P20. Night shift work and sleep quality in a prospective cohort of female nurses.

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Background: Though the acute effects of night-shift work on sleep quality directly after the shift are well described, less is known about the chronic effects of night-shift work on sleep. We conducted a study in which we associated frequency and cumulative years of working in night shifts with multiple proxies for sleep duration and quality, including lifetime sleep medication use.

Methods: The Nightingale study is a Dutch prospective cohort study among 59,947 female nurses. We assessed the association between ever and recently working night shifts and sleep duration, sleep quality (measured using the MOS Sleep scale), and lifetime use of sleep medication and melatonin. We explored trends of all outcomes with cumulative years of working in night shifts and average frequency of night shifts worked per week.

Results: We observed an elevated odds ratio (OR) of lifetime use of sleep medication for nurses that ever worked night shifts (OR 1.24 CI 1.13, 1.35) or that recently worked night shifts (OR 1.13 CI 1.05, 1.22). The odds ratio for melatonin use was also elevated for nurses that ever or recently worked night shifts, respectively 1.55 (CI 1.40, 1.71) and 1.72 (CI 1.59, 1,86). The OR for lifetime use of sleep medication increased with cumulative years of conducting night-work and with average frequency of night shifts per week (p-value for trend <0.001 for both). Working night shifts was not related to non-optimal self-reported sleep length and sleep quality in our study.

Discussion: We observed an association between (years and intensity of) night-shift work and lifetime use of sleep medication or melatonin. As no effect was observed with our direct measures of sleep quality, our results suggest that the use of prescribed and over the counter medication at least partly mitigate potential negative effect of night shift work on sleep quality.

P22. Associations between night shift work and weight change within the Nightingale Study.

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Background: Night shift work has been associated with increased risk of diabetes and cardiovascular disease, which may be (partly) explained by weight gain following night work. This study prospectively examines associations of different domains of night shift work with weight change.

Methods: The Nightingale Study, a cohort study among 59947 Dutch female nurses, was designed to study adverse health outcomes associated with night shift work exposure in detail. At baseline (2011), participants (median age 49) completed a questionnaire including job history. A follow-up questionnaire (2017), was completed by 63% of the cohort. Associations of night work with weight change (kilogram) and development of overweight/obesity (≥25kg/m2) between 2011 and 2017 were assessed using linear and logistic regression analyses, adjusted for age (baseline).

Results: Women who never worked night shifts on average gained 3.51 kg (sd 5.52) during follow-up, while women who ever worked nights gained 3.62 kg (sd 5.75) (p=.16). At baseline 7959 women worked night shifts. Compared with women who had worked night shifts for 1-9 years at baseline, weight gain increased 0.52 kg (95% CI 0.16-0.88) and 0.64 kg (95% CI 0.22-1.06) for those with durations of 10-19 years and 20+ years, respectively. Compared with never night workers, women with healthy weight who worked night shifts at baseline, had an OR of 1.19 (95% CI 1.06-1.34) for developing overweight/obesity. Overweight women working night shifts showed an OR of 1.33 (95% CI 1.10-1.59) for developing obesity.

Conclusion: Night shift work status and duration were associated with a slightly increased risk of weight gain and developing overweight/obesity. Our findings may contribute to understanding mechanisms underlying cardiometabolic risks resulting from night shift work.

P23. Night shift work and risk of colorectal cancer: results from a prospective cohort study among 59,947 female nurses in the Netherlands.

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Background: Shift work that involves night work has been classified as probably carcinogenic, among others due to the suppression of melatonin secretion. Although experimental studies suggest that melatonin inhibits proliferation of intestinal tumors, epidemiological evidence for a relationship between night work and colorectal cancer (CRC) risk is lacking.

Methods: We prospectively examined the association between night work exposure and CRC in the Nightingale study. In 2011, 59,947 Dutch female nurses completed a questionnaire, including lifetime occupational history with detailed information on night shift work. Up to July 2021, 321 CRC cases were recorded through linkage with the Netherlands Cancer Registry. We excluded participants with prevalent cancer. Data were analyzed using a complete case approach. Age-adjusted hazard ratios (HR) and 95% confidence intervals (CI) for associations between night work variables (ever/never night shifts, duration, cumulative no. night shifts) and CRC risk were estimated using Cox regression.

Results: The analysis included 56,830 nurses, of whom 81% ever worked night shifts with a mean duration of 11.9 years and a mean of 5.4 night shifts per month. Night work duration was missing in 27% and cumulative no. night shifts in 30% of the participants. Compared with nurses who never worked night shifts, the risk of CRC for nurses who ever worked night shifts was not increased (HR=1.19; 95%CI=0.88-1.59; p=.26). Neither increasing night work duration (1-9, 10-19, or 20+ years) nor an increase in cumulative no. night shifts (in tertiles: min. 12 to max. 13,104 nights) was associated with CRC risk.

Conclusion: Our preliminary results suggest that lifetime night work exposure is not associated with increased CRC risk in female nurses. Longer follow-up time and multiple imputation of missing exposure variables may alter our risk estimates. Updated results including multiple imputation, adjustment for confounders, and assessment of dose-response effects will be presented at WEON.

P24. Socio-economic participation of persons with hemophilia: results from the sixth Hemophilia in the Netherlands study.

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Background: Treatment availability and comprehensive care have resulted in improved clinical outcomes for persons with the congenital bleeding disorder hemophilia. Recent data on socio-economic participation of this patient group in the Netherlands are lacking. As part of the sixth nationwide 'Haemophilia in the Netherlands' (HiN) study we assessed participation in education, in the labor market and social participation for persons with hemophilia compared with the general male population.

Methods: Dutch adults and children (5-75 years) of all hemophilia severities (n = 1009) participated in a questionnaire that included socio-demographic, occupational and educational variables. Clinical characteristics were extracted from electronic medical records. General population data were extracted from Statistics Netherlands. Social participation was assessed with the PROMIS Ability to Participate in Social Roles and Activities short form, with a minimal important difference (MID) set at 1.0.

Results: Data from 906 adults and children were analysed. Participation in education was higher than in the general male population for persons aged 20-24 years (68%; 95% CI: 57-79, general male population: 53%). Educational attainment was higher compared to Dutch males, especially for severe hemophilia. Absenteeism from school was more common than in the general population. The employment-to-population ratio (64.3%; 95% CI: 58.6-70.0) and occupational disability (14.7%; 95% CI: 10.5-18.9) were worse for severe hemophilia compared to the general population (73.2% and 4.8%, respectively), but similar to the general population for non-severe hemophilia. Unemployment was 5.4% (95% CI: 3.5-7.3; general male population: 3.4%). Absenteeism from work was less common than in the general male population (37.7%; 95% CI: 31.4-43.9 vs. 45.2%). Mean PROMIS score was similar to or higher than in the general population (54.2 vs. 50).

Conclusion: Likely as a result of comprehensive care, socio-economic participation of persons with non-severe hemophilia was similar to the general male population. Some participation outcomes for persons with severe hemophilia were reduced.

P36. Approaches to estimating clearance rates for Human Papillomavirus groupings: a systematic review and real data examples.

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Background: The clearance rate (CR) is an important metric for quantifying human papillomavirus (HPV) clearance. Approaches to estimating CRs for HPV groupings differ between studies. We aimed to identify the approaches used in literature to estimating grouped HPV CRs. Moreover, we investigated whether these approaches resulted in different estimations of CRs using data from existing studies.

Methods:In this systematic review, articles were included if they reported CRs of HPV groupings. Identified approaches were applied to data of the HAVANA cohort, comprising of adolescent girls, and H2M cohort, comprising of men who have sex with men. CRs were estimated for six HPV groupings: bivalent-, quadrivalent- and nonavalent vaccine-types, and low-risk-, high-risk- and any HPV.

