WEON 2017
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1.
Abstracts Oral Presentations
WEON 2017
Identifying patient safety risks in care transitions. Validity and reliability of clinician based record review in merged primary and secondary care patients’ records.

Objective
Inadequate information transfer during transitions in healthcare is a major patient safety issue. Aim of this study was to assess reliability and validity of identifying transitional safety incidents (TSIs) by clinician-based review of medical records.

Study design and settings
A digital transitional medical record was created including the medical records of both the general practitioner and the hospital. In total, 301 patients were randomly selected, who had visited their general practitioner and the departments of either gastroenterology or cardiology of the University Medical Centre Utrecht, the Netherlands in 2013. Six trained reviewers, clinicians from either general practice or hospital specialty, reviewed these transitional medical records on presence of TSIs. To assess inter-rater reliability, 10% of medical records were independently reviewed twice. To assess validity, the identified TSIs were compared with a reference standard of three objectively identifiable and systematically assessed TSIs (presence and timeliness of hospital correspondence, repeated diagnostic testing and communication of medication prescription changes).

Results
The reviewers identified TSIs in 52 (17%) of all transitional medical records. Variation between reviewers was high (range: 3–28 TSIs out of 48-51 medical records). Positive agreement between reviewers was 0%, negative agreement 80%, and ICC -0.18. The reviewers identified 43 (22%) of 194 objectively identifiable TSIs.

Conclusion
Clinician based assessment of medical records is not a reliable method to identify TSIs. Health care professionals from different settings differ in what they regard as a TSI, showing contrasting views on the healthcare system and risks. Differences can also be explained by insufficient training and the open identification method used in our study. Our priorities are to produce a more complete transitional medical record, to develop a more systematic identification process, improve training and to select a more homogenous group of reviewers.

BL End, a pooled analysis of 14 cohort studies

The association between the Mediterranean diet and risk of developing bladder cancer

Background
In Europe, 124,000 people are diagnosed and over 40,000 people are dying from bladder cancer each year, making this disease the sixth leading cause of cancer. Bladder cancer is the most expensive malignancy to treat from diagnosis until death, because of its high recurrence rates. Since most of the metabolites of ingested food come into direct contact with the bladder mucosa, diet may have an important role in the development of bladder cancer.

Aim
To investigate the potential association between adherence to the Mediterranean diet and the risk of developing bladder cancer, using data of 14 prospective cohort studies in a meta-analysis.

Methods
Data was analysed from the BLEND consortium study. Worldwide, BLEND is one of the largest nutritional databases, including 11,261 cases and 675,532 non-cases/controls from 18 case-control studies and 6 cohort studies from countries all over the world. An overall analysis, a gender-stratified analysis and an analysis stratified for both gender and disease stage will be performed, using logistic regression models to estimate the association between adherence to the Mediterranean diet and the risk of developing bladder cancer by calculating odds ratios (ORs) and 95% confidence intervals (95% CIs) for each study. A meta-analysis approach will be used in all three conditions to pool the weighted ORs of the different studies and calculate an overall estimate and the accessory 95% CI of the effects of the Mediterranean diet on the risk of developing bladder cancer.
Results
Results will be presented at the WEON 2017.

O03
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Design of the BRAGATSTON study: automated quantification of coronary artery calcifications on radiotherapy planning CTs for cardiovascular risk prediction in breast cancer patients

Context Cardiovascular disease (CVD) is the second most common cause of death in breast cancer patients. Certain adjuvant treatments (e.g. anthracyclins, radiotherapy) increase the risk of CVD, in particular in patients with pre-existing CVD risk factors. Early identification of these patients enables targeted cardiopreventive interventions, and switching to less cardiotoxic treatments. The strongest independent CVD risk factor is the presence and amount of coronary artery calcium (CAC). In clinical practice, CAC is quantified on cardiac CTs. Breast cancer patients treated with radiotherapy routinely undergo planning CTs. These inferior quality CTs may give the opportunity to routinely assess CAC.

Design Work package 1: Software for automated CAC quantification on breast planning CTs will be developed. Work package 2: In a retrospective multicenter cohort study (UMC Utrecht, Erasmus MC, Radboudumc), the association between CAC measured on breast planning CTs (n=15,000) and incident (non-)fatal CVD events will be evaluated. To assess the added predictive value of CAC over classic CVD risk factors, a case-cohort analysis will be performed among all patients with CVD events (n=200) and a random sample of the cohort (n=600). Work package 3: Within the UMBRELLA cohort, a survey among 100 patients will be conducted to explore preferences regarding disclosure of CAC scores.

Impact This study aims to provide a low cost tool for accurate detection of patients at high CVD risk. Patients and doctors can act upon this, by adapting the treatment and/or by adopting cardiopreventive interventions. Hereby, the burden of CVD in breast cancer survivors can be reduced and better overall survival rates can be achieved.

Discussion In the era of personalized medicine, it would be of great value to develop a simple and universal tool to detect patients with increased CVD risk and predict the individual survival benefit of a given treatment strategy accounting for this risk.

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O04
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Height and cancer risk in persons with Lynch syndrome: challenges within an international collaboration
Context: Lynch syndrome (LS) is caused by an inherited mutation in DNA mismatch repair (MMR) or EPCAM genes. It predisposes mutation carriers to an increased risk of early onset (colorectal) cancer. However, cancer risks differ between and within families with the same mutated gene, which indicates an influence of environmental factors. To investigate whether height influences LS related cancer risk in (combined) subgroups of gender and mutated gene, an international collaboration was set up in which data of three studies will be harmonized.

Design: Data of the Dutch GEOLynch cohort study, the American/Canadian/Australasian Colon Cancer Family Registry (CCFR) and the American Ohio Colorectal Cancer Prevention Initiative (OCCPI) will be harmonized to establish a database of >2900 adult participants with a proven MMR or EPCAM gene mutation. All studies collected information about participants’ height, cancer diagnoses and the mutated gene that caused LS. Additionally, data about participants’ characteristics has been collected.

Impact: Combining data of the mentioned studies will help to determine the influence of height on cancer risk in persons with LS. In addition, it will increase the power to investigate the association by subgroups.

Discussion: The three studies were designed with a different aim, hence collected data differently and considered different time points in their questionnaires. This may hamper comparability and thus harmonization of variables between studies. Moreover, since it is probably the process leading to tallness instead of tallness itself that may influence cancer risk, it is not clear when the exposure to height starts, i.e. when the participants start to be at risk. This will influence the method used for data analyses. In addition, if the retrospectively collected data will be used, ascertainment of participants was mostly non-random with respect to disease status, which also has consequences for the data analyses.

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Exploring physical and mental determinants of drop-out among nursing students in Rotterdam, the Netherlands: the SPRiNG cohort

Introduction
Drop-out from the nursing profession is increasing. Research regarding retaining nurses in their profession is scarce. The SPRiNG cohort follows three cohorts of third year nursing students until one year after graduation to examine the causes of drop-out from education/work. This study aims to gain insight in the determinants of (first signs of) health problems, productivity loss and drop-out and to describe the baseline characteristics of the first cohort.

Methods
For the first cohort 272 nursing students were invited to participate in a prospective cohort study (figure 1). Validated questionnaires were used for data collection, with special emphasis on mental and physical health, capacity and resilience. Content areas included: skill discretion, decision authority, psychological job demands, distress, work engagement, physical workload, musculoskeletal complaints, sickness absenteeism, presenteeism, and physical activity.

Results
Of the 272 third grade students 225 agreed to participate in the study. The mean age of the cohort was 23 years (standard deviation 4.4 ) and comprised of 198 female students (88%) of which 50% was living with their siblings. 194 students (86%) were native Dutch speakers. Even when they were ill, 68% of the students followed internships. 77 students (34%) considered at some point leaving nursing school.

Discussion
This baseline measurement of the SPRiNG cohort is the first step in developing an innovative validated predictive model for retaining students in the nursing profession. Intended further steps are exploring unknown reasons for drop-out through qualitative research, a systematic review of

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effective interventions, and testing of the most promising ones in an RCT. These steps will lead to a prediction model to prevent drop-out from nursing education and nursing profession as part of an intervention toolbox.

O06

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Do markers of non-alcoholic fatty liver improve the prediction of cardiovascular disease?

Context
For the identification of patients at increased cardiovascular risk, a risk estimation system is used to calculate an individual’s 10-year risk of cardiovascular disease (CVD). Based on this risk, physicians decide whether preventive treatment is indicated. The discrimination of the most commonly used risk estimation systems leaves room for improvement (area under the receiver operating characteristic-curve: 0.75-0.80). Non-alcoholic fatty liver (NAFL) is increasingly prevalent worldwide and is associated with a 64% increased cardiovascular risk. The aim of this study is to examine whether cardiovascular risk prediction can be improved when markers of NAFL are added to the Dutch risk estimation system SCORE-NL 2011.

Design
Data is used from the Dutch EPIC-NL cohort (contributor to the European Prospective Investigation into Cancer and Nutrition study), which comprises 38,994 men and women aged 20 to 70 years at recruitment in 1993-1997. Exclusion criteria are prevalent CVD, preventive treatment at baseline, age below 40 years, missing follow-up or no consent to linkage with disease registries. The main outcome is defined as a fatal or non-fatal CVD event in 10 years of follow-up, obtained by linkage to national registers (n=3,572). Serological markers of liver function and prediction scores for NAFL are added to SCORE-NL 2011 using backward selection. The quality of the prediction models is evaluated by measures of discrimination, calibration and reclassification, in comparison with SCORE-NL 2011.

Impact
This study is expected to provide evidence whether cardiovascular risk prediction improves when markers of NAFL are added to the risk estimation system SCORE-NL 2011 and whether this results in a more accurate indication for preventive treatment. In case of improvement, this might lead to a revision of future guidelines.

Discussion
An important challenge is to model the pragmatic adaptations of the SCORE-NL 2011 algorithm described in the current guideline on cardiovascular risk management.

O07

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CONSUMPTION OF ALCOHOLIC AND NON-ALCOHOLIC BEVERAGES IN RELATION TO LIVER FAT CONTENT: THE NEO STUDY

Introduction: Non-alcoholic fatty liver (NAFL) is associated with increased risk of cardiovascular disease. Although it is clear that high alcohol consumption increases liver fat, the effect on liver fat in the general population is not completely elucidated. Moreover, energy-containing non-alcoholic beverages may also contribute to liver fat accumulation. We aimed to study alcoholic
beverage consumption and replacement with non-alcoholic beverages in relation to hepatic triglyceride content (HTGC) in middle-aged men and women.

**Methods:** In this cross-sectional analysis of the Netherlands Epidemiology of Obesity study, HTGC was assessed by proton-MR spectroscopy. Habitual consumption of alcoholic and non-alcoholic beverages (coffee, tea, milk, sugar-sweetened beverages, non-alcoholic beer) was assessed using a food frequency questionnaire. All beverages were converted to units, each alcoholic unit containing 10 grams of alcohol, and to percent of total energy intake (En%). We performed linear regression to examine associations between alcoholic beverages and HTGC, adjusted for sex, age, smoking, education, ethnicity, physical activity, and total energy intake. We studied replacement of alcoholic beverages with non-alcoholic beverages per unit/day and per 10 En%/day.

**Results:** A total of 1,967 participants (47% men) were analysed, with a mean (SD) age of 55 (6) years, BMI of 26 (4) kg/m2, and HTGC of 5.7% (7.9). One unit of alcoholic beverages per day was associated with 1.09 times more HTGC (95%CI: 1.06, 1.13). Replacing one unit of alcoholic beverages with one unit of non-alcoholic beverages was associated with less HTGC (0.95; 0.89, 1.01). Replacing 10 En% of alcoholic beverages with 10 En% of non-alcoholic beverages was not associated with less liver fat (0.99; 0.97, 1.02).

**Discussion:** In a population-based cohort, consumption of alcoholic beverages was associated with more liver fat. However, in isocaloric replacement, non-alcoholic beverages were similarly associated with liver fat, suggesting that both alcohol and energy intake contribute to liver fat accumulation.

**Introduction**

**Hospital performance on length-of-stay, readmission, and mortality: are these related?**

**Frequently used quality indicators to assess hospital performance are mortality, readmission and long length-of-stay (LOS). To interpret individual indicators it is important to know whether these are related or reflect different processes. Interpretation is further complicated as hospital-level associations may not reflect what happens at patient-level (ecological fallacy). Therefore, we will assess associations between in-hospital mortality, readmission and long LOS, on hospital and patient-level to gain more insight how to interpret individual indicators.**

**Methods**

We analyzed administrative admission data of the Dutch National Medical Registration (LMR) from 2007-2012. Disease-specific patient admissions were considered (stroke, colorectal carcinoma, heart failure (HF), acute myocardial infarction (AMI) and hip and knee replacements (THA/TKA) in osteoarthritis patients) based on different patterns of quality indicators. Logistic regression analysis was used to assess whether patients with long LOS have higher chances of readmission (acute, 30-days) and in-hospital mortality, adjusted for case-mix and hospital. Pearson correlation coefficients were used to quantify the hospital-level correlation between the risk-standardized long LOS, readmissions and in-hospital mortality rates.

**Results**

Table 1 shows that indicators are related. However, associations varied between diseases and hospital-level associations differed in magnitude or direction from patient-level associations. For example stroke patients with long LOS had 58% lower in-hospital mortality, whereas an association in the opposite direction was found at hospital level (r=0.39). Within each separate hospital we found that patient with a higher LOS had a decreased odds on in-hospital mortality, but that the LOS varied across hospitals.

**Discussion**

Evaluation of hospital performance based on a single indicator does not provide a balanced view on quality of care, if not interpreted in the context of other indicators and assessed for disease-specific admissions. Furthermore, we have to be careful drawing conclusions from hospital-level associations without knowing patient-level associations as the ecological fallacy is at play.
Decline of kidney function preceding dialysis initiation in chronic kidney disease patients: a systematic review and meta-analysis

Introduction: Cohort studies in non-dialysis CKD patients point to substantial heterogeneity in rates of kidney function decline preceding dialysis. By design, these decline rates can be studied in either, CKD3-5 cohorts or dialysis-based cohorts. In the former, patients are followed from a certain point in the pre-dialysis phase and only a part of the patients starts dialysis therapy, while in the latter all patients initiated dialysis. Decline rates obtained from dialysis-based cohorts could give an overestimation, ie faster decline rate, of the true underlying kidney function decline prior to dialysis initiation. We performed a systematic review and meta-analysis, assessing and comparing the rate of kidney function decline (eGFR) prior to dialysis initiation in CKD patients, in both these cohorts.

Methods: Systematic literature searches in PubMed, EMBASE, Web of Science and Cochrane identified eligible cohort studies. Main outcome was weighted annual eGFR decline (ml/min/1.73m2/year) prior to dialysis initiation in adult CKD patients. Random-effects meta-analysis was performed using linear mixed models. With random-effects meta-regression analysis rates of eGFR decline were compared between patients from CKD3-5 cohorts and dialysis-based cohorts.

Results: Systematic searches identified 1231 unique publications with sixty publications included in the analysis. Mean follow-up until dialysis initiation was between 0.2-8.2 years. Mean baseline eGFR in CKD3-5 cohorts was between 10-45 mL/min/1.73m2. Meta-analysis of the mean annual eGFR decline preceding dialysis initiation showed a lower weighted eGFR decline of 2.4 (95%-confidence interval: 2.2-2.6) mL/min/1.73m2/year in CKD3-5 cohorts (n=43) when compared to a decline of 8.5 (6.8-10.1) mL/min/1.73m2/year in dialysis-based cohorts (n=17). This difference was confirmed with meta-regression analysis (difference=6.0 (4.8-7.2)mL/min/1.73m2).

Conclusion: Reported mean annual eGFR decline prior to dialysis initiation is greater and clearly

Prediabetes is associated with white matter abnormalities: The Maastricht Study

Introduction: Type 2 diabetes mellitus (T2DM) is known to be associated with cerebral small vessel disease (CSVD) and brain atrophy; however information on prediabetes is scarce. Therefore, we investigated whether both prediabetes and T2DM were associated with CSVD and brain atrophy.

Methods: We used cross-sectional data from The Maastricht Study, a population-based cohort study (n=2243, 1372 with normal glucose metabolism, 347 with prediabetes, and 524 with T2DM (oversampled), mean age 59.8 ±8.2 year, 48.4% female). We measured the volumes of white matter hyperintensities (WMH), white matter (WM), grey matter (GM) and cerebrospinal fluid (CSF) on images acquired by 3T-MRI. Diabetes status was determined by use of an oral glucose tolerance test. We used linear regression analyses to assess the association between (pre-)diabetes and brain tissue volumes, and adjusted for age, sex, intracranial volume, educational level and cardiovascular risk factors.

Results: Prediabetes and T2DM were associated with larger WMH volumes (β 0.11 [0.02;0.20], p=0.02, and 0.23 [0.15;0.31], p<0.001, respectively), and smaller WM volumes (β -0.32 [-0.59;-0.06], p=0.02 and -0.66 [-0.90;-0.41], p<0.001, respectively) in fully adjusted models, while we found no association with GM volume (β 0.17 [-0.09;0.44], p=0.19 and -0.18 [-0.42;0.07], p=0.16, respectively). T2DM was associated with a larger CSF volume (β 0.78 [0.51;1.05], p<0.001), while prediabetes was not (β 0.13 [-0.16;0.42], p=0.39).

Conclusions: Both prediabetes and T2DM are independently associated with higher WMH and lower WM volumes, not with GM volumes. These data suggest that, in a middle-aged population, structural brain changes in the white matter occur before onset of T2DM.
overestimated in patients from dialysis-based cohorts compared to CKD3-5 cohorts. Importantly, guidance for clinical decision-making regarding dialysis initiation should be based on eGFR decline data from CKD3-5 cohorts.

The risk of cardiovascular disease following breast cancer by Framingham risk score: EPIC-NL cohort

Objective: Cardiovascular disease (CVD) is the most common non-cancer condition following breast cancer, however, it’s unclear which women are at increased risk. This study assessed the risk of CVD following breast cancer for women with a low, moderate, or high Framingham risk score.

Methods: 1,103 women diagnosed with breast cancer (T1) after EPIC-NL enrolment between 1993 to 1997 (T0) were included. For every one of those, three to four women without breast cancer (n = 4,328) were matched on age at T1, year of T1, and time between T0 and T1. Framingham risk score was calculated at T0 and used to categorize women as low (<10%), moderate (10% - 20%), or high (>20%) risk. Time at risk was the time between T1 and first CVD event (hospitalization or death) since T1. Cox proportional hazard models were used to estimate the risk of CVD, adjusted for age at T1 and body mass index at T0.

Results: For all 5,431 women, median age was 63 years (interquartile range (IQR): 56-68) at T1 and median time between T0 and T1 was 8 years (IQR = 4-11). Median follow-up since T1 was 5 years (IQR = 2-9) for women with breast cancer and 6 years (IQR = 3-10) for women without breast cancer, during which 92 (8.3%) and 325 (7.5%) CVD events occurred respectively. In the low Framingham risk group, women with breast cancer (n = 676) had a 1.44 (95% CI = 1.00 - 2.06) higher risk of CVD than women without breast cancer (n = 2,856). In the moderate and high Framingham risk groups, the risk of CVD did not differ between women with breast cancer and women without breast cancer.

