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**Oral presentations**  
**June 12-14, 2024**

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## Utilization of Healthcare in Children Born to Lymphoma Survivors in Sweden

Joshua Philipp Entrop<sup>1</sup>, Viktor Wintzell<sup>1</sup>, Caroline E Dietrich<sup>1</sup>, Anna Marklund<sup>2</sup>, Ingrid Glimelius<sup>3</sup>, Tarec C El-Galaly<sup>1,4,5</sup>, Karin E Smedby<sup>1</sup>, Sandra Eloranta<sup>1</sup>

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**Background:** Advances in lymphoma treatment lead to a rising population of young lymphoma survivors in childbearing ages who might be concerned about the impact of their disease on their children's health. Hence, our study aims to investigate the impact of lymphoma and its treatments on birth outcomes and health of children born to lymphoma survivors.

**Methods:** We analyzed data on in- and outpatient diagnoses up to age five from Swedish national health registers using tree-based scan statistics to identify disease clusters prompting the utilization of healthcare comparing children born to lymphoma survivors (diagnosed 2000-2015) and children born lymphoma-free parents. Children born to lymphoma survivors were identified using the Swedish Lymphoma and national population registers. Each child born to a lymphoma survivor was matched on maternal age at childbirth to five children born to lymphoma-free parents.

**Results:** We identified a total of 1 040 children born to lymphoma survivors and 5 200 children born to matched comparators, of whom 792 and 3 834 had at least one in- or outpatient diagnosis before age five, respectively. Children born to lymphoma survivors had a 13% higher rate of healthcare utilization (Rate Ratio: 1.13, 95% CI: 1.05-1.22) than children born to lymphoma-free parents. However, the panorama of diseases requiring healthcare utilization was broad and we could not identify any specific disease cluster with significantly elevated risk ( $P < 0.05$ ) using tree-based scan statistics.

**Conclusion:** Children born to lymphoma survivors have an overall increased healthcare utilization up to age five, distributed across a broad range of diseases.

Pediatric and perinatal Epidemiology, Auditorium 35.01.44 - Building 35, June 14, 2024, 10:30 - 12:00

## Risk and trajectories of postpartum depression in parents of twins compared to parents of singletons

Sofie Egsgaard<sup>1,2</sup>, Associate Professor Mette Bliddal<sup>2,3</sup>, Lars Christian Lund<sup>2</sup>, Simone Vigod<sup>4</sup>, Trine Munk-Olsen<sup>1,5</sup>

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**Background:** Becoming twin parents has been linked to an increased risk of postpartum depression (PPD), yet the magnitude and temporal onset in the postpartum period compared to singleton parents is unknown.

**Methods:** Using the Danish health registers, we identified parents (mothers and coparents separately) based on all singleton and twin livebirths between 1997-2019. Postpartum depression was defined by incident depression diagnosis or redeemed antidepressant prescriptions from date of childbirth through 365 days postpartum. We performed a parametric time-to-event analysis based on Poisson regression. The primary time scale was time since birth, which was modelled using restricted cubic splines. From this model, we obtained unadjusted and adjusted incidence and cumulative incidence rates of PPD in twin and singleton parents, from which we estimated the hazard ratio (HR) and cumulative risk ratio (RR) over the first year postpartum.

**Results:** The study population consisted of mothers and coparents from 27,055 twin and 1,347,702 singleton births. In adjusted analyses, the HR peaked at two months postpartum (1.27, 95% confidence interval (CI) 1.10–1.47) for mothers, and at seven months (1.23 95% CI 1.03–1.47) for coparents. Both mothers and coparents had a 12-month RR of 1.15 (95% CI 1.04–1.27 for mothers and 1.02–1.29 for coparents).

**Conclusions:** Mothers and coparents of twins had increased risk of PPD compared to singleton parents. This elevated risk was driven by an immediate increase after birth among mothers, and an increase in the later postpartum period among coparents, raising a possibility of diverse causes of PPD onset.

Mental health and psychiatric disorders, Auditorium 35.01.44 - Building 35, June 12, 2024, 16:15 - 17:00



## Intergenerational effects in the associations between childhood body mass index trajectories and adult coronary heart disease

Research Associate Julie Aarestrup<sup>1</sup>, Lise Bjerregaard<sup>1</sup>, Jennifer Baker<sup>1</sup>

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**Background:** Although there is familial transmission of coronary heart disease (CHD) risks, less is known about its effects on associations between early life body size and CHD risks. We examined if parental CHD history modified associations between offspring childhood body mass index (BMI) trajectories and CHD.

**Methods:** We included 58,071 girls and 60,850 boys from the Copenhagen School Health Records Register, born 1952-1996. Five sex-specific latent class BMI trajectories at 6-15 years were identified: below-average (23%), average (37%), above-average (24%), overweight (12%), and obesity (5%). CHD diagnoses ( $\geq 25$  years) were obtained through register linkages. Sex-specific hazard ratios (HR) and 95% confidence intervals (CI) were estimated using Cox regressions. Potential intergenerational effects were evaluated using interaction tests.

**Results:** During follow-up, 1043 women and 1999 men were diagnosed with CHD. There were no interactions between parental CHD and childhood BMI trajectory on offspring CHD risks ( $P(\text{women})=0.65$ ,  $P(\text{men})=0.72$ ). In models adjusted for parental CHD, among women, the childhood BMI trajectories at levels of above-average (HR=1.29, 95%CI: 1.09-1.53), overweight (HR=1.51, 95%CI: 1.23-1.86) and obesity (HR=1.90, 95%CI: 1.39-2.60) had increased CHD risks compared with the average trajectory. Similar patterns were observed among men. No associations were found with the below-average BMI trajectory.

**Conclusion:** Parental CHD history did not modify associations between offspring childhood BMI trajectories and CHD. Even after accounting for parental CHD history, childhood BMI trajectories above average were adversely associated with CHD. These findings underscore the importance of childhood BMI as a CHD risk indicator, independent of the intergenerational transmission of CHD risk.

Life course epidemiology, Auditorium 35.01.44 - Building 35, June 13, 2024, 13:15 - 14:45

## Register-based job exposure matrix studies to examine the impact of psychosocial working conditions on physical and mental health. Experiences from Denmark and Sweden.

Professor Reiner Rugulies<sup>1,2</sup>, Jeppe Karl Sørensen<sup>1</sup>, Elisabeth Framke<sup>1,3</sup>, Kristina Alexanderson<sup>4</sup>, Kristin Farrants<sup>4</sup>, Ida E.H. Madsen<sup>1,5</sup>

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### Background and Aim:

Survey-based occupational cohort studies face challenges in terms of non-response, attrition, reporting bias, and lack of repeated exposure measurements. One alternative is using annually updated job exposure matrices (JEMs) in registry-based nationwide cohort studies. We provide an overview of key research findings in Denmark and Sweden since 2019.

### Methods:

Based on Danish survey data, we created JEMs for key psychosocial work exposures (e.g., job control, job strain, effort-reward imbalance, emotional demands, workplace violence). We assigned the JEMs to nationwide occupational registers, creating two cohorts: an inception cohort of 960,000 individuals, aged 15 to 30 (Danish Work Life Course Cohort, DaWCo), and a cohort of 1.6 million individuals, aged 30 to 59 (Job Exposure Matrix Analyses of Psychosocial Factors and Healthy Ageing in Denmark, JEMPAD). We updated the JEMs annually from 1995 to 2009 and followed participants in health and labour market registers until 2018. We further linked the JEMPAD-JEM to a Swedish cohort of 3.9 million workers.

### Results:

In Denmark, low job control was associated with risk of depressive disorder, whereas the combination of job strain and effort-reward imbalance was associated with risk of chronic somatic disease. High emotional demands were associated with risk of depressive disorder in Denmark and with sickness absence due to mental disorders in Sweden.

### Conclusion:

Using JEMs in Nordic registers is a promising approach for occupational psychosocial health research. The advantages of JEMs need to be balanced against their limitations, though, in particular risk of exposure misclassification.

Occupational epidemiology, Auditorium 35.01.44 - Building 35, June 12, 2024, 14:30 - 16:00

## Educational differences in healthcare use among survivors after breast, prostate, lung, and colon cancer - a SEQUEL cohort study

Anne Katrine Graudal Levinsen<sup>1</sup>, Trille Kjær<sup>1</sup>, Thomas Maltesen<sup>1</sup>, Erik Jakobsen<sup>2</sup>, Ismail Gögenur<sup>3</sup>, Michael Borre<sup>4</sup>, Peer Christiansen<sup>4</sup>, Robert Zachariae<sup>5</sup>, Søren Laurberg<sup>6</sup>, Peter Christensen<sup>6</sup>, Niels Kroman<sup>7</sup>, Signe Larsen<sup>1</sup>, Thea Degett<sup>1</sup>, Lisbet Hölmich<sup>8</sup>, Peter Brown<sup>9</sup>, Christoffer Johansen<sup>10</sup>, Susanne Kjær<sup>1</sup>, Lau Thygesen<sup>11</sup>, Susanne Dalton<sup>1</sup>

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**Background:** The growing population of cancer survivors is likely to increase the future workload for healthcare professionals. We investigated educational differences in healthcare use among survivors and compared with cancer-free individuals.

**Methods:** We established a cohort of 127,472 breast, prostate, lung, and colon cancer survivors, and 637,258 cancer-free individuals (ratio 1:5). Each cohort member was followed until emigration, new primary cancer, death, 10 years after diagnosis, or end of study (December 31st, 2018). Information on education and number of consultations with general practitioner (GP), private practicing specialists (PPSs), hospital and acute healthcare was extracted from national registers. Using Poisson regression, we compared healthcare use between survivors and cancer-free individuals and investigated the association between education and healthcare use among survivors after relevant adjustments.

**Results:** Cancer survivors had statistically significant more GP, hospital, and acute healthcare contacts than cancer-free individuals up to 10 years after diagnosis, while the use of PPS was similar. During the first 1-4 years after diagnosis, survivors with short compared to long education had significantly more GP consultations (e.g., breast, rate ratios (RR) = 1.28, 95% CI = 1.25–1.30) and acute contacts (e.g., prostate, RR = 1.26, 95% CI = 1.15–1.38). One-to-four-year survivors with short compared to long education had less consultations with PPS, with no association for hospital contacts.

**Conclusion:** Survivors used more healthcare than their cancer-free counterparts. Survivors with short education had more GP and acute healthcare contacts than survivors with long education. Knowledge on survivors' healthcare-seeking behavior is crucial to optimize post-cancer healthcare use.

Social epidemiology I, Auditorium 35.01.06 - Building 35, June 12, 2024, 14:30 - 16:00

## Validity of self-reported night shift work among women with and without breast cancer

Phd Student Jesper Medom Vestergaard<sup>1,2</sup>, Jesper Nikolai Dietrich Haug<sup>1</sup>, Annett Dalbøge<sup>1,9</sup>, Jens Peter Ellekilde Bonde<sup>3</sup>, Anne Helene Garde<sup>4,6</sup>, Johnni Hansen<sup>5</sup>, Åse Marie Hansen<sup>4,6</sup>, Ann Dyreborg Larsen<sup>4</sup>, Mikko Härmä<sup>7</sup>, Sadie Costello<sup>8</sup>, Henrik Albert Kolstad<sup>1,9</sup>

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**Background** Differential exposure misclassification is a potential challenge in case-control studies relying on recall of previous exposures. The objective is to estimate the validity of self-reported ever-night shift work among women with and without breast cancer.

