P1. The score after ten years of registration of systematic review protocols.

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Background: With the exponential growth of published systematic reviews (SR), there is a high potential for overlapping and redundant duplication of work. Prospective protocol registration gives the opportunity to assess the added value of a new study or review, thereby potentially reducing research waste and simultaneously increasing transparency and research quality. The PROSPERO database for SR protocol registration was launched 10 years ago. This study aims to assess the proportion SRs of intervention studies with protocol registration (or publication) and explore associations of SR characteristics with protocol registration status.

Methods: PubMed was searched for SRs of human intervention studies published in January 2020 and January 2021. After random sampling and eligibility screening, data extraction on publication and journal characteristics; and protocol registration status was performed. Both descriptive and multivariate comparative statistical analysis were performed.

Results: A total of 357 SRs (2020: n=163; 2021: n=194) were included. Of these SRs, 38% had a protocol. SRs that reported PRISMA have higher odds of having a protocol than SRs that did not report PRISMA (OR 2.6; 95% CI: 1.20 to 5.69). SRs with a higher journal impact factor, have a higher odds of having a protocol (OR 1.12; 95% CI 1.02 to 1.23). Most SR protocols were registered in PROSPERO (n=129; 96%).

Conclusions: We found that only 38% of recently published SRs of interventions reported a registered or published protocol. Protocol registration was significantly associated with a higher impact factor of the journal publishing the SR and a more frequent reporting of use of PRISMA guidelines. Further research is needed to gain understanding of the benefits and informativeness of SRs protocols amongst different stakeholders, to guide strategies to increase the uptake of SR protocol registration.

Protocol registration: osf.io/9kj7r/

P2. Genetic association studies in critically ill patients: protocol for a systematic review.

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Background: Patients in the intensive care unit (ICU) are highly heterogeneous in characteristics, clinical course and outcomes. Genetic variability may partly explain the variability in disease courses observed among critically ill patients and may identify subgroups exhibiting similar disease courses. The aim of this study is to conduct a systematic review of all genetic association studies of critically ill patients with their outcomes.

Methods: This systematic review will be conducted and reported according to the HuGE Review Handbook V1.0. We will search PubMed, Embase and the Cochrane libraries for relevant studies. All types of genetic association studies that included acutely admitted medical and surgical adult ICU patients will be considered for this systematic review. All studies will be selected according to predefined selection criteria and will be evaluated and assessed for risk of bias independently by two reviewers using a newly developed quality assessment tool based on guidelines from the HuGE Review Handbook V1.0 with some modifications reflecting recent insights. This quality assessment tool consists of twelve questions representing the following domains: selection bias, information bias, confounding, multiple testing and replication and Hardy-Weinberg Equilibrium. We will provide an overview of all included studies by reporting the characteristics of the study designs, the patients included in the studies, the genetic variables and the outcomes evaluated. PROSPERO registration number: CRD42021209744.

Conclusion: The proposed systematic review will be able to give an overview of genetic loci which are associated with some degree of organ failure and will enable easier access to published results. These results might encourage external validation of earlier findings, and will help direct choice of genes of interest for future genetic studies on organ failure and/or critically ill patients.

P3. Exploratory analyses in etiologic research: considerations for assessment of credibility.

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Exploratory analyses in etiologic research are not always optimally reported. Since these analyses are usually done to generate new research questions, it is tempting to quickly perform a statistical test (or multiple tests) to get a first answer to the problem. However, when such 'quick-test' results are presented in a research article, their interpretation
may be ad hoc and unintentionally overconfident. We provide six considerations that should be central to reporting and the discussion about the credibility of exploratory analyses. These points focus on the defined research problem, the established protocol, the cautious assessment of statistical criteria, the interpretation of findings, the completeness of reporting, and the impact of exploratory findings on future etiologic research.

P4. Calculating diagnostic performance measures in clustered data: A simulation study.

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Background: Diagnostic performance measures (sensitivity, specificity, and positive/negative predictive values) are routinely reported in the medical literature, however, ramifications of clustering are not always properly accounted for. Clustering takes place for example when patients contribute multiple specimens each or the research involves multiple surgical teams or hospitals. Specimens coming from the same patient (surgical team, hospital, etc.) tend to share certain characteristics, making within-patient observations more similar than between-patient ones. Moreover, clustered data need to be considered with respect to balancedness (i.e., equal number of specimens per patient?) and missingness (what mechanisms are at work: MCAR/MAR/MNAR?). Disregarding the clustered nature of the data and thus implicitly assuming that specimens are independent can lead to erroneous conclusions, i.e., imprecise estimates and too narrow CIs. Several methods that address clustering are available, but it's far from clear which one to use under what conditions.

Methods: We compare methods that adjust for clustering when calculating diagnostic performance (e.g., variance adjustment methods, robust standard errors, logistic mixed effects modeling, generalized estimating equations, cluster bootstrap). We simulate a large number of patient samples given a set of population parameters (patient- and specimen-level disease prevalence, disease-, specimen-, and test status), calculate each performance measure and their 95% CI using each method in each sample, and evaluate coverage probabilities and CI length. Crucially, we assess robustness of performance as a function of population parameters, clustering, balancedness, and missingness.

Results and conclusion: Our objectives are to provide healthcare professionals with practical guidelines
(1) to determine if clustering presents an issue in their data set,
(2) to choose the optimal method given their needs and constraints, and
(3) to minimize error and bias in the design and analysis of screening and diagnostic studies.
Our implementation of the methods using R will be shared.

P5. Distinguishing acute heart failure from COPD exacerbations in COPD patients with acute dyspnoea: Integrating a supportive AI screening tool in the systematic literature review process.

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Background: Acute Exacerbations of COPD (AECOPD) and Acute Heart Failure (AHF) are difficult to distinguish, since both AECOPD and AHF manifest themselves with acute dyspnoea in COPD patients. This complicates timely and appropriate initiation of treatment. It is therefore important to provide an overview of markers that can help distinguishing AHF from AECOPD in dyspnoeic COPD patients.