Conclusion: This study shows that, among women with a low risk of CVD, breast cancer increases the risk of CVD hospitalization or death.
female donors was analysed using life tables and time-varying Cox proportional hazards models.

Results
The cohort for the primary analyses consisted of 40,013 patients who received 77,276 red blood cell transfusions. The full cohort included 64,946 patients who received 285,355 transfusions. For male patients the time-dependent “per transfusion” hazard ratio for death after a red blood cell transfusion from an ever-pregnant female donor, compared to a male donor, was 1.128 (95% confidence interval (CI): 1.009 to 1.260) and for a never-pregnant female donor compared to a male donor this was 0.928 (CI: 0.809 to 1.064). For female patients this was 0.993 (CI: 0.870 to 1.133) for an ever-pregnant female donor and 1.007 (CI: 0.882 to 1.149) for a never-pregnant female donor. Analyses of the single transfusion cohort and the full cohort yielded similar results.

Discussion
Our results confirm the association of red blood cell transfusions from female donors with decreased survival of male patients, but also limit this association to female donors with a history of pregnancy and male patients under the age of 50. This opens new avenues for further mechanistic research and, in the future, might lead to changes in transfusion strategy.

O13
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Unravelling biological mechanisms underlying associations of inactivity with persistent fatigue in colorectal cancer survivors: a molecular-epidemiological approach

Context: Persistent fatigue is the most common and distressing health problem after cancer, and affects over 1 in 3 colorectal cancer (CRC) survivors. Replacing sedentary behavior (daytime sitting/lying) by physical activity may reduce fatigue in CRC survivors, but the underlying biological mechanisms remain to be elucidated. In two ongoing projects, we are investigating whether the following parameters of hypothesized mechanisms underlie associations of inactivity with fatigue in CRC survivors (Figure 1):
1. Plasma metabolites of energy and fat metabolism, muscle protein metabolism and chronic inflammation, and anthropometric measures of adiposity and muscle function;
2. Magnetic resonance imaging (MRI)-derived concentrations of brain metabolites and parameters of white matter integrity.

Design: Both projects are embedded within an ongoing prospective cohort study in CRC survivors (EnCoRe study) with repeated measurements at 6-weeks (n=250), 6-months (n=204), 1-year (n=166) and 2-years (n=74) post-treatment. Sedentary behavior and physical activity are assessed by accelerometers and fatigue by questionnaires. Within Project 1, available anthropometric measurements and plasma concentrations of ~150 metabolites (targeted metabolomics) are used. Confounder-adjusted linear mixed-modelling will be applied to identify metabolites and anthropometric measures longitudinally associated with inactivity and persistent fatigue, and mediation analysis will be conducted. Within Project 2, we have selected 12 fatigued and 12 non-fatigued participants and measure brain metabolite concentrations (MR spectroscopy) and parameters of white matter integrity (diffusion MRI). Linear regression will be applied to identify MRI-derived parameters associated with inactivity and fatigue.

Impact: These projects will provide novel knowledge on biological mechanisms linking inactivity to fatigue in CRC survivors. This will provide leads for developing effective mechanism-tailored interventions to reduce persistent fatigue in CRC survivors.

Discussion: Our molecular-epidemiological approach can also be applied by other researchers with similar objectives. In our experience, a multidisciplinary team with scientists from all relevant areas is imperative for the success of these projects.
Coffee consumption and bladder cancer risk; which groups are at risk?

Context:
Contradicting studies have not established whether coffee consumption is a risk factor for bladder cancer (BC). Studies have found an associated risk in males, with females largely unaffected even at high coffee consumption. These conflicting studies might stem from both antioxidant and carcinogenic components of coffee and their overall weighting on the end product not being fully understood.

Design:
The Bladder Cancer Epidemiology and Nutritional Determinants Study (BLEND) consortium at Maastricht University includes 24 observational studies with information on BC and diet for roughly 700,000 people across 3 continents. We aim to observe the relationship between coffee consumption and risk of BC, ensuring confounders are taken into account and that identified risk groups (such as males) are analysed separately. Coffee consumption will be measured by cups per week and will be analysed by meta-analysis using the random-effects model for both cohort and case-control studies separately.

Phase 1 will identify if there’s a significant relationship between continuous coffee consumption and BC cases. Phase 2 will identify if heavy drinkers (≥4 cups of coffee per day) have a significantly higher risk of BC than non-heavy drinkers (<4 cups of coffee per day).

Impact:
Coffee is a popular beverage and especially prevalent in the ageing developed world. BC costs on average $65,000 to treat per person. Thus, to reduce the financial burden, establishing dietary factors which may impact the incidence of BC will be helpful for public health officials.

Discussion:
Coffee preparation varies around the world, especially with regards to what defines a ‘cup’. This will be taken into consideration when the results are discussed at WEON.

The Sarphati Cohort: a dynamic cohort of 150,000 children in Amsterdam

Context: Overweight, including obesity, forms a serious health threat in the Netherlands and worldwide. In Amsterdam, 19% of children are overweight. Sarphati Amsterdam is a newly established, unique collaboration between the city of Amsterdam and its research institutions, focusing on innovative multidisciplinary research beneficial to preventing non-communicable diseases effectively and sustainably. The Sarphati Cohort, a dynamic cohort study, systematically monitors growth and its determinants from birth until adulthood, in order to identify causes of overweight and evaluate interventions to combat overweight.

Design: Data collection within the Sarphati Cohort is linked to routine consultations with Youth Health Care (YHC). YHC monitors the health of all ~150,000 children in Amsterdam. Within the Sarphati Cohort their development is closely tracked until they reach the age of 18. The inclusion of ~11,000 newborns annually gives the Sarphati Cohort its dynamic character. Growth and its determinants (e.g. sleep, nutrition, physical activity) will be systematically monitored during 17 consultations from birth until adulthood. In addition to this core set of data, data will be collected through age-specific questionnaires (figure). More extensive research is possible in subcohorts.

Impact: With the Sarphati Cohort, Sarphati Amsterdam facilitates excellent research in the field of overweight that will contribute to the ambitious policy objectives of the city of Amsterdam to promote healthy behaviour and improve the quality of life of young people.

Discussion
The core set-consultation data collection (0-4 years) has started in November 2016. Age-specific questionnaires are currently being developed. During the conference, we will present the implications and challenges we face with regards to the:

1. implementation of data collection in the daily practice of YHC
2. use of questionnaires, relevant for both care and research
3. use of medical records for research
4. privacy and legal aspects concerning the inclusion of all children in Amsterdam

O16
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The impact of aspects of methods design on study results: The case of the nested case control study

Context
Contradicting results are a common issue in explanatory epidemiological research. Study results are largely influenced by the design (object and methods) applied. Often the object of a causal study is expressed as ‘the future occurrence of an outcome as a causal function of current exposure(s)’ and the data collection method is either a randomized controlled trial (RCT), a cohort study (census) or a case-cohort study (sampling). More appropriate is to design the object as ‘the present occurrence of an outcome as a causal function of past exposure(s)’, and an incidence density study (case-control study redefined, sampling) is the appropriate method of data collection.

We wonder to what extent different designs within one study population lead to different (contradicting) results and we will address the difficulties in relation to the different designs.

Design
We applied both objects and the different methods (census, sampling) to the same study population i.e. the PIPO birth cohort, investigating the association between breastfeeding and receiving a doctor’s diagnosis of asthma.

First, we considered the current incidence approach, where we applied 2 methods to sample population time ‘at risk’: each time a case occurred, leading to matching on age and incidence density sampling without matching.

Secondly, we considered the future incidence approach. We applied 3 methods: census-approach, case-cohort sampling and cumulative sampling.

Impact
The current incidence design allows to reconstruct covariates prior to disease manifestation within a correct time frame. For the future incidence approach, assessing covariates (possibly important confounders) and defining T0 was problematic.

Discussion
We argue that in causal research the most appropriate object design is based on current incidence density and the method of data collection should match this object. Assessing covariates is different and not appropriate in the future (cumulative) incidence approach. Possible impact on measures of association, will be studied next.

O17
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Green and built environmental infrastructure as predictor of psychosocial stress in children and adolescents

Introduction: There is evidence that living in green areas can alter stress levels. Unfortunately studies in children are lacking, while we know that childhood stress might negatively affect normal development and promote disease in adulthood. Therefore, the aim of this study was to investigate whether environmental infrastructure is a predictor of psychosocial stress in children and adolescents.

Methods: In a longitudinal design, 175 Flemish children and adolescents (50.9% boys) aged 6.7-12.2 years at baseline were followed up for three years (2012-2015). Information about stress was obtained using questionnaires (behavioural and emotional) and hair cortisol, an objective stress biomarker. The environmental infrastructure e.g. nature, agriculture, industry, residency and traffic, in a 100-m to 4-km radius around a participant’s home was estimated with Graphical Information Systems. Cross-sectional and longitudinal
associations were tested using multivariable linear regression and mixed model, while adjusting for age, sex and socioeconomic status.

Results: In cross-sectional analysis, a higher exposure to nature and agriculture resulted in increased feelings of happiness (β=0.17, p=0.01), less negative emotions (β=-0.15, p=0.02), lower hair cortisol (β=-0.18, p=0.03), less conduct problems (β=-0.13, p=0.049) and less hyperactivity problems (β=-0.14, p=0.03). In longitudinal analysis, similar positive findings were seen for nature and happiness (p=0.049), while negative associations were seen between industry and anger (p=0.03) and negative emotions (p=0.01). No associations were seen between traffic and stress.

Conclusion: Based on the results, we might conclude that a higher exposure to green environment, e.g. nature and agriculture, and less to built environment close to a child’s home may have a beneficial effect on their stress level.

O18

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Selective citation in the published literature on the association between swimming in chlorinated water and childhood asthma: a citation analysis

Introduction: Development of knowledge depends on an unbiased representation of evidence. Selective citation may thwart this unbiased representation. The research on the relationship between swimming and childhood asthma has raised some controversy in recent years, raising the question about the role of selective citation in this area. Specifically, we aimed to assess which factors determine the citation of previous publications in this field.

Methods: We identified all published literature on the relation between swimming in chlorinated water and childhood asthma. We extracted data on article characteristics that were related to the content (such as study outcome, article type sample size), that were content-unrelated (e.g. funding source, impact factor), and on author characteristics (e.g. gender, authority). We also looked at self-citation. To assess the impact of these factors on citation, we performed a series of univariate random-effects logistic regressions, with the potential citation paths as unit of analysis. We repeated these analyses while adjusting for article type.

Results: There was strong evidence for self-citation in this network: articles that had at least one author in common, cited each other 5.2 times more often than articles that did not. Similarly, the chance of being cited was higher for articles that were empirical rather than narrative (odds ratio [OR] 4.2), that reported a high sample size (OR 5.8), and that were written by authors with a high authority (OR 4.1). There was some evidence for citation bias in the network, with positive articles being cited 1.8 times more often, but this finding was not robust and depended on the type of analysis.

Conclusions: There is clear evidence of selective citation in this research field. Authors particularly prefer to cite their own work rather than that of others. The evidence for citation bias in this field was not very strong and inconsistent.

O19

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AIRbezen@school: a study on the association between DRY COUGH (DC) and TRAFFIC RELATED PARTICULATE MATTER (TRP) measured by leaf SIRM values

Introduction
Exposure to TRP has been associated with adverse effects on different health outcomes. In environmental epidemiological research (EER) individual health effects are determinable on condition of individual assessment of both exposure and outcome. Considering the respiratory system in children, as gatekeeper, which is primarily affected by TRP, we investigated the association between a common respiratory symptom, DC in absence of a
common cold, and TRP-exposure, at home and at school in an urban environment.

Methods
In this study we used strawberry plants as monitoring stations for measuring TRP as particulate matter deposits on their leaves. We delivered the plants (30/school) at a selection of schools (n=12), 10 plants remained at school and 20 were taken home with the children of the same class. After one month in the open air the leaves (5 leaves/plant) were collected and examined in the lab in a biomonitoring analysis called Saturation Isotherm Remanent Magnetization (SIRM). Leaf SIRM has previously been proven to be a reliable proxy for TRP.

We collected information on the respiratory health outcomes by means of ISAAC-questionnaires.

Results
Incidence Density Ratio’s (IDR) were calculated and logistic regression was performed to measure the strength of the TRP-DC-association, adjusted for smoking. The result for the TRP-DC-association at school was positive (IDR=3.6; 95% confidence interval (CI), [1.4-9.1]) whereas there was hardly an association at home between TRP and DC (IDR=1.2; 95% CI [.49-3.15]).

Discussion
We found a positive association between TRP-exposure (as measured by leaf SIRM) and the occurrence of DC in the school outdoor environment but not in the outdoor environment at home. We hypothesise that this might be explained by differences in the activity pattern.

The AIRbezen@school method characterised by low budget, extended scale (n>100) and subject based exposure measurement, offers, as result of that combination, a new perspective for further EER.

O20
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Working life expectancy with and without disability among older workers in the Netherlands and United States

Introduction: Due to population aging, many countries are reforming their policies by abolishing early retirement routes and raising statutory retirement ages. As health deteriorates with age, many older workers may experience that health limits their workability. The necessity to continue working may depend on the flexibility and generosity of a national pension system. Flexibility refers to retirement opportunities and their entitlement conditions, and generosity to the post-retirement income as percentage of pre-retirement income. It is expected that in countries with low flexibility and generosity, workers with disabilities stay in the workforce longer. This study examines this duration.

Methods: Two countries were selected with high versus low flexibility and generosity: the Netherlands and the United States, respectively. Data from the Longitudinal Aging Study Amsterdam (LASA) and the Health and Retirement Study (HRS) were used. Participants aged 55-65 years at baseline (2002) with a paid job were selected and followed up to 2012/2014 (n=385 and n=2335, respectively). Two health states were distinguished based on the common disability indication difficulty climbing stairs. Hazard Ratios (HRs) were estimated with Cox-regression analyses in SPSS and Working Life Expectancies at age 55 (WLE55s) were estimated using the MSM and ELECT packages in R.

Results: In the Netherlands, workers with disability retire earlier (HR 1.40; 95%CI 1.00-1.94) compared to workers without disability, and total WLE55 was 5.4 years of which 0.7 with disability. In the US, workers with disability retire earlier as well, although the effect size is smaller (HR 1.22; 95%CI 1.11-1.34) and workers work more years with disability (2.7 years of total WLE55 of 8.5 years).

Discussion: This study provides insight in the effect of the flexibility and generosity of pension systems on important work-related outcomes. Societies with low flexibility and generosity should be aware that disabled workers need special attention regarding their work environment.
Vitamin K antagonist use and rate of renal function decline and time until start of dialysis in incident pre-dialysis patients.

Introduction:
Post-hoc analyses of recent trials on novel oral anticoagulants versus vitamin K antagonists showed that patients with a mildly decreased kidney function receiving vitamin K antagonists exhibit a greater decline in renal function than patients receiving novel oral anticoagulants. Whether these vitamin K antagonist effects are the same in pre-dialysis patients is unknown. Therefore, the aim of this study was to investigate the association between vitamin K antagonist use and rate of renal function decline and time until start of dialysis in incident pre-dialysis patients.

Methods:
Data from the PREdialysis PAatient REcord (PREPARE) study, a multicenter follow-up study of patients with chronic kidney disease who started pre-dialysis care in The Netherlands (1999–2011), were analyzed. Cox proportional hazards models were used to estimate the hazard ratio (HR) with 95% confidence intervals (95% CIs) for starting dialysis and linear mixed models were used to compare renal function decline between vitamin K antagonist users and non-users. Adjustments were made for potential confounders. Missing data were imputed with multiple imputation.

Results:
In PREPARE, vitamin K antagonist use was known for 984 patients. Of these patients, 101 used a vitamin K antagonist. The HR for start of dialysis of vitamin K antagonist use compared to non-use was 1.20 (95% CI 0.85 to 1.69) after adjustment for confounders. For all patients the average change in renal function was -1.45 (95% CI -1.80 to -1.10) ml/min/1.73m2 per year. Using vitamin K antagonists at baseline was associated with an extra change of -0.09 (95% CI -1.32 to 1.13) ml/min/1.73m2 per year as compared with non-users.

Conclusion:
The use of vitamin K antagonists was not associated with an earlier start of dialysis or an accelerated kidney function decline as compared with non-use in incident pre-dialysis patients.

Excess early postnatal weight gain and blood pressure in healthy young children

Background: Blood pressure (BP) tracks from childhood to adulthood and early BP trajectories predict cardiovascular disease risk later in life. Excess postnatal weight gain is associated with vascular changes early in life, however to what extent it is associated to children’s BP is largely unknown.

Methods and Results: In 775 healthy 5-year-old children of the Wheezing-Illnesses-Study-Leidsche Rijn (WHISTLER) birth cohort systolic and diastolic BP (SBP;DBP) were measured in sitting and supine postures, and Z-scores of individual weight gain rates adjusted for length gain rates (WLG) were calculated by using at least two weight and length measurements from birth until 3 months of age. Linear regression analyses were conducted to investigate associations between WLG and BP adjusted for sex and ethnicity.

Each standard deviation increase in WLG resulted in 0.9 mmHg (95% CI 0.2;1.5) higher sitting SBP after adjustment for confounders. WLG was not associated to supine SBP or DBP. Especially in children in the lowest birth size decile, high excess weight gain resulted in higher SBP values compared to those children with low WLG.

Conclusion: Children with more excess weight gain in the first three months of life, particularly those with a low birth size, have higher systolic blood pressure at the age of 5 years.
**Age at menarche and coronary heart disease risk: a pan-European case-cohort study**

Background: There is uncertainty whether the association between age at menarche (AAM) and coronary heart disease (CHD) risk is linear or U-shaped. Traditional CHD risk factors have been suggested to mediate the association. In this observational study we investigated the association between AAM and CHD risk and performed mediation analysis in order to determine what mechanisms underlie the relation between AAM and CHD risk.

Methods: In a case-cohort study nested in the European Prospective Investigation into Cancer and Nutrition (EPIC) study, 15,013 women, of whom 4,458 incident cases were included. AAM was divided in the categories ≤ 11, 12, 13, 14, 15, 16 and ≥ 17 years. The outcome was the first fatal or non-fatal CHD event. Prentice weighted Cox proportional hazard modeling was used to assess the association between AAM and CHD risk and was adjusted for age, lifestyle and reproductive risk factors, with AAM of 13 years as reference category.

We performed mediation analysis with BMI, weight and height.

Results: AAM was significantly associated with CHD risk, with HR’s of 1.38 (95% CI: 1.19-1.61), 1.18 (95% CI: 1.03-1.35) and 1.35 (95% CI: 1.04-1.77) for AAM groups ≤11, 12 and ≥17 years, respectively (Table 1). This association is U-shaped (p-value quadratic trend < 0.001). BMI, weight and height mediate the relation between AAM and CHD risk and was adjusted for age, lifestyle and reproductive risk factors, with AAM of 13 years as reference category.

