic types.

Methods: The main cohort consisted of 45,810 cancer-free adults who participated in the second survey of the Nord-Trøndelag Health Study (1995-97, Norway), and were followed-up for lung cancer incidence until December 2014. Additional 12,017 subjects without information on physical activity were excluded and 33,793 subjects were left in sub-cohort. Lung cancer cases were ascertained from the Cancer Register. Cox regression was used to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) for lung cancer overall and histologic subtypes.

Results: In total, 549 participants developed lung cancer during the follow-up (median 18.3 years). Total sitting time daily was not associated with the incidence of overall, small cell (SCLC) or non-small cell lung cancer (NSCLC) after adjustment for smoking, physical activity and other major confounders. Compared with participants sitting <8 hours per day and being physically active, participants sitting ≥8 hours per day and being physically inactive (no activity or ≤2 hours light activity per week) had increased incidence of lung cancer (overall: adjusted HR = 1.44, 95% CI: 1.07-1.94; SCLC: adjusted HR = 2.58, 95% CI: 1.23-5.41; NSCLC: adjusted HR = 1.36 with 95% CI: 0.92-2.01).

Conclusions: We observed that total sitting time was not associated with lung cancer risk. Most sedentary people who are both prolonged sitting and leisurely inactive may have increased risk of lung cancer. However, our results should be interpreted with caution, as residual confounding of smoking cannot be excluded.

*This abstract has also been presented as thematic poster at the European Respiratory Congress in Paris.

A8

Menopausal hormone therapy and breast cancer risk: effect modification by body mass through life*

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Introduction: It is not known whether increased breast cancer risk caused by menopausal hormone therapy (HT) depends on body mass patterns through life.

Aims: To study body mass patterns from childhood until postmenopausal age, and assess whether the association of HT use with breast cancer risk could be modified by different patterns of body mass through life.

Methods: In a prospective study of 483,241 Norwegian women aged 50-69 years at baseline, 7,656 women developed breast cancer during follow-up (2006-2013). We combined baseline information on recalled body mass in childhood/adolescence and current (baseline) body mass index (BMI) to construct mutually exclusive life-course body mass patterns. We assessed associations of current HT use with breast cancer risk according to baseline BMI and life-course patterns of body mass, and estimated relative excess risk due to interaction (RERI).

Results: Within all levels of baseline BMI, HT use was associated with increased risk. Considering life-course body mass patterns as a single exposure, we used women who "remained at normal weight" through life as the reference, and found that being "overweight as young" was associated with lower risk (hazard ratio (HR) 0.85, 95% confidence interval (CI) 0.76-0.94), whereas women who "gained weight" had higher risk (HR 1.20, 95% CI 1.12-1.28). Compared to never users of HT who were "overweight as young", HT users who either "remained at normal weight" or "gained weight" in adulthood were at higher risk than expected when adding the separate risks (RERI 0.52, 95% CI 0.09-0.95, and RERI 0.37, 95% CI -0.07-0.80), suggesting effect modification.

Conclusions: Thus, we found that women who remain at normal weight or gain weight in adulthood may be more susceptible to the risk increasing effect of HT compared to women who were overweight as young.

***Reference:**
Sandvei, M.S., Vatten, L.J., Bjelland, E.K. et al. *Eur J Epidemiol* (2018). https://doi.org/10.1007/s10654-018-0431-7

A9

Lifetime indoor tanning and risk of cutaneous squamous cell carcinoma

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Introduction: Many studies have investigated sun exposure and risk of cutaneous squamous cell carcinoma (SCC). However, the available evidence is sparse as regards indoor tanning exposure and SCC risk, and based mainly on case-control studies. Furthermore, no previous study has prospectively investigated the association between indoor tanning and SCC risk among individuals with and without a history of other cancer.

Aim: We aimed to investigate the dose-response association between lifetime use of indoor tanning devices and SCC risk in women overall, and separately in women with and without a history of cancer to assess whether a history of other cancer influenced the association.

Methods: We used the Norwegian Women and Cancer cohort study with complete follow-up of cancer data from the Cancer Registry of Norway until end of 2015. We performed Cox regression stratified by birth-cohort to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between lifetime indoor tanning and SCC risk, adjusted for host pigmentation factors and sun exposure. Cumulative use of indoor tanning devices, and cumulative number of sunburns and sunbathing vacations, were modelled as time-varying variables.

Results: We included 159 419 women (born 1927-1963), of whom 597 were diagnosed with SCC in the period 1991-2015 (mean follow-up = 16.5 years). SCC risk increased with increasing cumulative number of indoor tanning sessions. Adjusted HRs were 1.68 (95% CI: 1.19-2.39; $p_{trend} = 0.002$) for highest use versus never use overall, and 1.63 (95% CI: 1.12-2.38; $p_{trend} = 0.004$) for women with no history of other cancer (n=105 460). In women with a history of other cancer (n=14 552), ever use of indoor tanning significantly increased SCC risk (adjusted HR = 3.84; 95% CI: 1.45-10.15).

Conclusions: This cohort study provides evidence of a dose-response association between indoor tanning and SCC risk. It showed for the first time a particular increase in SCC risk in women with a history of cancer, a result that should be further investigated.

A10

Is paternal alcohol intake suitable as an IV for offspring alcohol intake?

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Introduction: Instrumental variable (IV) estimation could help clarify why alcohol intake is associated with a lower risk of ischemic heart disease (IHD) in observational studies.

Aims: To evaluate if paternal alcohol intake is suitable as an IV for studying the effect of offspring alcohol intake on the risk of IHD.

Methods: We identified kinship among 330,632 participants in Norwegian health surveys (1987–2003). Ordinary least squares linear regression (unstandardized beta coefficient with 95% CIs) assessed the strength of the relation between paternal and offspring alcohol intake, and the relation between paternal drinking and covariates measured in the offspring.

Results: We identified 15,667 father – offspring pairs. A one unit increase in paternal drinking frequency (range of values 0–4) was associated with a 0.15 (0.16, 0.18) increase in offspring drinking frequency. Offspring whose father reported drinking regularly (values 2 – 4) had higher levels of attained education in comparison with offspring whose father reported not do be drinking regularly (values 0–1). They were also more likely to smoke, and less likely to be obese, physically inactive, have elevated resting heart rate, high serum triglycerides, high total cholesterol, and low serum HDL-cholesterol.

Conclusions: Offspring of fathers who drank alcohol regularly were different from offspring of fathers who did not drink regularly in the sense that they had obtained higher education and were healthier, with the notable exception of smoking. Based on these findings, we conclude that paternal alcohol intake is not suitable as an IV for studying the effect of offspring alcohol intake on IHD. The patterning of alcohol with other health behaviours within families is however an interesting prospect for future studies.

A11

Higher levels of estimated cardiorespiratory fitness is associated with reduced risk of atrial fibrillation: The HUNT study

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Introduction: Atrial fibrillation (AF) is the most common heart arrhythmia and is associated with increased morbidity and mortality. Obtaining high levels of cardiorespiratory fitness (CRF) may protect against AF development, but is not feasible to measure directly in a large population. However, nonexercise prediction models offers a viable option for estimating CRF (eCRF).

Aims: To investigate the association between (1) eCRF and AF, and (2) long-term change in eCRF and AF.

Methods: We prospectively followed 39 844 men (44.7%) and women (55.3%) from HUNT3 (2006-08) until first onset of AF diagnosis or end of follow up in 2015. AF diagnosis were collected through hospital registers. We performed cox proportional hazard regression to assess the association between eCRF in HUNT3, as well as change in eCRF from HUNT2 (1995-97) to HUNT3, and AF incidence. Two previously published nonexercise prediction models were used to calculate eCRF in HUNT2 and HUNT3, respectively. eCRF were divided into quintiles, with the 1st quintile set as reference. Change in eCRF were categorized according to being below or above the median in HUNT2 and HUNT3, yielding four groups: (1) persistently below (ref.), (2) above to below, (3) below to above, and (4) persistently above.

Results: Higher levels of eCRF were associated with lower risk of AF. The highest risk reduction was 31% for men (4th quintile, HR 0.69, 95% CI 0.53-0.89) and 47% for women (5th quintile, HR 0.53, 95% CI 0.38–0.74), respectively. Participants with eCRF below median at HUNT2 and above at HUNT3 had 30% reduced risk of AF compared to those who were persistently below, (HR 0.70, 95% CI 0.55–0.91 both sex combined). Being persistently above median at both HUNT2 and HUNT3 were associated with 18% lower risk (HR 0.82, 95% CI 0.69–0.98).

Conclusions: Higher levels of eCRF is associated with lower risk of AF. Participants with the lowest decline in eCRF during a 10-year period were least likely to experience future AF events.

A12

Associations of changes in cardiorespiratory fitness and depressive symptoms with white matter hyperintensities: the HUNT Study

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Introduction: White matter hyperintensities (WMH) are markers of white matter injury that occur with increasing age, and are associated with dementia and depression. Higher levels of cardio-respiratory fitness (CRF) have been associated with less WMH, whereas depression has been linked to increased WMH burden. Little is known about whether longitudinal changes in CRF and depressive symptoms are associated with WMH.

Aims: We investigated how changes in CRF and depressive symptoms over 12 years are associated with WMH volume in a middle-aged cohort drawn from the general population.

Methods: 718 participants (52.6% women, 51-67 years) from the Nord-Trøndelag Health Study (HUNT) MRI cohort were included. CRF derived from a non-exercise algorithm and depressive symptoms obtained with the Hospital Anxiety and Depression Scale were assessed twice; at HUNT2 (1995-97) and HUNT3 (2006-08), whereas WMH volume was assessed shortly after HUNT3. WMH volume was manually delineated from brain transversal fluid-attenuated recovery (FLAIR) MRI scans obtained at 1.5T. Due to the skewed distribution of WMH volume, gamma regression with identity link was used to assess unstandardized beta coefficients (*b*) and 95% confidence intervals (CI).

Results: In the fully adjusted model, each unit increase in CRF was associated with smaller WMH volume (*b*=-27.4, 95% CI -45.0, -9.86). Participants who remained above the age- and sex-specific median of the CRF distribution from HUNT2 to HUNT3 had smaller WMH volume (*b*=-186.4, 95% CI -325.6, -47.2). The same applied to participants with CRF below the median at HUNT2 but at above median CRF at HUNT3 (*b*=-229.4, 95% CI -386.9, -71.9), and participants with CRF above the median at HUNT2 but not at HUNT3 (*b*=-171.3, 95% CI -338.4, -4.28). Changes in depressive symptoms were not associated with WMH volume.

Conclusions: Maintaining or increasing fitness during midlife appears to prevent white matter injury. Individuals who have had a higher fitness but have experienced a decline over time still appear to be protected, indicating that having high fitness at some time during midlife is more beneficial than remaining at a low level of fitness. Changes in depressive symptoms during midlife do not appear to be associated with WMH.

A13

Estimation of causal effects using the co-twin regression model

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Introduction: The co-twin control design provides unique possibilities to estimate causal effects because it is regarded to control for familial confounding due to shared genetics and environmental factors by design. Differing findings in co-twin control analyses and analyses of genetically unrelated individuals have typically been interpreted as evidence of familial confounding. However, any change in effect estimate in co-twin control analyses compared to analyses of genetically unrelated individuals can also be ascribed to collider bias, carryover effects and/or having estimated a direct rather than total causal effect estimate.