Methods: An extensive literature search without restrictions was performed in PubMed, Web of Science, Scopus, Embase, CINAHL, and the Cochrane Library. An AI tool (Nature Mach Intell 2021;3:125–133) was used for the title and abstract screening and applies a researcher-in-the-loop text mining algorithm. This algorithm continuously provides the next study with the highest probability of being relevant, based on previous decisions of the first reviewer. After the tool provided 100 irrelevant studies in a row, the screening was stopped. A second reviewer checked a random 20% of the first reviewer's decisions to assess their reliability. Full-text eligibility was independently assessed manually by two reviewers.

Results: The first reviewer screened 1,063 (23%) titles and abstracts of 4,695 identified studies. Subsequently, 3,632 studies (77%) were automatically excluded. The reliability of the first reviewer's decisions was strong (Kappa = 0.83), therefore the training of the algorithm was considered adequate. After full-text screening, 29 studies were included for data extraction. These yielded 16 unique markers able to detect AHF in dyspnoeic COPD patients (e.g. NT-proBNP and hs-TnT blood levels, cardiac murmur).

Conclusion: Applying innovative review methods is inevitable, as medical scientific output increases exponentially. The AI tool allows screening of a large set of studies by accelerating the screening process. This review has identified markers that distinguish AHF from AECOPD. These will support the initiation of timely and appropriate treatment of AHF and/or AECOPD in dyspnoeic COPD patients, and will therefore lead to better health outcomes.

P7. Depression and Anxiety and the Incidence of Cancer: A two-stage individual participant data meta-analysis of the direct association.

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Background: Over the last decades, it has been repeatedly suggested that depression and anxiety may lead to the onset of cancer, through mechanisms such as mutation, DNA repair, neuroendocrine processes, or unhealthy behaviors. With two-stage individual participant data (IPD) meta-analyses, we aimed to test whether depression and anxiety (diagnoses and symptoms) increase the risk for all cancers combined, smoking-related cancers, alcohol-related cancers and cancer of the following sites: breast, lung, prostate, and colorectal.

Method: IPD meta-analyses were performed with fourteen cohort studies in the PSY-CA consortium (N = 330,914, person years = 2,965,559, cancer incidences = 26,590). At stage 1, Cox regression models were fitted in each cohort for each predictor (depression diagnosis, depression symptoms, anxiety diagnosis, and anxiety symptoms) and cancer outcome (outlined above). Two models were tested: a minimally-adjusted model (correcting for sociodemographic covariates) and a maximally-adjusted model (additionally correcting for several health behaviors and relevant cancer-specific confounders). At stage 2, effect estimates (from stage 1) were entered into random-effects meta-analyses.

Results: Depression and anxiety were associated with higher incidence of lung cancer and smoking-related cancers in the minimally-adjusted models, both for diagnoses and symptoms of depression and anxiety, but these associations became weaker when adjusting for health-related behaviors such as smoking in the maximally-adjusted models. Depression and anxiety were not related to any other cancer outcome.

Conclusion: Depression and anxiety are risk factors for lung cancer and smoking-related cancers, but the strength of these associations decreased when adjusting for health-related behaviors such as smoking. Further research is necessary to test whether health-related behaviors interact or mediate the association between depression/anxiety and lung cancer/smoking-related cancers.

P8. Role of innate and adaptive immune system in migraine: A population-based cohort study.

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Introduction: Within the multifactorial etiology of migraine, accumulating evidence points towards a role for the immune system. However, the specific contribution of innate and adaptive immunity to migraine remains unclear. Hence, we investigated the association of innate and adaptive immunity with migraine. Additionally, we explored the role of the balance between the two components of the immune system in migraine.

Methods: We measured white-blood-cell type based immunity markers and calculated their derived ratios using blood samples collected during attack-free periods and assessed the prevalence of migraine using a structured interview with participants of the prospective population-based Rotterdam Study. We assessed neutrophil and platelet counts as a proxy for innate and lymphocyte count as a proxy for adaptive immunity. The balance between the two components was assessed by the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and systemic immune-inflammation index (SII). We investigated associations of blood cell counts, and their derived ratios with migraine (and migraine subgroups) using logistic regression models adjusting for age, sex and other variables.

Results: Among 6593 participants (mean age 65.6 ± 11.2 years, 56.7 % female), 995 (15.1%) had migraine. We found no association between neutrophil (Odds Ratio [OR] per standard deviation increase 1.02 95% Confidence Interval [CI]: 0.94-1.10), platelet (OR 1.01 CI: 0.93 – 1.09) or lymphocyte counts (OR 1.01 CI: 0.93 – 1.09) and migraine status. Similarly, no associations were observed between NLR (OR 1.01 CI: 0.94 – 1.09), PLR (OR 1.00 CI: 0.93 – 1.08) and SII (OR 1.01 CI: 0.94 – 1.09) and migraine status. In the analyses where migraine subgroups were the outcome, a significant association was observed between the platelet count and migraine with aura (OR 1.17, CI: 1.01 – 1.35).

Conclusion: Our results do not support the involvement of innate and adaptive immunity in migraine. Platelet count and migraine with aura relationship needs further investigation.

P9. Impact of phosphate binders on quality of life in dialysis patients.

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Background: Phosphate binders contribute significantly to dialysis patients' high pill burden, complicate medication regimens, and have unpleasant taste and large size which may affect patients' quality of life. This study explores the association between phosphate binder pill burden and health-related quality of life (HRQoL) in dialysis patients.

Methods: We conducted a cross-sectional multi-centre cohort study in 21 Dutch dialysis centres within the DOMESTICO study. Phosphate binder pill burden was extracted from electronic patient records. Primary outcome was HRQoL measured with the Short Form 12 physical and mental component summary scores (PCS and MCS). Secondary endpoints were severity of gastro-intestinal symptoms, itching, and dry mouth, and mental health symptoms, measured with the Dialysis Symptom Index, and self-rated health measured on a visual analogue scale.