**Methods** 225 women diagnosed with breast cancer and 1800 matched controls without breast cancer employed within the Danish hospital regions during 2007-2016 participated in a questionnaire-based survey administered in 2015-2016. Their reported night shift work status was linked with objective payroll register day-by-day working hour data from the Danish Working Hour Database (DWHD) and the Danish Cancer Registry. For the breast cancer patients and their matched controls, we estimated sensitivity and specificity for ever working night shifts using the payroll data as the gold standard. We used quantitative bias analysis to estimate the impact on relative risk estimates for a hypothetical population.

**Results** For breast cancer patients, we observed a sensitivity of ever-night shifts of 86.2% and a specificity of never-night shifts of 82.6%. For controls, the sensitivity was 80.6% and the specificity 83.7%. Odds ratio for breast cancer in a hypothetical population decreased from 1.12 (95% CI 1.03-1.21) to 1.05 (95% CI 0.95-1.16) when corrected by the sensitivity and specificity estimates.

**Conclusion** Female breast cancer patients had slightly better recall of previous night shift work than controls. Additionally, both breast cancer patients and controls recalled previous never-night shift work with low specificity. The net effect of this misclassification is a small over-estimation of the relative breast cancer risk due to night shift work.

Occupational epidemiology, Auditorium 35.01.44 - Building 35, June 12, 2024, 14:30 - 16:00

## Constructing causal life course models: Comparing data-driven and theory-driven approaches

Anne Helby Petersen<sup>1</sup>, Claus Thorn Ekstrøm<sup>1</sup>, Peter Spirtes<sup>3</sup>, Merete Osler<sup>2,1</sup>

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### Background:

Life-course epidemiology relies on specifying complex (causal) models that describe how variables interplay over time. The models are constructed by referring to established empirical or theoretical results, which is time-consuming and inherently confirmatory. We compare this traditional approach to a data-driven alternative – causal discovery – which uses machine learning algorithms to recover (parts of) the causal data generating mechanism.

### Methods:

We focused on a longitudinal study concerning depression and heart disease etiology in a cohort of Danish men (Metropolit Study, 1953-2017). Two subject-field experts constructed theory-driven models (DAGs). We used the temporal Peter-Clark (TPC) algorithm to construct data-driven models. We compared the resulting graphs in terms of agreement on edges (direct causal relationships). In a post hoc assessment, we classified all edges found by TPC, but not by the experts, according to plausibility.

### Results:

The data-driven approach recovered 10 out of 30 edges proposed by the experts, all with the correct causal direction. Only 3 out of 20 remaining edges included in the data-driven model (but not in the expert model) were classified as implausible. The data-driven method recovered 6 out of 7 edges that the experts had high confidence in.

### Conclusion:

The data-driven method recovered some, but not all, causal relationships from the expert model. It was especially good at recovering edges that the experts were confident in. Most of the additional edges proposed by the data-driven method were deemed plausible. Hence, data-driven causal discovery is a useful compliment to traditional theory-driven approaches for constructing causal models.

Plenary session: "Constructing causal life course models: Comparing data-driven and theory-driven approaches", Chr. Hansen-auditorium Building 34, June 13, 2024, 09:45 - 10:15

## Validation of the “Indication for Use” (INDO) Variable in the Danish National Prescription Registry

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<sup>1</sup>University of Southern Denmark

**Background:** Despite its potential value in register-based pharmacoepidemiologic research, recorded information on “indication for use” (INDO) in the Danish National Prescription Registry has rarely been used, likely because of questions about the variable’s validity, which to our knowledge no study has systematically assessed.

**Methods:** We extracted data on 80,814 prescriptions from the software systems (PharmaNet and C2) of five Danish community pharmacies filled between 4 and 16 February 2019 and 2020. Using the indication information recorded in the pharmacy software systems as the gold standard, we evaluated the extent and quality of the corresponding information from the Prescription Registry.

**Results:** Of all prescriptions identified, we captured >99% in the Prescription Registry. The proportion of prescriptions with recorded indication codes in the Prescription Registry was 82% (n = 66,164) but was lower for C2 than PharmaNet. Correcting for the overrepresentation of C2 data in our sample, the estimated proportion of registration was ≈88%. Almost 100% (66,158 of 66,164) of the prescriptions with recorded indication codes in the Prescription Registry had correctly recorded indication codes. Nonspecific indication codes were present in 5.6%–36% of selected drugs and drug classes.

**Conclusions:** Prescriptions filled at Danish community pharmacies are accurately captured by the Danish National Prescription Registry, and the recorded information on indication is generally valid and usable in research. However, minor concerns remain about missingness, nonspecific recorded indication codes, and lower validity, and a higher proportion of missingness of recorded indication codes is expected before 2017.

Creating and validating register-based variables, Auditorium 35.01.05 - Building 35, June 12, 2024, 16:15 - 17:00

## Risk of homelessness after prison release and recidivism: A Danish nationwide, register-based, cohort study

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### Background

Transitional periods between and across services have been linked to homelessness. We aimed to association of previous homelessness and psychiatric disorders with the risk of post-release homelessness. We also examined the association between post-release homelessness and recidivism.

### Methods

We did a register-based nationwide cohort study of people aged at least 15 years released for the first time from prison in Denmark during 2001-2021. Information on release date, homeless shelter contact, psychiatric disorders, and new convictions were obtained from the population-based registers. We estimated incidence rate (IR) and incidence rate ratio (IRR) using Poisson regression analysis adjusting for confounders and calculated cumulative incidences.

### Results

The study cohort included 37,382 individuals aged 15-41 years of age who were released from prison during 2001-2021, accounting for 202,197 person-years at risk. Overall, 1843 (4.9%) individuals became homeless. One year after release from prison, 2.1% had at least one homeless shelter contact, and it was 20.7% in those with homelessness prior to the index-imprisonment. The IRR of post-release homelessness was 16.4, 95% CI 14.8-18.2 adjusted for sex, age, and calendar year for individuals with prior homelessness compared with individuals without. Individuals who additionally had a mental illness had a higher IRR (22.6, 95% CI 19.7-25.9) compared with those without either. Within two years post-release, the cumulative probability of recidivism was 73.2% (95% CI 72.8-73.7).

### Conclusion

Particularly attention to mental health and pre-prison homelessness and unstable housing is warranted for individuals incarcerated, to reduce the risk of further homelessness and other negative outcomes post-release.

## Bettering scientific reporting by replacing p values with simple, informative, objective and flexible Bayes factors

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<sup>1</sup>Danish Cancer Society, <sup>2</sup>Statens Serum Institut

**BACKGROUND:** The Bayesian equivalent of a significance test for H1: an unrestricted parameter value versus H0: of a specific parameter value based only on data D can be obtained from a recently developed asymptotic Bayes factor (BF) (PMID=36959371).  $BF = \text{Probability}(H1|D)/\text{Probability}(H0|D)$  and is a Bayesian equivalent of a likelihood ratio.

**METHODS:** Based on the same asymptotics as the ubiquitous chi-square tests, this BF only depends on the difference in deviance between the models corresponding to H0 and H1 (chisquare) and the dimension d of H1. It can be calculated using functions in the EpiForsk R package.

**RESULTS:** This BF is monotone in chisquare (and hence the p-value p) for fixed d. The expression for BF depends on a parameter lambda which expresses the ratio between the information in the prior and the data (likelihood). By default  $\lambda = \min(d/\text{chisquare}, \lambda_{\max}=0.255)$ . The value 0.255 corresponds to a watershed (evidence shed) of 2; that is, we prefer H1 when  $\text{chisquare} > d \times 2$  and prefer H0 when  $\text{chisquare} \leq d \times 2$ , similar to having a BF that is a continuous version of the Akaike Information Criterion for model selection.

**CONCLUSION:** This BF is a tool to turn p-values into evidence, also retrospectively. Evidence is communicated clearly, because BF is a ratio of evidence. BF generally favours H0 more than is the case for significance testing, especially for large d. It therefore avoids unnecessary interaction terms. It easily facilitates inference according to what the user specifies as a practical null result.

Statistical and epidemiological challenges and innovations, Auditorium 35.01.06 - Building 35, June 13, 2024, 13:15 - 14:45



## Validation of obstetric diagnosis and procedure codes in the Danish National Patient Registry in 2017

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### Background and aim

Data from the Danish Medical Birth Register are extensively used for epidemiological research. We aimed to systematically evaluate the validity of variables related to pregnancy, delivery, and key characteristics of the infant in the Danish National Patient Register, which feed into the birth register, using maternal medical records as reference standard.

### Methods

We reviewed medical records of 1264 women giving birth in the Region of Southern Denmark during 2017. We calculated positive (PPV) and negative (NPV) predictive values, sensitivity, and specificity to estimate the validity of 49 selected variables

### Results

The PPV was  $\geq 0.90$  on most pregnancy-related variables including parity, pre-gestational BMI, diabetes disorders, and previous cesarean section, while it was lower for hypertensive disorders, especially mild to moderate preeclampsia (0.49, 95% CI 0.32-0.66). Sensitivity ranged from 0.80 to 1.00 on all pregnancy-related variables, except hypertensive disorders (sensitivity 0.38-0.71, lowest for severe preeclampsia). On most delivery-related variables including obstetric surgical procedures (eg cesarean section and induction of labor), pharmacological pain-relief, and gestational age at delivery, PPVs ranged from 0.98 to 1.00 and the corresponding sensitivities from 0.87 to 1.00. Regarding infant-related variables, both APGAR score registered five minutes after delivery and birthweight yielded a PPV of 1.00.

### Conclusion

Obstetric coding in the Danish National Patient Register shows very high validity and completeness making it a valuable source for epidemiologic research.

Creating and validating register-based variables, Auditorium 35.01.05 - Building 35, June 12, 2024, 16:15 - 17:00

## Risk of hypersensitivity pneumonitis and interstitial lung diseases following occupational organic dust exposure

Inge Brosbøl Iversen<sup>1</sup>, Jesper Medom Vestergaard<sup>1</sup>, Ioannis Basinas<sup>2</sup>, Johan Ohlander<sup>3</sup>, Susan Peters<sup>3</sup>, Elisabeth Bendstrup<sup>4</sup>, Jens Peter Ellekilde Bonde<sup>5</sup>, Vivi Schlünssen<sup>6</sup>, Finn Rasmussen<sup>7</sup>, Zara Ann Stokholm<sup>1</sup>, Michael Brun Andersen<sup>8,9</sup>, Hans Kromhout<sup>3</sup>, Henrik Albert Kolstad<sup>1,10</sup>

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**Background and aim:** Organic dust, including particulate matter of microbial origin, has traditionally been integrated as a causal premise for hypersensitivity pneumonitis, thereby challenging systematic analyses of true causal associations. To address this issue, we examined the risk of hypersensitivity pneumonitis as well as all interstitial lung diseases (ILDs) combined following occupational organic dust exposure.

**Methods:** We included all Danish workers born 1956 or later and assigned annual levels of exposure to generic organic dust and endotoxin (a component of the cell wall of Gram-negative bacteria) from 1976 to 2015 using job exposure matrices. Incident cases of hypersensitivity pneumonitis and other ILDs were identified in the Danish National Patient Register from 1994 to 2015. Exposure-response relations were examined for cumulative exposure and duration of exposure.

**Results:** For generic organic dust, we observed increasing risk with increasing cumulative exposure with incidence rate ratios (IRR) per 10 unit-years of 1.19 (95% confidence interval (CI) 1.12-1.27) for hypersensitivity pneumonitis and 1.05 (95% CI 1.03-1.07) for all ILDs. We found increasing risk with increasing cumulative endotoxin exposure for hypersensitivity pneumonitis and all ILDs with IRRs per 5000 EU/m<sup>3</sup>-years of 1.55 (95% CI 1.38-1.73) and 1.16 (95% CI 1.08-1.25), respectively. For both exposures, risks also increased with increasing duration of exposure.