Aim: To compare the causal interpretations and possible sources of bias when applying 1) the widely used within- and between (WB) model and 2) a re-specified co-twin model for studies of binary exposures and time-to-event outcomes under a causal structure that includes between twins shared confounders, mediators and colliders.

Methods: Using data on smoking and its known causal effect on all-cause mortality from the Norwegian Twin Register, we compared the effect estimates from a Cox regression model as applied to the entire cohort of twins when studied as genetically unrelated / non-clustered (HR=1.51, 95% CI=1.35-1.71), to two different models taking genetics and clustering into account: 1) The traditional Cox regression model with shared frailty including WB pair parameters, and 2) A Cox regression model with shared frailty including adjustment for the co-twin's exposure level.

Results: For the WB regression model, colliders and carryover effects may have a sizeable impact on effect estimates (HR=1.23, 95% CI=0.73-2.07). The effect estimate represents a direct causal effect and may be biased due to conditioning on colliders and/or lack of adjustment for carryover effects from the co-twin's exposure. It is possible to eliminate these types of biases through a re-specification of the model that includes the adjustment for the co-twin's exposure level (HR=1.49, 95% CI=1.12-1.99).

Conclusion: The WB model could not reproduce the causal effect of smoking on all-cause mortality. The co-twin model is a re-specification of the traditional WB model in which the co-twin's exposure level is conditioned upon. The model produced unbiased and precise effect estimates interpretable as total causal effects.

A14

Causal inference in continuous time: an example on prostate cancer therapy

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Introduction: In marginal structural models (MSMs), time is traditionally treated as a discrete parameter. In survival analysis on the other hand, we study processes that develop in continuous time. Therefore, Røysland developed the continuous-time MSMs, along with continuous-time weights. The continuous-time weights are conceptually similar to the inverse probability weights that are used in discrete time MSMs. Here, we show how causal effect estimates can be derived by using continuous-time weights. Then, we describe how additive hazard models can be used to find such effect estimates. Finally, we apply this strategy to compare medium to long-term differences between the two prostate cancer treatments radical prostatectomy and radiation therapy, based on the cohort diagnosed in 2004, registered by the Norwegian Cancer Registry.

Aims: To find a clinically relevant application on continuous-time MSMs. To compare the long-term failure rates of the prostate cancer treatments radical prostatectomy and radiation therapy.

Methods: We use continuous-time MSMs to assess causal cumulative incidences under the two treatment regimens. We estimate the cumulative incidences non-parametrically by re-weighting Nelson-Aalen estimators, and thus keep modeling assumptions at a minimum.

Results: We find that the cumulative incidence of treatment failure is similar between surgery and radiation, accounting for the competing risk of other death.

Conclusions: Continuous-time MSMs is a theoretically appealing and practically feasible method for performing causal survival analysis. The observed failure rate difference between the treatment arms are likely due to confounding.

A15

Prolonged length of emergency department stay and risk of death within 30 days – an instrumental variable analysis

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Introduction: Emergency department (ED) crowding may delay treatment and lengthen ED stays and influence patient prognosis. The association between prolonged length of ED stay and mortality is difficult to assess since patients with the most urgent need of care are likely to be prioritized and will have shorter ED stays. The use of instrumental variables is a way to obtain causal information from observational data with unobserved confounding. We suggest using indicators of ED capacity strain as sources of variation in length of ED stay that are arguably not associated with the patient's medical condition.

Aims: Does prolonged length of ED stay increase 30-days risk of death? In addition, we studied effect differences for patient groups presumably sensitive to timing of treatment such as acute cardiovascular diagnoses (CVD) and infection diagnoses.

Methods: We used indicators of capacity strain based on the situation in the time leading up to the index patient's arrival. These are likely to capture exogenous factors for the index patient's length of ED stay, given adjustment for arrival hour, weekday, holiday, day after holiday, and the combination of month-year dummy variables. The analysis was done using two-stage ordinary linear regression. Both stages were adjusted for age, sex, prior admission within 30 days and medical area of condition.

Results: Among 153 659 arrivals at St. Olav's University Hospital, 2011-June 2018, we found no overall association between prolonged length of ED stay and risk of death. Subgroup analysis revealed no association for patients hospitalized with CVD or infection diagnosis.

Conclusions: Our study does not suggest that prolonged stay due to a strained service leads to higher mortality.

A16

Evidence of a causal relationship between body mass index and psoriasis: a Mendelian randomization study

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Introduction: Psoriasis has been associated with greater adiposity, but the direction of causality has not been established.

Aims: We aimed to investigate a possible causal relationship between body mass index (BMI) and psoriasis using Mendelian Randomization (MR).

Methods: We used a genetic instrument for BMI comprising 97 single nucleotide polymorphisms (SNPs), and conducted one-sample MR using individual-level data from 401,171 individuals in the UK Biobank and the Nord-Trøndelag Health Study (HUNT), Norway. We also performed two-sample MR with summary-level data (356,926 individuals) from published BMI and psoriasis GWA studies, and meta-analysed the one-sample and two-sample MR estimates using a fixed effect model. To explore a potential reverse causal direction, we conducted MR analyses with genetic instruments comprising variants from recent genome-wide analyses for psoriasis to examine if genetic liability to psoriasis has an effect on BMI.

Results: In observational analyses, higher measured BMI was associated a higher prevalence of psoriasis in both UK Biobank and HUNT (meta-analysis OR 1.04 (95% CI 1.03-1.04) per 1 kg/m^2 higher BMI; P=1.73x10^{-60}). MR analyses provided evidence that higher BMI causally increases the odds of psoriasis (OR 1.09 (95% CI 1.06-1.12) per 1 kg/m^2 higher BMI; P=4.67x10^{-9}). In contrast, MR estimates provided evidence for only a small effect of genetic risk of psoriasis on BMI (0.03 kg/m^2 (95% CI 0.01-0.06) higher BMI per doubling odds of psoriasis; P=0.01).

Conclusions: Our study, using genetic variants as instrumental variables for BMI, shows that higher BMI leads to a higher risk of psoriasis. Therapies and lifestyle interventions aimed at controlling weight should be further prioritised for the prevention or treatment of psoriasis.

A17

Causal association of lipid fractions with estimated glomerular filtration rate. A multivariable Mendelian randomization analysis of the HUNT Study, Norway

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Introduction: In observational studies, higher low-density lipoprotein cholesterol (LDL-C), lower high-density lipoprotein cholesterol (HDL-C) and higher triglyceride (TG) levels have been associated with lower estimated glomerular filtration rate (eGFR).

Aim: We aimed to investigate the causal associations between serum lipid levels and eGFR, using multivariable Mendelian randomization (MR) to disentangle the effects of the separate lipid fractions.

Methods: In a two-sample MR approach, we obtained information from the Global Lipids Genetics Consortium (n=188,577) on associations of 185 independent variants that showed genome wide significant association with at least one of the three lipid traits (LDL-C, HDL-C and TG). Associations of these variants with eGFR were estimated in 69,570 participants from HUNT. Causal associations of serum lipid levels with eGFR were estimated both using standard inverse-variance weighted (IVW) MR and multivariable MR. Evidence of pleiotropy was evaluated using MR-Egger regression. All analyses were adjusted for age and sex. The estimates (β [95% CI]) represent the difference in eGFR (mL/min/1.73 m^2) per 1 standard deviation higher lipid levels.

Results: In observational analyses, higher measured LDL-C (-0.0033 [-0.0039, -0.0028], $P<10^{-16}$) and TG (-0.0015 [-0.0018, -0.0013], $P<10^{-16}$) were associated with lower eGFR, and higher HDL-C was associated with higher eGFR (0.0033 [0.0028, 0.0039], $P<10^{-16}$), but the associations were of weak magnitude. The IVW method showed little evidence that LDL-C (0.441 [-0.100, 0.982], P=0.11), HDL-C (-0.214 [-0.800, 0.373], P=0.47) or TG (0.663 [-0.057, 1.383], P=0.07) may influence eGFR. Similarly, multivariable MR provided no strong evidence for causal associations of LDL-C (0.346 [-0.209, 0.901], P=0.22), HDL-C (0.015 [-0.627, 0.657], P=0.96) or TG (0.566 [-0.245, 1.377], P=0.17) with eGFR. MR-Egger regression showed little evidence of pleiotropy in any of the analyses.

Conclusion: Our findings do not support that serum lipid concentrations may substantially influence eGFR. Further research should use Mendelian randomization in larger well-phenotyped cohorts to replicate and extend our findings.

A18

Cardiovascular disease after hypertensive disorders of pregnancy: the role of conventional cardiovascular risk factors. The HUNT Study in Norway

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Introduction: Women with a history of hypertensive disorders of pregnancy (HDP) have an increased risk of cardiovascular disease (CVD). It is uncertain how much of the excess CVD risk in women with a history of HDP that is explained by conventional cardiovascular risk factors.

Aims: In this study we aimed to quantify the excess risk of CVD in women with a history of HDP, and estimate the proportion explained by adverse levels of conventional, modifiable cardiovascular risk factors: body mass index (BMI), blood pressure, glucose and lipids.

Methods: We linked data from the population-based HUNT Study, validated hospital records, the Cause of Death Registry and the Medical Birth Registry of Norway for 21 766 women with normotensive pregnancies and 2199 women with a history of HDP. We used Cox proportional hazards models to estimate the hazard ratio (HR) for CVD comparing women with and without a history of HDP, and an inverse odds ratio weighting approach to estimate the proportion of excess risk in women with a history of HDP that was explained by conventional CVD risk factors.

Results: From age 40 to 70, women with a history of HDP had an increased risk of CVD compared to women with only normotensive pregnancies (HR=1.57, 95% confidence interval: 1.32 – 1.87), but not at older age (p for interaction by age=0.015). Blood pressure and BMI accounted for up to 77% of the excess risk of CVD in women with history of HDP, while glucose and lipids accounted for smaller proportions.

Conclusion: The excess risk of CVD in women with history of HDP is largely explained by conventional cardiovascular risk factors, in particular hypertension and adiposity, indicating that these risk factors are important targets for cardiovascular prevention in women with history of HDP.

A19

Evaluation of the NORRISK2 model for cardiovascular risk prediction in South-Asians living in Norway

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Introduction: The NORRISK 2 model estimates an individual's 10-year risk of cardiovascular disease (CVD) based on known risk factors. It was developed from the Cohort of Norway (CONOR) surveys 1994-1999 linked to CVDNOR, a database of cardiovascular hospital discharge diagnoses and mortality in Norway in 1994-2014. The model is included in Norwegian guidelines, but has not been validated in immigrants in Norway.

Aims: To evaluate the NORRISK 2 model in immigrants from South Asia and compare with Norwegian born men and women.

Methods: We included participants aged 30-74 years from The Oslo Health Study (HUBRO), The Oslo Immigrant Health Study (IHUBRO) and the Romsås in Motion Study (MoRo II), all part of CONOR. The study population consists of 7823 women and 6429 men born in Norway and 832 women and 1192 men born in South Asia, linked to CVDNOR and the Norwegian Patient Registry. An endpoint was defined as the first occurrence of hospitalization with AMI or acute cerebral stroke or death from coronary heart disease or death from acute cerebral stroke as underlying cause. Due to limited number of cases, we calculated13-year risk of CVD instead of the original 10-year risk by the NORRISK 2 model. We validated the model by Harrell's C and calibration plots based on predicted minus observed cumulative risk within quintiles of predicted risk.