We performed mediation analysis with BMI, weight and height.

Conclusions: Early and late menarche were associated with an increased risk of CHD, and the association was mediated by BMI, weight and height. The directional differences in the explained proportions for early and late menarche suggest that different mechanisms exist for the effect of early and late menarche on CHD risk.

**CLINICAL PROFILE OF POST-LOAD GLUCOSE CURVES AND THEIR ASSOCIATION WITH CARDIOMETABOLIC RISK FACTORS OVER TIME.**

Background: Subclasses of different glycaemic disturbances could explain variation in characteristics of people with prediabetes and type II diabetes (T2DM). We aimed to identify subgroups with distinct glucose curves following an oral glucose tolerance test (OGTT) or a mixed meal test (MMT) and describe their baseline clinical characteristics and associations with cardiometabolic risk factors overtime.

Methods: The study included 2179 people with prediabetes and 819 newly diagnosed T2DM patients within the Diabetes Research on Patient Stratification (DIRECT) Study. Latent class trajectory analysis was used to identify subgroups of glucose curves from OGTT for those with prediabetes and MMT for T2DM patients at baseline. Using general linear models, these subgroups were associated with clinical characteristics at baseline and insulin resistance (HOMA-IR) or HbA1c at 18 months, adjusted for potential confounders.

Methods: The study included 2179 people with prediabetes and 819 newly diagnosed T2DM patients within the Diabetes Research on Patient Stratification (DIRECT) Study. Latent class trajectory analysis was used to identify subgroups of glucose curves from OGTT for those with prediabetes and MMT for T2DM patients at baseline. Using general linear models, these subgroups were associated with clinical characteristics at baseline and insulin resistance (HOMA-IR) or HbA1c at 18 months, adjusted for potential confounders.

Results: We identified five subgroups from OGTT and three from MMT, labelled in order of increasing peak values as C1 to C5 (OGTT) and T1 to T3 (MMT).
C4 and C5 had similar fasting glucose (6.0 and 6.2 mmol/l) but different 2-hour glucose (5.5 and 8.4 mmol/l). C5 had higher BMI and Hba1c than C4. C3 compared to C2, had similar fasting glucose (5.7 mmol/l), different 2-hour glucose (5.4 and 7.7 mmol/l), higher BMI and Hba1c. In both analyses, medium (C3 and T2) and highest (C5 and T3) peak curves had highest BMI and Hba1c. At 18 months, change in HOMA-IR were higher in C5 [beta=1.72; 95%CI=1.28-2.16], C4 [beta=0.70; 95%CI=0.35-1.06], C3 [beta=1.04; 95%CI=0.73-1.35], C2 [beta=0.38; 95%CI=0.13-0.64] compared to C1. At 18 months, Hba1c (mmol/l) increased from T2 [beta=1.88; 95%CI=-0.44-4.20] to T3 [beta=2.93; 95%CI=0.10-5.75] relative to T1.

Conclusions: Using OGGT and MMT, different glycemic profiles can be identified with different clinical characteristics and cardiometabolic risk. Subgroups with highest 2-hour glucose had greater cardiometabolic risk than those with high fasting levels only.

Vitamin D and calcium intake in relation to colorectal tumor risk in persons with Lynch syndrome

Introduction
Although vitamin D and calcium influence sporadic colorectal carcinogenesis, the role in the development of hereditary colorectal cancer is unknown. We investigated the association of dietary vitamin D and calcium intake, alone and in combination, with colorectal tumors in persons with Lynch syndrome (LS).

Methods

In the Geolynch prospective cohort study, 466 persons with LS completed a food frequency questionnaire and a lifestyle questionnaire between 2006 and 2008 and were followed up for colorectal tumors until 2014. Vitamin D and calcium intake were calculated using the Dutch food composition table. Information about carcinoma and adenoma occurrences was collected by reviewing medical records.

Cox proportional hazard models were used to estimate adjusted hazard ratios (HRs) and 95% confidence intervals (CI). Using robust sandwich variance estimates to control for dependency within families, models were adjusted for age, gender, education level, total energy intake, smoking status, physical activity level, and stratified by number of colonoscopies during follow-up.

Results
During a median follow-up of 59 months, 198 persons with LS developed a colorectal tumor. A high vitamin D intake compared with a low vitamin D intake (≥ 3.8 ug/day versus < 3.8 ug/day) showed a HR (95% CI) of 0.73 (0.51-1.05), while a high calcium intake compared with a low calcium intake (≥ 956 mg/day versus < 956 mg/day) resulted in a HR (95% CI) of 0.80 (0.61-1.06). Persons with both a high vitamin D as well as a high calcium intake were associated with a lower colorectal tumor risk (HR (95% CI) = 0.63 (0.41–0.95)) compared with those with a low vitamin D as well as a low calcium intake.

Conclusion
The results of this prospective study indicate that a combined high intake of dietary vitamin D and calcium is associated with a lower colorectal tumor risk in persons with LS.

Adherence to the Mediterranean diet and risk of lung cancer in the Netherlands Cohort Study

Introduction

Although Mediterranean diet is considered protective against colorectal cancer, its role in lung cancer is less clear. We aimed to investigate the association of adherence to the Mediterranean diet with lung cancer risk in the Netherlands Cohort Study in a nested case-control study.

Methods

The Netherlands Cohort Study is a prospective cohort study of 28,710 men and 30,672 women aged 55 to 70 years at baseline in 1986. A total of 1,395 lung cancer cases were identified by linkage with the Dutch Cancer Registry. The Mediterranean diet was assessed using a validated food frequency questionnaire at baseline, with higher adherence defined as above the median. Cox proportional hazards regression was used to estimate adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for lung cancer risk.

Results
A higher adherence to the Mediterranean diet was associated with a lower risk of lung cancer (HR = 0.83, 95% CI: 0.74-0.93 for the highest vs. lowest quintile). The association was more pronounced among never smokers (HR = 0.73, 95% CI: 0.58-0.92) than among former smokers (HR = 0.91, 95% CI: 0.72-1.14) or current smokers (HR = 0.95, 95% CI: 0.78-1.17).

Conclusion
The findings suggest that adherence to the Mediterranean diet is protective against lung cancer, particularly among never smokers.
The Mediterranean diet (MD) has been associated with numerous health benefits, including reductions in cardiovascular disease risk and mortality. However, evidence on a cancer-protective effect is limited and inconclusive. Therefore, we prospectively investigated the association between MD adherence and lung cancer risk.

Methods
Analyses were performed using data collected in the Netherlands Cohort Study, which was initiated in 1986. At baseline, 58279 men and 62573 women, aged between 55 and 69 years, completed a self-administered questionnaire concerning diet, lifestyle and other cancer risk factors. Incident cancers were detected until 20.3 years of follow-up using annual computerized record linkage with the Netherlands Cancer Registry and the Dutch pathology database (PALGA). Dietary habits over the preceding year were assessed at baseline using a 150-item semi-quantitative food frequency questionnaire. The alternate Mediterranean diet score excluding alcohol (aMEDr) was calculated to estimate MD adherence. In total, 2861 lung cancer cases and 3720 subcohort members were included in the multivariable Cox proportional hazards models.

Results
High versus low MD adherence was associated with reduced lung cancer risks in men and women with hazard ratios of 0.91 (95% confidence interval (CI): 0.72 – 1.15) and 0.73 (95% CI: 0.49 – 1.09), respectively, though the reductions were not statistically significant. Combining both sexes, the inverse association was most pronounced in never smokers, but lacked statistical significance. Subtype-specific analyses indicated variability in associations for the histological subtypes, especially in men. However, heterogeneity tests were not statistically significant.

Discussion
Even though the observed inverse associations were not statistically significant, our study is in agreement with the hypothesis that higher MD adherence might be associated with a reduced lung cancer risk and that this association is not restricted to Mediterranean populations. The inverse associations seemed strongest in women and seemed to vary between the histological subtypes in men.
not clear cell RCC risk. An early diagnosis of kidney stones was associated with an increased RCC risk.

O28

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The association between fluid intake and age at diagnosis for bladder cancer patients from the West Midlands Bladder Cancer Prognosis Programme (BCPP).

Introduction:
Bladder cancer (BC) is the ninth most common cancer in the UK. BC occurs more often in elderly and because of the increasingly aging population, coupled with having the largest per-patient lifetime cost of all cancers and the recurring nature of BC, it will likely form a large burden on healthcare systems in the future. In this study, the relation between total fluid intake and clinical characteristics of BC is further examined for both non-muscle invasive BC (NMIBC) and muscle invasive BC (MIBC).

Methods:

For this study, data from the West Midlands Bladder Cancer Prognosis Programme (BCPP) is used. The BCPP is an epidemiological prospective cohort study with 1550 participants from nine different hospitals and was initiated by the Cancer Research UK Bladder Cancer Group, based at the University of Birmingham. Participants were included if they had abnormal cystoscopy findings suggestive of bladder cancer.

Results:
In total, 1108 patients were included in the analyses of which 878 NMIBC patients and 230 MIBC patients. Multilevel regression models were used to calculate predicted means, corrected for sex, age and smoking status. A random intercept was also included to correct for possible differences between hospital sites. After adjustment, the highest quintile for alcohol consumption was on average 4.6 years younger at diagnosis (95% CI: -6.9 to -2.3) and 7.6 years younger at diagnosis (95% CI: -11.7 to -3.4) compared to non-alcohol drinkers for NMIBC and MIBC respectively. A significant P-trend was observed for both NMIBC patients and MIBC patients (p-value: 0.00).

Discussion:
Current results suggest that alcohol consumption is associated with a bladder cancer diagnosis at a younger age. There seems to be a linear relationship between alcohol consumption and age at diagnosis for NMIBC and MIBC patients. More results could be presented at the WEON 2017.

O29

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The UMBRELLA Fit study: the effects of exercise on breast cancer patients’ quality of life, using the cmRCT design

Context: Meta-analyses of randomized controlled trials have shown beneficial effects of physical exercise on fatigue and quality of life in breast cancer survivors. However, these effects were often small, which might partly be explained by contamination in the control group (controls who adopt the behaviour of the intervention group). Additionally, since blinding in an exercise trial is not possible this often results in difficult accrual and drop-out after randomization. The cohort multiple Randomized Controlled Trial (cmRCT) is an alternative for conventional randomized controlled trials and has the potential to overcome these disadvantages.

Design: The UMBRELLA Fit study is performed within a breast cancer cohort, UMBRELLA. In UMBRELLA, breast cancer patients who visit the radiotherapy department of the University Medical Center (UMC) Utrecht are asked to give consent for collection of medical information, providing patient reported outcomes through regular questionnaires
and to be randomized into future intervention studies. A subset of inactive patients (12 or 18 months after enrollment in UMBRELLA) who gave broad consent are randomly allocated to the intervention or control group (n=83/group). Patients randomized to the intervention group are offered a 12-week structured exercise programme and encouraged to adopt an active lifestyle. The control group is not informed. To evaluate intervention effectiveness, results of regular cohort measurements will be used.

Impact: The UMBRELLA Fit study provides the opportunity to examine the feasibility of the cmRCT design in exercise-oncology research. Results may be generalizable to other lifestyle intervention studies where blinding is not possible.

Discussion: UMBRELLA Fit studies the effect of a 12-week supervised exercise intervention on breast cancer survivors’ quality of life on the short- (6 months) and long-term (24 months), using the cmRCT design. The design will be explained in more detail. First experiences and operational challenges will be presented since recruitment is still ongoing.

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**O30**

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**Implementing a risk prediction tool in obstetric care**

Context
Five complications, preeclampsia, gestational diabetes mellitus, preterm birth and inadequate birth weight (either small or large for gestational age) are responsible for most adverse obstetric outcomes. Obstetric outcomes can be improved by risk-dependent care: patient-specific risk profiles combined with appropriate follow-up. Individual risk stratification is achieved using externally validated prediction models for preeclampsia and gestational diabetes mellitus. Risks of preterm birth and inadequate birth weight will be assessed using a list of risk factors composed by the Limburg Obstetric Quality System.

Design
External validation of prediction models and assessment of former care-as-usual has been achieved in a prospective multicenter cohort study (EXPECT 1, 2013-2015). Risk-dependent care will be implemented and analyzed in a second prospective multicenter cohort study (EXPECT 2, 2017-2019). Impact of risk-dependent care will be analyzed by comparing both cohorts regarding obstetric outcomes, maternal health-related quality of life, patient satisfaction and health care costs. Similar to EXPECT 1, all women who are ≥18 years old with a gestational age <16 weeks are eligible for inclusion.

Impact
Risk stratification is an important aspect of the Dutch obstetric care system. Modernization of risk stratification using prediction models combined with risk-dependent follow-up can lead to improved outcomes for both mother and child. Additionally, individual risk-assessment increases the opportunity of shared decision making. This may result in an increase of patient satisfaction. Furthermore, health care consumption and thereby costs will change.

Discussion
A combination of clinical and lifestyle interventions, along with increased awareness, can lead to significant reductions of maternal and neonatal mortality and morbidity. However, risk-dependent care can only lead to improved outcomes if they change behavior of both caregivers and pregnant women. Moreover, risk-dependent care is hypothesized as cost-effective if low risk pregnancies are treated as such.

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**O31**

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**The future of null-hypothesis significance testing II**

Context: Last year at WEON, I presented our thoughts on the future of null-hypothesis significance testing (NHST). NHST is still the leading paradigm in biomedical and other empirical sciences, despite criticism by leading epidemiologists and statisticians that NHST is a form of indirect inference. I concluded that educational papers haven’t changed practice and that action is
needed. However, it is unclear how a strategy for a paradigm shift should look like. We aim to study, which barriers and facilitators related to the use of NHST are experienced by stakeholders within science and how we can achieve a paradigm shift.

Design: We will conduct interviews and focus groups with editors of scientific journals, researchers, representatives of funding agencies and lecturers of statistics. This will provide us with information about the barriers and facilitators but also will enable us to identify early adopters; persons who are willing to change their behaviour with respect to drawing conclusions from empirical studies and can serve as role models for the rest of the scientific society. These early adopters will be invited to join work conferences in which we will develop the actual strategy to shift the paradigm.

Impact: There is growing awareness and debate about this topic, so the project is very timely. The potential impact of this study is tremendous, although we acknowledge that the subject is controversial and that it will not be easy to shift a paradigm that has been dominant for so many years.

Discussion: This project is suited to explore which alternatives for NHST will eventually be acceptable for all empirical researchers. Key is that we don’t replace one default binary (reject or accept) tool by another, but instead create a culture in which researchers put more thought into what they conclude from their data.

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O32
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Keeping Adolescent Girls and Young Women HIV free through distribution of HIV Self-Tests to male partners, creation of male-friendly clinics, and targeted PrEP.

Context:
Despite high risk for HIV-acquisition, South African adolescent girls and young women (AGYW) are often unaware of their male partner’s status. HIV testing rates among young men is low.

Design:
We aim to implement and assess three interventions: 1) AGYW-negotiated home-based HIV-self-testing of sexual partners 2) male-friendly clinic to promote linkage to care of HIV positive men 3) pre-exposure prophylaxis (PrEP) to AGYW in relationship with an HIV positive partner or partner with unknown HIV status. In a first phase, we performed formative research to understand the contextual factors and to develop two videos to be used during implementation. In the second phase, we will assess uptake and adherence of the interventions and its impact on AGYW’s HIV risk assessment. We propose an adaptive design based on on-going qualitative research to ensure maximal uptake of the interventions.

Impact:
Home-based HIV self-testing of male partners will improve the accuracy of AGYW’s perceived HIV-risk and empower them to take up HIV prevention. The initiation of a male-friendly evening clinic will improve linkage to care of HIV positive men. Targeted PrEP for AGYW at high HIV-risk will allow HIV-negative AGYW to stay HIV-free.

Discussion:
We propose a prospective cohort of AGYW and their male partners to quantitatively assess the interventions, and a mixed-method approach to identify the main barriers and facilitators. Major challenges expected are (1) ethical issues due to difficulty in accurately capturing potential adverse events (gender violence, relation break-up,…), (2) ethical issues in approaching male partners through contact information provided by AGYW, (3) selection bias due to difficulties in reaching the male partners and an expected poor response rate when contacted by study staff, (4) selection bias in AGYW due to expected differential response rate depending on ability to deliver HIV self-test to partner, (5) limited counselling opportunities.
Predicting trajectories of functional decline in 60-70 year old people

Introduction: Early identification of people at risk of functional decline is essential for delivering targeted preventive interventions. Studying trajectories of functional decline over time provides more information on distinct subgroups than studying merely onset of the decline. The aim of this study is to identify and predict trajectories of functional decline over nine years in males and females aged 60-70 years.

Methods: We included 403 participants (55% females) from the on-going InCHIANTI cohort study and 395 (53% females) from the on-going LASA cohort study aged 60-70 years, with data on two or more measurements of functional ability during nine-year follow-up. Functional ability was scored with six items on activities of daily living. We performed Latent Class Growth Analysis to identify trajectories of functional decline and applied multinomial regression models to develop prediction models of identified trajectories. Analyses were stratified for sex.

Results: In males and females three distinct trajectories were identified: no/little decline (219 males, 241 females), intermediate decline (114 males, 158 females), and severe decline (36 males, 30 females). The final model in males included three predictors: gait speed, fear of falling, and alcohol intake (no/little decline, area under receiver operating curve [AUC] 0.68, 95%CI 0.62-0.73; intermediate decline, AUC 0.63, 95%CI 0.56-0.69; severe decline, AUC 0.79, 95%CI 0.71-0.87). The final model in females included age, living alone, economic satisfaction, balance, gait speed, physical activity, BMI, and cardiovascular disease (no/little decline, AUC 0.80, 95%CI 0.75-0.85; intermediate decline, AUC 0.74, 95%CI 0.69-0.79; severe decline, AUC 0.95, 95%CI 0.91-0.99).

Discussion: In people aged 60-70 years, already three distinct trajectories of functional decline can be identified across nine-year follow-up. Predictors of trajectories differed between males and females. Ongoing work is validating these predictors in other populations of young older people and using the predictors to identify young older people for early preventive interventions.

Comparison of the population attributable fraction, average attributable fraction and attribution method to assess the contribution of specific diseases to disability in cross-sectional studies

Introduction: The aim of this study was to compare 3 methods for estimating the contribution of diseases to disability in cross-sectional studies: the population attributable fraction (PAF), the average attributable fraction (AAF) and the attribution method (AM). This information is useful to better interpret results obtained from cross-sectional data, and to help policymakers decide on public health strategies.