Results: From 26 articles, 54 theoretically possible approaches to estimating CRs were identified. These approaches varied regarding the nature of infections included (i.e., prevalent/incident), and the definition of clearance events and person-time. Application of the nine most used approaches to HAVANA (n=1,394) and H2M (n=745) cohorts demonstrated strong variation in CR estimates depending on the approach used. For example, for grouped high-risk HPV in the H2M cohort, CRs ranged from 52.4 to 120.0 clearances/1000 person-months. CRs also varied in the HAVANA cohort, but differences were less pronounced; CRs ranged from 24.1 to 57.7 clearances/1000 pm.

Conclusions: Various approaches to estimating CR of HPV groupings are used in literature and these yielded different CR estimates in our data-example. These differences depended on the study population. We advise clear reporting of methodology and urge caution in comparing CRs between studies.

P37. Towards more efficient multi-arm exercise trials in oncology: application of a Bayesian adaptive decision-theoretic approach.

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Purpose: Efficient designs are needed to reduce sample sizes and costs of trials comparing multiple complex treatments. This study illustrates a Bayesian adaptive decision-theoretic design using a multi-arm exercise oncology trial.

Methods: In the PACES trial, 230 women with breast cancer receiving adjuvant chemotherapy were randomized to a supervised resistance and aerobic exercise intervention (OnTrack), a homebased physical activity program (OncoMove) or usual care. Data was re-analyzed using a Bayesian adaptive decision-theoretic approach incorporating interim analyses for trial continuation after every stage of 36 patients. Endpoint for the re-analyses was dose modifications (any versus none). We considered a symmetric setting aiming to identify the arm with the lowest proportion of patients requiring dose modifications, and an asymmetric setting aiming to identify exercise arms with an absolute risk reduction in dose modifications of ≥10% compared to usual care. Interim decisions for continuation were based on expected absolute increases in the probability of a correct decision in the next stage, with continuation thresholds of 1% and 0.1%. Settings with and without early dropping of arms were considered.

Results: Dose modifications occurred in 34% of patients in the usual care and OncoMove arms versus 12% in OnTrack. Frequentist analysis showed these proportions to be statistically significant (p=0.002). Using the 0.1% continuation threshold, the Bayesian adaptive decision-theoretic analyses required 72 patients to identify OnTrack as the most effective arm in the symmetric setting. In the asymmetric setting, 144 patients were required to identify OnTrack as the only exercise arm superior to usual care.

Conclusion: A Bayesian adaptive decision-theoretic approach was shown to substantially reduce the sample size of a three-arm exercise oncology trial. This design is worth considering for multi-arm trials.

P38. Associations between late-onset preeclampsia and the use of calcium-based antacids and proton pump inhibitors during pregnancy: a prospective cohort study.

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Background: Preeclampsia is one of the leading causes of maternal morbidity and mortality. Calcium-based antacids and proton pump inhibitors (PPIs) are commonly used during pregnancy to treat symptoms of gastroesophageal reflux disease. Both have been hypothesized to reduce the risk of preeclampsia. We aimed to determine the associations of calcium-based antacid and PPI use during pregnancy with late-onset preeclampsia, taking into account dosage and timing of use.

Methods: We included 9,058 pregnant women participating in the PRIDE Study (2012-2019) or pREGnant (2014-2019), two prospective cohorts in The Netherlands. Data were collected through web-based questionnaires and obstetric records. We estimated risk ratios (RRs) for late-onset preeclampsia for any use and trajectories of calcium-based antacid and PPI use before gestational day 238, as well as hazard ratios for time-varying exposures after gestational day 237, adjusted for a minimally sufficient set of confounders and weighted using inverse probability of censoring weights.

Results: Late-onset preeclampsia was diagnosed in 2.6% of pregnancies . Any use of calcium-based antacids (RR 1.2 [95% CI 0.9-1.6]) or PPIs (RR 1.4 [95% CI 0.8-2.4]) before gestational day 238 was not associated with late-onset preeclampsia. However, use of low-dose calcium-based antacids in gestational weeks 0-16 (<1g/day; RR 1.8 [95% CI 1.1-2.9]) and any use of PPIs in gestational weeks 17-33 (RR 1.6 [95% CI 1.0-2.8]) seemed to increase the risk of late-onset preeclampsia. We did not observe any associations between late-onset preeclampsia and use of calcium-based antacids and PPIs after gestational day 237.

Conclusions: In this prospective cohort study, use of calcium-based antacids and PPIs during pregnancy was not found to reduce the risk of late-onset preeclampsia.

P39. Distribution of absolute risks provided by prediction models developed using supervised machine learning.

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Background: Prediction models are used extensively in healthcare to support diagnosis and prognosis, as well as to guide treatments. Regression techniques, such as logistic regression, were traditionally use for model building, however, over the past years, machine learning models have gained considerable popularity. While several studies suggest that machine learning could outperform traditional statistical models at population level, few studies have compared the distribution of individual risks across commonly used supervised machine learning algorithms.

Methods: We used individual participant data from prospective diagnostic studies of patients suspected of deep vein thrombosis (DVT) to develop five models. The outcome was the presence of DVT at initial assessment. We a-priori selected the following predictors for inclusion in the model: age, sex, d-dimer, previous history of DVT, alternative diagnosis, and cancer. As modeling technique, we selected logistic regression (LR), random forest (RR), support vector machine (SVM), extreme gradient boosting (XGBoost), and neural networks (NN). We compared discrimination, calibration, and distribution of individual risk prediction between models. All statistical analyses were performed in R version 4.0.3 with R base, rms, pROC, and caret packages.

Results: Among the 10,002 included patients, 1875 (19%) were confirmed cases of DVT. All five models achieved similar discrimination (AUC 0.82). However, models were often miscalibrated for higher predicted probabilities. Absolute risks provided by the SVM model were often close to the prevalence of DVT in our dataset.

Conclusion: Previous research found considerable uncertainty on absolute risks prediction when generated by regression-based models. This study found that commonly used machine learning models could yield different individual risk predictions. Our findings indicate the importance of assessing the reliability of individual risk predictions across different modeling techniques, before further validation.

P40. Prenatal risk factors for Alzheimer's Disease-related brain pathology.

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Background: Adverse exposures during prenatal development may impact the developing brain, preventing it from developing to its full potential. This may limit the reserve capacity of the brain, a structural buffer encompassing brain size and neuronal numbers, which can compensate for the neurodegeneration associated with Alzheimer's disease in late life. The prenatal environment may play an essential role in determining the risk for developing Alzheimer's disease. In this systematic review, we created an overview of the current evidence for the association between prenatal exposures and structural brain measures related to Alzheimer's disease in humans.

Methods: MEDLINE and Embase were systematically searched to identify studies in humans that reported one or more prenatal exposure(s) in association with whole brain volume, temporal lobe volume and/or hippocampal volume measured with structural magnetic resonance imaging at any age of outcome assessment. Risk of bias was assessed using the Newcastle Ottawa Scale, and we followed PRISMA reporting guidelines.

Results: We identified 81 eligible studies in the following prenatal exposure categories: alcohol (N=31), maternal smoking (N=7), drugs (N=14), mental health problems (N=7), maternal diet (N=8), medical conditions (N=10), infections (N=6) and environmental exposures (N=3). Evidence for an association with whole brain volume, hippocampal volume, and/or temporal lobe volume was found for maternal smoking, prenatal opioid and cocaine exposure, nutrient shortage, placental function, maternal anemia, rhesus/ABO incompatibility, pre-eclampsia and prenatal alcohol exposure. Most of these associations were negative, pointing at hampered brain development (% difference between -4 and -22%).

Conclusion: Our results substantiate the association between adverse prenatal exposures and smaller whole brain, temporal lobe and hippocampal volumes. These smaller volumes suggest lower brain reserves after adverse prenatal exposures, potentially increasing the risk of developing Alzheimer's disease in later life. Our findings underline the importance of the prenatal environment in shaping the risk for late-life neurodegenerative disease.