Results: The predicted 13-year risk by the NORRISK 2 model was 4.0% (95% CI 3.7-4.3) compared with observed 7.2% (5.8-9.0) in South Asian men and 1.1% (1.0-1.2) predicted versus 2.6% (1.6-4.0) observed in South Asian women. Corresponding results for Norwegian-born were 6.4% (6.2-6.6) predicted versus 5.9% (5.3-6.5) observed in men and 2.8% (2.7-2.8) predicted versus 2.3% (2.0-2.7) observed in women. NORRISK2 underestimated risk in all quintiles of predicted risk in South Asian men and women. Harrell's C was 0.79 in men and women from South-Asia and 0.79 in Norwegian-born men and 0.81 in Norwegian-born women.

Conclusions: NORRISK2 underestimated 13-year CVD risk in South-Asians. Discrimination ability was good. An updated model for men and women born in South Asia is warranted.

A20

Asthma, asthma control and risk of acute myocardial infarction: results from the Nord-Trøndelag Health Study (HUNT)

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Introduction: Asthma, a chronic inflammatory airway disease, shares several common pathophysiological mechanisms with acute myocardial infarction (AMI). Research of the prospective association between asthma and AMI is lacking and no previous studies have assessed the dose-response association between levels of asthma control and risk of AMI.

Aims: To assess the prospective associations between asthma, levels of asthma control and risk of AMI.

Methods: We followed 56 975 adults without previous history of AMI at baseline from Nord-Trøndelag Health Study (HUNT) in Norway**.** Self-reported asthma was categorized into 3 groups: those who reported ever having asthma, those who reported doctor-diagnosed asthma, and those who reported active asthma (i.e., being on asthma medication). Levels of asthma control were defined as controlled, partly controlled, and uncontrolled based on the Global Initiative for Asthma (GINA) guidelines. AMI was ascertained by linking HUNT data with hospital records.

Results: A total of 2 390 AMI events (4.2%) occurred during a mean (SD) follow-up of 16.3 (6.1) years. Adults with active asthma had an estimated 24% higher risk of developing AMI (hazard ratio (HR) 1.24, 95% confidence interval (CI) 1.02 -1.51) compared with adults without asthma. There was a dose-response association between asthma control and AMI risk, with highest risk in adults with uncontrolled asthma (HR 1.50, 95% CI 0.94 – 2.40) compared with adults with controlled asthma.

Conclusions: Our study suggests that active asthma and poor asthma control are associated with moderately increased risk of AMI in a dose-response manner. Further studies are needed to assess the underlying mechanisms and the role of asthma control and medications in the risk of AMI.

B1

Energy and macronutrient intake and associations with body mass index and fat mass index: The seventh Tromsø Study 2015-16

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Introduction: High total energy intake and sedentary lifestyle are associated with overweight and obesity. The most frequently used measure of overweight is body mass index (BMI), which does not distinguish between fat mass and lean mass, important indicators of cardiovascular health.

Aim: To investigate energy- and macronutrient intake, in categories of BMI and fat mass index (FMI) adjusted for self-reported leisure-time physical activity level (LTPA) and age, among women and men.

Methods: All Tromsø municipality inhabitants ≥ 40 years were invited to the seventh Tromsø Study survey (Tromsø 7) in 2015-16. Altogether 21 083 participated (65%), of whom 52% were women. Height and weight were measured for all participants. A total of 15 146 (72%) submitted a 13-page validated food frequency questionnaire including 261 questions on food and drink intake covering a Norwegian diet. Nutrient intake was calculated by the food and nutrient database Kostberegnings-systemet (KBS) at the University of Oslo. Body composition was measured with Dual-Energy X-ray absorptiometry (DEXA) and was available for 3600 participants. Physical activity level was included as self-reported LTPA defined by the four-level Saltin and Grimby questionnaire (sedentary, light, moderate and vigorous physical activity). We compared mean energy (MJ/day) and macronutrient intake (E%) in, and between, BMI- and FMI categories for women and men, adjusted for age and self-reported LTPA.

Results: Mean energy intake was 9.0 and 10.7 MJ/day, and mean BMI was 26.8 and 27.6 kg/m^2 in women and men, respectively. Preliminary analysis adjusted for age and LTPA showed differences in mean energy and macronutrient intake in categories of BMI. Results for the association between macronutrient intake in different measures of overweight will be presented.

Conclusion: In preliminary analysis of Tromsø 7, we found differences in total energy intake and E% for macronutrients in different measures of overweight.

B2

Quantifying the impact of genes on BMI during the obesity epidemic

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Introduction: While secular trends can change the prevalence of obesity for the entire population simultaneously, genetic differences could make some individuals more susceptible to an obesogenic environment than others.

Aims: To assess to what extent recent secular trends affected the genetically predisposed and non-predisposed differently.

Methods: Our data consists of repeated measurements of body mass index (BMI) from 1963-2008 among 118 958 participants from the Nord-Trøndelag Health Study linked to the Tuberculosis Register. Genetic data was available for 69 301 participants. We calculated a weighted genetic risk score for BMI using 96 single nucleotide polymorphisms previously identified to be associated with BMI and divided the study population into quintiles of genetic predisposition to high BMI. We estimated the associations with BMI for genetic predisposition, age and time or birth cohort using linear mixed models for men and women, respectively.

Results: Obesity increased markedly in Norway starting between the mid-1980s and mid-1990s. Men and women are getting heavier with both age and birth cohort, where cohorts born after 1970 have a substantially higher BMI already in young adulthood. There was a substantial difference in phenotypic BMI between the highest and lowest quintiles of genetic susceptibility for all ages at each time period, and the difference increased gradually from the 1960s to the 2000s. For the more recent birth cohorts, the association between the GRS and BMI amplified in the last decades. For men and women respectively aged 20-29 years, the most genetically predisposed had 1.12 (0.89-1.34) resp. 1.70 (1.43-1.97) kg/m^2 higher BMI than the least genetically predisposed in the 1960s compared to 2.29 (1.76-2.83) resp. 3.14 (2.54-3.73) kg/m^2 in the 2000s. For men and women respectively aged 40-49 years, the differences in BMI were 1.25 (0.99-1.50) resp. 1.73 (1.42-2.04) kg/m^2 in the 1960s and 1.94 (1.67-2.21) resp. 2.20 (1.86-2.53) kg/m^2 in the 2000s.

Conclusion: The population BMI increased substantially over the period for both men and women irrespective of genetic background. Our study suggests that the genetically predisposed are at greater risk for higher phenotypic BMI and that the gene by obesogenic environment interaction amplifies this effect primarily amongst today's youth.

B3

Associations of fathers and their offsprings weight gain with non-allergic asthma

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Introduction: We previously found that a father's overweight in puberty was associated with non-allergic asthma in his future offspring (Johannessen et al. Fathers' overweight and offspring asthma – an intergenerational perspective. European Resp. Journal 2017, 50:PA2615).

Aims: We explored the associations of both fathers and their offsprings personal weight gain during different periods of life with offspring non-allergic asthma.

Methods: We analysed questionnaire data from 3018 adult offspring (age 18-50) and their 2153 fathers (age 39-66) participating in the RHINESSA/RHINE generation study in 10 ECRHS centres in North Europe, Spain and Australia. The associations of fathers' and their offsprings weight gain was assessed by 9 body silhouettes (from lean to obese) self-reported for childhood, puberty and adult ages with non-allergic asthma in the offspring. It was analysed using a logistic regression model adjusted for parents and offspring variables, and cluster by family.

Results: Non-allergic asthma was related to a weight gain of ≥2 body silhouettes from 8 years to puberty, both for fathers' weight gain (OR 1.69; 95% CI 1.05-2.72; adjusted for fathers asthma, offspring body mass index, smoking and education) and for their offspring weight gain (1.77 [1.12-2.79], adjusted for parents´ education, smoking and asthma, and fathers´ weight gain from age 8 to puberty). If the father was overweight at puberty, in addition to having gained weight, non-allergic asthma in the offspring was more than tripled (3.53[1.80-6.94]; weight gain and adjustment as given above). No effect of weight gain from puberty or within adulthood in fathers' or their offspring was observed.

Conclusions: Non-allergic asthma was associated with weight gain from childhood to puberty. This was found both for personal weight gain and for having a father who gained weight.

B4

Associations between parental polygenic obesity risk and offspring's weight at birth, early and late adolescence – The HUNT Study, Norway

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Introduction and aims: Obesity develops in a complex interplay between genetic and environmental factors. We aimed to examine how genetic predisposition influences obesity development early in life, by estimating the association between polygenic obesity risk and weight at birth (ponderal index) and throughout adolescence (BMI).

Methods: We included 8561 parent-offspring trios who participated in the HUNT/Young-HUNT surveys in 1995-97 or 2006-08 when the offspring were 13-19 years of age. Additional weight data were included from a follow-up study in 2000-01 and from birth for 1026 and 8370 offspring participants, respectively. A weighted parental genetic risk score (GRS) based on maternal and paternal genetic data was constructed from 96 SNPs that have been robustly associated with adult BMI previously. Linear mixed effect models were employed to study sex-specific associations between parental GRS and children's ponderal index at birth and BMI at adolescents (ranging from 13-19 years).

Results: The parental GRS was positively associated with BMI in both boys and girls at all ages from 13 to 19 years. The estimates were of similar magnitude as associations between parents´ own GRS and their BMI at age 42. No association was found between the parental GRS and ponderal index at birth, nor did parental education modify any associations.

Conclusions: Genetic predisposition for adult obesity, expressed by a parental genetic risk score for BMI, had an adverse effect on adolescent BMI that was similar in boys and girls at all ages from 13 to 19 years, but was not associated with ponderal index at birth.

B5

Predictors for stroke mortality. A comparison of the Oslo-study 1972/73 and the Oslo II-study in 2000

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Introduction: Stroke mortality comprises different specific diagnoses as cerebral infarction, different haemorrhagic conditions, and unspecified stroke. The prediction by oral health indicators versus established cardiovascular (CVD) risk factors is assessed in the Oslo II-study 12 ½ year follow-up.

Aims: Compare previously published results of 21-years follow-up of the Oslo-study of 1972/73 to the 12 ½- year follow-up of the Oslo II-study with the addition of oral health to known CVD risk factors.

Methods: In the Oslo-study of 1972/73, 30,025 men in Oslo were invited and a 21-year follow-up was done of 14,403 men with regard to incidence and mortality for stroke and myocardial infarction. In Oslo II in 2000, 12,764 men aged 58 to 77 years were invited to a health screening which included general medical measurements and questionnaire information. Mortality data were supplied by Statistics Norway for the 12 ½- year follow-up of the attending 6,530 men of whom 364 men with prior stroke were withdrawn from the analyses. Cox proportional hazards analyses were used to establish prediction models for mortality.