Methods: Data on 9 chronic conditions and on disability for 5,170 adults aged 55-65 years living in household who participated in the 2008-09 cross-sectional Disability-Health Survey in France were used. A weighting factor was applied to obtain representative estimates for the French population. Disability was defined as any limitation reported in the Global Activity Limitation Indicator. PAFs were calculated using Levin’s formula, taking into account the prevalence of the disease and the relative risk of being disabled when reporting the disease. AAFs defined as the expected proportion of disability preventable by the additional elimination of the disease of interest, after adjustment for a random collection of other disorders were computed with the macro developed by Rückinger for SAS using a logistic model. The function
“BinAddHaz” in the R package “addhaz” was used to calculate the contributions of diseases with the attribution method based on a binomial additive hazards model.

Results: The results are in table 1. The PAFs, the AAFs and the contributions of diseases obtained with the AM summed up to 85.6%, 72.9% and 75.0%, respectively. Comparing the AAFs with the AM, diseases contributions were very close, and the ranking of diseases was exactly the same. PAFs were higher than AAFs and AM and the only difference in ranking was a switch between neurologic and urologic diseases.

Conclusion: All three methods would lead to the same conclusions. The advantages and the disadvantages of each method will be discussed.

O35
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Personality as a moderator of the relation between childhood abuse and body mass index in early adulthood

Introduction: Childhood abuse and personality have both been related to body mass index (BMI). However, the interplay between these factors is an understudied subject. In this study, we will examine whether personality moderates the relation between childhood abuse and BMI. Further, we will investigate whether this moderation is mediated by physical activity.

Methods: Data are from the fourth wave (n=13,478; 51.5% female; mean age=29.0 years) of the National Longitudinal Study of Adolescent to Adult Health (Add Health). Sexual, physical and verbal abuse experienced before age 18, personality (i.e. extraversion, neuroticism, agreeableness, conscientiousness and openness) and physical activity were measured by self-reported questionnaires. Participants’ BMI was determined based on their measured weight and height. Regression analyses were performed to determine the relation between (1) abuse, personality and their interaction with BMI and (2) these predictors and physical activity. Analyses were adjusted for age, ethnicity, parental and participants’ education and stratified by gender.

Results: Occurrence of verbal abuse, physical abuse and sexual abuse was reported by 47.1%, 18.4% and 5.0% of the participants, respectively. The mean BMI of the sample was 29.1 kg/m^2. Verbal abuse was related to higher BMI in females. Conscientiousness was related to lower BMI in both sexes. There was a negative interaction between verbal abuse and extraversion in both females and males. Further, there was a positive interaction between both physical and verbal abuse and agreeableness in females and a positive interaction between physical abuse and both conscientiousness and openness in males. Physical activity was related to lower BMI in males, but the interaction terms of abuse and personality were not related to physical activity.

Discussion: Personality traits moderate the relation between childhood abuse and BMI in an abuse- and trait-specific fashion. Moderation of the relation is not mediated by physical activity.

O36
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Distinct trajectories of physical performance measures in young older adults

Introduction: Physical performance is multidimensional and reflects the ability to perform tasks/activities that requires muscle strength and/or balance. It is unknown what the degree of interdependency across these physical domains is, whether there is a common mechanism responsible for decline in each domain and whether this is true to a similar extent. The aims of this study were 1) to unravel distinct trajectories of three physical performance measures among people aged 60-70 years and 2) to check for common mechanisms of decline by comparing degree of overlap between these measures.

Methods: We used data of 185 males and 205 females from the Longitudinal Aging Study Amsterdam who were assessed four times over nine years. Performance on chair stand, gait speed and hand grip strength (HGS) was analyzed. Gender-specific latent class growth models were conducted in Mplus for each of the outcomes separately to
obtain distinct trajectories. Degree of overlap was assessed by cross-tables.

Results: Chair stand analyses revealed two trajectories, one small subgroup showing declining performance over time (10 males, 38 females) and one fairly stable (168 males, 155 females). We identified three trajectories for gait speed: fast baseline speed with no decline (47 males, 27 females), intermediate baseline speed with no decline (132 males, 130 females), and slow baseline speed with decline (6 males, 47 females). For HGS we identified three declining trajectories differing in baseline performance: high (17 males, 75 females), intermediate HGS (111 males, 118 females), and low HGS (55 males, 10 females). Overlap of participants being assigned to the most favourable or unfavourable trajectories was minimal (3.3%).

Discussion: In the young old, few people showed a decline in physical performance measures over nine years of follow-up. There was minimal overlap in participants between the three measures, suggesting different underlying mechanisms for decline over domains.

O37
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Prediction models for short- and long-term outcome after carotid revascularization: systematic literature review and independent external validation

Introduction:
Carotid artery stenting (CAS) and endarterectomy (CEA) reduce the risk of future stroke in patients who suffered a stroke or transient ischemic attack (TIA) due to internal carotid artery stenosis. Prediction of outcome after CAS or CEA could aid in choosing the appropriate treatment in individual patients. We identified existing prediction models for short- and long-term outcome after CAS or CEA and externally validated three models for short-term outcome.

Methods:
The Framingham Risk Score and the Pooled Cohort Equations over-predict risk in women with hypertensive disorders of pregnancy, which is solved by updating the models.

Introduction: The AHA guidelines for Prevention of Cardiovascular Disease (CVD) in Women describe hypertensive disorders of pregnancy (HDP) as a failed stress test, which might unmask early CVD. Therefore, prediction of CVD in these women should be optimal. However, the validity of CVD risk prediction models in women with HDP is not established. Therefore, we aimed to assess the prognostic performance of the Framingham Risk Score (FRS) and the Pooled Cohort Equations (PCE) in women with and without HDP and, when necessary, update the models.

Methods: Data were used from 29,425 women out of the EPIC-NL cohort; we excluded those who had never been pregnant. In total, 6,302 answered the question: ‘Did you suffer from high blood pressure during pregnancy?’ with ‘Yes’; and 17,369 with ‘No’. Data were multiple imputed with MICE in R. First, we calculated the 10-year predicted risk and compared this with the observed risk. Subsequently, the models were updated in three steps: 1) recalibrating the baseline hazard and linear predictor, 2) additionally adding a common factor, and 3) refitting the full model. The performance of all models was assessed in terms of calibration (calibration plot, expected:observed ratio) and discrimination (c-statistic).

Results: The Table shows that the observed risk is 1.3-1.4 times higher in women with HDP. The original models over-predict risk in all women, either with or without HDP. Calibration plots improved most after recalibrating the baseline hazard and the linear predictor with a common factor, which is confirmed by the expected:observed ratio shown in the Table. Discrimination was already quite good and improved only slightly after refitting.

Conclusion: FRS and the PCE over-predict risk in women both with and without HDP and after recalibrating and refitting the models they both perform well in women with HDP as well as in women without HDP.

A Mendelian Randomization Study of Plasma phylloquinone levels and Type 2 Diabetes

Introduction: Higher dietary phylloquinone intake is associated with lower type 2 Diabetes (T2D) incidence. However, observational studies have to be interpreted carefully since there is a chance of reverse causation and confounding. The aim of this study is to investigate the causal effect of serum phylloquinone levels on T2D incidence via a Mendelian Randomization approach.

Methods: We used data from the European Prospective Investigation into Cancer and Nutrition (EPIC)-InterAct case-cohort study comprising 10,071 diabetes cases and 13,309 subcohort members from eight European countries. A weighted genetic risk score (wGRS) was made of four SNPs (rs2192574, rs6862071, rs4645543 and rs2108622) known to be related to serum phylloquinone levels in a GWAS study. We assessed the association between the wGRS and T2D incidence using a Prentice-weighted Cox regression analysis. Estimates from this Cox regression analysis, and estimates for the relation of the SNPs with plasma phylloquinone were used for inverse-variance weighted (IVW) analysis to obtain a hazard ratio (HR) for the unconfounded relation between serum phylloquinone levels and T2D incidence(figure 1). All analyses were adjusted for sex, center, principal components of ancestry, triglycerides, hours fasting and genetic platform.

Results: The median follow-up time was 10.9 years. The wGRS was unrelated to potential confounders of the observational relation between phylloquinone and T2D. A higher wGRS reflects higher serum phylloquinone levels according to a previous GWAS (β 0.44 (95%CI:0.06,0.82). A higher wGRS related to a lower T2D incidence: HR 0.87 (95%CI: 0.78, 0.97) per point higher of the wGRS. The hazard ratio for the unconfounded relation between serum phylloquinone levels and T2D
incidence, resulting from the IVW analysis, was 0.87 (95%CI: 0.78, 0.97).

Conclusion: This study showed that increased serum phylloquinone levels may be associated with a reduced T2D risk.

Survival bias in Mendelian randomisation: a simulation study

Introduction: The number of studies utilizing genetic variants as instrumental variables is rapidly increasing. While it has previously been theorized that collider stratification bias by age may distort results from Mendelian randomisation (MR) analyses, this has received little attention in the literature. We aimed to quantify the effects of this possible threat to MR-studies using odds ratios typically found in cardiovascular epidemiology.

Methods: Using Monte Carlo simulations, we assessed the extent to which the association between a genetic instrument and an outcome of interest is biased when the analysis is restricted to individuals having survived until a certain age (Figure). We illustrate the bias for a range of scenarios, incorporating varying degrees of i. age-at-inclusion, ii. phenotypic variance explained by the genetic instrument, and iii. odds ratios for uncorrelated risk factors. For all scenarios, simulations were repeated 1,000 times using 10,000 randomly generated observations.

Results: Collider stratification bias by age leads to biased estimation of the causal effect of the genetic instrument on the outcome of interest, with increasing age-at-inclusion, variance explained, and greater odds ratios leading to ever greater bias. This burden is estimated to more than double when age-at-inclusion increases from 70-75 to 85-90 years of age, and is accompanied by a decrease in statistical power.

Discussion/Conclusion: Using a simple framework, we were able to show that collider-stratification bias may seriously distort results from MR-studies performed in the oldest old. We describe considerations how to assess the presence of collider stratification bias in MR-studies. Given that these mechanisms should hold true for any sufficiently selected population, our findings support the position that a critical appraisal of possible collider stratification bias is warranted when considering populations for MR-analyses.

When will a breast cancer patient be cured? A prediction model for conditional relative survival

Introduction
Cancer patients and survivors often experience problems in getting a life insurance. Patients with a poor prognosis less often get accepted. However, it is reasonable to assume that survival rates will change as time passes, especially for patients with an initial poor prognosis. In this study, we generate a prediction model for conditional relative survival of breast cancer patients, which can be used in clinical practice, but also by insurance companies to take objective decisions whether or not to accept patients for a life insurance.

Methods
All women diagnosed with non-metastatic invasive breast cancer between 2005-2008 treated with surgery were selected from the Netherlands Cancer Registry. For patients diagnosed in 2005, a separate model was generated for patients free of disease during follow-up. Crude conditional relative survival was estimated using the Ederer II method, with life tables of the general Dutch population as
background (when 100%: a patient has equal survival as a general individual). Excess mortality ratios were obtained using general linear models with Poisson distribution. The model will be validated by bootstrapping.

Results
The 2005-2008 cohort included 48,121 patients. The 2005 subcohort consisted of 10,261 patients. Average 10-year conditional relative survival rates in the 2005-2008 cohort ranged from 87-93% from diagnosis to 7 years after diagnosis. In patients free of disease during follow-up (2005 subcohort) 10-year survival ranged from 87-96%. Survival rates increase even more over time in patients with an initial poorer prognosis, such as stage III (Figure). The prediction models, including several predictive variables, provide survival rates for individual patients.

Discussion
These data do not only give patients enhanced insight in their prognosis, but can also provide clinicians a more objective basis to deem a patient cured of disease. In addition, this study provides insurance companies accurate data for use in life insurance application processes.

The impact of smoking cessation before and after diagnosis on non-muscle-invasive bladder cancer recurrence: a cohort study

Abstract
Introduction: Smoking is a major risk factor for bladder cancer, but the relationship between smoking behaviour and bladder cancer recurrence after successful initial treatment is largely unknown. We investigated the effect of smoking behaviour before diagnosis, and smoking cessation after diagnosis, in relation to the risk of recurrence of non-muscle-invasive bladder cancer (NMIBC).

Methods: 723 NMIBC patients from the prospective Bladder Cancer Prognosis Programme (BCPP) cohort provided complete data on nature of any recurrence and smoking behaviour before and up to 5 years after diagnosis. The impact of smoking behaviour on NMIBC recurrence was explored by multivariable Cox regression models investigating time-to-first NMIBC recurrence and number of recurrent NMIBCs.

Results: Over a median follow-up period of 4.21 years, 403 pathologically confirmed NMIBC recurrences occurred in 210 patients (29%). Continuing smokers (HR=1.31, 95% CI=0.80-2.15) were at a slightly increased risk of recurrence compared to never smokers. Smoking cessation before diagnosis decreased the risk of recurrence with a HR for quitting more than 40 years prior to diagnosis of 0.66 (95%CI=0.43-1.01). Only 25 current smokers at diagnosis quit smoking (14%) during follow-up and smoking cessation after diagnosis did not decrease risk of recurrence compared to continuing smokers (p=0.783).

Conclusions: This report describes the first prospective evidence on the association between post-diagnosis smoking behaviour and NMIBC recurrence. Smoking cessation before diagnosis decreased the risk of recurrence with a HR for quitting more than 40 years prior to diagnosis of 0.66 (95%CI=0.43-1.01). Only 25 current smokers at diagnosis quit smoking (14%) during follow-up and smoking cessation after diagnosis did not decrease risk of recurrence compared to continuing smokers (p=0.783).

Nonetheless, the number of patients quitting smoking post-diagnosis was strikingly low. This points towards an important role for urologists in promoting smoking cessation in NMIBC patients and for early smoking cessation programmes in general.
Dietary patterns and risk of recurrence and progression in non-muscle invasive bladder cancer

Introduction: The association of dietary factors with urinary bladder cancer prognosis has scarcely been investigated, and results of studies conducted to date are inconsistent. We investigated whether empirically derived dietary patterns are associated with risks of recurrence and progression in non-muscle invasive bladder cancer patients.

Methods: Data from 595 newly diagnosed non-muscle invasive bladder cancer patients from an ongoing prospective study were used to derive dietary patterns using exploratory factor analysis. Factor scores were calculated and then categorized in sex-specific tertiles. Multivariable adjusted proportional hazards regression models were used to estimate hazard ratios and 95% confidence intervals for the associations between tertiles of adherence to the dietary patterns and recurrence and progression.

Results: We identified four dietary patterns: “fruits and vegetables”, “Western”, “low-fat”, and “Tex-Mex”. Patients in the highest tertile of adherence to the Western pattern experienced a 1.54 times higher risk of recurrence (95% CI 1.11-2.14) compared to patients in the lowest tertile. No statistically significant associations of a Western diet with risk of progression, or of the other dietary patterns with risk of recurrence and progression were found.

Discussion: Overall, we found that a Western diet was associated with a higher risk of recurrence, which supports the hypothesis that a Western diet plays a role in the etiology and prognosis of many cancers. However, diet-disease associations are complex, so further studies are needed to confirm our findings.
the only cardiovascular risk factor independently associated with MI risk (RR: 3.8, 95%CI: 1.6-9.2).

CONCLUSION
MI rate increased linearly with MHD. The risk per Gy was in line with previously reported dose-response relationships.

O45
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Risk stratification for advanced colorectal neoplasia according to FIT, age and gender in the Flemish colorectal cancer screening program (FCCSP).

Introduction: The faecal immunochemical test for haemoglobin (FIT), for detecting precancerous lesions and colorectal cancer (CRC) enables continuous quantification. Current CRC screening programs are based upon a binary FIT-result (≥75ng/ml, <75ng/ml). Since there are several identified risk factors for CRC, this study is evaluating the possibility of establishing a risk matrix based upon the FIT-result, age and gender. This could lead to more insight in a tailored referral approach after screening for CRC in Flanders.

Methods: In this retrospective study, 30,638 positive FIT results of participants of the Flemish colorectal cancer screening program who also underwent a colonoscopy were analysed, from October 2013 until December 2015. All participants were allocated to the non-advanced colorectal neoplasia group (NACRN) or the advanced colorectal neoplasia group (ACRN). Results: Median FIT results were significantly higher in the ACRN group (615 ng/ml, IQR 231-1000 ng/ml) compared to the NACR group (231 ng/ml, IQR 126-565 ng/ml) (P<.001). Multivariate logistic regression analyses identified the variables ‘FIT’ (≥1000 ng/ml: OR 7.00, CI 6.03-8.16), ‘age’ (70-74: OR 1.58, CI 1.44-1.75) and ‘gender’ (male: OR 1.07, CI 1.00-1.14) as independent predictive factors for the detection of ACRN. 64 risk categories were established based upon the included variables. Risk for the detection of ACRN increased by a factor of (OR) 14.19 [CI 6.91-29.12] between highest and lowest risk categories. Conclusion: The differences in risk within the matrix can be used to stratify between the detection probability of ACRN and prioritise referrals accordingly. Participants and their general practitioners (GPs) could be informed about their individual risks concerning the detection of ACRN when tested positive by FIT. This can increase the positive predictive value and the follow up rate by colonoscopy after a positive FIT, which is rather low in Flanders. It also provides GPs with more insight in the risk differences per patient, which could validate their clinical decision making.

O46
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Hospital of diagnosis affects the probability of cystectomy and survival of patients with muscle-invasive bladder cancer.

Introduction: Since 2010 the surgical treatment of bladder cancer started to be centralized in hospitals that fulfil the volume criteria as set by the Dutch Association of Urology. However, patients with bladder cancer can be diagnosed in every hospital. According to the Dutch guideline, the standard treatment for patients with muscle-invasive bladder cancer is removal of the bladder, i.e. cystectomy. The aim of this study is to evaluate the effect of hospital of diagnosis on the probability of cystectomy and its impact on survival.

Methods: Patients diagnosed with muscle-invasive bladder cancer (MIBC; T2-4a, N0/X,M0/X) between 2009 and 2014 were identified through the Netherlands Cancer Registry. Multilevel logistic regression analysis was used to investigate the probability of undergoing a cystectomy between hospitals on survival. Cox proportional hazard regression analysis was used to assess the effect of variation in the probability of undergoing a cystectomy between hospitals on survival.

Results: A total of 6,282 MIBC patients were included in the study. The probability of undergoing a cystectomy differed significantly by hospital of diagnosis in all periods (p<0.0001 in 2009-2010 and 2011-2012, p=0.004 in 2013-2014). The variation in the more recent period (2013-2014) was lower compared to 2009-2010 (Intraclass correlation coefficient, 3.2% versus 5.3%). Survival of patients who were diagnosed in the tertile of hospitals with the highest probability of patients undergoing
cystectomy was 10-12% better compared to survival of patients diagnosed in the tertile of hospitals with the lowest probability of cystectomies (p=0.04 in first two periods and p=0.06 in 2013-2014).

Discussion: Variation in probability of undergoing a cystectomy exists between hospitals of diagnosis but decreased over time. However, this variation still affects survival. This indicates that clinical management of potentially curable bladder cancer patients can be improved.