P41. Associations of maternal urinary bisphenol and phthalate concentrations with offspring reproductive development.

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Background: The endocrine-disrupting chemicals bisphenols and phthalates are among the most produced chemical compounds worldwide. Fetal exposure to bisphenols and phthalates may influence the development of reproductive system, potentially leading to an effect on infant reproductive abnormalities, ovarian and testicular development and pubertal development. OBJECTIVES: We examined the associations of maternal gestational urinary bisphenols and phthalates with offspring reproductive development from infancy until 13 years.

Methods: In a population-based, prospective cohort study of 1059 mother-child pairs, we measured maternal urinary bisphenol and phthalate concentrations in each trimester. Information on cryptorchidism or hypospadias after birth was obtained from medical records. At 9.7 years, we measured testicular and ovarian volume by MRI. At 13.5 years, we measured child Tanner stages and age at first menstruation through questionnaire. We performed analyses for boys and girls separately.

Results: In boys, no associations of maternal phthalate or bisphenol concentrations in pregnancy with offspring cryptorchidism and hypospadias were found. Higher maternal gestational high-molecular-weight phthalate and total bisphenol concentratoins, but not phtalic acid or low-molecular weight phthalate concentrations, were associated with larger child testicular volume at 10 years (p-values<0.05). Higher maternal phthalic acid and total bisphenol concentrations were associated with faster offspring genital development and pubic hair development at 13 years, respectively (p-values <0.05). In girls, we found no associations of maternal urinary bisphenol and phthalate concentrations with ovarian volume or menstrual age. Only higher maternal gestational urinary high-molecular-weight phthalate concentrations were associated with faster pubic hair development (p-value<0.05), but not with breast development at 13 years.

Conclusion: Higher maternal urinary concentrations of phthalates and bisphenols throughout pregnancy are associated with sex-specific alterations in offspring pubertal development, with pronounced effects among boys. These effects on puberty might contribute to the development of adverse long-term health effects.

P42. Impact of extreme temperatures on birth outcomes in the Netherlands: a nationwide population-based study.

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Background: Adverse birth outcomes have been highlighted in the literature as one of the potential health effects of extreme weather events related to climate change. Nevertheless, little is still known on the effect of such weather events —specifically, extreme temperatures— on birth outcomes. The aim of this study is to investigate the effects of prenatal exposure to extreme temperatures on birth outcomes, i.e., low birth weight, small-for-gestational-age (SGA), and preterm birth, using nationwide registry data from the Netherlands.

Methods: Retrospective population-based cohort study including over 2 million singleton births occurred in the Netherlands between 2003 and 2017. Daily weather measurements were linked to the perinatal registry using maternal postcode. To address the existence of nonlinearities and threshold effects in temperature we used a temperature-bins approach based on daily maximum temperature. Logistic regression models accounting for maternal characteristics, weather conditions and underlying trends were used to investigate the effect of temperature on birth outcomes. Interaction terms were used to investigate heterogeneity in the effect across levels of neighbourhood socioeconomic status (SES).

Results: This study finds that spending an additional day in the gestational period with a temperature above 28 °C, relative to a day in the 8–12 °C range, increases the risk of LBW (OR[95%CI]= 1.005[1.003-1.007]) and preterm birth (OR[95%CI]= 1.007[1.005-1.009]). We did not find a detrimental effect of extreme temperature on SGA. We found that the observed effect was driven by exposure during the third trimester. The effect was most detrimental for women living in low SES neighbourhoods.

Conclusion: We found that exposure to extreme temperature during pregnancy increases the risk of adverse birth outcomes in the Netherlands. The effect was more pronounced for women in low SES areas. The projected increases in extreme temperatures may further exacerbate socioeconomic health disparities in early life.

P43. Associations between the urban exposome and type 2 diabetes: A penalised regression by LASSO and a deep learning approach.

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Background: Type 2 diabetes (T2D) is a chronic disease with high individual and societal burden. Risk of T2D is partly driven by urban characteristics, such as air pollution, or indirectly through their influence on lifestyle behaviours. Environmental characteristics are generally studied individually in their association with T2D, but occur simultaneously in real life, potentially in nonlinear and non-additive ways. We therefore took a holistic approach and aimed to identify which factors of urban exposome predict T2D by applying a variable selection method by penalized regression LASSO and an artificial neural networks (ANN) approach to assess nonlinear associations.

Methods: A cross-sectional analysis was conducted using baseline data from 14,829 participants of the Occupational and Environmental Health Cohort study living across the Netherlands. Self-reported questionnaire data was used to define participants diagnosed with T2D (n=676(4.6%)). Geocoded exposures linked to individual home addresses of 86 environmental characteristics were estimated, including air pollution, traffic noise, green-space, chemicals in drinking water, built environmental and neighborhood socio-demographic characteristics. Nested cross-validation was used to determine the optimal model parameters of both approaches (ANN and LASSO), and the cross-validated predictive accuracies were compared. LASSO was followed by a stability selection procedure. The complete results of the ANN model will be added later.

Results: Living in neighborhoods with higher average home values was associated with a lower risk of being diagnosed with T2D (b=-0,26, stability selection probability=0,96). Residents of neighborhoods where the outdoor temperature was higher during heatwaves had a higher risk of T2D (b=0,04, p=0.81). Higher risk of T2D was also associated with living in highly urbanized neighborhoods (b=0,16, p=0.69) or in neighborhoods with a higher share of non-Western immigrants (b=0,05, p=0.52).

Conclusion: Neighborhood socio-economic characteristics, as well as the outdoor temperature is associated with the risk of T2D. Further investigation is required to explore the underlying mechanisms.

P44. Ethnic and socioeconomic inequalities in relation to air pollution exposure in the Netherlands.

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Background: Air pollution (AP) contributes to a large disease burden and some populations are disproportionately exposed. It is unclear to what extent AP exposure differs across ethnic groups in the Netherlands and how this intersects with socioeconomic position (SEP). First, we aimed to identify differences in AP exposure between ethnic groups in the Netherlands. Second, we examined the interrelationship between ethnicity and SEP in relation to AP exposure.

Methods: We assessed exposure to AP at the home address for all registered residents of the Netherlands in 2019. AP concentrations were estimated by dispersion models of the National Institute of Public Health and the Environment (RIVM). Exposure estimations of particulate matter smaller than 10 or 2.5 micrometer (PM10, PM2.5), nitrogen dioxide (NO2), and elemental carbon (EC) were linked to demographic data gathered by Statistics Netherlands. Absolute and relative differences in AP exposure across ethnic groups were assessed. We evaluated whether ethnicity, SEP, age, gender, and urbanicity were associated with AP exposure and tested for interactions.

Results: The total group consisted of 17,277,817 participants, a quarter of whom had a migration background. The mean(SD) exposure concentrations (µg/m3) were: PM2.5 10.1(1.1); PM10 17.6(1.5); NO2 17.5(4.3); EC 0.6(0.1). For the 40 largest minority ethnic groups, mean concentrations of all pollutants were higher than for ethnic Dutch, with up to 1.4-fold differences for NO2. Non-Dutch ethnicity, SEP, urbanicity, age and gender were associated with AP exposure. There was a significant interaction between ethnicity and SEP, indicating that the association between SEP and AP exposure differed by ethnic group.

Conclusion: Exposure to PM10, PM2.5, NO2, and EC was consistently higher in minority ethnic groups compared to ethnic Dutch. The association between SEP and AP exposure was dependent on ethnicity. Further research is needed to understand the health implications of these inequalities and to design mitigation policies.

P47. Clinical prediction models for mortality in COVID-19 patients: an external validation and individual participant data meta-analysis (COVID-PRECISE).

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Objective: To externally validate existing prognostic models for predicting short-term mortality in patients admitted to hospital for SARS-CoV-2 infection.

Design: Two-stage individual participant data meta-analysis.

Setting: Secondary and tertiary care.

Participants: 46,914 patients across 18 countries, admitted to a hospital with a PCR confirmed SARS-CoV-2 infection.