Results: Published results from the 21-year follow-up concluded that the risk-factor profile differed according to the underlying subtype of stroke. Cerebral infarction clearly shared with myocardial infarction the classical risk factors. Oslo II results for total stroke mortality (n=130) was also given separately for cerebral haemorrhage all combined (n=49), cerebral infarction (n=31), and unspecified stroke (n=50). Results from Cox analyses using the backward elimination procedure showed that oral health by tooth extractions >10 was a predictor for cerebral infarction hazard rate (HR) = 2.92, 95% confidence interval (CI) (1.24-6.89). This was independent of HDL-C (inversely) HR= 0.21, 95% CI (0.06-0.76), frequent alcohol consumption HR= 3.58, 95% CI (1.40-9.13), and diabetes HR= 4.28, 95% CI (1.68-10.89). Predictors for cerebral haemorrhage were age, CRP, and BMI (inversely) and age, total cholesterol (inversely) for unspecified stroke. Overall, stroke mortality was predicted by age, HDL-C, CRP, and diabetes.

Conclusions: Oral health measured by more than ten extracted teeth was found to be an independent predictor for cerebral infarction. The pattern of risk factors varied between the specific stroke diagnoses indicting cause-specific differences.

B6

Gender contrasts in adverse effect of diabetes on the risk of incident myocardial infarction. The Tromsø study 1979-2012

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Introduction: Diabetes is associated with increased risk of coronary heart disease (CHD). The relative risk has been found to be higher in women than men, and the more pronounced adverse effect has even been claimed to eliminate the female advantage in risk. However, few previous studies have quantified the difference in risk between men and women among individuals with diabetes.

Aims: To evaluate interaction between gender and diabetes in relation to the risk of incident myocardial infarction (MI).

Methods: Population-based prospective study of 33,859 individuals (51% women) in Tromsø, Norway. Median follow-up time at ages 35-94 years was 17.6 years; 2,746 individuals (854 women) were diagnosed with MI during follow-up. At their last visit, a total of 1063 individuals (3.1%) reported they had diabetes (530 men, 533 women); 170 (74 women) were later diagnosed with MI. Incidence rate ratios (IRR) were calculated as estimates of relative risk in Poisson regression analysis of person-years at risk. Interaction terms were included in the model to evaluate heterogeneity in risk estimates across subgroups.

Results: Adjusted for age, gender and established CHD risk factors, diabetes was associated with a doubling in risk of MI (IRR=2.18, 95% CI=1.86-2.55). The adverse effect was slightly more pronounced for women than men (IRR of 2.55 vs. 1.96, p=0.11, test for interaction). Accordingly, the gender contrast in risk was less pronounced among individuals with diabetes (IRR of 1.63 vs 2.11), but the elevated risk in men remained significant. Considering combined categories of interacting factors, women with diabetes had a risk level close to men without diabetes, but men with diabetes had a risk about four times as high as women without diabetes. Some heterogeneity across age groups was seen, but risk estimates were imprecise. These results are preliminary. Gender heterogeneity in associations with adjustment factors may influence risk estimates. Analyses based on data with 5 year extended follow-up are planned.

Conclusions: In terms of relative risk, the association between diabetes and risk of MI was more pronounced for women than men, but the female advantage in risk of MI was not erased in persons with diabetes.

B7

Time trends in stroke incidence rates in Norway 2001-2014: Analyses from the CVDNOR project

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Introduction: Declining trends in stroke mortality have been observed in Norway since the 1970s. National trends of stroke incidence are lacking.

Aims: To describe national time trends in incidence of fatal and non-fatal ischemic stroke, haemorrhagic stroke, subarachnoid bleeding and unspecified stroke in the period 2001-2014, by sex and age group.

Methods: National hospital discharge diagnoses in the CVDNOR database and in the National Patient registry were linked to the National Cause of Death Registry. All hospitalizations with stroke as main or secondary diagnosis and out-of-hospital deaths with stroke as underlying cause for individuals ≥ 25 years were obtained during 1994-2014. Incident stroke was defined as hospitalization or out-of-hospital-death due to stroke with no prior hospitalization for stroke or stroke sequela during the previous seven years. Incidence rate ratios were estimated by Poisson regression analyses. We used direct standardization against the 2001 Norwegian population. Preliminary analyses of change in incidence rates over time are presented.

Results: During 2001 to 2014 the number of incident total stroke cases declined from 12,137 to 10,166. The proportion due to out-of-hospital deaths declined from 10% to 7%. Of total stroke cases in 2014, 73% were ischemic, 14% haemorrhagic, 5% subarachnoid haemorrhages and 8% unspecified strokes. The age-standardized incidence of total stroke declined from 324 to 232 per 100 000 person years among men and from 234 to 163 among women. In individuals 45-84 years, incidence rates of total, ischemic and haemorrhagic stroke declined. Incidence rates in the age group 85 + years declined for total and ischemic stroke, but increased for haemorrhagic strokes in men and did not change significantly in women. In the youngest age group 25-44 years, incidence rates of total and haemorrhagic stroke did not change significantly, and for ischemic stroke incidence rates increased in men and did not change significantly in women.

Conclusions: The total stroke incidence rates decreased from 2001 to 2014 in the Norwegian population 45 years and older. Increased incidence rates of haemorrhagic stroke in men 85 + years and of ischemic stroke in men below 45 years needs further investigation.

B8

Concurrent changes in physical activity and body weight in relation to all-cause and cardiovascular mortality: the HUNT Study

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Introduction: It is well known that body weight and physical activity are closely related. Some evidence indicates that overweight and obese individuals who are physically active have lower mortality than normal weight inactive individuals, but conflicting results have been reported. However, no previous study has investigated the interplay between concurrent long-term changes in body weight and leisure time physical activity in relation to mortality.

Aims: The aim of this study was to investigate the joint effect of concurrent changes in leisure-time physical activity and body weight on all-cause and cardiovascular mortality.

Methods: The study population comprised 34 257 individuals who participated in the first (HUNT1, 1984-86) and second (HUNT2, 1995-97) waves of the HUNT Study, followed until December 31, 2013. Changes in weight and leisure time physical activity from HUNT1 to HUNT2 served as the exposures. Participants in the HUNT Study were linked with the Norwegian Cause of Death Registry at Statistics Norway to prospectively assess incident cases of death in the cohort. We used Cox regression to calculate hazard ratios (HR) with 95% confidence intervals (CI).

Results: During a median follow-up of 17 years (535 359 person years), 8449 deaths occurred in total. Of these, 3263 died from cardiovascular disease. Compared to participants with stable weight who remained active, participants who remained inactive had a HR for all-cause mortality of 1.54 (95% CI: 1.28-1.85) if they gained weight and 1.29 (95% CI: 1.08-1.53) if they were weight stable, whereas participants who gained weight and remained active had a HR of 1.00 (95% CI: 0.94-1.06). The corresponding HRs for cardiovascular mortality were 1.57 (95% CI: 1.17-2.12), 1.37 (95% CI: 1.05-1.79) and 1.06 (95% CI: 0.96-1.16), respectively.

Conclusions: Our results show that the risk of all-cause and cardiovascular mortality is particularly evident among people who gain weight while remaining inactive during a 10-12 year period. These findings suggest that there is an interplay between concurrent long-term changes in physical activity and weight gain that should receive particular attention in the prevention of premature mortality.

B9

Folate related birth defects and future maternal cardiovascular mortality

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Introduction: Low levels of plasma folate increase homocysteine levels and may be linked to cardio-vascular disease (CVD). Maternal periconceptional folic acid supplementation prevents offspring Neural tube defects (NTD), and possibly other birth defects.

Aim: We aimed at evaluating premature (40-69 years) CVD mortality in mothers whose first infant had folate-related birth defects, taking account of number of life-time births (1 vs >1).

Methods: We used linked data from the Swedish and Norwegian Medical Birth and Cause of Death Registries (Sweden: 1973-2010, Norway: 1967-2014), and linked successive births to their mothers. Major birth defects were defined according to the European network of congenital anomaly registries, folate-related defects were defined as NTDs, oral clefts, cardiac defects, or limb reduction defects. Women were followed to 2010/2014 for pregnancies and mortality, and Cox regression analyses were used to evaluate associations between a birth defect and maternal premature CVD mortality, adjusting for confounders.

Results: Among 2,237,648 women (Norway: 42.4%, Sweden: 57.6%) there were 48,903 premature deaths and 5,961 (2.7 per 1000) premature CVD deaths (Norway: 3.9 per 1000, Sweden: 1.8 per 1000). A folate-related defect in first birth was significantly associated with increased premature CVD mortality (adjusted HR (adjHR) 1.3; 95% CI 1.0-1.8), seemingly driven by cardiac defects (adjHR 2.1; 1.3 to 3.2). The relation was, however, limited to one-child mothers: Folate-related and cardiac defects in first and only birth: adjHR 3.3; 2.1 to 5.1 and adjHR 5.0; 2.7 to 9.0, respectively; vs mothers with >1 birth: adjHR 1.0; 0.6 to 1.5 and adjHR 1.4; 0.8 to 2.6. Excluding women with diabetes in first pregnancy and foreign born women only slightly attenuated results. A similar relation for fathers' CVD mortality by offspring birth defects was not found.

Conclusion: We found no indication that folate-related defects predict maternal CVD mortality, but factors associated with birth defects, reduced fertility and increased diabetes risk may be important.

B10

Health impact of air pollution in early life – A Nordic collaboration (NordicWelfAir)

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Introduction: Epidemiological studies have reported adverse health effects at levels even below recommended air quality limits, but the associations at low levels are uncertain. The Nordic region represents low exposure levels adding challenges on study power, especially for susceptible subgroups.

Aims: We aim to study health effects of air pollution on (i) birth outcomes and (ii) childhood asthma to evaluate (iii) the concentration-response relationships at Nordic levels.

Methods: In Denmark and Sweden we will make use of the National Population Register, Medical Birth Register, Prescribed Drug Register and Patient Register. These will be linked together giving study samples of 3 mill and 250.000 participants, respectively. Norway will use the Norwegian mother and child study (MoBa) with 100.000 participants linked to the same registers, whereas Finland will link the Population Register and Medical Birth Register to their Social Security Institution Register, Hospital Discharge Register and Register of Primary Health Care providing 1,75 mill participants. Through combining modelled air pollutants (PM10, PM2.5, PM10-2.5, NO2, ozone and black carbon) with residential address history we will link exposures with birth outcomes and childhood asthma. Susceptible populations will be defined by low socioeconomic status, lifestyle factors and gender.

Results: Annual modelled population weighted means (SD) of PM2.5 levels in 2015 have been reported to be 9.2 $\mu g/m^3$ (0.7 $\mu g/m^3$) in Denmark, 6.2 (1.7) in Norway, 5.9 (1.5) in Sweden and 5.1 $\mu g/m^3$ (1.2 $\mu g/m^3$) in Finland. The levels in rural areas are generally lower.

Conclusions: The Nordic registers provide an excellent platform for cross-border Nordic co-operation and sufficient study size to investigate health effects of low exposure levels in early life, also among susceptible subgroups.

B11

The association of osteoporosis with mortality in a COPD cohort. The HUNT Study, Norway

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Introduction: In patients with chronic obstructive pulmonary disease (COPD), comorbidities increase mortality.

Aims: To examine whether osteoporosis (OP) influences mortality in COPD patients in a population-based study.