O47

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Evaluation of universal and sex-specific clinical decision limits for high-sensitivity cardiac troponin I and T: a protocol for systematic review and best-evidence synthesis

Context: The European Society of Cardiology guidelines recommend the 99th percentile upper reference limits of high-sensitivity cardiac troponin I (hs-cTnI) or T (hs-cTnT) from a healthy reference population as the clinical decision limit for diagnosing an acute myocardial infarction (AMI). Regarding these clinical decision limits (hs-cTnI:26ng/L;hs-cTnT:14ng/L) two concerns has been raised which may harm the diagnosis of AMI. 1)The 99th percentile upper reference limits of hs-cTnI and hs-cTnT are not derived from the same ‘healthy’ reference population, and are therefore not biologically equivalent. This may result in a too low, or even worse, too high clinical decision limit for hs-cTnI or hs-cTnT. 2)Nowadays, an universal clinical decision limit of hs-cTn is used in clinical practice. There is concern whether a ‘one size fits all’ cut-off value of hs-cTn is sufficiently sensitive to diagnose AMI in women.

The objective of the present study is to perform a systematic review and narrative synthesis to establish universal and sex-specific 99th percentile upper reference limits of hs-cTnI and hs-cTnT.

Design: Reference cohorts designed to assess the universal and/or sex-specific 99th percentile upper reference limits of hs-cTnI(Abbott) and/or hs-cTnT(Roche) from healthy reference individuals ≥18 years will be included. A comprehensive search of MEDLINE and EMBASE will be conducted. Quality of the studies will be assessed using the Sandoval-criteria. Universal and sex-specific 99th percentile upper reference limits will be assessed. Due to substantial heterogeneity in applied methods, data synthesis will be conducted according to Slavin’s best-evidence synthesis approach.

Impact and Discussion: This systematic review and best-evidence synthesis will establish universal and sex-specific clinical decision limits for hs-cTnI and hs-cTnT. This study could provide support whether the currently used clinical decision limits of 26ng/L for hs-cTnI and/or 14ng/L for hs-cTnT should be reconsidered, or that sex-specific clinical decision limits needs further study in randomized controlled trials.

O48

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Associations between SNPs and erythrocyte traits including hemoglobin in humans: a systematic literature review.

Introduction: Erythrocytes contain hemoglobin (Hb), a protein that can bind oxygen and also carbon dioxide, and are therefore important for the transport of oxygen to and a substantial part of carbon dioxide from cells. Several genetic loci have been shown to be associated with Hb and other erythrocyte parameters. The aim of this study was to systematically review existing literature on
associations between single nucleotide polymorphisms (SNPs) and erythrocyte traits, including Hb, in humans.  
Methods: A literature search on SNPs associated with Hb and/or erythrocyte traits in Medline and Embase was developed by a medical information specialist. Title/abstract screening was performed by two independent researchers. Full text screening is currently ongoing. Studies will be included if: investigating a(n) causality/association/correlation, population-based, investigating a human population that is Caucasian or of mixed ethnic descent and written in English, Dutch or German. Disagreements will be resolved by consensus or by a third independent researcher who makes the final decision. Relevant studies will be assessed on risk of bias with the Quality Assessment Tool for Quantitative Studies.  
Results: 3,597 studies have been screened on title/abstract. 138 full texts remained and are currently being screened for relevance. Three studies are already included, of which two found an association between SNPs of the HFE gene and an increased transferrin saturation and serum ferritin. The third study found associations between SNPs of the CACNA2D3, TF, CCND3, HBS1L, HFE, HIST1H1T, HIST1H2BJ, SLC17A1, TRIM38, SH2B3 and TMPRSS6 genes, rs1682676, rs2673289 and mean corpuscular volume, Hb, ferritin, hematocrit, serum iron and transferrin (more preliminary results will be available before the conference).  
Discussion/Conclusion: This review will provide an overview of SNPs that are associated with erythrocyte traits including Hb. This information might be useful to discriminate between individuals who are more/less affected by things such as blood loss and iron deficiency.

O49
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Genetic polymorphisms associated with the risk of COPD, a systematic review with meta-meta-analyses

Context: Although smoking is the key risk factor for development of COPD, not all smokers develop the disease. It has been suggested that genetic factors may play a role in the aetiology. The aim of the current study is to review all published meta-analyses on genetic polymorphisms associated with the development of COPD, emphysema or chronic bronchitis (CB). Where appropriate, most comprehensive risk estimates will be determined with meta-meta-analysis.  
Design: PubMed, Web of Science and EMBASE will be systematically searched to identify meta-analyses reporting on genetic polymorphisms in humans associated with development of COPD, emphysema or CB, published in English, Dutch or German. Study quality will be assessed using the AMSTAR checklist. The most comprehensive risk estimates will be selected to be included: (1) results from one publication if one most comprehensive publication exists, or (2) determined by pooling results of primary studies included in the identified meta-analyses, whereby duplicates will be removed. Where available, estimates will be stratified by smoking status, ethnicity and gender.  
Impact: Results of our research will provide a comprehensive overview of the current state of knowledge with regard to genetic risk factors of COPD. The results can be used to identify gaps in knowledge to further understand the aetiology of this disease. Furthermore, such information can be used to tailor interventions focusing on disease prevention.  
Discussion: Although combining results in meta-meta-analysis will lead to more comprehensive estimates, it will remain important to keep an eye on sources of heterogeneity, some of which may be introduced through this approach.

O50
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Maternal obesity during gestation and effects on offspring development, behavior and physical health. Systematic review of animal studies.

Context
At present, over 15% of all women are obese. Multiple observational studies show that maternal obesity during gestation may impact long-term offspring health, development and behavior: e.g. offspring may be more likely to be obese themselves, have shorter life expectancy, developmental delay and attention problems. However, observational studies in humans are hampered by confounders including heritability and postnatal environment. Therefore animal studies may provide more insight in a possible causal relationship between maternal diet during gestation and offspring health, development and behavior. A systematic review of the existing animal evidence is presently lacking, and would allow us to assess the aggregated strength and consistency of effects. We aimed to examine the effect of maternal overweight on offspring’s physical health, development and behavior.

Design
We performed a systematic literature search in EMBASE and MEDLINE. Our search yielded 1793 unique publications. Two authors independently screened the references. Data extraction was performed in two steps. In the first step, we extracted study characteristics and recorded the type of outcome measures. In the second step, we selected the most relevant outcomes to perform further (meta-)analyses, based on biological and clinical relevance. The methodological quality of the studies was assessed using the SYRCLE Risk of Bias tool. At time of presentation, the study will be still ongoing.

Impact
This systematic review will provide new perspectives on the etiology of offspring physical health problems, developmental delay and behavioral disorders. This is critical from a public health view, since the rate of obesity in women of reproductive age increases.

Discussion and conclusion
This is a large explorative review with no initial restriction in terms of outcome measures. We will discuss the study design and decisions together with results of meta-analyses on offspring development and behavior parameters.
Long term impact of chronic Q-fever and Q-fever fatigue syndrome on psychosocial functioning

Introduction
Approximately 1-5% of acute Q-fever patients develop chronic Q-fever. Estimates show that 20% of acute Q-fever patients develop persistent fatigue, i.e. Q-fever fatigue syndrome (QFS). Both conditions can have long term impact on psychosocial functioning. Objective is to identify which psychosocial aspects are most affected on the long term and which factors mediate this impact.

Methods
Cross-sectional research of patients with chronic Q-fever or QFS (average 7 years after acute infection) in comparison with diabetes type II patients (average 7 years after diagnosis) and the general population. Quality of life, anxiety and social functioning were measured with validated questionnaires. Multivariate linear regression was used to identify significant differences between groups, to correct for gender, age, education level and co morbidity and to identify factors (fatigue, functional impairment, cognitive impairment) that mediate the impact on psychosocial functioning.

Results
Quality of life of Q-fever patients 7 years after acute infection is significantly lower compared to diabetes patients and the general population (p<0.05) (Fig. 1), even after correction for age, gender, education level and co morbidity. This effect is significantly mediated by the level of fatigue (between 86-99%) in both chronic Q-fever and QFS patients. Functional impairment and cognitive functioning also mediate this effect (between 17-63%), but not as strong as fatigue. Analysis show similar trends for anxiety and social functioning.

Discussion
Chronic Q-fever and QFS patients have significantly lower quality of life and social functioning and higher levels of anxiety compared to diabetes patients and the general population. This impact is particularly mediated by the level of fatigue experienced by chronic Q fever and QFS patients.
reported a positive intention to request a HBV test and 48.7% was willing to participate if the costs were maximal € 70.-. Clarity regarding HBV status, not having symptoms, fatalism, self-efficacy, and perceived risk of having HBV were the strongest predictors to request a HBV test. Shame and stigma regarding HBV, perceived severity, fatalism, perceived burden of participating in HBV screening, social influence of Islamic religious leaders, and not having symptoms had the greatest predictive value for the intention to participate in HBV screening. LR showed superior predictive performances with area under the curve scores of 0.742 (RF: 0.698) for intention to request a HBV test and 0.712 (RF: 0.677) for intention to participate in HBV screening. Conclusion RDS enabled us to successfully reach and study determinants among Moroccan-Dutch immigrants. To enhance screening uptake of Moroccan Dutch, HBV promoting activities should (1) incorporate clarity regarding HBV status, (2) stress the risk of having HBV despite feeling healthy, (3) emphasize mother to child transmission as the main route of transmission, and (4) include Islamic religious leaders to help decrease elements of fatalism, shame, and stigma.

Introduction School closure is often considered as an option to mitigate influenza epidemics because of its potential to reduce transmission in children and then in the community. The policy is however highly debated because of controversial evidence. Moreover, the specific mechanisms leading to mitigation are not clearly identified.

Methods
We introduced a stochastic spatial age-specific metapopulation model to assess the role of holiday-associated behavioral changes and how they affect the seasonal influenza dynamics. The model is applied to Belgium, parameterized with country-specific data on social mixing and travel, and calibrated to 2008/2009 influenza season. It includes behavioral changes occurring during weekend vs. week, and holiday vs. school-term. Several experimental scenarios are explored to identify the relevant mechanisms, like:
• the travel changes model, where only variations in travel behaviour are considered
• the mixing changes model, where only variations in social mixing are considered
• the regular weekday model, where no variations are considered, and social mixing and travel behavior are fixed as for regular weekday.

Results Stochastic numerical simulations show that holidays delay the peak of the season and mitigate its impact. Changes in mixing patterns are responsible for the observed effects, whereas changes in travel behavior do not alter the epidemic. Christmas holidays have the largest impact on the epidemic, however later school breaks may help in reducing the epidemic size. The extension of Christmas holiday of 1 week may further mitigate the epidemic.

Discussion Changes in the way individuals establish contacts during holidays are the key ingredient explaining the mitigating effect of regular school closure. Our findings highlight the need to quantify these changes in different demographic and epidemic contexts in order to provide accurate and reliable evaluations of closure effectiveness. They also suggest strategic policies in the distribution of holiday periods to minimize the epidemic impact.

OS5
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Pediatric HIV-encephalopathy in Malawi: longitudinal patterns of cognitive development in HIV infected, HIV exposed and unexposed children.

Introduction: A major consequence of perinatal HIV infection is the impact on the child’s central nervous
Apart from the viral infection itself, psycho-social and contextual factors also impact cognitive development. Even though more than 80% of HIV-infected children live in sub-Saharan Africa, only a limited number of studies have investigated cognitive development of HIV-infected children in those countries. Data on the impact of HIV in infants is especially scarce.

Methods: We performed a longitudinal, prospective, observational cohort study of 96 HIV-infected children and compared their cognitive development to 289 HIV-exposed and 170 non-exposed controls in urban Malawi. Using a linear mixed model, we assessed the longitudinal patterns of cognitive development and identified predictors that may impact development. Raw scores on the Bayley Scales of Infant Development, 3rd edition (BSID-III), were used to assess cognition in all children at 3.5, 6, 9, 12, 15, 18 and 24 months of age.

Results: Initial cognitive scores were lowest in HIV-infected children (8.39 (SE: 4.49)), intermediate in HIV-exposed (13.12 (SE: 2.42)) and highest in unexposed controls (18.26 (SE: 3.26)). The growth rate in cognition was higher in controls and in exposed children compared to HIV-infected children. Among HIV-infected children, predictors of cognitive development were care by the biological mother, antiretroviral treatment (ART) and nevirapine use, while malnutrition had a negative impact. The positive influence of ART diminished over time. The HIV-exposed children initially also benefited from care of the biological mother. Their cognitive growth was negatively influenced by stunting.

Conclusion: HIV-infected children lag behind in cognition from the start, and never catch up with their healthy peers. Psycho-social and contextual factors should not be ignored. Future interventions should not only focus on ART, but also on malnutrition and prolonged care by the mother.

Diagnostic indicators of Buruli ulcer in patients with skin lesions in a Buruli ulcer endemic region

Introduction. Buruli ulcer (BU) is a neglected tropical skin disease caused by Mycobacterium ulcerans mostly affecting rural regions of West and Central Africa. In most BU endemic settings, a diagnosis is made on clinical and epidemiological grounds, after which treatment with BU-specific antibiotics is initiated empirically. Following the current decline in BU incidence, clinical expertise in the recognition of BU is likely to wane, potentially resulting in diagnostic misclassification. In this context, laboratory confirmation of BU becomes increasingly important. We therefore aimed to determine the diagnostic accuracy of clinical, epidemiological and microbiological signs of BU.

Methods. A total of 226 consecutive patients with skin lesions compatible with BU were recruited between March 2012 and March 2015 in two BU hospitals and 10 decentralized health posts in southern Benin. The laboratory tests included direct smear examination, PCR, culture and histopathology. The clinical and epidemiological indicators recorded were the WHO diagnostic criteria plus additional signs associated with BU. In the absence of a gold standard, the accuracy of each test was estimated using a composite reference standard (CRS) which included clinical information, laboratory results and an evaluation by an expert panel.

Results and discussion. Among the 205 patients with complete data, clinicians recognized BU with a sensitivity of 88% (95%CI 81%-93%) which was higher than the sensitivity of any of the microbiological tests. In our study setting, 22%
(95%CI 13%-33%) of patients initially clinically not suspected to have BU were classified as BU by the CRS.

Conclusion. In clinical practice, patients that are clinically not suspected to have BU are not assessed by microbiological or histological assays, nor treated for BU. A wider clinical suspicion should therefore be recommended to reduce the false omission rate allowing improved patient management.

O57

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Impact of Chronic Bronchitis in Chronic Obstructive Pulmonary Disease

Introduction
Research on the association between chronic bronchitis and Chronic Obstructive Pulmonary Disease (COPD)-exacerbations has led to discordant results. Furthermore, the impact of chronic bronchitis on mortality in COPD subjects is unclear.

Methods
Within the Rotterdam Study, a population-based cohort study among subjects aged ≥45 years, chronic bronchitis was defined as having a productive cough for at least three months for two consecutive years. Logistic regression and Cox proportional hazard models were adjusted for age, sex and packyears.

Results
Of 972 included COPD subjects, 752 had no chronic phlegm production (CB-) and 220 had chronic phlegm production of whom 172 met the definition of chronic bronchitis (CB+). CB+ subjects were older, more frequently current smokers and had more packyears than CB- subjects. During follow-up, CB+ subjects had larger decline in lung function (-38 ml per year, 95%CI -61.7; -14.6). CB+ subjects had an increased risk of frequent exacerbations (OR 4.0 95%CI 2.7; 5.9). Survival was significantly worse in female CB+ subjects compared to female CB- subjects. Regarding cause-specific mortality, CB+ subjects had an increased risk of respiratory mortality (HR 2.16, 95%CI 1.12;4.17).

Conclusion
COPD subjects with chronic bronchitis have an increased risk of exacerbations and (respiratory) mortality compared to COPD subjects without chronic phlegm production.

O58

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What can we expect from prediction models in obstetric care: Simulated results in pre-eclampsia

Objective: The HYPITAT trial showed that induction of labor in women with gestational hypertension (GH) or mild preeclampsia (PE) at term prevented complications without increasing the c-section rate. Our aim was to develop a prediction model to stratify the risk of developing severe maternal morbidity, and to evaluate the impact of use of the model to select low-risk women eligible for expectant management.

Methods: Data from the HYPITAT trial was used to develop a prediction model for severe maternal morbidity. To simulate model application we considered different cut-off values of predicted probability of severe maternal morbidity. For low risk women, with a predicted probability below the cut-off, the model recommendation would be expectant management. Induction of labour would be recommended for those above the cut-off. Rates of severe maternal morbidity were compared for situations where the model recommendation and
the clinical conduct agreed versus when they disagreed (Figure).

- Results: The AUC for the model was 0.71 (95% CI: 0.69 - 0.73) and 0.69 (95% CI: 0.67 - 0.71) after internal validation through bootstrapping. Calibration was good. For the simulation we used a cut-off of 13.5% for the predicted probability of severe maternal morbidity. When the model recommendation agreed with the clinical conduct severe maternal morbidity occurred in 117 of 468 (25%) of the cases and in 237 of 685 (34.6%) in case of disagreement (difference 9.6%; 95% CI: 4.2% - 15.0%).

- Conclusion: The HYPITAT study encourages induction of labor in all term GH and mild PE women. We have shown instead that by identifying low risk women through the use of prediction models, expectant management becomes a viable alternative with no increase of severe maternal morbidity rates.

O59
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Plasma n-3 and n-6 polyunsaturated fatty acids and risk of type 2 diabetes in cardiac patients: a 3-year prospective analysis in the Alpha Omega Cohort

Background Dietary guidelines promote the consumption of polyunsaturated fatty acids (PUFA) for the prevention of coronary heart disease. Whether plasma n-3 and n-6 PUFA is associated with diabetes risk in a high-risk population of cardiac patients in still unknown.

Methods We included 3,751 post-myocardial infarction patients from the Alpha Omega Cohort aged 60-80 (80% male) who were free of diabetes at baseline (2002-2006) and who had complete data on the fatty acid composition of plasma cholesteryl esters (CE). PUFA in plasma CE was measured through gas chromatography and incident T2D was ascertained through self-reported physician diagnosis and medication use. Multivariable Cox regression models were used to study the associations between quintiles of individual and total plasma n-3 and n-6 PUFA and incident T2D, adjusting for demographics and lifestyle characteristics. Restricted cubic spline (RCS) analysis was performed to visualize the shape of the observed associations.

Results During a median follow-up 3.4 years, 201 cases of T2D occurred. Total and individual plasma n-3 PUFA were not associated with incident T2D. Among n-6 PUFA, plasma linoleic acid (HRQ5vsQ1: 0.44; 95%CI: 0.27 - 0.73) was inversely associated with incident T2D and was also most abundant in plasma CE (median= 50.08%). Contrary, plasma γ-linolenic acid (HRQ5vsQ1: 1.77; 95%CI: 1.06 - 2.93) and plasma dihomo-γ-linolenic acid (HRQ5vsQ1: 1.77; 95%CI: 1.10 - 2.87) were positively associated with incident T2D, but constituted only small proportions in plasma CE (median= 0.96% and 0.81%, respectively). RCS analysis showed linear associations for linoleic acid and γ-linolenic acid whereas dihomo-γ-linolenic acid was more U-shaped.