Results: In total 388 patients were included. Mean age was 62±16 years, 128 (33%) were female and 293 (77%) underwent haemodialysis. . Mean PCS was 37.0±10.0, mean MCS 47.4±10.1, and mean self-rated health 62±20. There was no difference in PCS and self-rated health score between patients with and without phosphate binders. Compared to patients without phosphate binders, patients using 1-3 pills reported lower scores for decreased appetite (β -0.5; 95%CI -0.9 to -0.2), implying better appetite. Patients using 4-6 pills also reported lower scores for decreased appetite (β -0.5; 95%CI -0.8 to -0.1) and for itching (β -0.5; 95%CI -0.9 to -0.1). Patients using >6 pills reported lower MCS (β -2.9; 95%CI -6.2 – 0.4) and higher scores for feeling nervous (β 0.6; 95%CI 0.1 – 1.1) and feeling sad (β 0.4; 95%CI 0.0 – 0.9).

Conclusions: Phosphate binder pill burden is not associated with physical quality of life. A higher pill burden is associated with better appetite and less itching. Patients using >6 pills per day report lower mental quality of life and felt nervous and sad more often.

P10. Associations between Childhood Adverse Experiences and Emotional and Behavioural Problems at Age 16 - a Network Analysis.

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Previous studies have shown that adverse experiences in childhood are associated with elevated levels of emotional- and behavioural problems. However, due to limitations of commonly used methods for modelling early life adversity, including sum scores, latent classes and single-adversity approaches, it is unclear how adverse experiences are conjunctively associated with emotional- and behavioural problems. In this study, we applied network analysis to examine associations between adverse experiences in childhood and emotional- and behavioural problems at age 16 in the Dutch Tracking Adolescents' Individual Lives Survey (TRAILS, N = 1203). Network analysis is a statistical approach that allows for estimating complex patterns of relationships between variables. In the resulting network model, peer rejection, emotional abuse, sexual abuse and parental mental health problems were directly associated with elevated emotional problems, whereas emotional abuse and familial conflicts were directly associated with behavioural problems. Other adversities were at most indirectly associated with emotional and behavioural problems. Moreover, we found three communities of strongly connected nodes: (1) parental divorce, parental addiction, and parental mental health problems; (2) financial difficulties, familial conflicts, and parental mental health problems; and (3) emotional abuse, emotional problems, behavioural problems. Our findings suggest that the association between childhood adversity and emotional and behavioural problems is driven by specific adverse experiences, which exert their effects within the context of associations with other AEs. The direction of these effects require further investigation. The findings in this study are an important step in understanding the potential mechanisms linking AEs with emotional- and behavioural problems.

P11. Impact of an HIV cure on HIV transmission among men who have sex with men (MSM) in the Netherlands

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When an HIV cure becomes available, it may have consequences for HIV transmission at the population level. A more plausible cure scenario is post-treatment control (PTC), whereby HIV remains suppressed after stopping antiretroviral treatment (ART). This study assessed the potential impact of PTC on the HIV epidemic among men who have sex with men (MSM) in the Netherlands. We developed a model of HIV transmission in a population stratified by sexual risk behavior and with access to ART, pre-exposure prophylaxis (PrEP) and PTC. PTC is targeted to individuals on ART who remain virally suppressed without ART but who may experience viral rebound, become infectious and start ART again if PTC fails. We examined how HIV prevalence (excluding individuals on PTC) was affected by PTC uptake and the average time to PTC failure. The model was calibrated to behavioral and HIV surveillance data for MSM in the Netherlands. An uptake of 15% of a perfect PTC that never fails can decrease HIV prevalence from 6.9% currently to 2.5% within 5 years after PTC Background. In case of an imperfect PTC, HIV prevalence will decrease if PTC uptake is similar to the current ART uptake and the average time to failure is more than 10 years. Likewise, HIV prevalence will decrease regardless of the average time to failure if ART uptake after failure and getting infected while on PrEP are similar. For the average time to failure of 3 years and a PTC uptake of 99%, HIV prevalence will increase if ART uptake after failure is the same as the current ART uptake. Strict monitoring is needed to prevent an increase in HIV prevalence among MSM after the Background of PTC. Without monitoring, HIV prevalence will decrease only if the average time to failure exceeds a decade.

P12. The experienced positive and negative influence of HIV on the quality of life of people living with HIV and key populations vulnerable to HIV: a qualitative study.

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Due to antiretroviral treatment (ART) and Undetectable equals Untransmittable (U=U) the burden experienced by people living with HIV (PLHIV) has changed. Due to pre-exposure prophylaxis (PrEP) the fear of acquiring HIV also changed for key populations who are living without but are vulnerable to HIV. This qualitative study aimed to explore the influence of HIV on the experienced quality of life (QoL) of PLHIV and key populations in the Netherlands.
We conducted semi-structured, in-depth interviews with 29 participants with HIV and 13 participants without HIV (i.e., men who have sex with men (MSM) and people injecting drugs). Interviews were conducted online (n=31) or face-to-face (n=11) and thematically analyzed.
PLHIV explained the positive influence of HIV as feeling grateful for life and being loved, being supported, and providing support to the community. The negative influence of HIV was described by both PLHIV and participants without HIV as negative effects of ART and challenges due to discussing HIV. In addition, PLHIV reported to experience social stigmatization, self-stigma, and challenges during the COVID-19 pandemic due to fear of problems with ART availability and concerns about the safety of COVID-19 vaccines. Finally, both PLHIV and participants without HIV described their gratefulness for ART, PrEP, and U=U because these treatment and prevention options reduced the fear of transmitting or acquiring HIV, and thus, the negative influence of HIV.
Our findings highlight that HIV may have a positive influence on QoL of PLHIV. In addition, HIV treatment and prevention options reduced the negative influence of HIV among PLHIV and key populations. It remains important to support HIV community organizations and to continue increasing availability of biomedical interventions options because they have a positive influence or further reduce the negative influence of HIV on QoL.