Methods: In total, 3437 and 2887 participants from the second and third survey of the Trøndelag Health study (1995-97, 2006-08) were identified as having COPD by GOLD (FEV1/FVC < 0.70) and Global Lung Initiative (GLI) lower limit of normal (LLN) criteria, respectively, and were followed-up for all-cause mortality until February 2018. Hip and forearm bone mineral density (BMD) measured by dual-energy X-ray absorptiometry (DXA) was categorized by WHO criteria with osteoporosis defined as T-score <-2.5. Multivariable Cox regression was used to calculate hazard ratios with 95% confidence intervals.

Results: The prevalence of osteoporosis was 16.7% and 15.4% in the COPD and GLI LLN cohorts. 85.3% and 77.0% had mild or moderate disease severity. For both cohorts having osteoporosis was associated with increased mortality. Mortality rate in the GOLD cohort was 34.5 per 1000 person-years for the non-OP group, and 77.6 per 1000 person-years for the OP group. The corresponding numbers for the GLI cohort was 33.3 and 81.7/1000 person-years.

Conclusions: COPD patients with osteoporosis had higher mortality than those without osteoporosis. These findings were similar among cohorts diagnosed by GOLD and GLI criteria.

B12

Comparison of pre- and post-bronchodilator lung function as predictors of mortality: the Nord-Trøndelag Health Study (HUNT)

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Introduction: Post-bronchodilator lung function is recommended for the diagnosis of COPD. However, often only pre-bronchodilator lung function is available in clinical practice or in epidemiological studies.

Aims: To investigate the discrimination ability of pre- and post-bronchodilator lung function to predict respiratory, cardiovascular, and all-cause mortality.

Methods: This study included people aged ≥40-year with potential bronchial obstruction (N=2538) and COPD (N=1262) who participated in the Nord-Trøndelag Health Study (HUNT2 1995-1997) followed through to December 31, 2015. The association of pre- and post-bronchodilator lung function (continuously as FEV_1 z-score and categorically as GOLD categories) with mortality was assessed using Cox proportional hazard models. The discrimination ability of pre- and post-bronchodilator lung function was compared using time-dependent receiver operating characteristics (ROC) curve. We compare the AUCs for crude lung function models because the clinical decision does not explicitly take into account other factors.

Results: Of the 2538 adults 283, 503, and 1387 died of respiratory, cardiovascular, and all-cause mortality, respectively, over the 20.4-year of follow-up. Worsening GOLD categories or GOLD grades among COPD were associated with higher mortality. The area under ROC curve for pre- and post-bronchodilator GOLD categories for all-cause mortality were 62.3 (95% confidence interval 60.6-63.8) and 64.5 (95% confidence interval 62.9-66.1) (p value <0.001) respectively, at the 20-year follow-up. The corresponding estimates for GOLD grades among COPD participants were 56.0 (95% confidence interval 53.9-57.9) and 57.0 (95% confidence interval 54.6-59.2) (p value =0.268).

Conclusions: Post-bronchodilator predicted mortality better than pre-bronchodilator lung function. However, among COPD, pre- and post-bronchodilator GOLD grades similarly predicted mortality.

B13

Incorporating genome-wide methylation and genotype data to elucidate how region-wise methylation level might influence allele-defined relative risks

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Introduction: The genetic code is tightly linked to epigenetic instructions as to which genes to express, when and where. The most studied epigenetic mark is DNA methylation at CpG dinucleotides. Today's technology enables a rapid assessment of DNA sequence and methylation levels at a single-site resolution for hundreds of thousands of sites in the human genome, in thousands of individuals at a time. This enormous wealth of data calls for new statistical approaches that can harness their full potential.

Aims: To integrate the DNA methylation data and genetic association analyses.

Methods: We propose a new method that treats the level of DNA methylation as an environmental exposure. We developed two new approaches to search for statistical interactions between a given SNP and DNA methylation (GxM), and between a parent-of-origin effect and DNA methylation (PoOxM). The new methods and approaches were implemented in the R package Haplin (https://people.uib.no/gjessing/genetics/software/haplin/).

Results: We tested the methods on genotype data from mother-father-child triads and DNA methylation data from the children only. The phenotype of choice was orofacial clefts (OFC). Our results show that identifying these interactive effects are dependent on the genomic region in which the CpGs reside and on the number of methylation level strata.

Conclusions: We found that including the methylation level around the SNP can significantly deacrease or increase the relative risk of the OFC. We discuss also that in such an analysis it is important to include control data.

B14

Evaluation of methods for analysis of 2x2 contingency tables

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Introduction: Literally hundreds of methods for hypothesis tests and confidence intervals for contingency tables are described in the literature. This is the case even for the seemingly simple 2 × 2 table. The Pearson chi squared test, the Fisher exact test, and the Wald confidence interval are widely used methods. Unfortunately, these methods are also commonly used in situations when they perform poorly, and better alternatives exist.

Aims: To show how to evaluate and choose appropriate methods for hypothesis testing and confidence interval estimation for 2x2 tables.

Methods: Important properties of a hypothesis test are the actual significance level and power. Important properties for a confidence interval are coverage probability, expected interval width, and symmetry. We have studied these properties for alternative methods.

Conclusion: For large samples, the asymptotic Pearson chi squared test performs well. Yates's continuity correction should never be used. In small samples, the traditional advice is the Fisher exact test. But unconditional tests are generally more powerful than Fisher's exact test for small samples. Unconditional tests also preserve the significance level. That is, the actual significance level does not exceed the nominal significance level, which is often 5%. Unconditional tests were but previously disadvantaged by being computationally demanding. Alternatively, Fisher's exact test with mid-p adjustment is easy to compute, and gives approximately the same results as an unconditional test.

The Wald confidence interval is a traditional choice for the difference between two proportions. But its coverage can dip substantially below the nominal coverage, which is usually 95%. The Agresti-Caffo interval and the Newcombe hybrid score interval are also easy to compute with closed form expressions. They have better coverage, and also narrower expected interval width, and better symmetry than the Wald interval.

Reference:

Fagerland MW, Lydersen S, Laake P (2017). Statistical Analysis of Contingency Tables. Chapman and Hall/CRC.

B15

A systematic approach to assess ethical issues in stem cell research

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Introduction: All research projects ought to be assessed for relevant ethical issues. We present a cheque list for ethics applied in Health Technology Assessments (HTA).

Aims: To present two HTA reports on stem cell therapy for diffuse systemic sclerosis and multiple sclerosis (MS) with regard to moral issues where the same cheque list for ethics was used with two different approaches.

Methods: A HTA report includes scientific evidence for effect and safety of the technology in question, and often includes appraisal issues such as health economy, organization, ethics, and law. A cheque list was developed in 2005 (1, 2) including 32 specific questions representing five categories and suggestions for approaches. The questions are subdivided into general moral questions, questions associated with the patients and others with a vested interest, questions associated with the methodology, questions associated with choice of methodology, and questions related to HTA work itself.

Results: In the MS report (3), ethics was discussed using five headings relating the cheque list questions to the current treatment alternative, the risks and benefits of the new treatment, particular aspects of the new treatment, vested groups and legislation. In the diffuse systemic sclerosis report (4), ethics was discussed using the perspectives of the patient, the doctor and treatment team, the hospital, and the society. For each of these five perspectives two specific questions of moral issues were selected: A) Is the introduction or use of the methodology offensive to the patients autonomy, their integrity, dignity or their (human) rights? B) Does the methodology in any way infringe on religious, social or cultural conviction.

Conclusions: The cheque list for ethics provides a systematic approach to assess different moral issues in medical research and relate them to each other to assure a useful discussion.

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C1

Survival and years of life lost in various aetiologies of dementia, mild cognitive impairment (MCI) and subjective cognitive decline (SCD) in Norway

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Introduction: Alzheimer's disease patients are reported to have higher survival rate compared to patients with vascular dementia or dementia with Lewy bodies. There is a paucity of studies investigating survival including persons with cognitive decline and dementia of various aetiologies.

Aims: We aimed to compare survival for patients with subjective cognitive decline, mild cognitive impairment, Alzheimer's disease, vascular dementia, mixed Alzheimer's/vascular dementia, dementia with Lewy bodies/Parkinson's disease, and other dementias compared to the general Norwegian population, taking into account the role of gender, cognitive function, function in everyday activities, comorbidity and education.

Methods: Patients (N=4682), ≥65 years, in the The Norwegian register of persons assessed for cognitive symptoms (NorCog) during 2009-2017 were followed for mortality in the National Registry until January 2018. Flexible parametric survival models were applied to estimate relative survival, life expectancy and years of life lost for diagnostic groups compared with the general population.

Results: Patients with vascular dementia or dementia with Lewy bodies/Parkinson's had the shortest survival, followed by mixed dementia, Alzheimer's disease, unspecified dementia, mild cognitive impairment and subjective cognitive decline. At age 70 years, men with vascular dementia or dementia with Lewy bodies/Parkinson's had life expectancy of 4.7 years, which corresponded to 10.3 years of life lost compared to the general population. Years of life lost for other diagnoses were 10.0 years for mixed dementia, 9.2 years for Alzheimer's disease, 9.3 years for other dementias, 5.2 years for mild cognitive impairment and 2.2 years for subjective cognitive decline. Corresponding years of life lost in women were: 12.7 years, 10.5 years, 9.8 years, 10.6 years, 7.8 years, and 2.6 years. Poor relative survival among dementia patients was associated with male gender, comorbidity, low cognitive function, and low function in activities of daily living.

Conclusions: Compared with the general population, patients with subjective cognitive decline had no significant loss in life expectancy, while patients with mild cognitive impairment and all dementia subtypes had large losses, especially those with a diagnosis of vascular dementia or dementia with Lewy bodies/Parkinson's.

C2

Prenatal exposure to benzodiazepines and z-hypnotics and child behavior problems at 5 years

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Introduction: Up to 15% of pregnant women experience anxiety or sleep disorders during pregnancy. The prevalence of pregnant women who use benzodiazepines or z-hypnotics during pregnancy to treat anxiety disorders or sleep problems is between 1.5 and 4%. When taken during pregnancy the medications cross the placenta, and consequently have the potential to impact on the fetal neurodevelopment. Little is known about the long-term effect of benzodiazepines and z-hypnotics exposure during pregnancy on behavioral problems in the children. One recent study using propensity score (PS) adjusted sibling-matched linear regression found a moderate effect of benzodiazepine anxiolytics exposure and internalizing problems at age 3 (β=0.26, CI=0.002-0.52). Despite the potential impact of the underlying maternal psychiatric disorder, most studies lack to control for this important confounder.

Aims: To examine whether prenatal exposure to benzodiazepines and z-hypnotics may increase the risk of externalizing and internalizing behavior problems in children at 5 years, while controlling for confounding by indication.

Methods: This study used data from The Norwegian Mother and Child Cohort Study (MoBa) linked to The Medical Birth Registry of Norway. The final study population included complete case data from 36 401 live-born children whose mothers had returned the 5-year follow up questionnaire. Children's behavior was measured by parental report on The Child Behavior Checklist at age 5. Children with T-score>63 were considered to have clinically relevant behavior problems. We applied PS weighting methods and log-binomial regression models to estimate risk ratios (RR) and bootstrapped 95% confidence intervals (CI). In addition, censoring weights were applied to account for drop out.