**Conclusion:** We observed exposure-response relations between generic organic dust and endotoxin exposure and both hypersensitivity pneumonitis and all ILDs. We consider the estimates for all ILDs most representative for the true associations, as the associations with hypersensitivity pneumonitis are predefined by the disease definition.

Occupational epidemiology, Auditorium 35.01.44 - Building 35, June 12, 2024, 14:30 - 16:00

## Time Trends of the Association of Body Mass Index with Mortality in 3.5 Million Young Swedish Adults

Dr. Innocent Baltazar Mboya<sup>1</sup>, Josef Fritz<sup>1,2</sup>, Marisa da Silva<sup>1</sup>, Ming Sun<sup>1</sup>, Christel Häggström<sup>3</sup>, Tanja Stocks<sup>1</sup>

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**Introduction:** Obesity has been suggested to be a weaker risk factor for all-cause mortality during later calendar years, but these findings might be influenced by differences in age, sex, and death causes distributions across calendar years. We aimed to investigate sex-specific time trends of the association between obesity in young adulthood and all-cause and cause-specific mortality.

**Methods:** We analyzed pooled nationwide data in Sweden for 3,472,310 individuals aged 17-39 years at baseline in 1963-2016, followed up through 2020. We used Cox regression and flexible parametric survival models to investigate the BMI-mortality association in sub-groups of sex and baseline calendar years (<1975, 1975-1985, ≥1985 in men and <1985, 1985-1994, ≥1995 in women).

**Results:** In men with obesity vs. normal weight, the all-cause mortality and other-causes mortality risk decreased over time, but it increased for CVD mortality, potentially because the calendar periods differed by age at death and main death causes distributions. For all-cause and other-causes mortality, higher age at death in the first calendar period coincided with generally higher risks with obesity at higher ages, and the opposite was observed for CVD mortality. Furthermore, the association with all-cause mortality for different ages in men showed no differences between calendar periods, suggesting no calendar effect after accounting for attained age. Similar, but less clear, results were observed in women.

**Conclusion:** The findings underscore the importance of accounting for the age and death causes distributions when investigating obesity-mortality time trends, to avoid misinterpreting the risks attributed to obesity over time.

Confounding and casual models, Auditorium 35.01.44 - Building 35, June 13, 2024, 10:45 - 12:15

## Duration and intensity of being breastfed and educational attainment, income and labour force participation: a prospective cohort and sibling study from Denmark

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**Background:** Breastfeeding improves cognitive ability in childhood, but whether this translates into long-term impact on socioeconomic outcomes remains unknown. We examined associations between durations of predominant and partial breastfeeding and educational attainment, income, and labour force participation in adulthood, and whether these varied by maternal education.

**Methods:** We followed 84,255 individuals born 1959-1967 with prospectively collected information on breastfeeding duration and intensity from the Copenhagen Infant Health Nurse Records. Socioeconomic outcome information came from national registers (1980-2020). Linear and Poisson regression were used, and models were adjusted for prenatal and postnatal variables, across three levels of maternal education.

**Results:** The duration of being breastfed exhibited associations with all outcomes, with most being more pronounced among mothers with low education. Compared with infants breastfed <1 month, those breastfed ≥5 months had 0.68 (95% confidence interval: 0.60-0.76), 0.55 (0.45-0.65), and 0.65 (0.46-0.84) additional years of education than infants born to mothers with low, medium, or high education, respectively. Moreover, infants breastfed ≥5 months had 2632, 2415, and 1237 GBP higher annual income and were 23% less likely outside of the labour force at age 50 years. These associations were stronger with longer durations of breastfeeding, and for predominant than partial breastfeeding.

**Conclusions:** Prolonged and higher breastfeeding intensity consistently exhibited dose-dependent associations with improved socioeconomic indicators in adulthood. Notably, these relationships were more pronounced among individuals whose mothers had lower educational attainment. Consequently, our findings suggest that breastfeeding may have a lasting positive influence on human capital, particularly for the most disadvantaged infants.

Confounding and casual models, Auditorium 35.01.44 - Building 35, June 13, 2024, 10:45 - 12:15

## Weight trajectories through adulthood and prostate cancer incidence, aggressiveness, and death

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### Background

There is inconclusive evidence whether body fatness is associated with prostate cancer (PCa) incidence but convincing evidence for a positive association with PCa death. Body fatness is often measured as body mass index at a single point in time. Instead, we investigated weight trajectories throughout adulthood.

### Methods

The Obesity and Disease Development Sweden (ODDS) study is a pooled cohort with ~4 million participants linked to national registries. We sampled 258,494 men, with minimum three weight observations between age 17-60 years, enrolled in 1963-2014, and followed up through 2019. We used linear mixed effects models with natural cubic splines and linear splines of age to estimate individual life and age span weight trajectories (intercept and slope) for inclusion in multivariable-adjusted Cox models.

### Results

During median 25 years of follow-up, 22,055 men were diagnosed with PCa at mean age of 70 (standard deviation=8) years. The hazard ratio (HR) with (95% confidence interval [CI]) of life span weight trajectory (quintile 1 vs. quintile 5) and aggressive PCa was 1.10 (1.00-1.21) and of PCa death 1.21 (1.07-1.35). These associations were driven by weight increase in the youngest age span (17 to <30). In cases only, the association of life span weight trajectory and PCa survival (HR 1.23 [1.07-1.42]) was driven by weight increase in the oldest age span (45-60).

### Conclusion

Our findings indicate that preventing weight increase that commonly occurs in young adulthood can reduce the risk of PCa incidence and death, while preventing weight increase in old adulthood can improve PCa survival.

## Trajectories of childhood poverty and patterns of psychiatric contacts in adolescence and young adulthood

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**Background:** Childhood poverty has been found to be associated with mental health. The purpose of this study was to explore the relationship between trajectories of childhood poverty and psychiatric hospital contacts in adolescence and young adulthood in Denmark.

**Methods:** This prospective cohort study included all children born in Denmark 1980-2000 (n=1,218,512). These were linked to nationwide registers. Trajectories of childhood poverty were identified using group-based trajectory modeling. Inpatient, outpatient and emergency contacts with psychiatric hospitals after the 16th birthday were identified and Cox regression models were used to estimate associations between childhood poverty and contacts with psychiatric hospitals. The combined effects of childhood poverty and parental mental illness were also estimated. All analyses were stratified by sex.

**Results:** Early and late childhood poverty was associated with a higher risk of psychiatric hospital contacts compared to the no poverty group. Persistent poverty was, however, associated with a lower risk of psychiatric hospital contacts. Those exposed to a combination of parental mental illness and childhood poverty had the highest risk of psychiatric contacts.

**Conclusion:** Early and late childhood poverty was associated with a higher risk of psychiatric contacts, whereas persistent poverty was associated with a lower risk of psychiatric contacts compared to those not exposed to childhood poverty. The findings for persistent poverty could be a result of underutilization in this group.

Life course epidemiology, Auditorium 35.01.44 - Building 35, June 13, 2024, 13:15 - 14:45

## Short-term exposure to ultrafine particles and asthma hospital admissions in children in Copenhagen, Denmark

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**BACKGROUND:** Ultrafine particles (UFP;  $<0.1 \mu\text{m}$  in diameter) are not regulated or commonly monitored, but may be harmful to human health, particularly for children. In this study, we aimed to examine the association between short-term exposure to UFP and asthma hospital admissions in children.

**METHODS:** Daily levels of UFP (2002-2018) were monitored at an urban background station in Copenhagen, Denmark. Asthma hospital admissions, demographic, and socio-economic information of children (0-18 years) were obtained from registries. We applied a case-crossover study design to estimate the association between hospital admissions and UFP exposure for up to six preceding days in all children, and stratified by age, sex, family income, mother's education, prior asthma, or prior respiratory infection.

**RESULTS:** We observed 15,903 asthma hospital admissions in total. An interquartile range increase in UFP was significantly associated with asthma hospital admissions, strongest at two-day means (risk ratio: 1.17 [95% confidence interval: 1.09, 1.25]). These associations remained unchanged when adjusting for particulate matter  $<2.5 \mu\text{m}$  in diameter (PM<sub>2.5</sub>) or nitrogen dioxide (NO<sub>2</sub>), for which we also detected significant positive associations. Associations with UFP were strongest for school-aged children.

**CONCLUSION:** In this large study in a low exposure setting, we find that short-term exposure to UFP can trigger asthma hospital admissions in children, independently of associations with PM<sub>2.5</sub> or NO<sub>2</sub>. This study adds strong evidence calling for the regulation of UFP to protect children's health in urban areas.

Pediatric and perinatal Epidemiology, Auditorium 35.01.44 - Building 35, June 14, 2024, 10:30 - 12:00

## Association between change in physical activity and hospital care among breast cancer survivors with type 2 diabetes in Sweden

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### Background

How change in physical activity (PA) from before to after a breast cancer diagnosis impacts subsequent healthcare utilization is unclear, particularly among women with type 2 diabetes (T2DM). We aimed to assess the association between change in PA and hospital care (hospitalizations and specialist outpatient visits) in this population.

### Methods

This cohort study included women with incident breast cancer in the Swedish National Cancer Register (2004-2019) with T2DM and PA in the National Diabetes Register 1-3 years before and after cancer diagnosis (n=2212). Women were grouped based on self-reported PA as: low maintainers, increasers, decreasers or high maintainers. Hospital care was ascertained from the National Patient Register. We used multivariable-adjusted Cox proportional hazards models to determine the association of change in PA with 1) hospitalizations overall and 2) incident hospitalization or outpatient specialist visits for specific chapters of the International Classification of Diseases (ICD-10).

### Results

During follow-up (median 3.3 years), there were 3604 hospitalizations (median 0.13/woman/year) and 20719 specialist visits (median 1.7/woman/year). Compared with low maintainers, the overall risk of hospitalization was lower among high maintainers (Hazard Ratio [95% Confidence Interval]: 0.68 [0.58-0.80]) and increasers (0.71 [0.58-0.87]), but not decreasers (0.94 [0.80-1.10]), but not increasers (0.96 [0.82-1.11]). The size and direction of effects were similar, irrespective of tumor stage, for the incident outcomes due to infections, malignancies, unspecific symptoms, and diseases of the blood and circulatory systems.

### Conclusion

Maintaining or increasing PA after a breast cancer diagnosis reduced the risk of hospital-care, consistent with recent mortality studies and further supports emphasizing PA throughout the cancer continuum.



## Physical activity and depression; evaluating the role of familial confounding with multicohort sibling data

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<sup>1</sup>University Of Helsinki

### Background

Research on the association between physical activity and depression has accumulated in the last decades. Still the nature of the association has remained elusive, and different statistical approaches have provided differing conclusions, ranging from bidirectional associations from regression-based studies to one prior twin-study reporting no causal association between physical activity and depression. Understanding the nature of the association is crucial for interventions and health-policy making. To address this we combined sibling and twin data to explore whether familial or genetic confounding affects the association.

### Methods

Data from MIDUS, NLSY79, NLSY-YA, GSOEP and WLS (combined number of sibling pairs ~ 15 000) were analyzed separately using multilevel regression with random intercepts and then combined using a random-effects meta-analysis. Physical activity levels at time T were used to predict depression at time T+1. Models were adjusted for sociodemographic variables, other health behaviors and physical health, in cumulative manner.

### Preliminary results

In the basic model, physical activity was associated with lower levels of depression (SMD= -.08). When adjusted for lifestyle factors and physical health, the association attenuated to non-significance. When comparing monozygotic twins from MIDUS, the association attenuated to non-significance after accounting for other covariates, and no support for reverse-causality was observed.

### Preliminary conclusions

Familial and genetic factors may confound the association between physical activity and depression. Thus, earlier studies may have overestimated the strength of the association.