P13. Sexualized drug use and STI and HIV incidence among men who have sex with men in Amsterdam, a cohort study.

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Background: Sexualized drug use (SDU), defined as the use of drugs before or during sex, is a rising phenomenon among men who have sex with men (MSM). We assessed the association between SDU and incident sexually transmitted infections (STIs) and human immunodeficiency virus (HIV) among MSM with many previous STIs and/or HIV.

Methods: We used data from the MS2 cohort study, conducted at the STI outpatient clinic of the Public Health Service of Amsterdam, the Netherlands, in 2014-2019. Eligible were adult MSM with ≥2 STIs in the preceding year or HIV. Participation encompassed 3-monthly clinic visits including STI screening and questionnaires on drug use. Primary outcomes were incident HIV, syphilis, Chlamydia trachomatis (Ct) and Neisseria gonorrhoeae (Ng). We studied the association between SDU and incident HIV and bacterial STIs, using Poisson regression models.

Results: 319 MSM (143 HIV-negative, 176 living with HIV) were included. 90.4% participants had engaged in SDU in preceding 3 months. 132 HIV-negative MSM and 172 MSM living with HIV attended ≥2 study visits. Eight participants acquired HIV during follow-up (incidence rate (IR) 2.9 per 100 person-years (py), 95% confidence interval (CI) 1.5-2.8). All seven about whom information on SDU was available had engaged in SDU in the 3 months prior to positive test. SDU was not associated with incident syphilis (IR 14.8/100py, incidence rate ratio (IRR) 1.4, 95%CI 0.7-2.8). SDU was associated with incident Ct (IR 45.7/100py, IRR 2.1, 95%CI 1.3-3.5) and Ng (IR 55.3/100py, IRR 2.1, 95%CI 1.3-3.2).

Conclusion: SDU among MSM was associated with incident Ct and Ng infections, and likely with incident HIV. HIV-negative MSM who engage in SDU should be advised to use HIV pre-exposure prophylaxis and have STI screening regularly. We suggest counseling on SDU among MSM with recurring STIs.

P14. How do different limiting mechanisms influence the transmission dynamics of schistosomiasis?

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Background: Schistosomiasis is a neglected tropical disease estimated to affect 200 million people worldwide causing severe morbidity. The transmission cycle of Schistosoma between the human host and the parasite is remarkably complex. Its peculiarity lies in the role of an intermediate host (freshwater snails), through which larvae are able to multiply and develop. Mathematical models help understand the complex mechanisms of Schistosomiasis transmission dynamics and can inform policy decisions for control and elimination. Several limiting mechanisms (such as density dependence in egg production, hosts immunity or vectorial capacity) impact the transmission dynamics. Clear evidence for density-dependence effects is lacking and which mechanisms have a predominant effect is subject of investigation. In this work we explore the impact of different limiting mechanisms on the transmission dynamics and on control interventions.

Methods: We implement a stochastic individual-based model in R programming language, to reproduce schistosomiasis transmission dynamics in an age-structured human population through an environmental reservoir of infective particles, including the role of the intermediate host.

Results: We show that different limiting mechanisms have a large impact on the resulting transmission dynamics of schistosomiasis, quantified as prevalence of infection, prevalence of heavy infection and mean worm burden. Interventions such as mass drug administration (MDA) have different effectiveness in reducing infection levels depending on the limiting mechanism assumed.

Conclusion: This work contributes to the understanding of schistosomiasis transmission dynamics in endemic settings and help informing policy makers on the effectiveness of control interventions.

P15. The prognostic value of glycemic control prior to cancer diagnosis on mortality among patients with type 2 diabetes in Dutch primary care.

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Background: One out of five cancer patients live with (pre)diabetes. Probably due to glycemic control (GC) is deprioritized in oncological care, limited study evaluated the role of GC among patients with cancer and type 2 diabetes (T2DM). A substantial of patients with comorbid cancer and T2DM are followed in primary care, where good quality of GC is feasible and may improve survival. This study therefore investigated the role of GC prior to cancer diagnosis on mortality among patients with cancer and T2DM in primary care.

Methods: The linkage of the benchmarking database of patients with T2DM (ZODIAC), the Netherlands Cancer Registry, and the Personal Records Database was used (1989–2019). Included were patients diagnosed with incident primary breast, colorectal, or prostate cancer. The target level of GC was defined according to the Dutch guideline. The hazard ratios and 95% CIs for mortality were estimated in multivariable Cox regression models, adjusting for individual expected survival relative to the general population as well as age, gender, diabetes duration, history of macrovascular events, body mass index, smoking, socioeconomic status, cancer stage, use of metformin, insulin, statin, and baseline year.

Results: The numbers of incident cancer patients included and the median follow-up years were breast (480, 7.4), colorectal (600, 6.5), and prostate (457, 6.9) respectively. The hazard ratios for having GC not at target compared with at target among cancer patients with T2DM were breast 0.90 (0.59–1.37), colorectal 1.52 (1.13–2.04), and prostate 1.08 (0.78–1.51) respectively.

Conclusions: In Dutch primary care for T2DM, a worse GC prior to colorectal cancer diagnosis was associated with 52% increased mortality compared with a good GC, suggesting its prognostic value. This association was not observed among patients with breast and prostate cancer.

P16. Beverage quality and risk of prediabetes and type 2 diabetes in the Rotterdam Study.

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Background: Several beverages have been associated with (pre)diabetes risk, with opposing effects. Whether overall beverage intake quality affects prediabetes and type 2 diabetes (T2D) risk is unknown. We examined associations of overall beverage intake quality with prediabetes and T2D risk in a Dutch population.