Results: In our sample, 273 (0.75%) children were exposed to benzodiazepines or z-hypnotics during pregnancy. PS-weighted analyses showed no significant increased risk of internalizing behavioral problems (16.5% among exposed, 10.4% among unexposed, RR: 1.39, 95% CI: 0.76, 2.52), and externalizing behavioral problems (16.5% among exposed, 9.9% among unexposed, RR: 1.59, 95% CI: 0.94-2.69).

Conclusion: Among this cohort of Norwegian children, we found no significant increased risk of externalizing and internalizing behavior problems by age 5 years after prenatal exposure to benzodiazepines or z-hypnotics.

C3

Psychiatric comorbidity and genetic correlations provide new insights into differences between attention-deficit/hyperactivity disorder and autism spectrum disorder

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Introduction: Psychiatric comorbidity is common in attention-deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD). The patterns of comorbid conditions in ADHD and ASD may reflect differences in underlying risk factors and mechanisms.

Aims: By examining psychiatric comorbidity in adults with ADHD and ASD based on epidemiological data combined with genetic correlations from GWAS, we aimed to achieve insights into specific vulnerabilities and possible underlying factors in these two neurodevelopmental disorders.

Methods: Cross-sectional analyses with data from linked population-based registries including all individuals born in Norway, 1967-1997 (n=1,701,206). Exposed groups were adults with ADHD (no ASD) and ASD (no ADHD). For the analyses, we excluded individuals with both ADHD and ASD (1,467; 0.1%). Outcomes were registered diagnoses of bipolar, anxiety, depression, personality, substance use disorder (SUD) and schizophrenia spectrum disorders from the Norwegian Patient Registry (2008-2015). Prevalence ratios (PRs) of these disorders were determined by Poisson regression, comparing exposure groups with the remaining adult population. Genetic correlations (r_g) were calculated from international GWAS by linkage disequilibrium score regression.

Results: We identified adults with ADHD (n=38,636; 2.3%), ASD (n=7,528; 0.4%) and the remaining population (n=1,653,575). For all psychiatric comorbidities except BD, PRs differed significantly between ADHD and ASD. The prevalence increase of SCZ was three times larger in ASD than in ADHD (PR_{ASD}=13.9, 95% CI, 12.7-15.2 versus PR_{ADHD}=4.4; 95% CI, 4.1-4.7, *P*<.001), while the increase of SUD was three times larger in ADHD than in ASD (PR_{ADHD} 6.2; 95% CI, 6.1-6.4 versus PR_{ASD} 1.9; 95% CI, 1.7-2.2, *P*<.001). For SCZ, the genetic correlation with ASD was almost twice that with ADHD, ($r_{g(ASD)}$: 0.211 (SE: 0.048, *P*=1.03E-05), $r_{g(ADHD)}$: 0.127 (SE: 0.036, *P*=.0004)). The genetic correlation of smoking (proxy for SUD) with ADHD was significantly higher than that with ASD ($r_{g(ADHD)}$: 0.478 (SE: 0.059, *P*=4.33E-16), $r_{g(ASD)}$: 0.063 (SE: 0.062, *P*=3.12E-01)).

Conclusions: The distinct psychiatric comorbidity patterns in adults with ADHD and ASD are supported by genetic correlations. This finding contributes to our understanding of these disorders as being distinct neurodevelopmental disorders with specific vulnerabilities.

C4

Neighborhood Built Environment Influence on Activity Participation and Mental Health in Childhood and Adolescence: A Systematic Review

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Introduction: Neighborhoods are important settings for health-promotion, particularly among the young ones. With the increased number of publications examining associations between the built environment and health, there is a growing need to summarize the evidence of built environment impact on health and well-being in childhood and adolescence in order to inform researchers, policy makers and practitioners.

Aims: To get an overview of neighborhood built environment determinants and their relationship with mental health and participation in health-promoting activities among children and adolescents.

Methods: We acquired relevant peer-reviewed articles, published after 2009, through searches in six databases, and 108 studies were included. We assigned the built environment determinants into predetermined categories based on previous research, and synthesized results based on multivariate analyzes. The number and percentage of positive, negative and non-significant associations between the determinants and the following outcomes were calculated: amount of general physical activity, active travel, outdoor play/activity, sport participation and mental health.

Results: We found that high walkability, low traffic and high safety, pedestrian infrastructure for walking/biking and short distance to facilities promoted active travel. Associations between the built environment and physical activity were inconsistent, and the low number of studies examining determinants of outdoor play/activity, sport participation and mental health-related provided limited evidence.

Conclusions: We conclude that policies and planning initiative should consider the determinants found to facilitate active travel behavior in order to promote health in childhood and adolescence. Additionally, we call for more research that addresses the built environment determinants of other health promoting activities, as well as positive mental health.

C5

The validity of FINDRISC as a prediction tool for diabetes in a contemporary Norwegian population. A 10-year follow-up of the HUNT Study

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Introduction: FINDRISC is a recommended risk-screening tool that has proved to be a reliable predictor for future and prevalent undiagnosed diabetes. Despite its widespread use, there is a lack of large, long-term cohort studies that have examined the risk of diabetes according to the current 0-26 point FINDRISC score.

Aims: We aimed to determine the validity of FINDRISC in an up-to-date risk environment, in different groups by age and sex, in a Norwegian population-based cohort study followed up from 2006-2008 to 2016.

Methods: We followed up 47,804 participants of the HUNT3 Survey (2006-2008) by linkage to information on glucose-lowering drug dispensing between 2004 and 2016 in the Norwegian Prescription Database. We estimated the C-index, sensitivity and specificity of FINDRISC as a predictor of incident diabetes, as indicated by incident use of glucose-lowering drugs. We estimated the 10-year cumulative incidence of diabetes by categories of FINDRISC, overall and by sex and age.

Results: The C-index (95% CI) of FINDRISC in predicting future diabetes was 0.77 (0.76-0.78) in the overall study population, 0.78 (0.76-0.80) in women and 0.77 (0.75-0.78) in men. At the conventional cut-off value of ≥15, FINDRISC had a sensitivity of 38% (44% in women and 34% in men) and a specificity of 90% (89% in women and 91% in men). The 10-year cumulative incidence (95% CI) of diabetes was 4.0% (3.8-4.2%) in the entire study population, 13.5% (12.5- 14.5%) for people with FINDRISC ≥15 and 2.8% (2.6-3.0%) for people with FINDRISC <15.

Conclusion: Our results indicate that the validity of FINDRISC is lower in a contemporary population than in the original cohorts in which it was developed, and that the risk of developing diabetes among people with FINDRISC ≥15 is substantially lower than assumed in official guidelines. Most people who develop T2D over a 10-year period have FINDRISC <15 and will therefore not be captured through screening using FINDRISC. By lowering the threshold for elevated FINDRISC to ≥11, we would identify 73% of those developing diabetes within the next 10 years, but 1/3 of the entire population would have an elevated FINDRISC score necessitating HbA1c or glucose measurements.

C6

Trends in diabetes prevalence. The Tromsø Study 1994-2016

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Introduction: The prevalence of type 2 diabetes is increasing worldwide. In Norway, register-based studies have reported an increased prevalence of type 2 diabetes and, recently, a decrease in incidence of type 2 diabetes.

Aim: To investigate long-term trends in self-reported diabetes, HbA1c levels and medication use in a population-based study.

Methods: We used self-report and laboratory data from adult women and men participating in one or more of four consecutive surveys of the population-based Tromsø Study; Tromsø 4 1994-95 (n=27158), Tromsø 5 2001 (n=8130), Tromsø 6 2007-08 (n=12984) and Tromsø 7 2015-16 (n=21083). Participants answered questionnaires including questions on diabetes and medication use. Non-fasting blood samples were collected and analysed for HbA1c at Department of Laboratory Medicine University Hospital North Norway. We included participants aged 40-89 years at each survey without missing values on the diabetes question in Tromsø 4 (n=16830), Tromsø 5 (n=7206), Tromsø 6 (n=12200), Tromsø 7 (n=20434) to study trends in diabetes prevalence. Moreover, we used HbA1c levels in Tromsø 4 (n=6720), Tromsø 5 (n=5833), Tromsø 6 (n=12003) and Tromsø 7 (n=20174) to study trends in diabetes unawareness (HbA1c ≥6.5% & no self-reported diabetes), and to study treatment target achievement (HbA1c≤7.0% & self-reported diabetes). We used generalized estimating equation models to study overall and group-specific age-adjusted trends in women and men in 10-year age-groups.

Results: In preliminary analyses, we found a statistically significant increase in prevalence of self-reported diabetes in both sexes and all age-groups. More results will be available.

Conclusion: In these preliminary analyses, using self-report and laboratory data from repeated cross-sectional surveys of an adult general population, we found an increase in prevalence of self-reported diabetes over the last two decades.

C7

Childhood-onset type 1 diabetes in Norway 1989-2014: individual level analysis of socioeconomic factors

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Introduction: There are few prospective studies at individual level assessing the association between parental education and incidence rates of type 1 diabetes.

Aims: Estimate the incidence of type 1 diabetes in children according to maternal education.

Methods: The study uses patients with type 1 diabetes identified in the Norwegian Childhood Diabetes Registry during the period 1989 to 2003 and link these to the National Registry and Statistics Norway. Data from the Norwegian prescription database is used to identify type 1 diabetes incident cases from 2005 to 2014 and link to the National Registry, under 15 years of age. Statistics Norway provided information on immigration, country of birth, education and occupation. We estimated incidence rates (IR) with 95% confidence intervals per 100,000 person years of follow-up, stratified by calendar year and mothers' educational level at child's birth. We use Poisson regression to estimate incidence rate ratios (IRR).

Results: Among the 6,090 type 1 diabetes incident cases, 53.4% were male. The incidence rate was 22.79 per 100,000 person-year (95% CI: 21.99–23.61) during the first study period (1989 to 2003), with an annual increase of 2.2%, and the IR was 30.82 (95% CI: 29.75-31.94) for the period 2005 to 2014, with no significant annual change. The IRR was 0.92 (95% CI: 0.85-0.99) for children of high educated mothers compared with children of mothers with 10 or less years of education. During the first period the IRR was 0.72 (95% CI: 0.63-0.82), in the same groups and there was no difference during the second period. The test for interaction period – maternal education was significant for the second period compared with the first period (p <0.001).

Conclusions: High maternal educational level was associated with lower risk of type 1 diabetes during the first period (1989-2003) but not during the second study period (2005-2014). Impact of maternal education on incidence of type 1 diabetes seems to have changed over time.

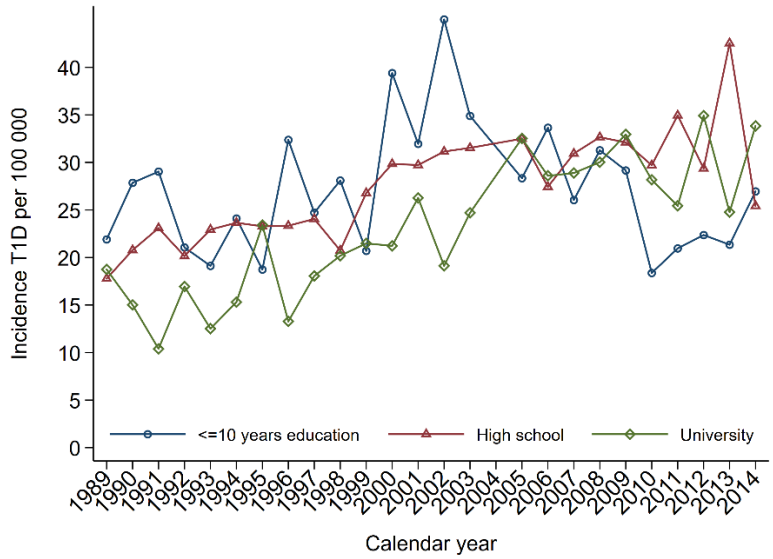

Figure 1. Incidence trends type 1 diabetes by mother's education at child birth, <=10 years education blue line, high school level red line and university level green line.