## Prenatal exposure to Selective Serotonin Reuptake Inhibitors and risk of Disorders of Gut-Brain Interaction in children and adolescents

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**Background and aim:** Given the important role of serotonin in gastrointestinal development and function, prenatal exposure to selective serotonin reuptake inhibitors (SSRIs) may impact development of Disorders of gut-brain interaction (DGBIs). Therefore, we aimed to examine the association between prenatal SSRI exposure and DGBI risk.

**Methods:** Using population-based registries, we included all single-birth Danish children born 1997–2015 with follow-up until occurrence of the outcome, age 15 years, death, emigration, or December 31, 2018. Children to mothers who continued SSRIs during pregnancy and children to mothers who discontinued SSRI use before pregnancy were compared using Cox regression. Main outcomes were the first diagnosis of a childhood DGBI (functional nausea and vomiting disorders, functional abdominal pain disorders, functional diarrhea, and functional constipation), or a physician-prescribed laxative.

**Results:** Among 1,158,560 children, 21,969 children (1.9%) were exposed to SSRIs prenatally and 30,174 children (2.6%) were born to mothers who discontinued SSRIs before pregnancy. Overall, the estimated 15-year cumulative incidence of any DGBI was 15.5% (95% CI, 14.9-16.2) in the SSRI-exposed group and 14.7% (14.0-15.3) in the unexposed group. SSRI-exposed children had an overall increased risk of DGBIs (HR 1.08, [1.02-1.14]), which was driven by functional constipation (HR 1.19, [1.10-1.28]) rather than functional nausea and vomiting (HR 0.97, [0.83-1.13]) or functional abdominal pain disorders (HR 0.90, [0.81-1.00]).

**Conclusions:** Prenatal SSRI exposure is associated with specific increases in functional constipation across childhood. The findings emphasize the importance of studying the long-term impact of maternal depression and fetal SSRI exposure on the development of common gastrointestinal disorders.

Pediatric and perinatal Epidemiology, Auditorium 35.01.44 - Building 35, June 14, 2024, 10:30 - 12:00

## Genetic confounding of the association between age at hormonal contraception initiation and depression

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**Background:** Previous studies found associations between earlier age at hormonal contraception (HC) use and increased depression risk. However multiple factors, including genetics, are associated with both early HC use and depression risk. Our goal was to evaluate the potential for genetic confounding by examining associations between polygenic scores for psychiatric disorders and first HC use by age in a nationally representative sample of females born in Denmark.

**Methods:** Data were obtained from the population-based subcohort of the iPSYCH2015 sample. We selected all unrelated females of European ancestry who had genetic data available, were alive and  $\geq 10$  years old by 31 Dec 2006 and free of select medical conditions (e.g. cancer, endometriosis) (N = 19,044). Information on redeemed prescriptions for HC were obtained from the Danish National Prescription Registry. Associations between polygenic scores for major depression, bipolar disorder, schizophrenia, and ADHD and HC initiation were estimated using Cox regressions.

**Results:** Polygenic liability for depression and ADHD were most strongly associated with HC initiation at ages 10-14 years (depression: Hazard Ratio [HR]=1.22, 95% Confidence Interval [CI]=1.17-1.28; ADHD: HR=1.25, 95% CI=1.19-1.31). The associations decreased with age, and by age 20-24 were no longer significant. Polygenic liability for bipolar and schizophrenia were associated only slightly with HC initiation at age 10-14 (bipolar: HR=1.02, 95% CI=1.00-1.05; schizophrenia: 1.02, 95% CI=1.00-1.04).

**Conclusion:** Genetic liability likely explains some of the association between age at HC use and depression, indicating that the proposed causal effect of HC on depression may be weaker than suggested by prior observation studies.

Confounding and casual models, Auditorium 35.01.44 - Building 35, June 13, 2024, 10:45 - 12:15

## Association between cannabis use disorder and schizophrenia stronger in young males than in females

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**Background:** Previous research suggests an increase in schizophrenia population attributable risk fraction (PARF) for cannabis use disorder (CUD). However, sex and age variations in CUD and schizophrenia suggest the importance of examining differences in PARFs in sex and age subgroups.

**Methods:** We conducted a nationwide Danish register-based cohort study including all individuals aged 16-49 at some point during 1972-2021. CUD and schizophrenia status was obtained from the registers. Hazard ratios (HR), incidence risk ratios (IRR), and PARFs were estimated. Joinpoint analyses were applied to sex-specific PARFs.

**Results:** We examined 6,907,859 individuals with 45,327 cases of incident schizophrenia during follow-up across 129,521,260 person-years. The overall adjusted HR (aHR) for CUD on schizophrenia was slightly higher among males (aHR=2.42, 95% CI=2.33-2.52) than females (aHR=2.02, 95% CI=1.89-2.17); however, among 16-20-year-olds, the adjusted IRR (aIRR) for males was more than twice that for females (males: aIRR=3.84, 95% CI=3.43-4.29; females: aIRR=1.81, 95% CI=1.53-2.15). During 1972-2021, the annual average percentage change in PARFs for CUD in schizophrenia incidence was 4.8 among males (95% CI=4.3-5.3; P<0.0001) and 3.2 among females (95% CI=2.5-3.8; P<0.0001). In 2021, among males, PARF was 15%; among females, it was around 4%.

**Conclusions:** Young males might be particularly susceptible to the effects of cannabis on schizophrenia. At a population level, assuming causality, one-fifth of cases of schizophrenia among young males might be prevented by averting CUD. Results highlight the importance of early detection and treatment of CUD and policy decisions regarding cannabis use and access, particularly for 16-25-year-olds.

Mental health and psychiatric disorders, Auditorium 35.01.44 - Building 35, June 12, 2024, 16:15 - 17:00

## Algorithm for forming hospital courses by combining sequential attendance contacts in the Danish National Patient Register: A consensus-driven methodological development study

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**Background and aim:** Studying complete hospital courses from register-data can cause methodological difficulties due to the lack of a contact linkage identifier. We aimed to develop an algorithm combining sequential attendance contacts in the Danish National Patient Register (DNPR) into hospital courses, spanning the entire duration and all contacts from hospital arrival to departure.

**Methods:** The algorithm was developed under the consensus of experts from research institutions across Denmark. It reads in 2nd and 3rd version DNPR data, deletes contacts without attendance, duplicates elective outpatient contacts corresponding to attendance dates, and modifies contact types (e.g., repeated acute contacts), among others. Thereafter, sequential contacts within 4 hours by the same person are marked as the same hospital course, consisting of one or more DNPR contacts. We tested the algorithm in a data set of adults living in Denmark during 2013–2021 and compared different hourly cut-offs.

**Results:** For the demonstration, we included 120.2m contacts from 5.7m persons, combined into 105.9m hospital courses. Of the final hospital courses, 6.4% were acute inpatients, 8.3% acute outpatients, 2.0% elective inpatients, and 83.3% elective outpatients. Using 4-hours as our recommendation, 3-, 5-, and 6-hour cut-offs for contact combining revealed only minor differences in the number of hospital courses ( $<\pm 0.4\%$ ), whereas 12- ( $<1.7\%$ ) and 24-hour cut-offs ( $<43.1\%$ ) had larger impact.

**Conclusion:** This new algorithm automates data reading, modification, and linkage of sequential attendance contacts into combined hospital courses. The algorithm will be made freely available from an online repository as a SAS Macro and R script.

Creating and validating register-based variables, Auditorium 35.01.05 - Building 35, June 12, 2024, 16:15 - 17:00

## Identifying Signature Features of Epidemic Diseases from 19th Century All-cause Mortality Data

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**Background and aim.** Deadly epidemics leave distinct marks on all-cause mortality. When cause-specific health data is unavailable, studies of all-cause mortality may be necessary for understanding epidemic and pandemic diseases in history.

**Methods.** We identified and cataloged every major epidemic in Denmark during the hundred-year period between 1814 and 1915, based on a recently digitized and compiled dataset of all 4 million burials in the period. Time-series of daily deaths for each county were constructed and excess mortality was estimated as the difference with a baseline average of the day-specific mortality in the surrounding 12 years. Baseline estimations were adjusted by iteratively removing datapoints above three standard deviations. A mortality crisis was defined as period with at least one day with a standard score above three. We determined plausible etiology each mortality crisis with more than 50 excess deaths by consultation with historical sources and investigation of the signature features of age-patterns, seasonality, timing, and geography.

**Results.** We identified 418 mortality crises, totaling 59,932 excess deaths over the 100-year study period (1.5% of all burials). These crises included pandemic influenza, cholera-outbreaks in 1853 and 1857, and annually repeating epidemics in 1826-1832.

**Conclusion.** While some these epidemics have been discussed elsewhere, our approach is based solely on all-cause mortality. In modern low-income settings where representative population health data may be unavailable, the use of mortality data to determine the signature features may guide policy and improve future mitigation strategies.

Mortality and cancer, Auditorium 35.01.06 - Building 35, June 14, 2024, 10:30 - 12:00

## Using causal modeling frameworks to investigate the association between long-term exposure to nitrogen dioxide and COVID-19 diseases

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<sup>1</sup>University Of Copenhagen

**Background:** Emerging evidence linked long-term exposure to air pollution and coronavirus (COVID-19) disease, yet the potential effects of actionable intervention on air pollution and their health benefits across socioeconomic groups remains underexplored. This study evaluate the effect of reducing long-term exposure to nitrogen dioxide (NO<sub>2</sub>) on the COVID-19 hospitalization and mortality, and assesses the attributable health impacts across demographic and socioeconomic subgroups in Denmark.

**Methods:** We followed all Danish residents aged 30 years or older in Denmark from March 1, 2020 for a year. Annual mean concentration of NO<sub>2</sub> at their residences in 2019 were estimated using the Danish DEHM/UBM model. We applied a G-computation model, utilizing binomial regression with inverse probability censoring weighting to model the risk of COVID-19 hospitalization and mortality under different hypothetical NO<sub>2</sub> reduction scenarios. We quantified the health benefits of different hypothetical interventions against the no intervention and further stratified by different demographic and socioeconomic subgroups.

**Results:** Implementing any NO<sub>2</sub> reduction intervention would significantly benefit Danish public health in the first year of COVID-19 pandemic. Compared to no intervention, aligned with World Health Organization's Air Quality guideline (10 µg/m<sup>3</sup>) would prevent 1059 [884-1234] COVID-19 hospitalizations and 467 [345-590] deaths. These benefits were more pronounced among male, older adults, low-income individuals, pension/cash receiver, and small families.

**Conclusion:** Reducing NO<sub>2</sub> would contribute significant health benefits for COVID-19 in Denmark, even in a country with relatively low air pollution levels.

Confounding and casual models, Auditorium 35.01.44 - Building 35, June 13, 2024, 10:45 - 12:15

## Sociodemographic differences in the response to changes in COVID-19 testing guidelines in Sweden

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### BACKGROUND:

During the COVID-19 pandemic, Sweden emphasized voluntary guidelines over mandates. We exploited a rapid change and reversal of the Public Health Agency of Sweden's COVID-19 testing guidelines for vaccinated and recently infected individuals as a quasi-experiment to examine sociodemographic differences in the response to changes in pandemic guidelines.

### METHODS:

We analysed daily polymerase chain reaction (PCR) tests from October 1st, 2021, to December 15th, 2021, for vaccinated or recently infected adults ( $\geq 20$  years;  $n=1,596,321$ ) from three Swedish regions (Stockholm, Örebro, and Dalarna). Using interrupted time series analysis, we estimated abrupt changes in testing rates at the two dates when the guidelines were changed (November 1st and November 22nd). Stratified analysis and meta-regression were employed to explore sociodemographic differences in the strength of the response.