Data sources: Multiple (clustered) cohorts in five continents, previously identified by a living systematic review of COVID-19 prediction models, or through PROSPERO, reference checking or expert knowledge.

Model selection: Prognostic models identified by the living systematic review and through contacting experts. We excluded models that had a high risk of bias in the participant domain of PROBAST or poor applicability.

Outcome measures: 30-day or in-hospital mortality.

Methods: We identified and validated eight existing prognostic models that use clinical characteristics or laboratory test results. We performed a two-stage individual participant meta-analysis of the estimated model concordance (c)-statistic, calibration slope, and observed vs expected ratio (O:E) across the included clusters.

Results: The heterogeneity of most performance estimates across clusters was large. The 4C Mortality Score by Knight et al. (pooled c-statistic .80, 95% prediction interval [PI] .72 to .86) and the clinical model by Wang et al. (pooled c-statistic .77, 95% PI .63 to .87) had the highest discrimination. We observed on average 29% fewer deaths than predicted by 4C (pooled O:E 0.71, 95% PI 0.21 to 2.39), 35% fewer than predicted by the Wang et al. model (pooled O:E 0.65, 95% PI 0.23 to 1.89), and 4% fewer than predicted by the Xie et al. model (pooled O:E 0.96, 95% PI 0.21 to 4.28).

Conclusion: The prognostic value of the included models varied greatly between the included data sources. The 4C Mortality Score by Knight et al. and the clinical model by Wang et al. appeared most promising, although local adjustments are needed.

P49. Multidimensional health status assessment of COVID-19 survivors at three and twelve months after hospital discharge: a monocentre retrospective cohort study.

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Background: SARS-CoV-2, the pathogen responsible for COVID-19, has been first detected in the Netherlands in February 2020. While the vast majority of COVID-19 patients recovers from the acute phase within 4 weeks, around 20% of COVID-19 survivors still experiences symptoms such as dyspnoea, fatigue and mental problems twelve months after infection. However, to what extent subjective as well as objective health complaints persist in the long-term and are mutually associated, remains largely unknown. Therefore, the aim of this monocentre retrospective cohort study is to describe the multidimensional health status of COVID-19 survivors visiting an outpatient clinic at three and twelve months after hospital discharge.

Methods: All COVID-19 patients admitted to the VieCuri Medical Centre between February 2020 and December 2020 were invited to the outpatient clinic visit at three and twelve months after hospital discharge. Multiple health variables were assessed at the outpatient clinic including pulmonary- and heart function, pulmonary abnormalities using chest CT-scans, blood markers, and general complaints according to the Federation of Medical Specialists standards. Multiple logistic and linear regression models were used to analyse the association between subjective and objective health outcomes at three and twelve months follow-up.

Results: First analyses showed that pulmonary abnormalities were present in 226 of the 278 COVID-19 survivors at three months after hospital discharge, with reticulation being the most dominant pattern (43%). Additionally, 104/270 patients and 18/56 patients showed a disturbed cardiac rhythm at three months and twelve months follow-up, respectively, with sinus bradycardia being the most common feature (16% and 17%, respectively).

Conclusion: Pulmonary abnormalities were seen in COVID-19 survivors at three months follow-up, whereas cardiac rhythm disturbances were still present at three and twelve months after hospital discharge. Further analyses will be done to describe the association between subjective and objective health outcomes at three and twelve months follow-up.

P50. Primary health care contact preceding the diagnosis of peripheral artery disease: do women present themselves differently than men before being referred to a specialist?

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Background: Women with peripheral artery disease (PAD) are often underdiagnosed, present themselves at their first visit with more advanced disease, and fare worse than men.

Objective: To investigate to what extent potential differences exist between women and men in the frequency of, and reasons for contact with a GP 6 months preceding PAD diagnosis as potential indicators of delay, and determine at what point the number of consultations differs.

Methods: Sampled from the Julius General Practitioner's Network, patients older than 18 years with PAD were included and compared with a reference. We applied a zero-inflated negative binomial (ZINB) regression model to compare the number of GP contacts between men and women in the two cohorts. Subsequently, the reasons for GP contact were compared.

Results: The study population comprised 4044 patients with PAD (43.5% women) and 10486 participants in the reference population (46.3% women). The number of GP contacts for a woman with PAD was 2.70 (95% CI: 2.42, 3.02). For a man, this decreased by 0.94 (CI: 0.87, 1,01); thus, the number of GP contacts in them was 2.54 (CI: 2.29, 2.82).
In the reference cohort, the number of GP contacts for a woman was 1.77 (95% CI: 1.62, 1.94) and decreased by 0.92 (CI: 0.87, 0.98) in men; so, men had 1.63 (CI: 1.50, 1.78) GP-contacts. 21.9% of GP contacts occur in the one month before referral for PAD.

Conclusions: Six months preceding the referral due to PAD, patients visit the GP more often than similar patients without a PAD. There were no differences between sex. Therefore, the underdiagnosis of PAD in women could not be explained by a delay in presentation to the GP.

P51. Sex differences in the relationship between New York Heart Association functional classification and survival in cardiovascular disease patients:
A mediation analysis of exercise capacity.

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Background: The New York Heart Association (NYHA) class has extensively been used for risk stratification in patients with cardiac symptoms, although its prognostic value differs between sexes and disease entities. The ability to exercise might explain the association between NYHA classification and survival. The aim was to assess to what extent sex-differences in exercise capacity explain the association between NYHA classification and survival in patients suspected of cardiovascular disease.

Methods: Electronic health record data from 7259 patients with cardiovascular symptoms was analysed. All patients had a documented NYHA class and underwent cardiac stress electrocardiography. A sex-stratified mediation analysis was performed to assess to what extent the proportional heart rate and workload during stress testing explained the association between NYHA classification and survival.

Results: In men, increments in NYHA class were related to higher mortality (NYHA II vs III/IV: hazard ratio [HR] 1.59 vs 3.64, referenced to NYHA I), whilst in women those with NYHA class II and III/IV had a similar mortality risk (HR 1.49 vs 1.41). The association between NYHA class and survival was mostly explained by the proportional workload (men vs women: 22.9%, 95% CI: 18.9%-27.3% vs 40.3%, 95% CI: 28.5%-68.6%) and less by proportional heart rate (men vs women: 2.5%, 95% CI: 1.3%-4.3% vs 8.0%, 95% CI: 4.1%-18.1%). Post-hoc analysis highlighted that NYHA classification explained a minor proportion of the association between proportional workload and mortality (men vs women: 15.1%, 95% CI: 12.0%-18.3% vs 4.4%, 95% CI: 1.5%-7.4%).

Conclusion: A significant mediation was observed in both sexes on the association between NYHA classification and mortality by proportional workload. The effect explained by NYHA classification on the association between survival and proportional workload is small. This implies that the NYHA classification is not a sole representation of a patient's functional capacity, but extends to their overall health status.

P52. Association of intima-media thickness measured at the common-carotid artery with incident carotid plaque: Pooled analysis of 20 prospective studies.

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Background: The association between common-carotid artery intima-media thickness (CCA-IMT) and incident carotid plaque has not been characterised fully. To provide clarity, we undertook an individual-participant-data meta-analysis of prospective studies from the Proof-ATHERO consortium to precisely quantify the relationship between CCA-IMT and development of carotid plaque.

Methods: Studies from the Proof-ATHERO consortium that recorded baseline CCA-IMT and incident carotid plaque were eligible for inclusion. We excluded participants with a history of cardiovascular disease or pre-existing carotid plaque at baseline. Study-specific odds ratios for incident carotid plaque were combined using random-effects meta-analysis.