C8

Maternal and Newborn Vitamin D-Binding Protein, Vitamin D levels, Vitamin D Receptor genotype, and Childhood Type 1 Diabetes

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Introduction: Several lines of circumstantial evidence link 25-hydroxyvitamin D (25[OH]D), vitamin D-Binding Protein (DBP), vitamin D-associated genes and type 1 diabetes (T1D), possibly via immunomodulatory mechanisms. However, no studies have jointly analysed these variables.

Aims: The primary aim was to investigate whether higher DBP levels, during pregnancy or at birth, were associated with lower risk of childhood onset T1D. Secondarily, we aimed to test whether vitamin D pathway genetic variants modified associations between DBP or 25(OH)D and T1D.

Methods: From a cohort of over 100,000 mother/child-pairs (MoBa), we included all available 189 pairs where the child later developed T1D, and 576 random control pairs. We measured 25(OH)D using liquid chromatography combined with tandem mass spectrometry (LC-MS/MS), and DBP using polyclonal radioimmunoassay, in cord blood samples and maternal plasma samples collected mid-pregnancy and at delivery. We genotyped mother and child for variants in or near genes involved in vitamin D metabolism (*GC, DHCR7, CYP2R1, CYP24A1, CYP27B1, VDR*). Logistic regression was used to estimate odds ratios adjusted for potential confounders (aORs).

Results: Higher maternal DBP levels at delivery were associated with lower risk of offspring T1D (OR=0.86, 95%CI: 0.74-0.98, per µM/L increase). Higher cord blood 25(OH)D levels were associated with lower T1D risk (OR=0.87, CI: 0.77-0.98 per 10 nmol/L increase) in children carrying the *VDR* rs11568820 *G/G* genotype (P[interaction]=0.01 between 25(OH)D level and *VDR* genotype). We detected no other significant gene-environment interactions.

Conclusions: Our findings for maternal DBP and childhood T1D is consistent with the only previous study on this topic, but potential mechanisms need further investigation. The observed interaction between 25(OH)D levels at birth and *VDR* genotype in predicting T1D risk is consistent with a recent independent study, and shows that the association between perinatal vitamin D status and T1D risk is complex.

C9

Improvement in work ability, psychological distress and pain sites in relation to low back pain prognosis: A longitudinal observational study in primary care

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Introduction: Knowledge of patients' characteristics is essential for better management of low back pain (LBP). Furthermore, addressing modifiable factors can help identify sub-groups for stratified management and support clinical decision-making. For most patients with LBP, there is a complex interaction between biological, psychological and social factors, which have shown individual prognostic value. However, clinical studies rarely incorporates all domains when studying treatment outcomes for patients with LBP.

Aims: To investigate the longitudinal relation between multisite pain, psychological distress and work ability with self-reported disability, pain and quality of life in patients attending physiotherapy. Secondary, to investigate the associations between changes in multisite pain, psychological distress and work ability with improvement in the outcome measures.

Methods: The study population included 165 patients with non-specific LBP seeking primary care physiotherapy, pooled from two clinical cohorts. Mixed-effects models were used to estimate longitudinal relations between the exposure variables and concurrent measures of self-reported outcomes at baseline and 3 months. Logistic regression was used to estimate odds ratios for minimal important difference in the outcomes.

Results: Higher work ability was associated with less disability -2.6 (95% CI: -3.3, -2.0), less pain: -0.4 (95% CI: -0.5, -0.3), and higher quality of life 0.03 (95% CI: 0.02, 0.04). Higher psychological distress and number of pain sites were associated with more severe disability: 10.9 (95% CI: 7.7, 14.1) and 1.9 (95% CI: 0.9, 2.8), higher pain: 1.9 (95% CI: 1.3, 2.5) and 0.4 (95% CI: 0.2, 0.5), and lower quality of life: -0.1 (95% CI: -0.2, -0.1) and -0.02 (95% CI: -0.03, -0.01), respectively. Improvement in work ability showed consistent associations with successful outcome for disability (OR: 4.8, 95% CI: 1.3, 18.1), pain (OR: 3.6, 95% CI: 1.1, 12.1) and quality of life (OR: 4.5, 95% CI: 1.4, 15.1) at 3 months. Reduced psychological distress was associated with improvement in pain only (OR 4.0, 95% CI: 1.3, 12.3).

Conclusions: More pain sites, higher psychological distress or lower work ability showed higher disability, more pain, and lower quality of life in patients with low back pain. Only improvement in work ability was consistently related to successful outcomes.

C10

Contact with primary health care physicians prior to a severe emergency hospitalisation

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Introduction: There is scarce knowledge on the use of primary health care prior to emergency hospitalisation.

Aims: To assess contacts with general practitioners (regular GP and municipal out-of-hours emergency services) during the year prior to hospitalisation for five common acute diagnoses (acute myocardial infarction; hip fracture; stroke; heart failure; and pneumonia) for patients aged 50 years and older.

Methods: Longitudinal population-based design with linked data from Norwegian national- and municipal registers. Register-based information on all health care contacts and use of municipality services for the inhabitants aged 50 and older in four municipalities in central Norway collected for a two-year period from 2012 to 2013. In total, 66952 participants were included: 53% female, and mean age (in 2012) 65 years (11.1SD). We used generalized estimation equation models (GEE) to investigate the use of health care during 1) the year and 2) the month prior to hospitalisation for each of the six patient groups. We used the estimates to calculate the predicted level of health care use at different time points prior to hospitalisation.

Results: Patients in the age group 50 years and older hospitalised for different severe conditions had a stable and frequent contact with general practitioners the year prior to the admission. Level and patterns of increase close to the time of hospital admission differed between the diagnose groups. The group hospitalised for heart failure stood out with a clear increasing share that visited their general practitioner and municipal out-of-hours emergency services the closer they got to the acute admission; OR 1.97 (CI 1.44-2.68) for seeing a GP the last month prior to hospitalisation compared to 6 months prior to hospitalisation. Nevertheless, 21% (heart failure) to 50% (hip fracture) of hospitalised patients were “non-users”; they visited neither their general practitioner nor municipal out-of-hours emergency services the last month prior to admission.

Conclusion: General practitioners are in frequent contact with patients hospitalised for different severe emergency conditions. This underscores the general practitioners vital role in these patients’ health care.

C11

Hordaland County Public Health Survey 2018 – some results

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Introduction: The Ministry of Health has asked the Norwegian Institute of Public Health (NIPH) to present plans for future county surveys. Before concluding, NIPH conducted a County Public Health Survey in Hordaland to determine if web-based methods only are sufficient.

Aims: The Hordaland County Survey (2018) had two main aims: To produce reliable and valid data for Hordaland County and to test the response rate and selection bias for a web-based only survey.

Methods: Sample sizes were determined on the assumption of a 20-25% response rate. Simple random sampling was used, however three municipalities and one city district in Bergen were over-sampled. Three samples were defined: 30,000 in Helsenorge.no platform, 33,000 using NIPH/University of Oslo (UiO) web-based survey solution, and finally, a smaller sample of 6000 to be followed up more closely by telephone interviews (CATI) (being the benchmark sample with a targeted 50+ % response rate). The survey was conducted in the period April 9th (telephone interviews starting May 2nd) to May 16th.

Results: The overall response rate was 41.3%; 40.8% and 41.6% for Helsenorge.no and NIPH/UiO solution respectively. Response from higher age groups (56+) were 53%. Younger men had the lowest response rate. Given the response rate, estimates could be calculated (with 95% confidence intervals) for 11 of 33 municipalities in Hordaland and all City Districts in Bergen. Follow up by telephone interviews (benchmark sample of 6000) did not increase the response rate substantially, with only 188 new respondents. There was a detectable difference in response on specific items between Helsenorge.no and the NIPH/UiO solution, e.g. a significant lower HSCL score, stratified on education, sex and age, was found in NIPH/UiO solution than in Helsenorge.no.

Conclusions: Using a web-based only survey method has a response rate higher than expected. Older age groups had a relatively high response rate, dispelling fear of digital age discrimination. A thorough analysis of selection bias must be conducted in order to understand strengths and limitations to web-based surveys and different survey solutions. CATI yielded few new respondents and will not be recommended for the future.

P1

Coffee consumption and overall and cause-specific mortality – the Norwegian Women and Cancer Study (NOWAC)

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Introduction: Coffee consumption has previously been reported to reduce overall and cause-specific mortality. We aimed to further investigate this association by coffee brewing methods and in a population with heavy coffee consumers.

Methods: The information on total, filtered, instant, and boiled coffee consumption from self-administered questionnaires was available from 117,228 women in the Norwegian Women and Cancer (NOWAC) Study. We used flexible parametric survival models to calculate hazard ratios (HR) and 95% confidence intervals (CI) for total, cardiovascular, and cancer mortality by total coffee consumption and brewing methods.

Results: During 3.2 million person-years of follow-up, a total of 13,818 deaths occurred. Compared to light coffee consumers (≤1 cup/day), we found a statistically significant inverse association with high-moderate total coffee consumption (more than 3 and up to 6 cups/day, HR=0.90; 95%CI 0.84-0.96) and total mortality. The positive association between heavy filtered coffee consumption (>6 cups/day) and total mortality observed in the entire sample (HR=1.09; 95%CI 1.01-1.18) was not found in never smokers (HR=0.85; 95%CI 0.68-1.06). Both high-moderate filtered and total coffee consumption were associated with a reduced risk of cardiovascular mortality (HR=0.80; 95%CI 0.67-0.94; HR=0.32; 95%CI 0.17-0.60, respectively), whereas no significant association was found for heavy coffee consumption. However, the association was stronger in the analyses of never smokers (>6 cups of coffee overall HR=0.32; 95%CI 0.17-0.60; >6 cups of filtered coffee/day HR=0.20; 95%CI 0.08-0.56). The consumption of over 6 cups/day of filtered, instant, and coffee overall was found to increase the risk of cancer deaths by 23% (95%CI: 11%-36%), 40% (95%CI: 9%-81), and 14% (95%CI: 3%-26%), respectively. However, these associations were not statistically significant in the subgroup analyses of never smokers: HR=1.06; 95%CI 0.82-1.38; HR=0.91; 95%CI 0.38-2.21; HR=1.09; 95%CI 0.88-1.36, respectively.

Conclusion: The data from the NOWAC study indicate that the consumption of filtered coffee reduces the risk of cardiovascular deaths, and that the observed positive association between coffee consumption and cancer mortality is most likely due to residual confounding by smoking.

P2

Sport participation among adolescents and its association with mental health in different age-groups: The Young-HUNT Study

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Introduction: Physical activity (PA) decline with increasing age during adolescence. Data on sport participation-rates is lacking, and more research on the impact of PA and sport participation on mental health among adolescents is needed.