Methods: We included 6,769 participants from the population-based Rotterdam Study (RS), aged ≥45 years and free of diabetes at baseline. Dietary intakes were estimated at baseline using food-frequency questionnaires. A Beverage Quality Index (BQI) was created consisting of 8 components, including beverage groups intake based on the Dutch Dietary guidelines and additional components for added sugar and total calories from beverages, with an score ranging from zero to ten per component, resulting in a total score between 0 (no adherence) and 80 (complete adherence). Data on outcomes were available from 1993 to 2015. Associations of BQI (per 10 points) with risk of prediabetes and T2D were assessed by using multivariable-adjusted Cox regression models, later stratified by sex and obesity status.

Results: Participants mean age was 62.0 ± 7.8 years and 59% were female. During follow-up, we documented 1139 prediabetes and 784 T2D cases. Mean (SD) of the BQI was 52.7 (11.7). Higher BQI score was not associated with prediabetes (HR: 0.95; 95% CI: 0.90, 1.01) or T2D risk (HR: 1.05; 95% CI 0.98, 1.12). In stratified analyses, higher BQI tended to be inversely associated prediabetes in men (HR: 0.91; 95% CI: 0.84, 0.99) and non-obese individuals (HR:0.94; 95% CI: 0.89, 1.01).

Conclusion: Higher BQI score was associated with a lower risk of prediabetes in men and in non-obese individuals. More studies are needed to confirm these findings, and the BQI needs to be validated in other cohorts.

P17. Alcohol consumption and microvascular dysfunction: a J-shaped association– The Maastricht Study.

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Background: Alcohol consumption may be a determinant of microvascular dysfunction (MVD), an important contributor to major clinical disease such as stroke, dementia, and retinopathy. Main objectives were 1) to study whether alcohol consumption was associated with MVD as assessed in the brain, retina, skin, kidney and in the blood; and 2) to investigate whether associations differed by history of cardiovascular disease or sex.

Methods: We used cross-sectional data from The Maastricht Study (N=3,120 participants, 50.9% men, mean age 60 years, 16.8% with a history of cardiovascular disease, and 27.5% with type 2 diabetes [the latter oversampled by design]). We used regression analyses to study the association between total alcohol, consumption (moderate versus light) and MVD, where all measures of MVD were combined into a total MVD composite score (expressed in SD). We adjusted for potential confounders (age, sex, educational level, diet, and key cardiovascular risk factors) and tested for interaction by history of cardiovascular disease and sex.

Results: The association between total alcohol consumption and MVD was J-shaped. After full adjustment, moderate versus light total alcohol consumption was significantly associated with less MVD (beta [95% confidence interval], -0.10 [-0.19; -0.01] SD). History of cardiovascular disease ($P_{interaction}<0.001$) and sex ($P_{interaction}=0.03$) modified the associations. In individuals with, versus without, a history of cardiovascular disease the mathematical minimum was at higher levels of alcohol consumption and moderate versus light alcohol consumption was considerably more strongly associated with less MVD. The shape of the J-curve, but not the strength of the association, differed by sex.

Conclusion: The present population-based study found a J-shaped association between alcohol consumption and MVD. Therefore, alcohol consumption may be a determinant of MVD. Hence, although increasing alcohol consumption cannot be recommended as a policy, this study suggests that prevention of MVD may be possible through dietary interventions.

P18. Prognostic value of coronary artery calcium in predicting cardiovascular diseases of patients with breast cancer.

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Background: Improved breast cancer screening methods and treatments have led to an increasing number of breast cancer survivors. Cardiovascular disease (CVD) is the leading cause of death in patients treated for breast cancer. Coronary artery calcification (CAC), an important risk factor (RF) for CVD, can be quantified from radiotherapy (RT) planning computed-tomography (CT) scans. CAC scores offers the opportunity for cheap and fast identification of breast cancer patients with an increased risk of CVD. However, until now, the added prognostic value of the CAC score to classic CVD RFs for predicting the risk of CVD in patients with breast cancer is unknown.

Methods: Patients with breast cancer participating in the Utrecht cohort for Multiple BReast cancer intErvention studies and Long-term evaluAtion (UMBRELLA) who received radiotherapy between 2007 and 2020, were sent a questionnaire about CVD RFs (i.e., hypertension, diabetes mellitus, dyslipidemia, former or current smoking, and history of CVD). Participants were classified as low, moderate or high risk based on the number of RFs. CAC scores were quantified from RT planning CT-scans using a deep learning algorithm, and patients were classified into four Agatston categories: 0, 1-10, 10-100, and >100 units. The area under the curve (AUC) and c-statistic will be used to examine the added value of CAC to classic risk factors.

Results: 1126 patients with a mean (SD) age of 56.4 (9.9) years were included, whereof 1122 patients were female (99.6%). A total of 892 patients had no CAC, whereas 90, 81, and 63 patients had CAC scores of 1 to 10, 10-100, and >100 respectively. 185 patients (16.4%) had a low CVD risk profile, whereas 701 (62.3%), and 240 (21.3%) had a moderate, and high CVD risk profile, respectively. Currently, data analysis is ongoing and results and conclusions of this study will be available at the congress.

P19. A higher glycemia level, lower adherence to healthy diet, lower cardiorespiratory fitness, smoking, and a higher systolic blood pressure are cross-sectionally associated with lower retinal sensitivity – The Maastricht Study.