Conclusion In the present study among Dutch drug-treated cardiac patients the most abundant n-6 PUFA linoleic acid was associated with lower T2D risk. Due to the complexity of the fatty acid metabolism, it remains to be elucidated whether the nature of the observed associations is predictive or aetiological.

O60
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Treated HIV-1-infection is independently associated with decreased erectile function among middle-aged men who have sex with men

Introduction
Several studies have reported that HIV-1-infected men who have sex with men (MSM) more often experience sexual dysfunction compared to HIV-1-uninfected MSM. We assessed whether treated HIV-1-infection is independently associated with decreased sexual functioning among middle-aged MSM.
Methods

Data from 399 HIV-1-infected MSM receiving ART and 366 HIV-1-uninfected MSM aged ≥45 years were used. The questionnaire included 3 questions (representing 3 sexual domains) on sexual functioning from the International Index of Erectile Function (IIEF), addressing erectile function, sexual desire, and sexual satisfaction (scale 1-5, higher score representing better function). The 3 separate questions were dichotomised using a cut-off of ≤2. Three multivariable logistic regression models were constructed to investigate the association between HIV-1 infection and the 3 domains. Variables associated with both HIV-1 infection and one of the outcomes (at p<0.20) were included in all 3 multivariable models. We explored HIV-1 and ART-related variables in the established multivariable models including only HIV-1-infected individuals.

Results

Decreased erectile function (13.0% vs. 3.4%, p<0.001), sexual desire (7.0% vs. 3.6% p=0.03), and sexual satisfaction (17.8% vs. 11.8%, p=0.02) were each more prevalent in HIV-1-infected than HIV-1-uninfected MSM. In multivariable logistic regression models including age, ethnicity, waist-to-hip ratio, noncommunicable comorbidities, depression, frailty, use of antidepressants, and antihypertensive medication, HIV-1 infection was independently associated with decreased erectile function (adjusted odds ratio (aOR) 2.53, 95%CI 1.23-5.21), but not decreased sexual desire (aOR 1.78, 95%CI 0.81-3.92), or decreased sexual satisfaction (aOR 1.35, 95%CI 0.84-2.17) (Table). Among HIV-1-infected participants, current (aOR 5.39, 95%CI 2.09-13.92) use of lopinavir/ritonavir was independently associated with decreased erectile function.

Conclusions

Among MSM aged ≥45 years, having treated HIV-1 infection was independently associated with decreased erectile function, but not with sexual desire or sexual satisfaction. Current exposure to lopinavir/ritonavir appeared to be an independent risk factor for decreased erectile function among the men with HIV.

O61

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External validation and clinical usefulness of first trimester prediction models for the risk of pre-eclampsia: a prospective cohort study

Introduction: Prediction models can help identify women at increased risk of pre-eclampsia who may benefit from preventive interventions. Although a number of prediction models for pre-eclampsia have been developed, few have been validated in independent populations. In this study, we assessed the external validity of all published first trimester prediction models for the risk of pre-eclampsia based on routinely collected maternal predictors. Moreover, we evaluated the potential utility of the best performing models in clinical practice.

Methods: We performed a multicentre prospective cohort study in The Netherlands between July 1, 2013 and December 31, 2015. Published prediction models were systematically selected from the literature. Pregnant women, ≥18 years of age, completed an online questionnaire consisting of predictors before 16 weeks of gestation. The outcome pre-eclampsia was established using medical records and a postpartum questionnaire. Predictive performance of each model was assessed by means of the c-statistic and a calibration plot. Clinical usefulness was evaluated by means of decision curve analysis and by calculating the potential impact at different risk thresholds.

Results: Ten prediction models were included for external validation. The validation cohort contained 2614 women of whom 76 developed pre-eclampsia (2.9%). Five models showed moderate discriminative performance with c-statistics ranging from 0.73 to 0.77. Adequate calibration was obtained after refitting of the models. The best models were clinical useful over a small range of predicted probabilities and may provide more benefit compared to risk selection as used in current guidelines.

Discussion: Five of the ten included first trimester prediction models for pre-eclampsia showed moderate predictive performance. Further research should focus on determination of an acceptable risk
threshold and impact analysis of implementation of the most optimal model in clinical practice.

O62
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Personalised prediction of future risk using early treatment response

Introduction: Clinician should assess the current level of asthma control and guideline defined level of future risk. Current level of asthma control can be easily assessed by the Asthma Control Questionnaire, a clinical tool to assess the level of future risk lacks. We aimed to develop, and externally validate, a risk prediction score for level of future risk, including baseline characteristics and information on early treatment response.

Methods: Data from a 12-month primary care cluster-randomized trial with asthmatics, aged 18-50. Early treatment response was assessed after 3 months. Future risk was defined as an ACQ ≥ 1.5 at the final visit, or the experience of one or more severe exacerbations during the final six months of the trial. Association was assessed with logistic regression and the predictive performance by area under the receiver operating curve (AUROC) and Hosmer-Lemeshow test. Based on the regression coefficients a risk prediction score was developed; externally validated in another similar dataset.

Results: Performance of the risk prediction score improved considering information on early treatment response (AUROC 0.84) compared to a model with only baseline characteristics (AUROC = 0.78). The final risk prediction score included six easy to obtain predictors; see figure 1. External validation yielded an AUROC of 0.77. The risk prediction score classified patients into three risk groups with absolute risks of 8.9% for low risk, 46.6% in intermediate risk and 64.4% in high level of future risk.

Conclusion: We developed and externally validated a risk prediction score, quantifying both the level of current asthma control and level of future risk. The risk prediction score can be used to identify patients with an increased future risk in a more explicit way, rather than just the presence or absence of risk factors.

O63
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Is the extended selection cohorts design a solution to difficulties in finding control groups? The evaluation of a multi-component school-based intervention to stimulate healthy diets

Context: To tackle the childhood obesity epidemic it is important to stimulate a healthy lifestyle among children. Jump-in is a multi-component school-based intervention stimulating physical activity and healthy eating habits among primary schoolchildren in Amsterdam. The healthy eating component includes a healthy nutrition school policy and workshops for parents and children. The current study aims to evaluate the effectiveness of the Jump-in healthy eating component.

Design: The study includes ten primary schools with high rates of obesity, often comprising children from ethnic minority families or families with a low socio-economic status. A quasi-experimental extended selection cohorts design is used to evaluate the Jump-in healthy eating intervention. As illustrated in Figure 1 this design includes two data collection waves. At baseline all classes are measured, after which the intervention is implemented. One year after baseline measurements, classes are measured again. These measurements are compared to the baseline measurement of the class in the subsequent grade, which then represents a same-age control group.

Dietary habits are assessed by questionnaires for parents and children and by photographs of the children’s lunchboxes.

Impact: A challenging factor in effect evaluation studies is the inclusion of comparable control schools. The extended selection cohorts design illustrates a solution to overcome this challenge in experimental research designs.
Discussion: An advantage of the extended selection cohorts design is that it ensures comparability in baseline characteristics. As control groups and the intervention groups belong to the same schools, the chance of selection bias is reduced. On the other hand, the design does not allow to control for general time trends in society, coinciding with the intervention. During the presentation, the researcher will further elaborate on the advantages and disadvantages of the extended selection cohorts design.

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Uptake and effectiveness of a Dementia Risk Reduction Program in middle-aged descendants of people with recently diagnosed Alzheimer’s Disease (AD) or vascular dementia. Design: Cluster randomized controlled trial, in which 26 memory clinics throughout the Netherlands are randomized to an active or passive recruitment strategy. The difference in uptake (e.g. percentage of eligible people that completed Dementia Risk Assessment) between the active (personal invitation by the medical doctor of their parent) and passive (poster in waiting room of memory clinic) strategy will be evaluated. Additionally, the effectiveness of the Dementia Risk Reduction Program on dementia risk factors between participants of the DRR Program (aged 40-70 years) and a matched (using propensity scores) control group, consisting of Lifelines participants (non-exposed to the DRR Program) will be investigated.

Impact: Accumulating evidence suggests that the neurodegenerative process leading to AD begins already in midlife. An average delay of two years in onset of AD could decrease the worldwide prevalence of AD by 22.8 million cases by the year 2050 and subsequently, decrease the amount of care and costs.

Discussion: Having a parent with recently diagnosed dementia might encourage people to participate in the DRR Program and improve their health behavior.

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Effectiveness, economic, and process evaluation of a combined nutrition and resistance exercise intervention for community-dwelling elderly: study design and methods

Context: The age related loss of skeletal muscle mass, sarcopenia, can lead to a decrease in physical functioning, decreased independence, and subsequently increased health care costs. The (cost-)effectiveness and implementation of an efficacious nutrition and resistance exercise intervention for
elderly, that has been translated to the real-life setting, will be studied.

Design:
A randomised, controlled, multicentre, phased intervention trial will be implemented in collaboration with local organisations, nutrition companies, and the community health service. In total 200 participants (≥ 65 years of age, (pre-)frail or experiencing difficulty in daily activities) will be included in phases in five municipalities in the Netherlands. The 12 week intervention consists of twice weekly group-based progressive resistance exercise guided by a physiotherapist, and increasing dietary protein intake at the main meals under supervision of a dietitian. After these 12 weeks, participants are stimulated to continue exercising and follow a nutrition course in the community. The control group receives this community program after 24 weeks. Outcomes are measured at baseline, 12 weeks and 24 weeks, and include physical functioning, quality of life, strength, and lean body mass. Cost-effectiveness is assessed based on QALY’s and Short Physical Performance Battery score. The implementation process is evaluated in participants and implementers using the process indicators recruitment, acceptability, applicability, integrity, dose, and context.

Impact:
Evaluating cost-effectiveness and implementation of this combined intervention provides valuable insight in the feasibility of this intervention for elderly in the Dutch public health and care setting, and its ability to improve and/or maintain physical functioning and quality of life.

Discussion:
Moving from an efficacious intervention to implementation in practice is a logical step, however, evaluation of both effectiveness and implementation in practice is necessary. An adequate set of process indicators has to be defined to describe the most relevant aspects of the implementation process.

Context
Research in an academic setting is different from research in a real-world setting. The difference relates to the content of the intervention and the context in which the intervention is implemented. In general, clinical trials are conducted under standardised conditions, whereas public health interventions are evaluated under real-world conditions. Consequently specific epidemiological methods are needed to address effectiveness in the real world in which the analysis of processes is necessary to evaluate intervention exposure and contribute to the interpretation of outcomes and the generalisability of study findings.

Design
In our book Epidemiology in Public Health Practice (2017), new and applied methods are described to evaluate public health interventions integrally. Logic models, causal diagrams, evaluation designs balancing external and internal validity and advanced methods like dose–response and mediation analysis contribute to the evidence-base. The extent to which the intervention is accepted by the target group, fits into the organisational structure and is supported by the wider political and sociocultural environment can be measured with process indicators like reach, acceptability and applicability. Economic evaluations provide insight into the question whether the intervention is worth the money.

Impact
Processes, effects and costs together give a richer picture of a successful programme. These results should be evaluated integrally to determine whether the implementation of the public health intervention has been successful from the viewpoints of policy, practice and research. To contribute to viable public health interventions and sustainable results, these three fields need to be covered in due balance within evaluations.

Discussion
Several researchers advocate research with more rapid public health and policy impact. They propose a shift towards research that provides contextually appropriate evidence on the effectiveness of interventions. The identification of a set of robust and standardised measures for so-called good practice characteristics that assess contextual factors could contribute to this.

066
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Epidemiological methods for evaluation research in public health practice
Evaluating DAG-dataset consistency to address confounding

Introduction
The classical approach to handle confounding in observational research includes the identification of the confounding variables and addressing it by regression techniques. An alternative way for confounding identification is the use of directed acyclic graphs (DAGs), which are a "language" for codifying causal assumptions and deriving their implications. However, it is essential to test a constructed DAG on consistency with the data. The aim of this study is to compare the classical approach with the DAG method and to show the benefit of consistency testing.

Methods
The research question of the study used for our comparison was whether fertility treatment is a risk factor of congenital anorectal malformations (ARM). Data were obtained from the AGORA data-and biobank including questionnaires and clinical data from children with congenital malformations, population-based controls, and their parents. In total 380 patients with ARM and 1973 control children were analysed. We used the web application “DAGitty” to construct the DAGs and the R-package “dagitty” to statistically test the implications of the constructed DAGs on conditional independencies (the so-called d(directional)-separation) and to determine adjustment sets for confounding correction of the effect of fertility treatment on ARM.

Results
The starting DAG was based on up-to-date knowledge. The conditional independencies of all testable relations according to this DAG were checked. Adapting the DAG to address the revealed violations resulted in an updated final DAG with no violations. Additional variables, which were not considered confounders in the original study, entered the adjustment set when using DAGs.

Discussion and conclusion(s)
Testing the implications of a DAG helps to evaluate the validity of causal assumptions and robustness of obtained adjustment sets. Proper use of DAGs provides a set of confounders, however demands critical thinking and testing its consequences.

Collider bias in metabolomics studies: a cautionary note

Introduction: Metabolomics studies are still expensive and therefore often performed as nested case-control studies in existing cohorts to examine secondary exposure-outcome relationships. If the selection criteria for the study population are common effects of these exposure-outcome relationships, collider bias can occur. We present an example to illustrate the effects of collider bias and the use of inverse probability weighting (IPW) to resolve these effects.

Methods: Metabolites were measured in a nested case-control design of 533 participants of 45-65 years selected on fasting glucose concentrations, of whom 176 with a normal fasting glucose (NFG; <6.1 mmol/L), 186 with impaired fasting glycaemia (IFG: 6.1 - 6.9 mmol/L) and 171 with high fasting glucose (HFG: ≥7 mmol/L). With linear regression we examined the associations between total body fat (TBF) and glycine concentrations, both related to glucose metabolism, adjusting for age and sex. Analyses were performed (1) in the total sample, (2) stratified or (3) adjusted for fasting glucose group, and (4) adjusted for the effects of collider bias using IPW.

Results: The association between TBF and glycine was markedly different within each of the fasting glucose groups at -2.0 (-3.0; -1.0) mmol/L/kg in NFG, -1.2 (-2.1; -0.2) in IFG, and 0.2 (-0.4; 0.8) in HFG. With linear regression we examined the associations between total body fat (TBF) and glycine concentrations, both related to glucose metabolism, adjusting for age and sex. Analyses were performed (1) in the total sample, (2) stratified or (3) adjusted for fasting glucose group, and (4) adjusted for the effects of collider bias using IPW.

Results: The association between TBF and glycine was markedly different within each of the fasting glucose groups at -2.0 (-3.0; -1.0) mmol/L/kg in NFG, -1.2 (-2.1; -0.2) in IFG, and 0.2 (-0.4; 0.8) in HFG. In the total sample the association was -1.1 (-1.6; -0.7) mmol/L/kg, and after adjusting for case status -0.8
IPW created a virtual population using the sampling frequencies of the fasting glucose groups from the original cohort, resulting in an estimate of $-1.9 \pm 0.9$. (Figure 1)

Conclusion: Metabolomics studies on secondary outcomes in case-control studies or case series are vulnerable to collider bias if the study population is oversampled with respect to a common effect of the exposure and outcome. In nested case-control studies or when the sampling frequencies are known, IPW can be used to correct for the effects of collider bias.

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Polysaturated fatty acid status at birth and allergy-related phenotypes in childhood: a pooled analysis of the MEFAB and RHEA birth cohorts

Introduction: Lower prenatal exposure to n-3 polysaturated fatty acids (PUFAs) relative to n-6 PUFAs has been hypothesized to influence later allergy development, but evidence remains largely inconsistent. Therefore, we investigated whether cord blood phospholipid PUFAs levels, reflecting fetal exposure in late pregnancy, are associated with mid-childhood wheeze, asthma, rhinitis, and eczema in the Dutch MEFAB (n=293) and Greek RHEA (n=213) birth cohorts.

Methods: Information on allergy-related phenotypes was collected at age 6-7 years using validated questionnaires. We estimated relative risk (RR) and 95% confidence intervals (CIs) for associations of PUFAs with child outcomes using multivariable generalized linear regression models.

Results: Mean ($\pm$ SD) levels of n-3 and n-6 PUFAs in MEFAB were 6.89 ± 1.59 and 32.16 ± 1.69 % of total fatty acids, respectively; the corresponding values for RHEA were 5.38 ± 1.12 and 32.06 ± 2.35 %. In pooled analyses, higher levels of the n-3 long-chain eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) and a higher total n-3:n-6 PUFAs ratio were associated with lower risk of current wheeze (RR 0.63 [95% CI 0.48-0.84] per SD increase in EPA+DHA and 0.56 [0.41-0.76] per unit increase in the n-3:n-6 ratio) and reduced asthma risk (RR 0.54 [0.34-0.85] for EPA+DHA and 0.46 [0.28-0.76] for the n-3:n-6 ratio). No associations were observed for other allergy-related symptoms. These results remained robust in sensitivity analyses.

Discussion: High EPA and DHA levels and a higher n-3:n-6 fatty acid ratio at birth might decrease the risk of wheeze and asthma in mid-childhood.

O70

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Development of a diagnostic multivariable model to screen for cerebellopontine angle lesions.

Introduction

We aimed to develop a diagnostic multivariable model to select patients with high risk for a
cerebellopontine angle (CPA) lesion from those with asymmetrical audiovestibular dysfunction (AAD), prior to MRI (to reduce the number of unnecessary MRIs).

Methods
We used a cohort of patients with AAD that underwent an MRI in the Radboudumc between 2005 and 2015. Data on demographics, symptoms and audiometry were collected. Multiple imputation of missings was performed by predictive mean matching, creating 10 imputation sets. Since events were few, LASSO was used to create a diagnostic multivariable model in each imputation set, resulting in selection of different variables per set. We categorized variables according to their frequency of selection and created 3 diagnostic models, i.e. model 1, 2 and 3 containing variables selected in 10, ≥5, or ≥1 imputation set(s), respectively, using mean regression coefficients over the 10 imputation sets. We assessed the models’ performances in the 10 imputation sets. Three diagnostic rules were generated, of which one was selected considering parsimony and performance. Its optimal threshold was selected by evaluating sensitivity and specificity.

Results
Data of 2214 patients were analyzed among which 69 (3.1%) subjects with a CPA lesion. We identified 4, 8 and 23 variables for model 1, 2 and 3, respectively (Figure 1). Corresponding c-indices were 0.66, 0.68 and 0.7, respectively. Applying the optimal threshold on the most parsimonious diagnostic rule achieved a sensitivity, specificity, positive and negative predictive value of 81%, 45%, 5% and 99%, respectively.

Discussion
We propose a diagnostic rule containing variables selected in all imputation sets as a first step in selecting patients with a high risk for a CPA lesion among those with AAD. The model needs to be externally validated, and its diagnostic accuracy preferably is improved, before it can be completely relied on in referring patients for MRI.