Results: We analysed data from 21,494 individuals in 20 studies (mean age 56 years [standard deviation 9]; 55% female; mean baseline CCA-IMT 0.71 mm [standard deviation 0.17]). Over a median follow-up of 5.9 years (5th-95th percentile 1.9-19.0), 8,278 individuals developed first-ever carotid plaque. Baseline CCA-IMT was approximately log-linearly associated with the odds of developing carotid plaque. The age-, sex-, and trial arm-adjusted odds ratio for carotid plaque per standard deviation higher baseline CCA-IMT was 1.40 (95% confidence interval 1.31-1.50; I2=63.9%). The corresponding odds ratio further adjusted for ethnicity, smoking, diabetes, body mass index, systolic blood pressure, low-density and high-density lipoprotein cholesterol, and lipid-lowering and antihypertensive medication was 1.34 (1.24-1.45; I2=59.4%; 14 studies; 16,297 participants; 6,381 incident plaques). We observed no significant effect modification across clinically relevant subgroups. Sensitivity analysis restricted to studies defining plaque as focal thickening yielded a comparable odds ratio (1.38; 1.29-1.47; I2=57.1%; 14 studies; 17,352 participants; 6,991 incident plaques).

Conclusion: Our large-scale individual-participant-data meta-analysis demonstrates that CCA-IMT is associated with the odds of developing first-ever carotid plaque, independent of traditional cardiovascular risk factors.

P53. Intima-media thickness at the near or far wall of the common-carotid-artery in cardiovascular risk assessment.

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Background: Current guidelines recommend measuring carotid intima-media thickness (IMT) at the far wall of the common-carotid-artery (CCA). However, available evidence from prospective cohort studies on the association with disease risk is conflicting. To provide clarity, we reliably quantify associations of near vs. far wall CCA-IMT with cardiovascular risk and their added predictive values.

Methods: We analyzed participant-level data of 16 prospective studies from the Proof-ATHERO consortium. We pooled study-specific hazard ratios for cardiovascular disease (CVD, defined as coronary heart disease or stroke) using random-effects meta-analysis.

Results: Individual records were available for 41,941 participants (mean age 61 years [SD=11]; 53% female; 16% with history of CVD; 10,423 CVD events, median follow-up 9.3 years). Mean baseline values of near and far wall CCA-IMT were 0.83 (SD=0.28) and 0.82 (SD=0.27) mm, differed by a mean of 0.02 mm (95% limits of agreement: -0.43 to 0.46) and were moderately correlated (r=0.44; 95% CI: 0.39-0.49). Near and far wall CCA-IMT were both approximately linearly associated with CVD risk. The respective hazard ratios per SD higher value were 1.18 (95% CI: 1.14-1.22; I^2=30.7%) and 1.20 (1.18-1.23; I^2=5.3%) when adjusted for age, sex, and history of CVD, and 1.09 (1.07-1.12; I^2=8.4%) and 1.14 (1.12-1.16; I^2=1.3%) in a multivariable adjusted model (all P<0.001). Assessing CCA-IMT at both walls provided a greater C-index improvement than assessing CCA-IMT at one wall only (+0.0046 vs. +0.0023 for near [P<0.001] or +0.0037 for far wall [P=0.006]).

Conclusion: The associations of near and far wall CCA-IMT with incident CVD were positive, approximately linear, and similarly strong. Improvement in risk discrimination was highest when CCA-IMT was measured at both walls.

P54. Medication prevalence in CHD patients in South America: systematic review and meta-analysis.

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Background: Coronary heart disease (CHD) is the most common cause of death globally, and clinical guidelines recommend the long-term use of cardioprotective medications in CHD patients for secondary prevention. Suboptimal use of these medications has been reported, but information from South America is scarce.

Methods: We conducted a systematic review on prevalence of CHD secondary prevention medication in South America. We searched in the databases PubMed, Embase, Cochrane, LILACS and SciELO for original articles reporting the prevalence of medication use in patients with established CHD. Cardioprotective medication classes included anti-platelet drugs, lipid-lowering drugs, antihypertensives, oral hypoglycaemics and insulin. Two independent reviews screened the articles on eligibility criteria. They also assessed the publications' risk of bias with a tool for prevalence studies that rates the fields study design, study population, participation rate, participant's characteristics, and outcome.
We meta-analysed the estimates of medication use prevalence from individual studies per class of medication using mixed meta-regression models. We also used mixed meta-regression models to analyse time-trends in medication use (with study year as co-variate); and factors associated with medication use (with sex, time since discharge, diagnosis category, urban region, and care setting as co-variates). Furthermore, we summarized the information on compliance to clinical guidelines reported in the studies.

Results: The search resulted in 7388 publications, from which 73 were included in the review. Medication prevalence varied by class: beta-blockers 73.4%(95%CI 66.8%–79.1%), ACEI/ARBs 55.8%(95%CI 49.7%–61.8), antiplatelets 84.6%(95%CI 79.6%–88.5%), aspirin 85.1%(95%CI 79.7%–89.3%) and statins 78.9%(95%CI 71.2%–84.9%). The use of beta-blockers, ACEI/ARBs and statins increased since 1993. Medication use was lower in community, public and rehabilitation settings compared to tertiary centres. Ten publications reported low medication use and nine reported adequate use.

P55. Women who smoke at the start of pregnancy are more likely referred to an obstetrician during pregnancy and birth: results from a cohort study.

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Background: Women who smoke during pregnancy make less use of prenatal care; the relation between smoking behavior and the use of other forms of maternal healthcare is unknown. The objective of this study is to investigate the association between women's smoking behavior and their use of healthcare during pregnancy, birth and six weeks postpartum.

Methods: We analyzed data from the Dutch Midwifery Case Registration System (VeCaS), period 2012-2019. We included women with a known smoking status, singleton pregnancies, and who had their first appointment before 24 weeks of gestation with a primary care midwife. We compared three groups: non smokers, early stoppers (stopped smoking in first trimester), and late- or non-stoppers (stopped smoking after first trimester or continued smoking). Descriptive statistics were used to report maternal healthcare utilization, statistical differences between the groups were calculated with Kruskal-Wallis tests. Multivariable logistic regression was conducted to assess the association between smoking behavior and referrals to primary or secondary care.

Results: We included 41 088 pregnant women. The groups differed significantly on maternal healthcare utilization. The late- or non-stoppers initiated prenatal care later and had less face-to-face consultations with primary care midwives. Compared to the non smokers, the early- and late- or non-stoppers had significant higher odds of referral to the obstetrician during pregnancy and birth. Postpartum, the odds of referral to the obstetrician were lower for the early- and late- or non-stoppers compared to the non smokers.

Conclusion: Although the early- and late- or non-stoppers initiated prenatal care later than the non smokers, they did receive adequate prenatal care. The results suggest that not smoking during pregnancy may decrease the odds of referral to secondary care. This indicates that smoking cessation already before pregnancy could affect the odds referral to secondary care.

P56. Diet, lung function level, lung function decline and respiratory symptoms in the Lifelines Cohort Study.

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Background: Associations between diet and respiratory health are widely investigated. However, generalizability of previous studies is limited by restricted study populations. Using Lifelines' general-population data, we investigated the cross-sectional and longitudinal associations between diet and lung function level, lung function decline and the prevalence, development, and remission of respiratory symptoms.

Methods: To investigate the association between diet and lung function level (FEV1, FVC, FEV1/FVC) or respiratory symptoms (wheeze, cough, phlegm, dyspnea, bronchitis) at baseline we included 87,436 and 128,154 adults respectively. In analyses on lung function decline and symptom development/remission after 4 years of followup we included 17,578 (≥ 30 years) and 76,269 adults. Diet was defined using the Lifelines Diet Score (LLDS) ranging from 0-48 with higher scores indicating healthier diet. Linear and logistic regression analyses adjusted for age, sex, height, SES, smoking status were used to test associations between LLDS and lung function level/decline and respiratory symptom prevalence/development/remission.
Results: There were significant positive associations between LLDS and lung function level across FEV1: 5.36 (4.79; 5.93), FVC: 5.19 (4.53; 5.85) and FEV1/FVC: 0.03 (0.02; 0.04). Higher LLDS was associated with less decline in FEV1: 0.26 (0.12; 0.40) and FVC: 0.25 (0.06; 0.44). Higher LLDS was significantly associated with a lower prevalence of all respiratory symptoms, as well as with lower development of cough, phlegm and bronchitis, and higher remission of wheeze, cough and phlegm.