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Diabetic retinopathy is preceded by subtle functional neurodegenerative changes, including reduced light sensitivity "lower retinal sensitivity". It is not yet understood if modifiable risk factors may be determinants of retinal sensitivity (RS). Using cross-sectional data from a cohort study, we investigated whether those risk factors were associated with RS. We used data from The Maastricht Study, up to 5,255 participants, 50.5% men, age 59.7±8.7 years, and 22.6% with type 2 diabetes (T2D). We determined HbA1c (mmol/mol) and total cholesterol (mmol/L) in fasting plasma samples. We assessed dietary intake and alcohol consumption with a food frequency questionnaire, and smoking status via a questionnaire. We measured cardiorespiratory fitness, defined as the maximum power output adjusted for body mass. We measured 24-hour ambulatory blood pressure (mm Hg). We assessed waist circumference (cm) and physical activity (hours/day). We estimated the RS using Heidelberg Edge Perimeter and defined RS as the mean (peri)macular RS of both eyes. We used linear regression analyses with adjustment for potential confounders and tested for interaction by sex and T2D. After full adjustment, greater HbA1c, lower healthy diet score and cardiorespiratory fitness, and current versus never smoking were significantly associated with lower RS, per SD-β[95% CI], -0.05[-0.08; -0.02], -0.06[-0.09; -0.03], -0.05[-0.08; -0.01], and -0.14[-0.22; -0.06], respectively; greater 24-hour ambulatory systolic blood pressure was significantly associated with lower RS in individuals with, but not in individuals without, T2D -0.06[-0.12; -0.04]. In contrast, greater total cholesterol was significantly associated with greater RS 0.05[0.02; 0.08]. Alcohol consumption, antihypertensive medication use, lower physical activity, and greater waist circumference were not associated with RS. Sex did not modify the associations. In this study, higher levels of glycemia or systolic blood pressure, lower adherence to a healthy diet, or cardiorespiratory fitness, and smoking were associated with a lower RS. Hence, early-stage prevention of these factors may contribute to the prevention of loss of RS.

P25. Dementia prediction in the general population using clinically accessible variables: a proof-of-concept study using machine learning. The AGES-Reykjavik Study.

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Background: Early identification of dementia is crucial for prompt intervention and better outcomes for high-risk individuals in the general population. The use of machine learning in dementia prediction has allowed for highly accurate models that could aid in early classification; however, they have focused on expensive predictors. Exploring predictors that are more accessible is crucial for the possible widespread use of machine learning models in clinical practice.

Methods: Data from 4,793 individuals without dementia or mild cognitive impairment at baseline were included from the AGES-Reykjavik Study. Cognitive, biometric, and MRI assessments were collected at baseline, with follow-up of incident dementia for a maximum of 12 years. Elastic net regression, random forest, support vector machine, Naïve Bayes, logistic regression, and elastic net Cox regression were explored as possible algorithms. Model 1 was fit using all variables, model 2 after feature selection, and model 3 without neuroimaging (clinically accessible model). Ten-fold cross-validation, repeated ten times, was implemented during training.

Results: During training, the Model 2 elastic net regression had the highest AUC [0.78; 95% CI: 0.76-0.80], sensitivity [72; 95% CI: 68-75], and specificity [72; 95% CI: 70-73]. For Model 3, the AUC remained high [AUC 0.75; 95% CI: 0.73-0.77]. Similar results were found in our test data for Model 3 [AUC 0.74; 95% CI: 0.71-0.77]; thus, the risk of overfitting was low. The elastic net Cox models showed similar discrimination [c-statistic 0.79] during testing. The most important variables included the presence of APOE e4 allele, memory functioning, and sex.

Conclusion: Supervised machine learning could be used to identify individuals at high-risk for dementia in the general population using easily accessible variables. Further external validation is needed.

P26. Associations between the social environment and cardiometabolic health outcomes: systematic review (and meta-analysis).

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Background: A number of studies has investigated the relationship between the social environment (i.e., the social relationships and social context in which groups of people live and interact) and lifestyle behaviours. However, to what extent this relation extends to cardiometabolic disease outcomes is unknown. This systematic review and meta-analysis summarizes the available evidence.

Methods: We systematically searched PubMed (Medline), Scopus, and Web of Science from inception to 16 February 2021. Outcomes were type 2 diabetes mellitus and cardiovascular diseases and determinants were social environmental factors (e.g., area-level deprivation and social network size). We assessed the quality of studies using the Newcastle-Ottawa Scale (NOS). We meta-analysed associations when ≥3 binary associations from high quality papers were available per social environment dimension. For the sake of this abstract, we only present results for stroke outcomes but full results will be available at the time of the conference.

Results: From 7671 records screened, 218 were included and 35 focused on stroke. Of these, 50% were of poor or fair quality. Among the 35 studies, 97 relevant associations were investigated. Economic and Social Disadvantage (ESD) was the dimension with the largest number of associations investigated (71%), followed by Social Relationships and Norms (16%), Discrimination and Segregation (8%), and Social Cohesion and Social Capital (2%). Limited evidence was found for the remaining dimensions (Crime and Safety, Civic Participation and Engagement and Disorder and Incivilities). Meta-analysis was only possible for ESD. More ESD was associated with higher stroke risk/prevalence (n=5; OR=1.10; 95% CI 1.03-1.17; I2=40%).

Conclusion: Higher levels of economic and social disadvantage seem to contribute to increased stroke risk. During the conference we will present full results of our study, including underexplored dimensions of the social environment.

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P27. The sex difference in self-rated health among older adults: Longitudinal analyses across different birth cohorts and educational levels.

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Background: Self-rated health forms an important aspect of healthy ageing, as it encompasses one's individual health judgement and is associated with various health outcomes. Women report a lower self-rated health compared to men. This sex difference seems to decrease with increasing age, but longitudinal studies are lacking. Besides variability by age, sex differences might vary over time or by educational level. This study aims to investigate sex differences in self-rated health among older adults in the Netherlands, including the longitudinal course, trends over time and a potential risk group regarding educational level.

Methods: Data from the Longitudinal Ageing Study Amsterdam (LASA) were used. Sex differences in self-rated health (RAND General Health Perception Questionnaire (RAND-GHPQ) scale) and modification thereof by birth cohort and educational level were analyzed via mixed models analyses using longitudinal data from birth cohort 1927-1937 with baseline age 55-81 years (n=3107) and birth cohort 1937-1947 with baseline age 55-65 years (n=1002).

Results: For both men and women, a decline in self-rated health was seen with increasing age. In addition, a higher self-rated health was seen for the more recent birth cohort and higher educational levels. No significant sex differences were found for all ages, birth cohorts and education levels.