Figure 1: The number of times each variable is retained in the prediction model over the 10 imputation sets.
Black indicates a predictor that is being selected in all imputation sets. Grey indicates a predictor selected > 5 times. White indicates a predictor selected ≥1 time.
2.
Abstracts Poster
Presentations
WEON 2017
Estimation of sojourn time and sensitivity in cancer screening: a systematic review

Introduction: Sojourn time (i.e. the duration of the preclinical detectable phase) and test sensitivity play an important role in the design and assessment of cancer screening programmes. As a result, many mathematical models have been developed to estimate these key parameters using data from screening studies. In this systematic review, we will present an overview of these methods with the aim to provide researchers guidance to select the most appropriate method matching their own study data.

Methods: We systematically searched PubMed and Embase for original studies of new mathematical models that estimated sojourn time using individual patient data from screening studies. Direct observation of sojourn time (e.g. growth rates, survival benefits) or microsimulation estimates were excluded. From the selected studies we categorized method and study design and extracted the required data, assumptions and outputs. Furthermore, as an example, sojourn time estimates of colorectal cancer were collected to investigate the impact of the used method on this estimate.

Results: Thirty-two papers met the inclusion criteria. We grouped the studies into five methodological categories: prevalence-incidence ratio (n=5); interval incidence rates (parametric) (n=18); interval incidence rates (non-parametric) (n=3); Markov Chain Monte Carlo estimation (n=4) and other (n=3). Twelve of these methods were applied to RCTs, seventeen to observational studies and three to case-control studies. Ten publications were found estimating the overall mean sojourn time of colorectal cancer based on eight studies, including two RCTs. The mean sojourn time estimates varied between 2.1 and 4.9 years. The sojourn time estimates of breast cancer will be presented at WEON 2017.

Discussion: Five major methodological categories were identified as models to estimate population sojourn time. Methods based on the prevalence-incidence ratio and using RCTs based on interval incidence resulted in lower sojourn time estimates than the other methodological categories.

Clustering of mental health, chronic illness, lifestyle, and social experiences in Dutch adolescents

Introduction: The Public Health Monitor Utrecht (VMU) provides a comprehensive view of the health of citizens in Utrecht (The Netherlands) and determinants that influence health. This monitor is used to make well-founded (policy) choices, prioritize themes or target groups, support insights, and evaluate work.

Research has shown a clustering of health behaviors in adolescents. The current study, which is part of the VMU, extends previous research by including a wider range of health (related) factors. We examined whether different subgroups of adolescents can be distinguished based on mental health, chronic illness, lifestyle, and social experiences. The second aim was to examine differences between the subgroups on perceived health and demographic factors.

Methods: Data of 3824 adolescents were obtained using a self-reported questionnaire at thirteen high schools in Utrecht. Adolescents filled out the questionnaire prior to a consult with a municipal youth health care worker. TwoStep Cluster analysis was performed to create subgroups of adolescents. The subgroups were compared on perceived health and demographics using ANOVA and Chi-square tests.

Results: Four different subgroups were distinguished. The Healthy cluster (21%), the Social...
couch potato cluster (35%; positive social experiences, but inactive), the Experimenters cluster (25%; substance use) and the Increased risk cluster (19%; cumulation of negative health factors). Subgroups differed significantly on perceived health and demographics.

Discussion: Most adolescents have a healthy profile. Adolescents in the Increased risk cluster are characterized by the co-occurrence of negative health factors and a less positive perceived health. Experimenting behavior may be part of a healthy development (Experimenters cluster) or may go hand in hand with more unhealthy behavior and less positive experiences (Increased risk cluster). Youth health care workers who discussed the results, recognized the distinguished subgroups in practice. The clustering insights help to offer personalized preventive care to adolescents.

P03
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Metabolomics: a search for biomarkers of visceral fat volume and liver fat content

Introduction: Excess visceral and liver fat are important risk factors for cardiometabolic disorders. Metabolomics might allow for easier quantification of these ectopic fat depots, instead of using invasive imaging studies or approximations such as waist circumference or the fatty liver index. In this study, we investigated metabolites as potential biomarkers of visceral adipose tissue volume (VAT) and hepatic triglyceride content (HTGC).

Methods: The present study is a cross-sectional analysis of a subset of the Netherlands Epidemiology of Obesity study. Metabolite profiles were determined using the Biocrates AbsoluteIDQ p150 kit in 176 individuals with normal fasting plasma glucose, without concomitant use of lipid or glucose lowering medication. VAT was assessed with magnetic resonance imaging (MRI) and HTGC with proton-MR spectroscopy. We used linear regression to investigate the associations of 190 individual metabolites and predefined metabolite ratios with VAT and HTGC, also adjusting for age, sex, total body fat, waist circumference and serum triglycerides, total and high density lipoprotein cholesterol concentrations, while correcting for multiple testing using the false discovery rate.

Results: After adjustment, three ratios of metabolites were associated with VAT, the strongest association being the ratio of lysophosphatidylcholines to total phosphatidylcholines (PCs) at -14.1 (95%CI: -21.7; -6.6) cm2 VAT per SD of metabolite concentration. Several individual metabolites were associated with HTGC, in particular the diacyl PCs, of which C32:1 was the strongest (HTGC was 31.2 (13.6; 51.5) % higher per SD of metabolite concentration), and variables related to aromatic amino acids, of which tyrosine was the strongest (HTGC was 27.9 (7.6; 52.0) % higher per SD of metabolite concentration).

Conclusion: Metabolomics can be used to identify potential biomarkers of visceral fat volume or liver fat content that may have added diagnostic value over current approximations. Replication studies and repeated measurements are required to validate the predictive value of these metabolites.

P04
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Patient experiences with shared decision-making on neoadjuvant chemotherapy in early breast cancer

Introduction: Chemotherapy for early breast cancer can be administered prior to or after breast surgery in neo-adjuvant (NAC) or adjuvant (AC) setting. Application of NAC is still infrequent and varies considerably between hospitals. This study investigated patients’ experiences and preferences in receiving information on chemotherapy-timing during treatment for early breast cancer.

Methods: A 35-item online questionnaire was distributed among female patients, aged 18+, diagnosed in 2013-2014 in 19 Dutch hospitals with
clinical stage II/III invasive breast cancer, of whom half and half had been treated with NAC and AC respectively (apart from breast surgery). Outcome measures were experienced information exchange, and patients’ involvement in the decision-making process. Besides, patients’ experiences and satisfaction with care were measured using the Cancer Therapy Satisfaction Questionnaire (CTSQ).

Results: Of 805 invited patients 49% responded (179 NAC, 215 AC). NAC-treated patients were younger; more often treated in a teaching/academic and high-volume hospital; had different tumour characteristics (more often node-positive, higher stage, more often multifocal); more often received breast conserving surgery in case of stage II (all p<0.05). All (100%) NAC-treated patients were informed about NAC compared to AC-treated patients (stage II:14%, stage III: 31%). Provided information on chemotherapy in general was rated sufficient (stage II: 85% NAC, 63% AC; stage III: 73% NAC, 75% AC). Respondents not always felt they had a choice in the timing of chemotherapy as being either NAC or AC (stage II: 54% NAC vs 36% AC; stage III: 36% NAC, 50% AC). Discussion (conclusion): Although patients rated the information they actually received on chemotherapy as sufficient, not all patients felt they decided together with their clinician on chemotherapy-timing. Lack of information on the possibility of NAC was revealed among most patients treated with AC. Better information-exchange will lead to a well-informed and shared decision on the timing of chemotherapy.

POS
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Advanced stage breast cancer is less often diagnosed in women attending breast cancer screening

Introduction
The contribution of screening mammography to a reduced rate of advanced stage breast cancer (ASBC) is questioned. Our aim was to assess incidence rates of ASBC in women attending breast cancer screening compared to non-attenders.

Methods
All women, aged ≥49, diagnosed with breast cancer between 2006-2011 were selected from the Netherlands Cancer Registry and linked to data of the screening programme. Screen-related cancers were diagnosed <24 months after a screening examination, all other breast cancers were defined as non-screen-related cancers. Two definitions of ASBC were used: 1) stages III and IV (versus stages 0, I, II), or 2) invasive tumour sizes ≥15 mm (versus <15 mm or DCIS). Incidence rates were age-adjusted, multivariable logistic regression was used to estimate ratios for advanced stage between subgroups.

Results
In total 72,612 breast cancers were included, of which 44,246 were screen-related cancers (61%) including 32,158 screen-detected cancers (73%). ASBC incidence was 38/100,000 in the screened population compared to 94/100,000 in the non-screened population (p<0.001). Non-screen related cancers had a three times higher risk to be ASBC compared to screen-related cancer (OR: 2.86, 95%CI: 2.72-3.00). Applying the second definition resulted in higher incidence rates of ASBC for both populations, but was still higher in the non-screened population (169/100,000 vs 210/100,000; OR:1.85, 95%CI:1.78-1.93).

Conclusion
ASBC incidence rates were higher in non-attenders compared to those who attended the screening program, supporting the stage shift related to early detection. Data on actual screening attendance is essential to show if screening is an effective tool. We conclude that despite critical evaluations of breast cancer screening programs, screening is a valuable tool with potential to reduce a woman’s breast cancer load.
Inter-laboratory variation in the histological grading of invasive breast carcinoma in the Netherlands

Introduction: Histological grading of invasive breast carcinoma (IBC) is used throughout all stages of patient management. To date, its clinical contribution has become increasingly important, yet the level of inter- and intra-observer agreement does not reach the high clinical standards. Insight into laboratory-specific variation in the distribution of the histological grade and the role of other clinico-pathological factors, will help to improve standardization among laboratories.

Methods: We extracted 46,562 synoptic pathology reports of resection specimens of IBC between 2013 and 2016 from PALGA, the Dutch Pathology Registry. Histological grade (I-III) was determined using the Bloom-Richardson grading system. Records with unknown tumor grade (n=422), synchronous ipsilateral tumors (n=4,170) and tumors with neoadjuvant treatment (n=5,807) were excluded. Odds ratios (OR) and 95% confidence intervals (CI) for the proportion of high-grade (grade II and III) vs low-grade (grade I) IBC per laboratory were calculated using logistic regression and adjusted for differences in case mix, including sex, age, tumor size, histological subtype, receptor status, HER2 status, type of surgery and presence of carcinoma in situ.

Results: In total, 36,163 IBC of 35,034 patients from 39 pathology laboratories were included for analysis. Inter-laboratory proportions of grade I, II and III ranged between 16.4-43.4% (median: 28.2%), 8.3-57.3% (median: 46.2%) and 15.9-34.3% (median: 24.3%), respectively. For five laboratories, the proportion of high-grade IBC was significantly different from the reference laboratory. After the correction for case-mix, the number of laboratories with a significant deviant proportion of high-grade IBC increased to eight; four labs became significant and one lab lost significance. In general, the influence of the case-mix correction on laboratory-specific risk estimates was limited. Multivariable-adjusted OR(95%CI) ranged from 0.43(0.30-0.61) to 1.59(1.04-2.43).

Discussion: The inter-laboratory variation of histological grading is apparent concerning both the distribution range and the number of labs with a deviant proportion of high-grade IBC.

Room for improvement in diagnosing vestibular schwannoma: a diagnostic review and decision analytical modeling study.

Introduction: Vestibular schwannoma (VS) is a benign tumor located between inner ear and brain. All patients with asymmetrical audiovestibular symptoms are screened for VS using MRI with a yield of approximately 3%, i.e. >95% of costly MRIs are negative. We aimed to 1) assess diagnostic accuracy of non-imaging screening tests that can be used to select high risk patients for MRI (to reduce the number of negative MRIs), and 2) quantify room for improvement (difference between costs of the current strategy and a hypothetical perfect strategy) in diagnosing VS. This can be used to assess whether investments in new strategies are potentially worthwhile.

Methods: We performed a systematic literature search to assess evidence for currently available diagnostic methods to select patients for MRI. We included studies comparing non-imaging screening tests to MRI as gold reference standard. Methodological quality was assessed using QUADAS-2 by two independent reviewers. We calculated sensitivity and specificity of all tests and obtained pooled estimates. To assess room for improvement, we established a decision analytical model comparing the current diagnostic strategy to a hypothetical perfect strategy.

Results: We analyzed 12 studies (4,549 patients) of poor to moderate quality. Five pure-tone audiometry protocols were studied; pooled estimates for sensitivity ranged from 89% [95% CI 80-99] to 94% [95% CI 72-99] and specificity from
39% [95% CI 23-58] to 58% [95% CI 49-65]. Due to heterogeneity we were unable to pool other tests, having low diagnostic accuracy. If we would be able to improve diagnostics so that only patients with a VS would receive MRI, savings would amount to €293 (95% CI €290-296) per patient (or, in case of the Netherlands: €3.2 million/year).

Discussion: None of the currently available non-imaging screening protocols appear accurate in detecting VS. Room for improvement is, however, large, making it worthwhile to invest in new potential diagnostic methods.

Causes of death registration for Hodgkin lymphoma patients - a comparison between medical records and cause-of-death registry data

Background
Accurate registration of causes of death (CODs) may be difficult in patients with a complicated disease history, including cancer survivors. We aimed to compare CODs of Hodgkin lymphoma (HL) patients using medical records and official death certificates as processed by Statistics Netherlands.

Methods
Our hospital-based cohort, including 3,019 HL patients treated between 1965-2000 before the age of 51 years was linked with Statistics Netherlands. We compared CODs from official death certificates (CODDC) with CODs obtained from hospital or general practitioners’ records (CODMR) for HL patients who died in the period 1980-2013. CODMR was available for 65% of deceased patients in this cohort. The level of agreement was assessed for common ICD-coded underlying CODs and original death certificates were reviewed when CODDC and CODMR showed discrepancy. Additionally, we examined the influence of using CODDC or CODMR on standardized mortality ratio (SMR) calculations.

Results
Linkage with the cause-of-death registry could be performed for 95.2% of 1,215 deceased HL patients. Agreement for the most common CODs, including selected malignant neoplasms, circulatory and respiratory disease was 71%. HL was more often reported as underlying COD on the death certificates (CODDC=32.7% vs. CODMR=22.8%, p<0.001), whereas the CODMR more often concerned circulatory disease or other diseases potentially related to HL treatment (CODDC=15.6% vs. CODMR=20.9%, p<0.001). Compared to SMRs based on CODDC, SMRs based on CODMR complemented with CODDC were higher for infectious diseases (SMR=12.4; 95% CI=8.4-17.4 vs. SMR=6.2; 95% CI=3.5-10.0, p<0.001) and circulatory disease (SMR=5.9; 95% CI=5.2-6.6 vs. SMR=4.6; 95% CI=4.0-5.2, p<0.05) and lower for HL (SMR=1030; 95% CI=917-1152 vs. SMR=1249; 95% CI=1124-1384, p<0.05).

Conclusions
We observed moderate to high levels of agreement between CODDC and CODMR for common CODs in our cohort; however, SMRs for several CODs were significantly influenced due to differential assignment of COD between the two sources.

Markers of Vascular Function are associated with Procoagulant Factors in the General Population

Objective: Vascular function has been associated with venous thrombosis. We investigated whether three measures of vascular function (estimated...
glomerular filtration rate (eGFR), urinary albumin-creatinine ratio (UACR), and pulse wave velocity (PWV) are associated with a procoagulant state.

Approach and results: In this cross-sectional analysis of the NEO Study eGFR, UACR, fibrinogen, and coagulation factors (F)VIII, FIX, and FXI were determined in all participants (n=6,536), and PWV was assessed in a random subset (n=2433). eGFR, UACR and PWV were analysed on a continuous scale and per percentile based categories; per 6 categories for eGFR (>50th [reference] to <1st) and UACR (<50th [reference], to >99th), and per 4 categories (<50th [reference] to >95th percentile) for PWV. Linear regression analysis was performed and adjusted for age, sex, total body fat, smoking, education, ethnicity, total cholesterol, CRP, and vitamin K antagonists use (FIX). Mean age was 56 years, mean eGFR 86.2 (12SD) ml/1.73m² and UACR 0.45 mg/mmol (IQR 0.30; 0.71). All coagulation factors showed a procoagulant shift with vascular function, for example FVIII concentration was 22 IU/dL (95% CI: 13-32) higher in the <1st percentile. Compared with the UACR<50th percentile, FVIII was 12 IU/dL (3-22) higher in the >99th percentile. PWV was only associated with procoagulant factors FIX an FXI in continuous analysis: to illustrate, per m/s difference in PWV, FIX concentrations were 1.96 IU/dL (95% CI 0.70-3.2) higher.

Conclusions: All tested measures of vascular function were associated with higher procoagulant levels, supporting that vascular function plays a role in the etiology of venous thrombosis.

Body fat distribution, in particular visceral fat, is associated with cardiometabolic risk factors in obese women

Introduction

Body fat distribution is, next to overall obesity, an important risk factor for cardiometabolic outcomes in the general population. In particular, visceral adipose tissue (VAT) is strongly associated with cardiometabolic risk factors. It is unclear whether body fat distribution is also important in obese individuals. We aimed to investigate the associations between measures of body fat distribution and cardiometabolic risk factors in obese men and women.

Methods

In this cross-sectional analysis of obese men and women (BMI≥30 kg/m²) included in the Netherlands Epidemiology of Obesity Study, waist circumference and waist hip ratio (WHR) were determined, in addition to amount of abdominal subcutaneous adipose tissue (aSAT) and VAT by MRI. Associations between these adiposity measures and the presence of at least one of the risk factors hypertension, hypertriglyceridemia, low HDL-cholesterol concentrations and hyperglycemia were examined using logistic regression analysis. Analyses were stratified by sex and adjusted for age, ethnicity, education, tobacco smoking, alcohol consumption, physical activity and depending on the association additionally for total body fat or VAT.

Results

We included 2,981 obese individuals (57%women) with a mean(SD) age of 56(6) years and BMI of 34.0(4.0) kg/m², after excluding individuals with missing values of cardiometabolic risk factors(n=33). VAT and aSAT measurements were available in 1,071 participants. There were 241 obese individuals without any other cardiometabolic risk factors. In obese women, all measures of body fat distribution except aSAT (OR per SD:0.76, 95%CI:0.53,1.10) were associated with having at least one cardiometabolic risk factor, of which VAT most strongly associated. One SD higher
VAT(64.0cm2) was associated with an OR of 5.77(95%CI: 3.02,11.01) of having at least one cardiometabolic risk factor. In obese men, associations showed a similar, but weaker pattern.

Discussion
In obese women, but less so in men, measures of body fat distribution, of which VAT most strongly, are associated with cardiometabolic risk factors.

P11
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Effect of glomerular filtration rate at dialysis initiation on survival in patients with advanced chronic kidney disease: what is the effect of lead-time bias?