Conclusions: Healthier dietary intake is associated with higher lung function level, less lung function decline, and lower prevalence of respiratory symptoms. Our findings highlight the relevance of diet in maintaining and promoting respiratory health. These results are useful in informing dietary guidelines for both general and patient populations.

P57. The mediation of health behaviors in the association of depression and anxiety with the risk of cancer: An individual participant data meta-analysis.

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Background: Although the behavioral mechanisms underlying the associations between depression, anxiety and cancer are highly plausible, few studies have empirically investigated whether and to what extent these associations can be explained by health behaviors. We aimed to examine mediation by health behaviors in the associations between depression, anxiety and the risk of overall cancer, and breast, prostate, lung, colorectal, smoking-related and alcohol-related cancers.

Methods: A two-stage individual participant data meta-analysis was performed based on 14 cohorts within the Psychosocial Factors and Cancer Incidence (PSY-CA) consortium that had a measure of depression or anxiety (N = 330,914, person years = up to 2,965,559, cancer incidences = 26,590). Health behaviors included smoking, physical activity, alcohol use, BMI, sedentary behavior and sleep. In stage one, path-specific regression estimates and their variances and covariances were obtained in each cohort. In stage two, output from each cohort was pooled using random-effects multivariate meta-analysis, and natural direct, natural indirect and total effects were calculated.

Results: Smoking, low physical activity and sedentary behavior mediated the total effects of depression and anxiety on lung and smoking-related cancers. Although total effects of depression and anxiety on incidence of overall cancer and other types of cancer were not statistically significant, there seemed to be mediation of health behaviors taking place in these associations, especially through smoking, alcohol use, low physical activity and a higher BMI.

Conclusion: Health behaviors, especially smoking, constitute prominent mediating pathways linking depression and anxiety to the risk of cancer. Promoting healthy behaviors is warranted for persons with depression or anxiety to lower their risk of cancer.

P58. Accelerometer-derived physical activity and sedentary time and cardiac biomarkers.

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Background: Cardiac biomarkers (troponins and NT-proBNP) are the standard for assessing cardiac injury. Chronically elevated cardiac biomarkers are associated with adverse outcomes like lower event-free survival. Physical activity may lower cardiac biomarkers. We investigated the relationship between amount and pattern of physical activity and sedentary time and cardiac biomarkers.

Methods: In the population-based Maastricht Study (n=2370, 51.3% male, 28.3% T2D) we determined cardiac biomarkers (hs-cTnI, hs-cTnT,NT-proBNP). Physical activity and sedentary time were measured by activPAL and divided into quartiles (quartile 1 (Q1) served as reference). The weekly pattern of moderate-to-vigorous physical activity and coefficient of variation was calculated. Linear regression analyses were conducted with adjustment for demographic, lifestyle, and cardiovascular risk factors.

Results: Higher amounts of total physical activity was associated with lower levels of hs-cTnI (Q2) and hs-cTnT (Q2). Higher levels of light intensity physical activity were associated with lower levels of hs-cTnI (Q2 and Q3) and with higher levels of hs-cTnT (Q4). Further, those with the highest levels of vigorous intensity physical activity had significantly higher levels of hs-cTnI and lower levels of NT-proBNP. Compared to the least sedentary, those in Q3 had significantly lower levels of hs-cTnI and individuals in Q2 and Q3 had lower levels of hs-cTnT.
The physical activity patterns, weekend warriors and regularly actives were associated with lower levels of NT-proBNP but not with hs-cTnI and hs-cTnT. Higher coefficient of variation was association with lower levels of hs-cTnI and higher levels of NT-proBNP, but not with hs-cTnT.

Conclusion: Physical activity and sedentary time were not consistently associated with cardiac biomarkers. However, a minimum of 150 minutes of moderate-to-vigorous physical activity was associated with less NT-proBNP. Furthermore, there was an association between the coefficient of variation and NT-proBNP, implying that more regularity of moderate-to-vigorous physical activity during the week is associated with lower levels of NT-proBNP.

P59. Participant recruitment and at-home-measurement of cardiometabolic markers: Challenges, costs, and key learnings from the Supreme Nudge parallel cluster-randomised controlled supermarket trial.

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Background: Recruitment and retention of participants for healthy lifestyle programs is known to be challenging. Insights from previous projects are therefore valuable, but rarely reported. We will present key learnings on the costs, feasibility and results of utilized recruitment strategies and insights on the feasibly of at-home-measurement of cardiometabolic markers, as part of the Supreme Nudge supermarket trial, promoting healthy lifestyle behaviours. This trial was conducted during the Covid-19 pandemic, which required adaptation to a contactless approach.

Methods: Participants were recruited from socially deprived areas around participating supermarkets (n=12). Further eligibility criteria included aged 30-80 years, being regular shopper at a participating supermarket, and speaking of the Dutch language. All utilized recruitment strategies, costs, and yields were logged, together with success rates in completion of at-home measurements (HbA1c, lipid profile and waist circumference).

Preliminary results: In total, 784 individuals registered for participation, 602 were eligible and 421 completed informed consent. Most participants were recruited via letters/flyers received at home (75%) and flyers received at the supermarket (12%). Less frequent reported strategies were in-store recruitment by a researcher (8%), news items (7%), word-of-mouth (6%), and social media (4%). Of paid strategies, flyers in the supermarket were the cheapest per participant included through this method (12 Euros) and least time-invasive for research staff (<1 hour), while most expensive were social media campaigns (194 Euros) and mailing of letters/flyers (89 Euros). In-store recruitment was high in staff hours per included participant (9 hours) as well as costs (50 Euros). The at-home-measurement of cardiometabolic markers was successfully completed for 89% (lipid profile), 95% (HbA1c) and 99% (waist circumference) of participants.

Conclusion: Utilizing a wide range of recruitment strategies which vary in required staff hours and cost is crucial in reaching a target population in socially deprived areas. At-home-measurement of cardiometabolic markers can be feasible.

P60. Longitudinal associations of adherence to World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) and Dutch Healthy Diet (DHD) recommendations with kynurenines in colorectal cancer survivors after treatment.

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Background: Studies have suggested that the tryptophan-kynurenine pathway, in which several nutrients are involved, might be related to the health-related quality of life in colorectal cancer (CRC). Emerging evidence indicates a plausible link between the diet and kynurenines. This study describes longitudinal associations of adherence to the dietary recommendations of the World Cancer Research Fund and the American Institute for Cancer Research (WCRF/AICR) and the Dutch Healthy Diet (DHD) recommendations with plasma kynurenines in CRC.

Methods: In a prospective cohort of stage I-III CRC survivors (n=247), three repeated measurements were executed at 6 weeks, 6 months and 1-year post-treatment. Dietary intake was measured using seven-day dietary records. Adherence to the WCRF/AICR dietary and DHD recommendations were operationalised into scores ranging from 0-5 and 0-140, respectively. An extensive panel of nine kynurenines was analysed in plasma using liquid chromatography-tandem mass spectrometry (LC/MS-MS). Linear mixed models adjusted for sociodemographic, clinical and lifestyle factors were used to analyse longitudinal associations between adherence to the dietary recommendations and kynurenines.

Results: Higher adherence to the DHD recommendations was associated with significantly lower HK concentrations (standardised beta (95%CI): -0.09; -0.16,-0.01), a lower kynurenine:tryptophan ratio (KTR, -0.08; -0.15,-.01), a lower hydroxykynurenine ratio (HKr, -0.09; -0.17,-0.02), and a higher 3-hydroxyanthranilic acid:HK ratio (HAA/HK, 0.12; 0.04,0.19). No significant associations were observed between adherence to the WCRF/AICR dietary recommendations and kynurenines.