Discussion: This study shows that among older adults in the Netherlands there is neither a sex difference or female disadvantage in self-rated health nor a higher risk thereof based on age, birth cohort or education level.

P28. Diverging death risks: mortality as a corollary of economic, social, cultural and person capital.

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Background: The persistence of socioeconomic differences in mortality may be due to the fact that they are not merely driven by education and income, but also by other economic and non-economic factors. This study proposes a capital-based approach and analyses the association of mortality risks with four types of resources: economic, social, cultural and person capital.

Methods: We used data of 2592 participants from the Disparities in the Netherlands (ViN) survey and annual mortality data from Statistics Netherlands for the period 2014 to 2020. Economic capital was measured through education, income, occupation, home equity, and liquid assets. Social capital was measured by strong ties, size of the core discussion network, and access to people in resourceful positions; cultural capital by life style, digital skills, and mastery of English, and person capital by self-rated health, impediments to climbing stairs, self-confidence, self-image, people's appearance, and body mass index. To accommodate the fact that each capital was formed by sets of indicators, we used Partial Least Squares (PLS) Cox Regression proportional hazard models.

Results: Simple regression analyses showed lower economic and person capital to be associated with increased mortality (Hazard Ratio (HR) 1.26; [1.05 -1.52] and 1.19 [1.03 - 1.37]). In multiple regression analysis, including all capital measures and sex, economic and person capital remained significant (HR 1.30 [1.08 - 1.56] and 1.18; [1.00 - 1.38]).The PLS weights showed that occupation and home equity were the most influential indicators for economic capital, and self-rated health and impediments to climbing stairs for person capital.

Conclusion: We found low economic and person capital to be associated with increased mortality. These findings provide preliminary empirical support for the assumption that a wider set of capital measures - hitherto seldom included simultaneously in epidemiological research - can provide a fuller explanation of divergent death risks.

P29. Prenatal famine exposure and cognitive function from age 68 to 74.

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Background: Previous findings in the Dutch famine birth cohort showed that people exposed to undernutrition in early gestation performed worse on a Stroop-like task administered during a stress-protocol around age 58. At age 73, especially men exposed to famine in early gestation more often self-reported cognitive problems. Here, we hypothesized that famine exposure in early gestation is associated with worse cognitive function in older age and a higher rate of cognitive decline. Given our previous findings, we tested these hypotheses in the total group as well as in men and women separately.

Methods: We assessed cognitive function using tasks repeatedly measured at age 68 and 74 (Stroop-like task, trail making task, 15-word task) or only at age 74 (Montreal cognitive assessment, self-perceived cognitive problems) in 73 men (n=34) and women (n=39) born as term singletons around the time of the 1944-45 Dutch famine. Participants exposed to famine in early gestation were compared to those prenatally unexposed (born before or conceived after the famine).

Results: Although cognitive function declined from age 68 to 74, cognitive task scores and rate of decline did not differ between those exposed or unexposed to famine. Men exposed to famine in early gestation more often reported cognitive problems at age 74 (OR 3.1 [95% CI 0.9 – 11.0]), although the difference here was just above the level of statistical significance.

Conclusion: We could not detect an association between famine exposure in early gestation and cognitive performance at older age or accelerated cognitive decline. The discrepancy with observations in Stroop performance at age 58 may be explained by participation bias and the fact that, unlike the previous assessment, the Stroop-task was not performed under stressful circumstances. Corresponding to previous findings, men exposed in early gestation more often reported cognitive problems, possibly indicative of future cognitive problems and dementia.

P30. Environmental noise exposure during pregnancy and embryonic and fetal growth: The Generation R study.

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Noise exposure is considered a risk factor for adverse health outcomes. Moreover, noise exposure during pregnancy has been associated with adverse birth outcomes, including lower birthweight and an increased risk of preterm birth. However, no studies have explored the association with embryonic and fetal growth during pregnancy, which may provide a window of opportunity for interventions.

We studied 7946 pregnant women from the Generation R Study, the Netherlands. Average noise exposure at the participants' home address during the pregnancy period was estimated using EU noise maps. Embryonic and fetal growth parameters (crown-rump length, head circumference, femur length and estimated fetal weight) were measured at multiple time points by ultrasound. Information on neonatal anthropometrics at birth (head circumference, length, and weight) and adverse birth outcomes (preterm birth, low birthweight, and small for gestational age) were retrieved from medical records. Linear mixed models were conducted to analyze the association between noise exposure and repeatedly measured fetal growth parameters. To analyze the association between noise exposure and first trimester growth and birth outcomes, linear and logistic regression models were used. Median total noise exposure levels were 55.3 decibel. Noise exposure during pregnancy was associated with larger crown-rump length in the first trimester, but not with repeatedly measured head circumference, length and weight. Noise exposure during pregnancy was moreover not associated with neonatal anthropometrics at birth, nor with adverse birth outcomes. We observed no evidence of an association between noise exposure during pregnancy and fetal growth nor with birth outcomes. Noise exposure during pregnancy was however associated with larger embryonic growth. Future research on the association between environmental exposures on fetal growth should include longitudinal embryonic and fetal growth parameters rather than birth outcomes alone.

P31. The effect of burns on children's growth trajectory: a nationwide study.

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Background: The objective of this study was to evaluate the short- and long-term effect of burn injury on children's height and weight, by comparing their pre- and post-burn growth trajectory.

Methods: We invited children (≤17 years old), who sustained a burn injury requiring surgical treatment and/or admission at one of the three Dutch burn centers in 2013 (n=175). As well as children who sustained a severe burn injury, covering >10% of the total body surface area (TBSA), throughout 2009-2018 (n=228). Data was collected from a survey on health-related topics, Youth Health Care records, and the Dutch Burn Repository R3. For all participants, height and weight were converted to Z scores using Dutch reference values. Linear mixed modelling, nested on individual level, was used to examine the associations between burn injury and children's height and weight Z scores.