### RESULTS:

Testing rates declined substantially when guideline against testing of vaccinated and recently infected individuals came into effect on November 1st (testing rate ratio: 0.50 [95% CI 0.41, 0.61]), and increased again from these lowered levels by a similar amount upon its reversal on November 22nd (testing rate ratio: 2.19 [95% CI: 1.69, 2.85]). Being Sweden-born, having higher household income, or higher education, were all associated with a stronger adherent response to the guideline changes. Adjusting for stratum-specific baseline testing rates and test-positivity did not influence the results.

### CONCLUSION:

The population was responsive to the rapid changes in testing guidelines, but with clear sociodemographic differences in the strength of the response.

Social epidemiology I, Auditorium 35.01.06 - Building 35, June 12, 2024, 14:30 - 16:00



## Treatment for urinary tract infections is associated to delayed diagnosis of urinary bladder cancer

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**Background:** Urinary tract infections (UTIs) have been associated with delayed diagnosis of bladder cancer. The aim was to investigate pre-diagnostic prescriptions of antibiotics for UTI and the relation to diagnostic delay of bladder cancer reflected by advanced disease at diagnosis.

**Methods:** We investigated patterns of UTI treatments among bladder cancer patients compared to a matched reference population, and among the bladder cancer patients investigated association between UTI treatments and more advanced disease. We selected bladder cancer patients diagnosed 2008-2019, and their matched referents from BladderBaSe 2.0. Filled prescriptions of treatment for UTI 3 year prior to diagnosis were retrieved from national registers. Generalized ordered logistic regression were used to calculate odds ratios (ORs) of a more advanced disease as an ordered outcome: non-muscle invasive bladder cancer (NMIBC), muscle-invasive bladder cancer (MIBC), and metastatic bladder cancer (MBC).

**Results:** The study population included 29921 bladder cancer patients and their matched 149467 referents. Patients had a higher proportion of UTI treatment as compared to their respective referents, with largest differences among those with MIBC and MBC. At least one UTI treatment versus none corresponded to an OR of 1.28 (95% CI 1.19 – 1.37) in men and 1.42 (95 % CI 1.27 – 1.58) in women on risk to a more advanced disease (MIBC or MBC), and higher number of treatments resulted in increased estimates in both sexes accordingly.

**Conclusion:** Further studies are needed focused on the predictive value of UTI treatments in combination with other predictors for decision aids in both gender.

Mortality and cancer, Auditorium 35.01.06 - Building 35, June 14, 2024, 10:30 - 12:00

## Hypersensitivity of self-controlled designs towards exposure misclassification when there is abundant chronic use - a simulation study

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### Background

Self-controlled designs, such as the case-crossover (CCO), case-time-control (CTC), and self-controlled case series (SCCS) only include individuals with discordant exposure. With minor exposure misclassification, chronic drug users may potentially confer a strong conservative bias and a false narrowing of the confidence interval.

### Aims

Our aim was to demonstrate both a hypersensitivity towards exposure misclassification and too narrow confidence intervals when chronic users are falsely included as discordant in self-controlled analyses.

### Methods

We used citalopram prescriptions from 41,835 users in Denmark and established formally true treatment episodes by using the recorded days' supply and assigning a grace period of 90 days to each prescription. Outcomes were simulated 1000 times using the true exposure classification with different baseline incidence rates (IR) incidence rate ratios (IRR). We also simulated different proportions of chronic users and exposure misclassifications. We introduced exposure misclassification by creating artificial treatment gaps.

### Results

The CCO, CTC and SCCS showed considerably more conservative bias than a cohort analysis. Under a scenario with 80% true chronic users, a baseline IR of 0.02 per person-year, and a true IRR of 10, the CCO yielded ORs of 10.3, 5.2, and 2.7 with misclassifications of 0%, 2%, and 5%. Corresponding IRRs were 10.0, 9.7, and 9.1 in a cohort design. Confidence intervals narrowed with increasing exposure misclassification. Bias was most strongly dependent on the degree of misclassification, proportion of chronic users, IRR and IR, in that order.

### Conclusion

Some self-controlled designs show hypersensitivity to exposure misclassification with high proportions of chronic users.

Statistical and epidemiological challenges and innovations, Auditorium 35.01.06 - Building 35, June 13, 2024, 13:15 - 14:45

## Preliminary results. Atopic dermatitis in childhood and reproductive health in young adult men: A cohort study in the Danish National Birth Cohort

MD Camilla Lomholt Kjersgaard<sup>1</sup>, Anne Gaml-Sørensen<sup>1</sup>, Linn Håkonsen Arendt<sup>1,2</sup>, Sandra Sjøgaard Tøttenborg<sup>3,4</sup>, Karin Sørig Hougaard<sup>4,5</sup>, Gunnar Toft<sup>6</sup>, Onyebuchi Arah<sup>1,7,8</sup>, Jens Peter Bonde<sup>3,4</sup>, Mette Deleuran<sup>9</sup>, Cecilia Høst Ramlau-Hansen<sup>1</sup>

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**Background and aim:** Atopic skin absorbs more allergens and endocrine disruptors than healthy intact skin. Combined with chronic systemic inflammation, it may negatively affect the reproductive hormone system. However, evidence to support this hypothesis is sparse, especially in men. We therefore investigated the association between childhood atopic dermatitis and later reproductive health.

**Methods:** This study is based on the Danish National Birth Cohort (DNBC) and its sub-cohort, the Fetal Programming of Semen Quality Cohort (FEPOS). It consists of men born between 1998 and 2000 whose mothers were recruited to the DNBC. In total, 1,058 men completed a comprehensive questionnaire regarding health and lifestyle. In a clinical examination, testes volume was measured, and height, weight, semen, and blood samples were collected. Information on atopic dermatitis was obtained from registers and as self-reported, doctor-diagnosed atopic dermatitis during childhood. The association between atopic dermatitis and semen characteristics, testes volume, and reproductive hormone levels were analyzed using negative binomial and linear regression models.

**Preliminary results:** Overall, 217 (21%) of the included men had childhood atopic dermatitis. We found slightly higher semen concentrations in men with atopic dermatitis in childhood than in unaffected men (17%, 95% confidence intervals 3% to 34%), and slightly lower FSH and LH. Testosterone and estradiol levels and the remaining reproductive health outcomes were comparable between men with and without atopic dermatitis.

**Conclusion:** The present study is reassuring for young men with atopic dermatitis as it suggests no clinically important effect of childhood atopic dermatitis on young men's reproductive health.

Life course epidemiology, Auditorium 35.01.44 - Building 35, June 13, 2024, 13:15 - 14:45

## Occupational daytime light exposure and risk of initiating antidepressant treatment

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### Background and aim

Light exposure may play a pivotal role in the manifestation and management of depressive symptoms. We examined the association between levels of occupational daylight exposure and the risk of filling a prescription for antidepressants.

### Methods

We conducted a register-based follow-up study of all gainfully employed individuals in Denmark (56°N) born in 1981 or later. We estimated annual occupational daytime (6:00-17:59h) white light exposure levels (lux) for each employment year from 1999-2015 using a quantitative job exposure matrix. Individuals were followed from the year 2000 or from the year after their first employment if later, until the first antidepressant treatment recorded in a national prescription database or until the end of the study in 2016. We calculated sex-specific incidence rate ratios (IRRs) by light level the previous year, adjusted for age, calendar year, family history of antidepressant treatment, smoking, and educational level.

### Results

We included 864,826 individuals who accumulated 4,679,410 person-years of follow-up. Among women, relative to those exposed to <250 lux, an IRR of 1.03 (95%CI=1.01-1.06) was seen among those exposed to 250-499 lux. Among those exposed to 500-999 lux and ≥1000 lux, IRRs of 0.83 (95%CI=0.71-0.96) and 0.84 (95% CI 0.69-1.03) were seen. In men, no association between light exposure and antidepressant treatment was suggested.

### Conclusion

We indicate a protective effect of high occupational daylight levels on the initiation of antidepressant treatment among women, potentially reflecting underlying biological mechanisms. These findings underline the significance of integrating considerations of light exposure into workplace policies and practices.

Occupational epidemiology, Auditorium 35.01.44 - Building 35, June 12, 2024, 14:30 - 16:00

## Lipid levels during adult lifetime in men and women with and without a subsequent incident myocardial infarction. The Tromsø Study 1974-2016.

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**Background:** The adverse effect of an unfavorable lipid profile on the risk of myocardial infarction (MI) is assumed to accumulate throughout life, but little is known about latency time. Population-based longitudinal data on serum lipid level were utilized to explore this issue.

**Methods:** Results were based on data for 26,130 individuals (50.5% women) participating in at least 2 of the 7 Tromsø health surveys, Norway. Diagnoses of MI at ages 35-97 years were obtained from national registers. A linear mixed model was applied to compare mean serum lipid levels during adult lifetime (20-89 years) between individuals with and without a subsequent incident MI.

**Results:** Already from ages 20-30 years, individuals with a subsequent incident MI had in average more unfavorable lipid levels. The contrast by MI was seen 20-35 years before incident MI, with a clear trend towards more severe adverse lipid levels, occurring at an earlier age, the lower age at diagnosis ( $p < 0.001$ , test for trend through ordered categories  $< 55$ ,  $55-74$ ,  $\geq 75$  years). This trend was particularly pronounced for the ratio between HDL-C vs. total cholesterol (both sexes) and triglyceride vs. HDL-C in proportion of total cholesterol (women). Men had in general more unfavorable lipid profile, especially before ages 55-60 years. However, the difference by MI status was equally large in women as men although the age pattern differed ( $p \leq 0.05$ , tests for 3-way interaction).

**Conclusions:** Compared to general population mean levels, both in men and women, an adverse lipid profile was seen 20-35 years before incident MI.

Life course epidemiology, Auditorium 35.01.44 - Building 35, June 13, 2024, 13:15 - 14:45

## Socioeconomic position and cause-specific mortality in 15-24-year-olds in Denmark 2010 to 2022: a nationwide study

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### BACKGROUND

It is well known that adult mortality is socioeconomically patterned. Literature on differences in youth mortality is however sparse. In contrast to mortality in adults, many deaths in youth are attributable to unnatural causes such as traffic accidents, alcohol intoxication or self-harm, causes that are in principle entirely preventable. We aimed at testing if socioeconomic background of 15-24 year-olds associated with mortality.

### METHODS

We conducted a nationwide cohort study consisting of all Danes 15 to 24 year old during 2010 to 2022. Participant and parental information were linked to obtain information on socioeconomic background (parents' education, employment status, and income) using annually updated registers. All-cause and cause-specific mortality included natural deaths (i.e. medical conditions and diseases), accidents, suicides, and homicides. Poisson-regression was used to calculate incidence rate ratios (IRR).

### RESULTS

Results revealed a dose-dependent relationship between socioeconomic position and mortality, observed for all measures of socioeconomic position, and for all-cause mortality as well as for deaths caused by natural causes, accidents, suicides, and homicides, respectively. Results were similar in strata of young men and young women and by age group (15-17 versus 18-24-year-olds).

### CONCLUSION

Young people from disadvantaged backgrounds have a markedly higher mortality from both natural and unnatural causes as compared to more affluent groups. Further, the socioeconomic position of parents is associated with premature mortality in a dose-dependent manner meaning that this is not only a concern for marginalised groups. Public health attention should be directed to respond to these inequities by concerning for youth health.

## Residual confounding: The example of parental age and miscarriage

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<sup>1</sup>Department of Public Health

### Background

Many scientific papers state, 'Residual confounding cannot be ruled out,' often using this term ambiguously to describe both unmeasured/unknown confounding and what we believe is the correct definition: confounding persisting despite attempts to control for the confounding variable. This study emphasizes the need for clarity by illustrating the example of confounding due to maternal age when investigating paternal age and miscarriage risk.