Conclusion: Our results suggest that higher adherence to the DHD recommendations is associated with more favourable concentrations of HK, KTR, HKr and HAA/HK ratio. Analyses on individual dietary components are ongoing to further elucidate the association between diet and kynurenines in CRC survivors.

P61. Cumulative risks of false positive recall and screen detected breast cancer after seven rounds of screening.

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Background: Breast cancer screening has been shown to reduce breast-cancer mortality, but is also associated with harms. It is, therefore, important to provide balanced, high-quality information to enable women to make an informed decision about participating. Since most women make a decision about participation and adhere to this for future invitations, presenting risks from multiple screening rounds is crucial.

Methods: This study included women invited for their first screening round in 2005. Individual screening data from 2005-2018 were gathered via the Netherlands Comprehensive Cancer Organisation on subsequent screening rounds. Survival analyses were used to calculate cumulative risks for a false-positive (FP) and a true positive (TP) result. Also, the detection and participation rate were calculated for women with a history of FP results.

Results: Data from 114931 women were analysed. Of the women who were invited seven times, 63% participated in all rounds. Over these seven rounds, the cumulative risk of a TP result was 4% and the cumulative risk of a FP result was 10%. In the rounds after a FP result, the detection rate was 58% higher compared to women with true negative (TN) screening outcomes. Also, women with a history of a FP result more often had another FP outcome (68 vs. 35 per 1000). However, participation was lower in the round following a FP result (72-81%) compared to the round following a TN result (91-93%).

Conclusion: Over the course of seven screening rounds in the Dutch breast cancer screening program, women had a 4% chance of a screen-detected breast cancer and a 10% chance of at least one FP result. The detection rate and the number of new FP results was higher among women with previous FP than in women with previous TN results, while the participation was lower.

P62. Optimizing the set of pairs of radiologists that double read screening mammograms.

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To investigate how radiologist performance characteristics can be leveraged to determine the optimal set of pairs of radiologists for the double-reading of screening mammograms.
We retrospectively analyzed two datasets of screening examinations of women who underwent mammography in Sweden and the United Kingdom (UK). The examinations were double read and for our study any examination that was flagged by either radiologist was classified as abnormal. Cancer detection rates (CDR) and abnormal interpretation rates (AIR) were evaluated for individuals and pairs. The individual radiologists were divided into four performance categories involving CDR and AIR, using the group average as cut-off for each metric. Therefore, radiologists were classified into high CDR & low AIR (HL), high CDR & high AIR (HH), low CDR & low AIR (LL), or low CDR & high AIR (LH). Random pair performance, for which any type of pair was equally likely, was compared to the performance of specific pairings.
For both datasets, the CDRs for the specific pairings were not statistically significantly different from the CDR from the random pairings. Some AIRs did show significant differences. Compared to random pairings, pairing strategies with opposite AIR radiologists resulted in a significant AIR reduction of 3.4% and 2.9% for the Swedish and UK dataset, respectively. The pairing strategy with fully opposite performance characteristic radiologists resulted in a significant 10.3% AIR reduction when compared to random pairing for the Swedish dataset but was not significant for the UK dataset.
Pairing radiologists based on their performance characteristics, as opposed to randomly, may improve grouped screening performance. Compared to random pairings, pairing strategies involving radiologists with opposite AIR characteristics reduced AIR with no significant loss in CDR. Depending on what type of readers and how many of them are involved, the feasibility of using performance metrics to pair radiologists may be considered.

P63. Determinants of extremely dense breast tissue.

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Background: High mammographic density is a risk factor for breast cancer and limits the detection of cancer with mammography. We aimed to clarify the inconsistencies regarding risk factors for mammographic density.

Methods: 2820 women with extremely dense breasts and 1206 age-matched women with entirely fatty breasts were recruited from the Dutch mammography screening program. Data on risk factors were collected by self-report questionnaires. Associations between risk factors and mammographic density were examined by multivariable logistic regression models.

Results: Women with a higher BMI (per 1-unit increase) were less likely to have extremely dense breasts (OR, 0.53; 95% CI, 0.51-0.55). Women <12 years at menarche were less likely to have extremely dense breasts than those ≥14 years (OR, 0.59; 95% CI, 0.40-0.88). Nulliparous women were more likely to have extremely dense breasts than parous women (OR, 1.79; 95% CI, 1.32-2.44). Premenopausal women were more likely to have extremely dense breasts than postmenopausal women (OR, 11.40; 95% CI, 6.67-19.30). Physically inactive women had the same risk of extremely dense breasts as physically active women (OR, 0.92; 95% CI, 0.51-1.65). Women who smoked >20 pack-years had the same risk of extremely dense breasts as women who never smoked (OR, 1.04; 95% CI, 0.72-1.50). Women who consumed >10 glasses/week alcohol had the same risk of extremely dense breasts as women who abstained from alcohol (OR, 0.89; 95% CI, 0.55-1.44).

Conclusion: This study supports existing evidence that BMI, parity and menopausal status are determinants of mammographic density. Additionally, this study clarifies that older age at menarche is a risk factor for mammographic density, and physical activity, smoking and alcohol consumption are not.

P64. The gap between rare and common cancers still exists: results from a population-based study in the Netherlands.

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Background: Epidemiological discrepancies between rare and common cancers exist, and studies on the burden of rare cancer compared to common cancer are scarce. The aim of this population-based study was to compare rare versus common adult solid cancers in the Netherlands, by providing incidence, prevalence and survival rates, evaluating trends in survival, and comparing individual entities within domains and families.

Methods: All adult patients with rare and common malignant solid cancers in the Netherlands between either 2010-2019 or 1995-2019 were identified from the Netherlands Cancer Registry. Data on patient, tumour, and treatment characteristics were collected, and relative survival and survival trends were analysed.

Results: A total of 170,628 patients with rare adult solid cancers and 806,023 patients with common adult solid cancers were included. Rare cancers accounted for 18% of all cancer diagnoses (mean incidence), and 15% of the total ten-year cancer prevalence during 2010-2019. Overall 5-year survival was worse for rare cancers than for common cancers (52.0% vs. 68.7%). Between 1995-1999 and 2015-2019, 5-year survival rates for rare cancers increased to a lesser extent (from 46.2% to 52.6%, i.e., 6.4%) than for common cancers (56.9% to 70.1%, i.e., 13.2%), and for most rare cancer domains compared to common cancer domains. The majority of rare cancer entities did not show an improvement in 5-year survival. Differences for individual entities between domains and families were found

Conclusion: Differences in survival between rare and common cancers indicate major challenges for rare cancer care and emphasize that improvement is highly needed. Observed inequalities need to be overcome by investing in early diagnosis, novel therapies, scientific research, and in establishing centres of expertise.

P65. Discontinuation of infliximab treatment in patients with inflammatory bowel disease: a comparison between patients who retransitioned to originator and those who remained on biosimilar.

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Background: Many inflammatory bowel disease (IBD) patients in clinical care transitioned from infliximab originator to biosimilar. However, some patients retransition to originator (stop biosimilar and reinitiate originator). Whether this unsatisfactory treatment response is related to the product or to the patient and disease is unclear. We aimed to compare the risk of infliximab discontinuation between patients who retransition to originator and those who remain on biosimilar.

Methods: IBD patients who transitioned from infliximab originator to biosimilar were eligible for inclusion. Patients who retransitioned to infliximab originator (index date) were included in the retransitioning cohort and matched with maximum 3 patients who remained on biosimilar (biosimilar remainder cohort). Patients were matched on: hospital, transitioning date and duration of biosimilar treatment until index date.
Patients were followed from index date until discontinuation of infliximab. Risk of discontinuation (overall discontinuation, switching to another biological or discontinuation without switching) was compared with conditional Cox proportional hazards model, adjusted for age, gender, duration of infliximab originator use and other biologicals used before infliximab.