Aims: To describe levels of PA and sport participation in a population-based sample of adolescents, and to explore how PA-level and sport participation is associated with mental health in different age-groups.

Methods: Data from adolescents (13 -19 years-old) participating in the young part of the Nord-Trøndelag Health Study (Y-HUNT) were used. Participants reported level of PA and frequency of participation in various sports. The associations between 1) PA-level (low (reference), medium or high) and 2) participation in sports (no sport (reference), team sport or individual sports) and mental health outcomes (psychological distress, low self-esteem and low life satisfaction) were evaluated using logistic regression analyses, stratified by gender and school level (junior- vs. senior high school).

Results: In total, 3785 boys and 3834 girls were included, mean age 15.8 years (SD 1.7). For both genders there was a lower participation-rate among senior high school students (>= 16 years) compared to junior high students (<=16 years) for team- and technical sports ($p<0.001$). A high level of PA, compared to a low level, was associated with reduced odds of psychological distress among senior high school students (OR = 0.56, 95% CI [0.41-0.77] for girls and OR = 0.44, 95% CI [026-0.74] for boys), and with reduced odds of low self-esteem and low life-satisfaction for all students. Participation in team sports, compared with no sport participation, was associated with mental health benefits among girls.

Conclusions: Our study suggests that a high level of PA is favorably associated with mental health, especially for students in senior high school. Team sport participation seems to have positive impact on mental health among girls and should therefore be encouraged.

P3

Transcriptional profiles of whole blood from women with ovarian cancer. A prospective nested case-control study from the NOWAC Post-genome Cohort

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Introduction: Ovarian cancer generally becomes symptomatic six months before diagnosis, and is often diagnosed at an advanced stage. There is limited knowledge about the transcriptional profile in peripheral blood at the early stages of disease.

Aims: The aim of our study was to explore gene expression in peripheral blood collected in the years preceding ovarian cancer diagnosis, in a nested case control design.

Methods: We used samples from the population representative Norwegian Women and Cancer (NOWAC) post-genome cohort. Between 2003 and 2006, a cohort of 50,000 women born between 1943 and 1957 made a single donation of whole blood in RNA-preserving buffer. We included samples from 87 women diagnosed with ovarian tumors, with controls matched on age and sample storage time. We applied different statistical methods (local in time statistics, linear models for microarrays, gene set enrichment analysis) to assess differences in gene expression between samples from women diagnosed with non-metastasized and metastasized ovarian cancer, and how these changed over time before diagnosis.

Results: Samples were collected up to 7 years before diagnosis of an ovarian tumor. Mean age at blood sampling was 53.3 years, and mean age at diagnosis was 59.9 years. Out of the 87 cases, 18 were borderline. Among the 69 invasive cancers, 59 had metastasized. Overall, there were modest differences in gene expression between groups. The largest variation in gene expression was between samples collected 4-5 years before diagnosis. This could suggest a transient immune response, but could also be a result of a higher number of cases being sampled in this period. The greatest transcriptional differences were found between women that had metastatic ovarian cancer at diagnosis and women diagnosed with non-metastatic ovarian cancer/borderline tumor.

Conclusions: In this prediagnostic study of gene expression in peripheral blood, greatest variation was found in year 4-5 before diagnosis and in association with metastatic disease at diagnosis.

P4

The "Healthy Soldier Effect": The role of self-selection and lifestyle factors

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Introduction: Military personnel often show lower mortality rates when they are compared to the general population. The phenomenon is termed “healthy soldier effect” (HSE) and is mainly due to selection on good health before and during military service and a demand to stay fit during service. However, self-selection might influence upon the HSE as conscripts as well as military careerists can choose between military branches and duty stations

Aims: To investigate the difference in relative mortality between vessel crews and land-based personnel in a cohort of 28 000 officers and enlisted men who served in the Royal Norwegian Navy at some time between 1950 and 2004.

Methods: We followed the cohort members for mortality from the first day of service in the Navy through 2015. Standardized mortality ratios (SMR) were calculated from national rates for vessel crews and land-based personnel separately. Poisson regression analysis was used to compare mortality rates according to personnel group. Relative risks expressed as rate ratios (RR) were calculated for vessel crews using land-based personnel as reference. Ninety-five percent confidence intervals (CI) were computed on the assumption of a Poisson distribution of the observed deaths.

Results: Mortality from all-causes combined, non-neoplastic diseases and external causes was significantly lowered in both personnel groups. While cancer mortality was lowered among land-based personnel (SMR=0.82), the vessel crews showed mortality risk above the expected rate (SMR=1.07). The relative risk of dying was generally higher among vessel crews compared to land-based personnel group, and this contrast was most pronounced for cancer (RR=1.33) and external cause mortality (RR=1.29).

Conclusions: We saw a weaker HSE among vessel crews than among land-based personnel. As both personnel groups have passed the medical screening for military service, we assume that the difference, at least in part, is due to self-selection as individuals with an unhealthy lifestyle might enlist for vessel service. This is supported by a previous study on the same cohort, which showed that vessel crews had 60% higher risk of incidence of lung cancer and of alcohol-related cancers, and mortality from non-neoplastic alcohol diseases than land-based personnel.

P5

The Norwegian Armed Forces Health Registry and data from medical screening for service suitability

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Introduction: Up to the year 2009 all young men in Norway were obliged to attend military medical screening. The Act on military service was changed in 2010, and since that time only a portion of eligible Norwegian citizens are called for military screening, depending of the Armed Forces military staff requirements. Screening include tests of physical fitness; mental and physical health; and intellectual ability. The data are stored in the Norwegian Armed Forces Health Registry (NAFHR) and are available for research within the regulations concerning the register.

Aims: To present the numbers of women and men who were included in the Norwegian Armed Forces Health Registry at military medical screening, and to illustrate the numbers of registrations on height, weight, intellectual performance, and physical performance by year of birth.

Methods: The statistics includes birth cohorts 1950-1998. Numbers of live born boys by year were collected from Statistics Norway.

Results: The NAFHR contains military medical screening data from approximately 1.3 million men and about 60 000 women born between 1950 and 1998. Data from military screening are available for about 70-75% of the men born between 1950-1959. Among men born between 1960-1992, approximately 85-95% have registrations on height, weight and/or intellectual performance, but measures on physical performance are very crude in this period. Among people born after 1992, about 30% go through the military medical examinations and is included in the register. Numbers of women who were screened for military service were about 500-1000 each year but reached ~5000-7000 per year in women born between 1989 and 1998.

Conclusion: The Norwegian Armed Forces Health Registry contains military medical screening data on approximately 1.4 million people born between 1950 and 1998. The coverage of each annual birth cohort varies somewhat because military screening and filing procedures have varied. Most of the men who were born in Norway between 1960-1992 are included in the Norwegian Armed Forces Health Registry.

P6

Relative mortality of Norwegian military veterans of foreign missions

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Introduction: The Norwegian Armed Forces has an obligation to monitor the overall impact of foreign service on the health of the deployed men and women. In partial fulfilment of this obligation, the Norwegian Armed Forces Medical Services conducts analyses of relative mortality rates for veterans with periodic updates. To enable such analyses, the Norwegian Armed Forces Health Registry (FHR) has incorporated information on time, place and duration of deployment on foreign missions starting from deployments in 1978.

Aims: To give an overview of mortality rates among Norwegian male veterans subsequent to first deployment on a foreign mission.

Methods: Standardized mortality ratios are calculated for different cause-of-death groupings, e.g. all-causes, neoplasms, cardiovascular diseases, external causes and suicide. The standardization involves referencing the veterans' mortality rates against national mortality rates with stratification of person years by sex, age (5-yr age group) and time (calendar year). Follow-up is through 2016, the last year for which complete cause-of-death records are available.

Results: Overall mortality from disease is lower for veterans than for the appropriate reference population. Low mortality from cardiovascular disease contributes heavily to this effect, while the difference in mortality from neoplasms is not statistically significant.

Conclusion: The lower disease-mortality for veterans primarily reflects better cardiovascular health than in the reference population.

P7

Tinnitus and chronic pain: The Tromsø Study

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Introduction: There are many similarities between tinnitus and pain. Both are subjective sensations that may turn chronic, they are often accompanied by hypersensitivity in their respective sensory system, and overlapping brain changes have been observed in the two conditions. Additionally, both conditions may be caused by functional changes in the central nervous system due to damage of peripheral structures. Several studies have pointed out these similarities between tinnitus and pain, but, to our knowledge, no population study has examined the empirical associations between the two conditions.

Aims: The aim of the present study is to explore the relationship between tinnitus and chronic pain in the general adult population, i.e. pain that has persisted for longer than three months.

Methods: The study uses data from the Tromsø Study: Tromsø 7, where 21 083 people of ages 40 and above participated (65% participation rate). Of these, data from 19 058 participants will be used in analyses, as these contain complete sets for all relevant variables. We will examine the distribution, intensity and bothersomeness of chronic pain in relation to tinnitus intensity and tinnitus annoyance. Linear regression models will be used to analyse the relationships. Directed Acyclic Graphs (DAGs) are used to identify confounding variables that should be adjusted for in the regression models.

Results: Preliminary results indicate an association between the presence of overall chronic pain and tinnitus annoyance, but no association with tinnitus intensity. Further results will be presented at the conference.

Conclusions: Both tinnitus and pain are frequently occurring phenomena. Thus, examining the relationship between the two conditions is a useful contribution on the path to discovering possible common mechanisms of their development. In this general population study, an association between chronic pain and tinnitus was indicated, but only with how annoying the tinnitus symptoms were perceived, not with the symptoms themselves. Further studies of the relationship between chronic pain and tinnitus are warranted.

P8

Reproductive factors and risk of melanoma: a population-based cohort study

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Introduction: The association between reproductive factors and risk of cutaneous melanoma (CM) is unclear.

Aims: To study the association between various reproductive factors and the risk of CM overall, and by histological subtype and anatomical site, in the Norwegian Woman and Cancer study (NOWAC).

Methods: We followed 165,712 women aged 30-75 at inclusion from 1991-2007 to the end of 2015. Multivariable Cox regression was used to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) for the associations between the reproductive factors age at menarche, menstrual cycle length, parity, age at first and last birth, menopausal status, breastfeeding duration and length of ovulatory life and cutaneous melanoma risk, overall and by histological subtypes and anatomical site.

Results: The mean age at cohort enrolment was 49 years. During the median follow-up of 18 years, 1,347 CM cases were identified. No reproductive factors were clearly associated with CM risk. When stratifying by histological subtype we observed significant heterogeneity ($p = 0.013$) in the effect of ovulatory life on the risk of superficial spreading melanoma (SSM) (HR 1.02, 95% CI 1.01-1.04 per year increase) and nodular melanoma (HR 0.97, 95% CI 0.94-1.01 per year increase). When stratifying by anatomical site, menopausal status (HR 0.54, 95% CI 0.31-0.92, postmenopausal compared to premenopausal) and menstrual cycle length (HR 1.07, 95% CI 1.01-1.13, per day increase) were associated with CM of the trunk, and significant heterogeneity between anatomical sites was observed for menopausal status ($p = 0.036$).

Conclusions: In this large Norwegian cohort study, we did not find convincing evidence of an association between reproductive factors and the risk of CM.