### Methods

Conducting a register-based study covering all pregnancies in Denmark from 1994 to 2022, we estimated hazard ratios (HR) for miscarriage based on paternal age. Cox regression models with gestational days as the time scale were employed, initiating at pregnancy week 5. To assess confounding by maternal age, we modeled it as a continuous linear term, using restricted cubic splines, and categorized it into 5-year and 1-year intervals.

### Results

Among 2,110,582 pregnancies, 201,862 resulted in miscarriage between gestational week 5 and 22. We found a statistically significant step-wise increase in miscarriage risk with higher paternal age when maternal age was categorized in 5-year intervals, with HR 5-10% higher for fathers over 35 years compared to those aged 25-30 years. This is in line with previous findings. This association persisted when maternal age was modeled linearly, but the association disappeared completely when adjusting in 1-year strata or using restricted cubic splines.

### Conclusion

The study underscores the necessity of accurately understanding residual confounding as persistent confounding by a factor after inadequate adjustment. A precise conceptualization is crucial for effectively addressing and mitigating residual confounding in scientific studies.

Confounding and casual models, Auditorium 35.01.44 - Building 35, June 13, 2024, 10:45 - 12:15

## In utero exposure to psychotropic medication and long-term offspring growth trajectories

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**Background:** The use of psychotropic medications during pregnancy is a matter of concern due to potential long-term developmental effects on offspring, including childhood growth, which is a key indicator of child health and development and an important influence on health and wellbeing later in life. Only few studies have examined the association with growth in early infancy and none in later childhood or adolescence.

**Objective:** This nationwide register-based cohort study aims to evaluate the long-term impact of prenatal exposure to psychotropic medications on the physical development of children, particularly focusing on height and weight trajectories from birth through adolescence.

**Methods:** Utilizing data from the Danish Medical Birth Register, we included singleton live births from 1998 to 2018. Psychotropic medication exposure from 30 days before conception until delivery, including antipsychotics, anxiolytics, antidepressants, and stimulants, was determined based on prescription records from the Danish National Prescription Registry. The Children's Database provided longitudinal measures of children's length/height and weight from birth up to 17 years. We applied a linear spline multilevel model to estimate and compare the growth trajectories of children exposed and not exposed to these medications, adjusting for potential confounders using propensity score stratification.

**Results:** The study includes over 1.16 million children, with a median of 7 height and weight measurements per child. Detailed findings on the developmental differences between exposed and non-exposed groups will be disclosed at the conference.

**Significance:** This research contributes vital insights into the developmental consequences of psychotropic medication use during pregnancy, informing clinical practices and guidelines.

Pediatric and perinatal Epidemiology, Auditorium 35.01.44 - Building 35, June 14, 2024, 10:30 - 12:00



## Is the sequence ratio an unbiased estimate of the incidence rate ratio? A simulation study

Thomas Delvin<sup>1,2</sup>, Sofie Egsgaard<sup>1</sup>, Jesper Hallas<sup>1</sup>, Helene Kildegaard<sup>1</sup>, [Lars Christian Lund](#)<sup>1</sup>, Martin Torp Rahbek<sup>1</sup>

<sup>1</sup>University Of Southern Denmark, <sup>2</sup>LEO Pharma

**Background and aim:** The sequence symmetry analysis (SSA) is an increasingly used method to detect adverse drug events. We aimed to evaluate the conditions under which the sequence ratio (SR) obtained from a SSA is an unbiased estimate of the true incidence rate ratio (IRR).

**Methods:** We simulated cohorts of one million individuals who could initiate an exposure drug and experience a very rare, rare, common, or frequent outcome of interest, corresponding to incidence rates of 1 event per 10,000, 1000, 200, and 10 person years. The outcome rate among exposed individuals was modified by a true IRR of 0.2, 0.5, 1.0, 2.0, and 5.0. We further evaluated scenarios where the outcome was fatal or the outcome reduced the rate of initiation of the exposure drug. Bias was calculated as  $\log(\text{SR}) - \log(\text{IRR})$ .

**Results:** The SR was close to unbiased for rare, common, and frequent events, except when the true IRR was 5.0 (mean SR 4.94 and 3.74 for common and frequent events). The SR was slightly biased when the outcome was very rare (bias +0.01 to +0.36). When the outcome was potentially fatal, bias increased with the probability of death (bias up to +2.32 for a probability of death of 0.9). We observed a corresponding upwards bias when the outcome reduced the probability of future exposure.

**Conclusion:** The SR is an unbiased estimate of the IRR, except when the true IRR is high, the outcome has a high mortality, or when the outcome reduces the probability of future exposure.

Statistical and epidemiological challenges and innovations, Auditorium 35.01.06 - Building 35, June 13, 2024, 13:15 - 14:45

## EQUITY OF REFERRALS TO TYPE 2 DIABETES REHABILITATION IN A UNIVERSAL WELFARE STATE

Mette Bender<sup>1</sup>, Karsten Vrangbæk, Henrik Brønnum-Hansen, Ingelise Andersen, Charlotte Glümer  
<sup>1</sup>University Of Copenhagen

**Background** Despite aims of equal access to treatment and care in the Nordic countries, marked socioeconomic inequality in the development of type 2 diabetes (T2D) complications persists. The study purpose was to estimate the associations of individual socioeconomic position and deprivation at the general practitioner (GP) level with referrals to T2D rehabilitation.

**Methods** In 2015-2018, 3390 people affiliated with 432 primary GPs living in the municipality of Copenhagen were identified through registry data as newly diagnosed with T2D. Of these, 656 (19%) individuals were referred to municipal rehabilitation services in 2015-2021. Individual socioeconomic position was measured by education, income, and employment. The Danish Deprivation Index (DADI) was used as a measure of GP-level deprivation.

**Results** Patients were more likely to be referred to municipal rehabilitation if they had low vs. high income (hazard ratio (HR) 2.87 [women], 1.64 [men]), were not employed vs. employed (HR 1.95 [women], 1.23 [men]) and were affiliated with GPs with a low vs. very high level of deprivation (HR 7.63 [women], 4.30 [men]).

**Conclusions** The results suggest that GPs practice proportionate universalism by allocating treatment to lower socioeconomic individuals in likely higher need of care. However, the overall HR for referrals was lower among GPs with more deprived patient populations, indicating unequal treatment of all citizens, which conflicts with the aims of general universal health care. Inequality in rehabilitation healthcare services must be further addressed and investigated to prevent exacerbating health disparities.

Social epidemiology I, Auditorium 35.01.06 - Building 35, June 12, 2024, 14:30 - 16:00

## An emulated target trial examining onset and offset of perceived job insecurity on the risk of sickness absence due to common mental disorders.

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**Background:** Perceived job insecurity is associated with poor mental health, but whether it affects sickness absence due to common mental disorders (CMD) is not well understood. We investigated onsets and offsets of perceived job insecurity compared to reporting being stably secure or stably insecure, and the risk of sickness absence due CMD.

**Methods:** Five target trials between 2008 and 2022 were emulated and pooled into one, investigating onsets and offsets of job insecurity from two consecutive waves of data from the Swedish Longitudinal Occupational Survey of Health. The participants were subsequently followed until a medically certified CMD sickness absence event, disability pension, death or end of follow up (2 years). Job insecurity onsets were compared to stable security while offsets were compared to stable insecurity. Statistical analysis included pooled logistic regression and inverse probability weighting on baseline covariates for 26 969 person-observations (1 633 for offsets vs. stably insecure).

**Results:** Compared to being stably secure, a job insecurity onset appeared to increase the risk of sickness absence for CMD after 24 months of follow up (risk ratio (RR) 1.48, 95% robust standard error confidence interval (CI) 0.91-2.06) while offsets compared to remaining stably insecure resulted in a RR below 1 (RR 0.86 95% CI 0.31-1.40).

**Conclusion:** Rather than having a disciplining effect on employees, job insecurity predominantly appeared to act as a stressor with negative consequences on mental health and in extension sickness absence due to common mental disorders. However, findings were uncertain why alternative explanations cannot be ruled out.

Occupational epidemiology, Auditorium 35.01.44 - Building 35, June 12, 2024, 14:30 - 16:00

## Income in epidemiological research: a guide to measurement and analytical treatment for mental health and mortality studies

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**Background:** Income is one of the most widely used indicators of socioeconomic position in studies of health inequalities. Despite its frequent use, no empirical-driven guidelines on how to operationalize and analytically handle income exist. In this study, we develop straightforward step-by-step graphical guidelines based on a comprehensive comparative examination.

**Methods:** We followed the entire working-age population (ages 30-65) residing in Denmark in 2010 (n = 2,700,651) until death, diagnosis of either severe mental disorder, or anxiety/depression, respectively, or censoring. Adjusted hazard ratios were estimated for four tax-reported income measures, examining variations due to the handling of extreme values, income categorization, and reference categories, both overall and stratified by sex.

**Results:** Across all income measures and handling strategies, lower baseline incomes were consistently associated with an elevated risk of experiencing adverse health outcomes. As income approached zero, the degree of corresponding household assets exhibited a sharp increase with very high values at each end of the income spectrum. Associations with health outcomes varied mostly for the lowest income categories. The variations depended on the handling of extreme values, income categorization, and choice of reference category. Notably, income measures differed in the strength of associations with adverse outcomes with some differences in these patterns between males and females.

**Conclusion:** The findings emphasize the need for methodological clarity in income-based health research. The step-by-step graphical guidelines, informed by these findings, offer a methodological framework aiming to enhance the precision, comparability, and relevance of future studies exploring the association between income and health.

Social epidemiology II, Auditorium 35.01.06 - Building 35, June 12, 2024, 16:15 - 17:00

## Comprehensive Nationwide Study on Mental Health before, during, and after the COVID-19 Pandemic

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**Background:** The COVID-19 pandemic and lockdowns prompted a major concern for mental health effects. We aimed to conduct a longitudinal study on the mental health of an entire population during the COVID-19 pandemic adjusting for pre-pandemic trends.

**Methods:** We followed all individuals in Denmark between 1990 and 2023. The main outcomes were rates of psychiatric admissions, use of psychotropic medication, suicide attempts, suicides, referrals to psychiatric hospitals, and patients in community-based private psychiatry or psychology practices. The impact of the pandemic and lockdowns was assessed with log-normal models, reporting Rate Ratios (RR) of the observed and the counterfactual rates.

**Results:** During the pandemic (March 11, 2020–June 30, 2023), the rates of psychiatric admissions, suicide attempts, suicides, patients in private practices, and referrals were not significantly increased compared to the pre-pandemic trend. During the first lockdown (March 11–May 19, 2020), rates were lower for psychiatric admissions (RR: 0.85, 95% CI: 0.80 to 0.90, p-value <0.001), suicide attempts (RR: 0.80, 95% CI: 0.69 to 0.94, p-value: 0.007), suicides (RR: 0.67, 95% CI: 0.52 to 0.86, p-value: 0.002), patients in private practices (RR: 0.88, 95% CI: 0.82 to 0.93, p-value <0.001), and referrals (RR: 0.69, 95% CI: 0.60 to 0.81, p-value < 0.001) compared to the pre-pandemic trend. However, the rate of psychotropic medication users increased during the pandemic compared to the pre-pandemic trend (RR: 1.06, 95% CI: 1.05 to 1.06, p-value < 0.001).

**Conclusion:** The COVID-19 pandemic and lockdowns did not severely influence pre-pandemic trends of the mental health burden.

Mental health and psychiatric disorders, Auditorium 35.01.44 - Building 35, June 12, 2024, 16:15 - 17:00

## Latent risk factor profiles in the Norwegian adult population over time and their association with premature NCD mortality – the NCDNOR project.