Results: Baseline characteristics of the retransitioning cohort (n=42) and the biosimilar remainder cohort (n=120) were similar, but dosing interval was shorter in the retransitioning cohort (44 versus 56 days). Infliximab discontinuation after 12 months was 25.0% in the retransitioning cohort and 8.8% in the biosimilar remainder cohort. Retransitioned patients had twofold increased risk of discontinuing infliximab (adjustedHR 2.2, 95% CI 1.1-4.3) compared with patients remaining on biosimilar. Risk of switching (adjustedHR 8.1, 95%CI 0.9-71.1) was higher than discontinuing without switching (adjustedHR 1.7, 95%CI 0.8-3.8).

Conclusions: Retransitioned patients have a twofold increased risk for infliximab discontinuation, including switching and discontinuing without switching. Thus, retransitioning is mainly patient- or disease-related and less likely product-related.

P66. Introducing the International Society for Pharmacoepidemiology Dutch student chapter.

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Background: Network-building while studying pharmacoepidemiology facilitates opportunities for future research and enriches students' prospects following graduation. From the listed ISPE student chapters, 2 institutions (out of 28) are located in Europe, of which one partly located in the US. This demonstrates a gap in opportunities for pharmacoepidemiology students in Europe to engage with each other.

Objectives: To establish and raise awareness of the Dutch ISPE student chapter and facilitate pharmacoepidemiologic research collaborations between students.

Methods: A screening was conducted of universities in the Netherlands that provide pharmacoepidemiology and epidemiology study programmes, followed by an enquiry to selected departments for their interest in a Dutch ISPE student chapter. Next, additional participants were contacted through snowball sampling. In teleconference meetings, the participants established the mission, vision, and outline of activities of the student chapter. A summary of activities of the student chapter will be shared as part of the Annual Report of ISPE student chapters.

Results: Out of 17 research universities in the Netherlands, 5 were identified as potential institutions hosting pharmacoepidemiology PhD students: University of Groningen, Utrecht University, Erasmus University Medical Center, Leiden University Medical Center and Maastricht University. They were contacted; PhD students from the University of Groningen (n = 1) and Utrecht University (n = 4) participated in the initial call and drafted an outline of the aims of the student chapter. In addition, they approached participants from personal networks to join. Students from each aforementioned university joined the initiative, and prepared the application submission and a plan to engage additional universities.

Conclusions: Setting up the Dutch student chapter has established a foundation for pharmacoepidemiology students across 5 institutions to engage with each other, with ongoing recruitment of students. Over the coming years, the student chapter aims to expand its network and cement the activities undertaken to support growing collaborations.

P67. The first opioid prescription and the prescribers of opioids after knee and hip arthroplasty.

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Background: Opioids are frequently prescribed after arthroplasty surgery, also in the Netherlands. This may increase the risk of opioid adverse effects. Therefore we aimed to describe the first prescribed opioid and the prescribers of opioids after knee and hip arthroplasty (KA/HA) between 2013-2018. Furthermore, we evaluated the association between the first prescribed opioid and the total amount of prescribed opioids and long term opioid use in the first postoperative year.

Methods: The Dutch Foundation for Pharmaceutical Statistics (SFK) was linked to the Dutch Arthroplasty Register (LROI). Stratified for KA/HA the first out of hospital opioid within 30 days of operation was assessed. The first opioid prescription was quantified as median morphine milligram equivalent (MME). Opioid prescribers were categorized: orthopedic surgeon, general practitioner (GP), and other. Long term opioid use was defined as ≥1 opioid prescription after 90 days. We used linear and logistic regression analyses controlled for confounders.

Results: 46,106 KAs and 42,893 HAs were included. After KA the first opioid prescription changed from tramadol to oxycodon between 2013-2018. Oxycodon increased from 44% to 85%, the MME of the first prescribed opioid remained the same. The MME of the first opioid prescription was associated with the total MME in the first postoperative year, but not with long term use, a 1% increase in MME resulted in a 0.5% increase in total MME. The orthopedic surgeon more often prescribed the first prescription, 44% of the prescriptions in 2013 to 69% in 2018. Consecutive prescriptions were mostly prescribed by GPs (>50%). Similar results were found after HA.

Conclusion: Oxycodon increased as a first prescription between 2013-2018. The first prescribed opioid was associated with an increase in the total MME in the first postoperative year. First prescriptions were mostly prescribed by an orthopedic surgeon, while consecutive prescriptions came from GPs.

P68. Preoperative opioid prescriptions before total knee and hip arthroplasty: a nationwide cohort study.

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Background: To determine the preoperative opioid prescription rate and their prescribers in patients one year prior to total knee or hip arthroplasty (TKA/THA) between 2013 and 2018, a nationwide study was performed.

Methods: The Dutch Foundation for Pharmaceutical Statistics (SFK) was linked to the Dutch Arthroplasty Register (LROI). All analyses were stratified for joint (knee/hip). Opioid prescription rates were given as defined daily dosages (DDD) and morphine milligram equivalent (MME). Opioid prescriptions were calculated per week and per operation year based on the time of prescription. Opioid prescribers were assessed per preoperative quarter and the prescribers were divided in the following categories: general practitioner (GP), orthopedic surgeons, rheumatologists, and others.

Results: 40,989 TKAs and 42,689 THAs were included. In 2013, 25% of TKA patients received ≥1 opioid prescription in the year before arthroplasty, this increased to 28% in 2018. For THA these numbers increased from 25% to 31%. In the year before TKA the prescription rates increased from 8.2 DDDs/person year (PY) to 10.4 DDDs/PY, mainly due to oxycodone prescriptions (0.9DDD/PY to 3.1DDD/PY). All other opioids remained relatively stable. When opioid exposure was expressed as MME/PY this increase was also seen (562 MME/PY to 781 MME/PY). In the year before surgery on average, the DDD/week prescribed increased from 0.19DDD/week in the 53rd week before surgery to 0.23 DDD/week in the week before surgery, and seemed to also increase between 2013 and 2018. Over 80% of preoperative prescriptions came from GPs. The proportion of preoperative prescriptions by an orthopedic surgeon increased between 2013-2018 (3%-7%). Similar changes were seen before THA.

Conclusion: In the Netherlands between 2013 and 2018 the preoperative opioid prescription rates increased, mainly due to a shift toward oxycodone prescriptions. Furthermore, over time orthopedic surgeons became more often the prescriber of preoperative opioids.

P69. The association of opioid use with risk of ICU admission and mortality in the adult Dutch population.

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Background: Opioid overdoses are on the rise in the Netherlands, and the burden of opioid use may extend beyond poisoning. Here, we investigate a relationship between opioid prescription status and one-year risk of unplanned intensive care unit (ICU) admission and death.

Methods: For this cohort study, comprised of several registries concerning the Dutch population, on 1 January 2018 alive adults were eligible and followed until either ICU admission, death, or 31 December 2018 occurred. Then, crude event rates and event specific hazard rates with 95% confidence interval (CI) in those with and without an opioid prescription–in the full cohort and in subgroups–were calculated.

Results: Rates of ICU admission and death in those with an opioid prescription were 5.87 and 62.2 per 1,000 person-years (PY) and rates of ICU admission and death in those without one were 2.03 and 6.34, respectively. Exposed residents had a 2.53-fold (95% CI 2.45-2.60) increased risk of ICU admission and a 7.11-fold (95% CI 7.02-7.19) increased mortality risk than unexposed residents. The risk of both outcomes was increased in users than in non-users regardless of the subgroup (adjusted hazard ratios greater than one) and it was influenced by the duration of opioid treatment; it was highest in chronic users (119 per 1,000 PY for death and 10.6 for ICU admission).

Conclusion: The risk of ICU admission and death was higher in opioid users than in non-users, however, other explanatory variables, not accounted for, may be present. Nevertheless, dangers of opioid use may be far-reaching.