Results: Children's height and weight Z scores remained within the normal range throughout the study period. During the first year post-burn, children's height and weight Z scores decreased by -0.21 (95%CI [-0.41,-0.01]) and -0.23 (95%CI [-0.46,-0.04]), respectively. Beyond the first year post-burn, estimates were consistent with a positive linear association between burn size and the overall effect of burn injury on participants' height and weight Z scores. Including a modest, but statistically significant, effect among participants with a burn injury covering ≤4.5% TBSA and >14.0% TBSA. Sensitivity analyses did not alter our findings.

Conclusion: Children were on track or even surpassed their growth potential. Our findings could therefore be considered reassuring to patients, parents, and clinicians.

P32. Early pregnancy metabolite profiles and gestational blood pressure.

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Background: Blood pressure plays a major role in both the etiology and prediction of gestational hypertensive disorders. Metabolomics might serve as a tool to identify underlying metabolic mechanisms in the etiology of higher blood pressure in pregnancy and individual metabolites might be useful in de prediction of gestational hypertensive disorders.

Methods: In a population-based, prospective cohort study among 803 pregnant women, LC-MS/MS was used to determine serum concentrations of amino-acids, non-esterified fatty acids, phospholipids and carnitines in early pregnancy. Blood pressure was measured in each trimester of pregnancy.

Results: Higher metabolite group and subgroup concentrations of diacyl-phosphatidylcholines, acyl-lysophosphatidylcholines and amino acids were association with higher systolic blood pressure throughout pregnancy (p-values <0.05). Higher diacyl-phosphatidylcholines, acyl-lysophosphatidylcholines, sphingomyelins and acyl-carnitine were associated with higher diastolic blood pressure throughout pregnancy (p-values <0.05). We identified 12 individual early-pregnancy non-esterified fatty acids and phospholipids and the metabolite ratio glutamine/glutamic acid, that were jointly associated with larger changes of diastolic and systolic blood pressure from first to third trimester. These metabolites did not improve the prediction of gestational hypertensive disorders in addition to clinical markers.

Conclusion: Altered early pregnancy serum metabolite profiles are associated with higher gestational blood pressure. These findings are important from an etiological perspective and, after further replication, might improve early identification of women at increased risk of gestational hypertensive disorders.

P33. Environmental risk factors for congenital solitary functioning kidney.

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A congenital solitary functioning kidney (CSFK) is a congenital anomaly which frequently leads to kidney injury. The aetiology is thought to be multifactorial, with both genetic and environmental factors involved. Known risk factors for CSFK and other congenital anomalies of the kidney and urinary tract (CAKUT) include maternal obesity and diabetes and use of assisted reproductive technologies to conceive. However, most previous studies were small and few investigated risk factors for CSFK specifically. We aimed to get more insight into the role of environmental risk factors in the aetiology of CSFK. Children with CSFK were recruited in 36 hospitals throughout The Netherlands and a population-based control group was collected via a diversity of municipalities. We asked parents of both cases and controls to fill out online or paper questionnaire about exposure to potential risk factors in the period before and during pregnancy. Directed acyclic graphs were used to identify minimum sets of confounders for each potential risk factor. Multiple imputation was used to deal with missing values. Questionnaires were available for 789 cases and 4100 controls born between 1990 and 2021. Our preliminary results indicate mildly increased odds ratios (ORs) for conception using IVF or ICSI and major life events during pregnancy. Use of multivitamins, folic acid supplements, or a combination of both in the first 8 weeks of gestation slightly reduced the risk of CSFK (ORs 0.6 (95% confidence interval (CI) 0.3-1.0), 0.8 (95% CI 0.6-1.1) and 0.7 (95% CI 0.5-1.1), respectively). Family history of CAKUT was strongly associated with CSFK (OR 4.8, 95% CI 3.0-7.7). Our results indicate that environmental factors may be involved in the aetiology of CSFK, although the estimated effect was mild for most factors studied. As family history of CAKUT was strongly associated with CSFK, a genetic component is likely as well.

P34. Congenital anomalies in the Netherlands 2009-2018: can increased prevalence in Limburg be explained with socio-economic, health, and environmental factors?.

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Background: n the Netherlands, national perinatal registrations, including congenital anomalies (CA), are collected and managed by Perined. In 2014, analyses of regional variations in CAs showed an increased prevalence in Limburg (relative risk (RR) 1.35 compared to other Dutch regions). Province Limburg commissioned epidemiologic research in order to explain the increased prevalence. This study aimed at:
1. Mapping the spatial distribution of CAs in the Netherlands;
2. Investigating whether known risk factors can explain the increased prevalence of CAs in Limburg compared to the Netherlands

Methods: Perined registrations of CAs for the period 2009-2018 were pseudoanonymised and analysed in the remote microdata environment of Statistics Netherlands (CBS). Individual child birth outcomes (including CA) were linked to parental age, migration status, education, household income, work sector, and municipality of residence (CBS microdata), as well as exposure to air pollutants around conception.
Spatial clusters of CAs on municipality and region level were explored using Bayesian Besag, York and Mollie (BYM) model. Next, the BYM model was fitted to the prevalence, standardized for age, education and migration status of the mothers to explore whether these factors could explain regional variation. Lastly, the confounding role of individual risk factors on the relationship between Limburg (vs other provinces in the Netherlands) and CAs (all and by type) was explored in logistic regression models.

Results: Data on 1,727,993 pregnancies ≥ 16 weeks were linked to socio-economic and environmental risk factors. Unadjusted RR for CAs in Limburg vs other Dutch provinces was 1.33 [95%CI 1.27-1.41]. Analyses of geographical clusters and contribution of the risk factors are to be presented to Province Limburg in May 2022 and remain under embargo until then.

Conclusion: The results are expected to provide insight on whether socio-economic factors and/or air pollutants are (partially) responsible for the increased prevalence of CAs in Limburg.