Dr. Knut Eirik Dalene<sup>1</sup>, Simon Lergenmuller<sup>2</sup>, Erik Sund<sup>3,4</sup>, Steinar Krogstad<sup>3,4</sup>, Laila Hopstock<sup>5</sup>, Wenche Nystad<sup>1</sup>, Inger Kristin Larsen<sup>2</sup>, Ulf Ekelund<sup>1,6</sup>, Haakon Meyer<sup>7,8</sup>, Hein Stigum<sup>8</sup>, Vidar Hjellvik<sup>1</sup>, Lars Jøran Kjerpeseth<sup>1</sup>, Inger Ariansen<sup>1</sup>

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### Background

Several modifiable risk factors for non-communicable disease (NCD) have been established. Yet, knowledge on risk factor clustering patterns, temporal change in these patterns, and how they are related to NCD-mortality remains largely unknown.

### Methods

We used data from Norwegian populations-based health-examination surveys included in the NCDNOR project and Latent Profile Analysis to identify underlying groups of individuals ('clusters') with similar exposure to key NCD risk factors. In total, 576,299 participants (52% women) aged 20-65 had data on smoking, physical activity, body mass index, blood pressure, total cholesterol, and triglycerides, of which 186,665, 372,312, and 18,468 participated 1974-1989, 1990-2004, and 2005-2019, respectively. We used flexible parametric survival models to estimate restricted mean survival time (RMST) differences between clusters.

### Results

We identified four distinct clusters containing 44% ('Healthy'), 45% ('Sub-optimal'), 4% ('Dyslipidemics'), and 7% ('Hypertensives') of the full sample, respectively, with significant between-cluster differences in exposure to the risk factors considered and in RMST. Compared to the 'Healthy' cluster, the RMSTs of the other three clusters were 1.3 (95% confidence interval (CI): 1.2, 1.4), 6.9 [95% CI: 6.4, 6.9], and 5.8 (95% CI: 6.1, 5.4) years shorter, respectively. Despite changes in exposure to individual risk factors, the clustering pattern was consistent over time with four clusters identified in 1974-1989, 1990-2004, and in 2005-2019.

### Conclusion

This study provides new insights into the clustering of NCD risk factors among Norwegian adults, their impact on mortality, and the evolution of these clusters over time.

Mortality and cancer, Auditorium 35.01.06 - Building 35, June 14, 2024, 10:30 - 12:00

## The Association Between Having Adult Children and Survival After Colon and Rectal Cancer Among Older Adults: A Danish Register-Based Cohort Study

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**Background:** Prior research links social support to survival in colorectal cancer patients, but the specific impact of having adult children remains unexplored. This study aims to investigate this association.

**Methods:** The study included individuals over 60 years diagnosed with colorectal cancer between 2001 and 2021 born after 1935 (N=39,495). Cox regression models were performed with adjustment of birth cohort, age at diagnosis, sex, education, residence, and cohabitation status. Patients were followed 0-1 and 1-5 years post-diagnosis. The association between the number of children and the sex of the adult children and survival was examined among those with adult children (N=34,404).

**Results:** Compared to having adult children, not having adult children was associated with a 1.34 [95%CI 1.22;1.47] and 1.35 [95%CI 1.18;1.54] times higher hazard of death for colon and rectal cancer patients, respectively, 0-1 year post-diagnosis. The corresponding estimates for 1-5 years post-diagnosis were 1.08 [95%CI 0.99;1.18] and 1.26 [95%CI 1.13;1.40]. For colon cancer patients, having one child was associated with a higher hazard of death compared to having two children (0-1 year post-diagnosis: 1.15 [95%CI 1.05;1.26] & 1-5 years post-diagnosis: 1.08 [95%CI 1.00;1.17]). Having three or more children was neither associated with a higher nor lower hazard of death. There was no association between the sex of the children and death.

**Conclusion:** Older colorectal cancer patients without adult children had a higher hazard of death compared to those with adult children, particularly in the first year post-diagnosis. The study provides new insights into social networks in colorectal cancer survival.

Social epidemiology I, Auditorium 35.01.06 - Building 35, June 12, 2024, 14:30 - 16:00

## Early life psychosocial stress and risk of asthma, celiac disease and type 1 diabetes in children

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**Background:** Maternal psychosocial stress has been associated with risk of childhood asthma. We aimed to confirm this and test whether maternal psychosocial stress is associated with risk of two other immune-mediated diseases in children: type 1 diabetes and celiac disease.

**Methods:** We studied 91,000 mother-child pairs in the Norwegian Mother, Father and Child Cohort study (births 2000-2009). Information on anxiety/depression and negative life events was obtained from questionnaires in gestational week 30 and at child age 6 months. The outcomes were diagnosed type 1 diabetes (n=551; Norwegian Childhood Diabetes Registry) and celiac disease (n=1429; Norwegian Patient Registry) before age 18y, and asthma at 12y defined based on the Norwegian Prescription Database. We estimated relative risks (aRR) with 95% CIs per standard deviation score, using binary log-linear regression adjusting for maternal type 1 diabetes and celiac disease, age, parity, education, smoking and BMI.

**Results:** Previously published associations with asthma at age 7y were extended to age 12y. Maternal symptoms of depression/anxiety (aRR=0.91,95%CI:0.71-1.17) and negative life events reported during pregnancy (aRR=1.04,95%CI:0.96-1.12) were not associated with type 1 diabetes. The same was seen for celiac disease in the child, with an aRRs of 0.97,95%CI:0.84-1.12 for maternal depression/anxiety during pregnancy and aRR=1.02,95%CI:0.98-1.07 for negative life events. There were also no associations with maternal psychosocial stress during the child's first 6 months of life.

**Conclusion:** Maternal psychosocial stress during pregnancy and 6 months postnatally were not associated with risk of childhood onset type 1 diabetes or celiac disease.

Pediatric and perinatal Epidemiology, Auditorium 35.01.44 - Building 35, June 14, 2024, 10:30 - 12:00



## The ICH E9(R1) Estimand Framework in the Context of Real-World Data and Observational Studies

Lotte Husemoen<sup>1</sup>, Antonia Morga<sup>2</sup>, Antonio Remiro-Azócar<sup>3</sup>, Frank Kleinjung<sup>4</sup>, Khadija Rerhou Rantell<sup>5</sup>, Amel Besseghir<sup>6</sup>, Barbara Rosettani<sup>7</sup>, Arthur Allignol<sup>8</sup>, Tatsiana Vaitsiakhovich<sup>9</sup>, Pepa Polavieja<sup>10</sup>

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### Background

Despite growing interest in Real-World Data (RWD) from regulatory agencies, health technology assessors and payers, concerns over the credibility and relevance of observational studies persist. Transparency issues in communicating key study attributes hinder proper assessment and reduce these studies' utility in healthcare decision making. While the Target Trial Emulation (TTE) and PICO frameworks are well known to epidemiologists, regulators are more familiar with the estimands framework introduced by the ICH E9(R1) addendum. Therefore, bridges between these "languages" are needed to clearly communicate the clinical question of interest, as different stakeholders have different objectives.

### Methods

We aim to introduce the ICH E9(R1) estimand framework, highlight its practical implementation in observational studies using RWD, and explore its relationship with other frameworks such as PICO and the TTE approach.

### Results

The estimand framework comprises five attributes: target population, treatment condition, endpoint, population level summary, and strategies for handling intercurrent events. Like PICO, it is used to specify the study objective and research question. Unlike PICO, it also places emphasis on the summary measure and the definition and handling of intercurrent events occurring during follow-up, e.g. treatment discontinuation, switching or additional medication. Moreover, the estimand framework clearly differentiates the "what" from the "how", a distinction less evident in the TTE framework.

### Conclusion

The estimands framework assists researchers in clearly defining scientific questions. It strengthens communication across stakeholders about key study attributes, and helps to align study objective, design, conduct, statistical analysis, and interpretation. It complements the PICO and TTE approaches.

Statistical and epidemiological challenges and innovations, Auditorium 35.01.06 - Building 35, June 13, 2024, 13:15 - 14:45

## Successful decline but increasing socioeconomic gap in hip fracture incidence in Oslo, Norway

Senior Researcher Kristin Holvik<sup>1</sup>, Ruth Aga<sup>1,2</sup>, Anne Johanne Sjøgaard<sup>1</sup>, Haakon Eduard Meyer<sup>1,3</sup>

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**Background and aim:** The city of Oslo has historically experienced the world's highest hip fracture incidence, but several measures have been implemented during the last decade, including fall and fracture prevention programmes. We examined trends in hip fracture incidence in Oslo 2012-2022 by sex and education level.

**Methods:** Annually updated sociodemographic information for the dynamic population aged 70+ years in Oslo 2012-2022 from Statistics Norway was linked with hip fractures from the Norwegian Patient Registry. Sex-specific age-adjusted annual incidence rates by attained education (primary, secondary, or tertiary education) were estimated using Poisson regression.

**Results:** A total of 7,905 individuals suffered a hip fracture in the 11-year period. The incidence declined steeply in both genders. The lowest rates were observed in 2020, the year characterized by strict COVID-19 restrictions in Oslo. By then, incidence rates had declined by 38% in women and 37% in men since 2012. However, meanwhile, the educational gap in hip fracture incidence increased progressively in women ( $p=0.024$  for women,  $p=0.46$  for men). Incidence rates were lowest among those with tertiary education throughout the period, and the drop in 2020 was particularly pronounced for this group, with a weaker trend among those with primary or secondary education. By 2022, the rates had rebounded to pre-pandemic levels.

**Conclusion:** There was a dramatic decline in hip fracture incidence in Oslo during the last decade, which was clearly more pronounced than the national decline in this period. The COVID-19 restrictions appeared preventive for hip fractures particularly among women with high education.

Social epidemiology I, Auditorium 35.01.06 - Building 35, June 12, 2024, 14:30 - 16:00

## Prevalence, Patterns, and Risk of Comorbidities and Death in Cancer Patients: A Nationwide Norwegian Registry Study – the NCDNOR Project

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**Background and aim:** Improved survival after cancer diagnosis increases the vulnerability to comorbidities, posing challenges to healthcare systems. While studies have investigated prevalence of comorbidities in cancer patients, knowledge on patterns and future risk is limited. This study examines patterns of comorbidities at first primary diagnosis of breast, prostate, skin, colorectal and lung cancers and estimates the five-year post-diagnosis probabilities of comorbidities (secondary cancers, cardiovascular diseases (CVD), chronic respiratory diseases (COPD), diabetes, and mental disorders (MD)) and death.

**Methods:** We included 270,223 individuals aged  $\geq 18$  years registered with a primary cancer in the Cancer Registry of Norway between 2009-2019, and comorbidities in other mandatory national health registries included in the NCDNOR project. Comorbidity patterns at diagnosis were analyzed using intersection diagrams, and future probabilities estimated through a multistate framework.

**Results:** Comorbidity prevalence at diagnosis ranged from 35%–83% and was highest in lung cancer patients. CVD was the most prevalent comorbidity, often co-occurring with MD, diabetes, or COPD. Comorbidity patterns differed by cancer type, age, and sex, with reduced prevalence in younger patients and women. Five years post-diagnosis, probability of death ranged from 6%–88%, and the probability of living with one, two, or  $\geq$ three comorbidities from 3%–38%, 5%–18%, and 3%–6%, respectively. CVD remained the most likely comorbidity, followed by MD and COPD.

**Conclusion:** In this study on patterns and risk of comorbidities and death in cancer patients, we showed a high variation in comorbidity burden by cancer type, age, and sex, emphasizing the need for tailored healthcare approaches.

Mortality and cancer, Auditorium 35.01.06 - Building 35, June 14, 2024, 10:30 - 12:00

## Exact confidence intervals for interval censored rates with small counts

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### Background and aim

Due to privacy concerns, data custodians prohibit reporting of small counts although relevant in studies of rare side-effects. For example, The Danish Health Data Authority requires counts between 1 and 4 events (both included) to be reported as “N<5”. Reporting a count of zero is allowed. We aim to provide exact confidence intervals for rates with small interval censored counts.

### Methods

“N<5” represents an interval censored observation. Since no information about the actual count may be revealed, one must assume that all four values are equally likely to have occurred. From this, we implement numerical computation of 95% confidence intervals (CI) for rates. We compare the limits with those obtained assuming the count is either 1 or 4. We show how the method can be applied with other interval censorings as well.

### Results

The 95% CI for a rate with “N<5” reported can be found as (0.100000078; 8.726159480) divided by the person-time at risk. For “N<3” the corresponding values are (0.050020345; 6.607959747). Assuming an observation of 500 person-years risk time and a count of “N<5”, the 95% CI of the rate is (0.2; 17.5) per 1,000 person-years. Using extreme values of 1 and 4, the limits of the 95% CI would be (0.05; 20.5) per 1,000 person-years.

### Conclusion

We provide precise intervals for rates, when the actual count of events may not be disclosed. Intervals are narrower than reporting an interval based on extreme values of the interval censored count.

Statistical and epidemiological challenges and innovations, Auditorium 35.01.06 - Building 35, June 13, 2024, 13:15 - 14:45

## Potential avoidable mortality among adults with intellectual disability

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### Background

Individuals with intellectual disabilities (ID) face pronounced health disparities and evidence shows a significantly higher mortality rate within this group. The aim of this study is to assess avoidable mortality patterns among persons with ID.

### Methods

This study is based on a Danish nationwide cohort of adults (aged 18-74 years) with ID (n=57,663) and an age- and sex-matched reference cohort (n=571,446) which was established by linkage between several registers. The cohorts were followed in the Register of Causes of Death between 2000 and 2021. Causes of death were categorized into preventable, treatable, or non-avoidable deaths using the OECD/Eurostat classification. We compared the observed and expected number of deaths by calculating standardized mortality ratio (SMR).

### Results

Among persons with ID the number of deaths was 9,400 whereof 5,437 (58%) were avoidable. SMR for preventable deaths, e.g. by reducing smoking and alcohol intake or by vaccination, was 2.63 (95CI, 2.51-2.73), and SMR for treatable deaths, e.g. by earlier diagnosis and treatment, was 6.00 (5.72-6.29). Non-avoidable mortality was also six-fold increased (SMR=6.03; 5.84-6.22). Preventable deaths were higher for persons with mild ID compared to severe ID, while treatable and non-avoidable mortality were highest for persons with severe ID.

### Conclusion

The study confirmed that individuals with ID have an amplified risk of mortality across all categories. There is an exigent need for health policy reforms and reasonable adjustment making it as easy for people with ID to access health promotion programs and health care services as it is for others.

Mortality and cancer, Auditorium 35.01.06 - Building 35, June 14, 2024, 10:30 - 12:00

## Infant mortality after assisted reproductive technology treatment – a Nordic collaborative study on 7,947,575 liveborn children

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### Background

An increasing proportion of children are born after assisted reproductive technology (ART) treatments. ART-conceived children have an increased risk of preterm birth and low birth weight, mainly due to higher twin birth rates among ART-children. ART-singletons carry an increased risk of poor perinatal outcomes compared to their naturally conceived (NC) counterparts. This study examines infant mortality after ART vs NC.

### Methods

A Nordic registry-based liveborn cohort of 171,836 ART-children and 7,775,739 NC-children from Denmark (1994–2014), Finland (1990–2014), Norway (1984–2015) and Sweden (1985–2015) was followed from livebirth until death, emigration, or one year of age. Among ART-children, 74% were singletons and 25% twins, and among NC-children 97% were singletons and 3% twins. Multiples with >2 children were excluded (<0.1%). Infant mortality was compared for ART- vs NC-singletons and ART- vs NC-twins using Cox proportional hazards regression yielding hazard ratios (HRs) with 95% confidence intervals (95% CIs).

### Results

Overall, 515 (4‰) ART- and 26,076 (3‰) NC-singletons and 615 (14‰) ART- and 3317 (17‰) NC-twins died during infancy. Median age at death was 3 (IQR 0–195) and 10 days (IQR 0–245) for ART- and NC-singletons, respectively, and 1 (IQR 0–151) and 2 days (IQR 0–161) for ART- and NC-twins, respectively. Adjusting for country, parity, maternal age, and birth year, the HR was 1.75 (95% CI 1.60–1.91) for ART-singletons vs NC-singletons, and 0.94 (95% CI 0.86–1.03) for ART-twins vs NC-twins.

### Conclusions

Infant mortality is rare among both ART and NC. Further studies should address mechanisms explaining the higher mortality in ART- vs NC-singletons.

## Sequential safety monitoring of drugs: a tool for prospective drug safety monitoring

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### Background

Large administrative healthcare databases can be used for near real-time sequential safety monitoring of drugs as an alternative approach to traditional spontaneous reporting based pharmacovigilance.

### Aim

We aimed to build and empirically test a prospective drug safety monitoring setup.

### Methods

We used Danish population-based health registers and performed sequential analysis of rofecoxib use and cardiovascular outcomes using a case-time-control and cohort study designs from January 2000 to September 2004. Each monitoring period added 6 months of data until the end of study period. In the case-time-control study, incident cases of myocardial infarction (MI) and ischemic stroke were identified and matched with up to 5 time-controls on age, sex, and calendar time. Exposure status on the date of diagnosis was assessed using a 60-day focal window with reference windows 120, 180 and 240 days prior to the diagnoses. In the cohort study, incident users of rofecoxib were matched up to 1:4 with ibuprofen users (active comparators) using high dimensional disease risk scores and were followed for 60 days.

### Results

The earliest association of rofecoxib use and risk of MI was seen in study period 2 for both study designs. However, a more precise association was seen in study period 4 onwards (cumulative OR1.39; 95%CI 1.06-1.83) for case-time-control and in study period 9 onwards (cumulative RR1.26; 95%CI1.01-1.56) for cohort study designs.

### Conclusion

Our prospective drug safety monitoring setup using the case-time-control design effectively showed that the risk of MI could have been established as early as two years after rofecoxib launch.

Statistical and epidemiological challenges and innovations, Auditorium 35.01.06 - Building 35, June 13, 2024, 13:15 - 14:45

## Life course socioeconomic position and cardiovascular disease: The combined influence of shared family factors, cognitive ability, and risk factors

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**Background:** Cardiovascular diseases (CVD) have been related to the number of times people experience social disadvantage over their life course, yet the combined influence of early life family factors, cognitive ability in addition to risk factors on this relationship has not been evaluated. We estimated CVD risk by life course socioeconomic position (SEP) and assessed the relationship before and after accounting separately and combined for within siblings, cognitive ability, and risk factors.

**Methods:** Norwegian citizens born between 1940 and 1960 having at least one sibling (n= 827 926) were included. Participants from conscription and Norwegian health surveys were analyzed in sub-cohorts. SEP was an index of 20 indicators from Statistics Norway, and categorized into four categories. Cox proportional hazards models were used, following participants from age 55 to the first event of fatal/non-fatal CVD or the end of 2020.

**Results:** Life course SEP was linearly related to CVD risk. Those in the lowest SEP group had 40 % (HR 1.40 (95% CI: 1.24-1.57) higher risk of CVD events compared to those in the highest. This attenuated to 30 %, 18 %, and 24 % when accounting for cognitive ability, within siblings and CVD risk factors separately. When accounting for all jointly, the increased risk was reduced to 10 %.

**Conclusion:** Life course SEP had a graded relationship with the risk of CVD events which was to a large extent attenuated by accounting for family factors, cognitive ability, and risk factors. This provides a comprehensive assessment of likely causal mechanisms.

Life course epidemiology, Auditorium 35.01.44 - Building 35, June 13, 2024, 13:15 - 14:45



## Social disparities in multimorbidity of noncommunicable diseases in Norway 2010-2020 – an emerging challenge in a single-disease-focused healthcare system. Data from the NCDNOR project.

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**Background/aim:** The cooccurrence of  $\geq 2$  noncommunicable diseases (NCD multimorbidity) is reportedly increasing worldwide, disproportionately affecting socioeconomically disadvantaged populations. The prevalence in Norway is largely unknown, however. Therefore, we have estimated the prevalence in Norway, overall and in relation to socioeconomic factors, of  $\geq 2$  of the following NCDs: cancer, cardiovascular disease (CVD), chronic obstructive pulmonary disease (COPD), asthma, diabetes, mild/moderate mental disorder, major mental disorder, and substance use disorder.

**Methods:** The study population was all Norwegian residents  $\geq 20$  years in 2010. Using linked data from nationwide registries on primary and specialist care, deaths and dispensed drugs, we estimated their prevalence of  $\geq 2$  NCDs in 2010 and 2020. Results were stratified by sex, age group, own/maternal education (low/medium/high), and combinations of education and income (quartiles).

**Results:** We included 3,537,421 residents. Multimorbidity prevalence increased across all age groups from 2010 (12.4% overall) to 2020 (28.6% overall). Both in 2010 and 2020, prevalence was incrementally higher with higher age and lower education (own and maternal). Within each level of education, individuals in the lowest income quartile had a higher prevalence than those in the highest income quartile. Main contributors to multimorbidity were mental disorders, substance use disorder and asthma in younger age, changing towards cancer, CVD, COPD and diabetes with increasing age. Sex differences were small for overall prevalence, socioeconomic gradient, and contribution of different NCDs to multimorbidity.

**Conclusion:** The prevalence of NCD multimorbidity in Norway is high and followed a clear socioeconomic gradient, representing an emerging challenge for our single-disease-focused healthcare system.

Social epidemiology I, Auditorium 35.01.06 - Building 35, June 12, 2024, 14:30 - 16:00

## Occupation and long-term decline in lung function: A large population study from Norway

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**Background:** Most research evaluating the relationship between occupational titles and lung disease has been done by cross-sectional studies. New estimates are also required because preventive measures have been implemented. Our aim is to investigate long-term decline in lung function across job titles in the general population in Norway.

**Methods:** Population-based study in Norway including two surveys: a baseline survey (2005-2007) and a follow-up survey (2017-2019). Our sample included 3854 adult workers (1676 men, mean age at baseline 41.6 years, age range 20-55 years), who attended both surveys, providing longitudinal data with about 11-year follow-up. We used mixed model analysis to investigate the relationship between occupational titles (white-collar workers as reference category) and decline in forced expiratory volume in one second percent predicted (FEV1% (GLI-2012)) during the 11-year follow-up. We adjusted for age, sex, and smoking.

**Results:** In the total sample (N=3854 workers), mean FEV1% at baseline and follow-up was 98.8% and 97.4%, respectively. Certain occupations, such as drivers, mobile plant operators, and agricultural workers, experienced a greater fall in FEV1% during the 11-year follow-up period when compared to the reference group of white-collar workers. Among agricultural workers, 46% and 36% reported respiratory problems at work at baseline and follow-up, respectively, whereas the corresponding numbers for white-collar workers were 17% and 11%.

**Conclusions:** In Norway, some workers continue to be at risk for lung diseases related to their jobs. This should lead to focused interventions. However, there were modest differences between occupations, suggesting that Norway's preventive efforts are effective.

Occupational epidemiology, Auditorium 35.01.44 - Building 35, June 12, 2024, 14:30 - 16:00

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