Introduction: Following current clinical guidelines, dialysis should be initiated based on disease-related symptoms, often between a glomerular filtration rate (GFR) of 5-10 mL/min/1.73m2. Little evidence exists about the optimal kidney function to start dialysis. Thus far, most observational studies have been limited by lead-time bias. Only a few studies have accounted for lead-time bias and showed contradictory results. We examined the effect of GFR at dialysis initiation on survival in CKD patients, and the role of lead-time bias therein. We used both kidney function based on 24-hour urine collection (mGFR) and estimated GFR (eGFR).

Methods: A total of 1143 patients with eGFR data at dialysis initiation and 852 patients with mGFR data were included from the NECOSAD cohort. Cox regression was used to adjust for potential confounders. To examine the effect of lead-time bias, survival was either counted from the time of dialysis initiation or from a common starting point (GFR=20 mL/min/1.73m2), using linear interpolation models.

Results: Without lead-time correction, no difference between early and late starters was present based on eGFR (HR 1.03 [95% confidence interval: 0.81-1.30]). However, after lead-time correction, early initiation showed a survival disadvantage (HR between 1.10 [0.82-1.48] and 1.33 [1.05-1.68]). Based on mGFR, the potential survival benefit for early starters without lead-time correction (HR 0.80 [0.62-1.03]) completely disappeared after lead-time correction (HR between 0.94 [0.65-1.34] and 1.21 [0.95-1.56]). Dialysis start time differed about a year between early and late initiation.

Conclusion: Lead-time bias is not only a methodological problem but has also clinical impact when assessing the optimal kidney function to start dialysis. Therefore, lead-time bias is extremely important to correct for. Taking account of lead-time bias, this controlled study showed that early dialysis initiation (eGFR>7.9; mGFR>6.6 ml/min/1.73m2) was not associated with an improvement in survival.

P12
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The influence of adjuvant systemic treatment on contralateral breast cancer risk and subtype

Introduction
Due to improved breast cancer survival, more patients are at risk of developing contralateral breast cancer (CBC). Studies have shown that treatment with adjuvant hormonal or chemotherapy reduces CBC risk. Little is known about the influence of adjuvant systemic therapies, including trastuzumab, on CBC subtype (estrogen receptor (ER), HER2).

Methods
We performed a large population-based cohort study among 83,245 Dutch women diagnosed with invasive breast cancer between 2003 and 2010, to evaluate the impact of adjuvant treatment on metachronous CBC risk and subtype (Figure 1). Patients and corresponding treatment and tumor characteristics were selected from the Netherlands Cancer Registry. Additional data on receptor status were obtained through linkage with the nationwide network and registry of histopathology (PALGA). CBC risk was quantified using cumulative
incidence and multivariable Cox regression analysis, adjusted for competing risks.

Results
During median follow-up of 7.7 years, 2,849 CBCs were observed. The cumulative incidence increased with 0.4% per year, reaching 4.0% after 10 years. Adjuvant treatment was associated with a markedly decreased CBC risk (chemotherapy: Hazard ratio (HR)=0.67, P<0.001; hormone therapy: HR=0.46, P<0.001; hormonal + chemotherapy: HR=0.37, P<0.001; chemotherapy + trastuzumab: HR=0.57, P<0.001). ER-concordance between first and contralateral breast cancer was high (OR=6.41, P<0.001). However, ER-concordance was altered when receiving hormone therapy after ER-positive first breast cancer, leaving a greater proportion ER-negative CBCs (23% vs. 7%). Sub-analyses showed that hormone therapy was only effective in reducing risk of ER-positive CBC (HR=0.25, P<0.001), and did not significantly affect development of ER-negative CBC (HR=0.87, P=0.324). No association between trastuzumab and CBC risk according to HER2 status was found.

Discussion
Adjuvant systemic treatment considerably reduced the risk of CBC. However, hormone therapy was only effective in reducing risk of ER-positive CBC, and did not affect the risk of developing ER-negative CBC, leaving a greater proportion ER-negative CBCs.

Risk factors for HGAIN among HIV-positive MSM in Amsterdam, the Netherlands

Background
High-grade anal intra-epithelial neoplasia (HGAIN) is a precursor for anal cancer, and is common among HIV-positive men who have sex with men (MSM). We studied risk factors for HGAIN among HIV-positive MSM screened by high resolution anoscopy (HRA).

Methods
MSM screened by HRA at three HIV clinics in Amsterdam, the Netherlands, were included. Findings of the first screening visit were analyzed.

HIV-parameters (CD4 count, nadir CD4, most recent plasma viral load (VL), combination antiretroviral therapy (cART) use, duration of cART use, years of viral suppression), any sexually transmitted infection (STI) in the preceding 6 months, smoking and number of sexual partners in preceding 6 months were assessed as risk factors for HGAIN, using uni- and multivariable logistic regression. A multilevel (by clinic) regression was done.

Results
From 2008 through 2015, 1681 MSM were screened for HGAIN; 713 at clinic A; 674 at clinic B; 294 at clinic C. The mean age was 49 years (SD 9.6), 96% used cART, median duration of cART use was 7.8 [IQR 4.0-12.4] years. The prevalence of HGAIN was 30% (499/1681 participants). Only an STI in the preceding 6 months was found to significantly increase the odds of HGAIN (aOR 1.66, 95% CI 1.02-2.71, P=0.043) in multivariable multilevel regression analyses. Time living with viral suppression was borderline significantly associated with HGAIN (1 to 5 years viral suppression OR 0.63 [95% CI 0.40-0.98], 5.01 to 10 years viral suppression OR 0.50 [95% CI 0.30-0.83], >10 years viral suppression OR 0.64 [0.39-1.07], compared to <1 year viral suppression, P=0.052).

Discussion
In this large group of HIV-infected MSM, only an STI in the preceding 6 months was significantly associated with HGAIN. Therefore, identifying those at low or high risk of having HGAIN based on HIV-related factors seems not possible.
Introduction: Dose changes in the label occur frequently (~20%) in the post-marketing phase of new substances; most often a downward adjustment related to safety concerns. However, limited information about dose changes is available for biopharmaceuticals. Therefore, the aim of this study was to evaluate post-marketing label changes in dosing information of biopharmaceuticals.

Methods: Biopharmaceuticals authorised between 2007 and 2014 via the European Medicines Agency (EMA) were included in this cohort study. The follow-up time consisted of the period from marketing authorisation until 31 December 2016 or date of withdrawal of the marketing authorisation. The outcome of the study was defined as label change in dosing information for the initially approved indication; an increase or decrease in daily dose or a change in dosing frequency. The assessment history as retrieved from the EMA website was used to determine if a label change in dosing information of a product had occurred. Incidence of changes, type of change and mean time to change were assessed.

Results: A total of 71 biopharmaceuticals were authorised during the study period. The mean follow-up time was six years (SD: 3). Dosing changed for the initial indication in the label during follow-up for seven products (cumulative incidence 10%). In three of the seven products the change concerned an increase in dose. Also, in three products a change in dosing frequency was identified. For the remaining product a recommendation was added that therapy could be initiated with or without a loading dose. The mean time to a label change was four years (SD: 2, range 1-7 years).

Conclusions: This study showed that in 10% of the biopharmaceuticals the dosing information in the label was changed an average of four years after marketing authorisation. In contrast with small molecules, these dose changes included dose increases and changes in dosing frequency.

Background: Patients are at risk for harm when treated simultaneously by healthcare providers from different health care organisations. Accordingly, improving transitional patient safety is an important objective in health care. To assess this improvement, valid measurement tools assessing transitional patient safety are needed.

Methods: First, PubMed, Cinahl, Embase and Psychinfo were systematically searched to identify all validated measurement tools and outcomes that measure aspects of transitional patient safety. Two researchers performed the title and abstract and full text selection. We used the COSMIN criteria to appraise the quality of these articles. Second, we inventoried all measurement tools and outcome measures that were used to assess current transitional patient safety or the effect of interventions targeting transitional patient safety.

Results: The initial search yielded 6871 studies, of which 17 assessed validity of measurement tools of aspects of transitional safety and 161 assessed the current transitional patient safety or effect of interventions. No validated tools solely measuring the full scope of transitional patient safety were found. In the validated measurement tools, the overall quality of content and structural validity was generally acceptable; other COSMIN criteria were mostly poor or not reported. In our measurement inventory, the most frequently used validated outcome measure was the Care Transition Measure (n=5). The most frequently used non-validated outcome measures were: medication discrepancies (n=84), hospital readmissions (n=44), emergency department visits (n= 29), adverse events (n=28), (mental or physical) health status (n=24), and patient satisfaction (n=21).

Conclusions: Although no validated measures exist measuring the full scope of transitional patient safety, we did find validated measurement tools on several aspects of transitional patient safety. Reporting of validity of transitional measurement tools was incomplete.

Measuring transitional patient safety from both the perspectives of the health care provider and the patient; a systematic review.
Association Of Resistance Exercise With The Incidence Of Hypercholesterolemia In Men

Introduction. Hypercholesterolemia is an important risk factor for cardiovascular disease. Beneficial effects of aerobic exercise (AE) are well-documented, however, evidence for the effects of resistance exercise (RE) on the incidence of hypercholesterolemia is limited. Therefore, this study sought to determine the associations of RE, independent of and combined with AE, with the risk of developing hypercholesterolemia in men.

Methods. This cohort included men, aged 18-83 years (mean 46), who received comprehensive medical examinations at the Cooper Clinic in Dallas, Texas. Baseline RE, AE, and meeting the 2008 US Physical Activity Guidelines (RE ≥2 days/week; AE ≥500 MET-minutes/week) were assessed by self-reported frequency and minutes of exercise. Hypercholesterolemia was defined as total cholesterol of ≥240 mg/dL or physician-diagnosed hypercholesterolemia during follow-up examinations. Cox proportional hazards regression was used to generate hazard ratios (HRs) and 95% confidence intervals (CIs).

Results. Twenty percent of the 7317 men developed hypercholesterolemia during a median follow-up of 4 years. Meeting the RE guidelines was associated with a 13% lower risk of hypercholesterolemia (HR 0.87; 95% CI 0.77-0.996) after adjustment for potential confounders and AE. In addition, after full adjustment, individuals performing less than 1 hour/week and 2 sessions/week of RE had a 32% and 31% lower risk of hypercholesterolemia (HR 0.68; 95% CI 0.54-0.86 and HR 0.69; 95% CI 0.54-0.88), respectively, compared to performing no RE. Whereas, higher levels of RE did not show additional benefits. Further, meeting guidelines for both RE and AE lowered the risk of hypercholesterolemia by 21% (HR 0.79; 95% CI 0.68-0.92), compared to meeting neither of the guidelines.

Discussion. Participating in RE for even less than 1 hour/week or 2 sessions/week, was associated with a significantly lower risk of developing hypercholesterolemia in men, independently of AE. These results suggest that RE should be added to habitual physical activity to prevent hypercholesterolemia.

Dietary Fatty Acids and Coronary Heart Disease Mortality in the Alpha Omega Cohort

Introduction

Replacement of saturated fatty acids (SFA) with unsaturated fatty acids (UFA), mainly polyunsaturated fatty acids (PUFA), is associated with a lower risk of coronary heart disease (CHD). Whether this replacement may also be of benefit for drug-treated CHD patients is not yet clear. In this study of Dutch CHD patients, we examined the risk of CHD mortality for the replacement of the sum of SFA and trans-fatty acids (TFA) by cis-UFA, cis-MUFA, and cis-monounsaturated fatty acids (MUFA).

Methods

We included 4,146 post-myocardial infarction patients aged 60-80 (79% male) from the Alpha Omega Cohort in whom diet was assessed at baseline (2002-2006) by a validated 203-item food-frequency questionnaire. Cause-specific mortality was monitored until January 2013. Iso-caloric replacement of the sum of SFA and TFA with cis-UFA, cis-MUFA, and cis-MUFA in relation to CHD mortality was statistically modelled in quintiles and continuously per 5 energy percent (en%). Hazard Ratios (HR) with 95% confidence intervals (95%CI) were obtained after adjustment for demographics, lifestyle characteristics, medication use, and dietary...
factors. The model for PUFA also included MUFA as a covariate, and vice versa.

Results:
During a median follow-up of 7.3 years 249 CHD deaths occurred. Comparing extreme quintiles, replacing the sum of SFA and TFA intake by cis-UFA was statistically inversely associated with CHD mortality. HRs (95% CI) were 0.39 (0.21-0.70) for cis-UFA, 0.54 (0.33-0.88) for cis-PUFA, and 0.77 (0.45-1.33) for cis-MUFA. When expressed per 5 en% (Figure), replacing the sum of SFA and TFA with either cis-UFA, cis-PUFA, or cis-MUFA was associated with a more than 30% lower risk of CHD mortality. Findings were similar were confined to statin users.

Conclusion:
In drug-treated CHD patients, replacement of SFA and TFA by cis-UFA is associated with a lower CHD mortality risk.

P18
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Built environmental characteristics and type 2 diabetes risk: a systematic review and meta-analysis

Background: Physical inactivity and poor dietary habits are established lifestyle-related risk factors of type 2 diabetes (T2D). Built environmental characteristics may influence these risk factors, and thus risk of T2D. We systematically reviewed the evidence on built environmental characteristics related to these lifestyle factors and T2D incidence, prevalence and glycaemic markers.

Methods: A literature search was performed in PubMed, Embase and Web of Science. We included studies reporting: 1) populations ≥18 years old, 2) T2D prevalence, T2D incidence, or glycaemic markers as outcomes, and 3) physical activity and/or food environment as determinants. After screening by two independent reviewers, data were extracted by one reviewer according to a standardized protocol and quality of the studies was assessed by two reviewers according to the Quality Assessment Tool for Quantitative Studies. When ≥3 studies investigated the same outcome and exposure, we performed meta-analyses using a random effects model.

Results: From 9827 studies 84 were eligible for inclusion and 23 were meta-analysed. Urban residence was associated with higher T2DM risk/prevalence (n=12, OR=1.54 (95% CI=1.3-1.9; I2=74%)) as compared to rural residence. Higher neighbourhood walkability was associated with lower T2DM risk/prevalence (n=8, OR=0.87 (95% CI=0.8-0.9; I2=0%)) and more green space tended to be associated with lower T2DM risk/prevalence (n=3, OR=0.84 (95% CI=0.6-1.2; I2=97%)). No convincing evidence was found of an association between food environment with T2DM risk/prevalence.

Conclusion: Urbanisation was associated with higher T2DM risk/prevalence. Physical activity environment was more consistently associated with T2DM risk/prevalence, than the food environment. In addition to other positive consequences of walkability and access to green space, these environmental characteristics may also contribute to T2D prevention. These results may be relevant for infrastructure planning.

P19
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Polyunsaturated fatty acid status at birth, childhood growth and cardiometabolic risk: a pooled analysis of the MEFAB and RHEA birth cohorts

Background: Prenatal exposure to polyunsaturated fatty acids (PUFAs) may influence childhood obesity development and cardiometabolic health.

Objective: To assess whether fetal PUFA exposure is associated with rapid growth in infancy, childhood obesity and clustered cardiometabolic risk.

Methods: In the Dutch MEFAB (n=255) and Greek RHEA (n=257) birth cohorts, we measured cord blood phospholipid n-3 and n-6 PUFAs levels, reflecting fetal exposure in late pregnancy. We defined rapid infant growth as a weight gain z-score >0.67 from birth to 6 months. We analyzed child body mass index (BMI) as a continuous outcome and in categories of overweight/obesity at 4 and 6 years. We computed a continuous cardiometabolic risk score at 6-7 years as the sum of waist circumference, non-hdl cholesterol and blood pressure z-scores.

Results: In pooled regression analyses, higher levels of the n-3 long-chain eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) and a higher total n-3:n-6 PUFA ratio were associated with lower risk of rapid infant growth (adjusted RR: 0.84 [95% CI: 0.72, 0.99] per SD increase in EPA+DHA and 0.83 [95% CI: 0.71, 0.97] per unit increase in the ratio). We found no associations of PUFAs with childhood BMI, overweight/obesity and cardiometabolic risk. The results were similar across cohorts, and remained robust in sensitivity analyses.

Conclusions: High EPA and DHA levels and a higher n-3:n-6 fatty acid ratio at birth might decrease the risk of rapid growth in infancy.
Moderate and heavy alcohol consumption are associated with decreased systolic function after 8 years of follow-up: The Hoorn Study

Background:
Excessive alcohol consumption is an important risk factor for cardiovascular disease, however, the underlying mechanisms are not well understood. We examined whether alcohol consumption is associated with cardiac structure and function in older adults at baseline and after 8 years of follow-up.

Methods:
We used data from the Hoorn Study, a population-based, prospective cohort study. Data on alcohol consumption were collected with a validated food frequency questionnaire in 2000/2001 (baseline for the current analyses). Echocardiography was performed in 2000/2001 in 582 participants and in 2007/2009 in 339 participants.

Participants were classified into 5 categories based on self-reported alcohol consumption (glasses per week): 0 (non-drinkers), 0-3 (light-drinkers), ≥3-7 (light to moderate drinkers), ≥7-14 (moderate drinkers) and ≥14 (heavy drinkers). Light drinking was considered the reference group. We studied the association of alcohol consumption with echocardiographic measures of left ventricular mass index, left ventricular ejection fraction and left atrium volume index cross-sectionally and prospectively after 8 years of follow-up using linear regression analyses, adjusting for potential confounders.

Results:
The mean age was 69.8±6.5 years and 50% was female. Cross-sectionally, alcohol consumption was not associated with any of the echocardiographic measures. After 7.4±0.5 years follow-up, moderate and heavy alcohol consumption were associated with a decreased ejection fraction of -5.1% (95% CI: -8.7, -1.4) for moderate and -4.8% (-8.8, -0.8) for heavy drinkers (Table). Heavy drinking was also associated with a decrease in left atrial volume index: -3.9mL/m² (CI: -7.6, -0.2). No longitudinal associations were found between alcohol consumption and left ventricular mass index.

Conclusion:
Both moderate and heavy drinking were associated with decreased systolic function after 8 years follow-up. The toxic effect of alcohol could lead to underfilling of the left atrium which could lead to lower systolic function. These findings may explain the increased cardiovascular risk among people with excessive alcohol use.


Background – High intake of dairy products has been associated with lower risk of diabetes in observational studies, although not consistently. Genetic lactase persistence (LP) enables digestion of dairy sugar (lactose). Therefore, a single nucleotide polymorphism (SNP) related to LP has been used as instrumental variable (unbiased proxy) for dairy intake to investigate if dairy intake is be causally related to incident diabetes.

Methods – The analysis included 21,900 individuals from 8 European countries of the European Prospective Investigation into Cancer and Nutrition (EPIC)-InterAct case-cohort study, among whom 9,742 incident diabetes cases were confirmed during on average 10-year follow-up. Participants were genotyped using the CardioMetabochip or Illumina 660W quad chip and the LP SNP of interest, rs4988235, was imputed. Baseline dietary intakes were assessed with food frequency questionnaires. IV estimates were derived by predicting dairy intakes based on the LP SNP genotype and using these predicted intakes in a Prentice weighed Cox-regression model to examine the causal association of dairy intakes with incident diabetes.

Results – Homozygous LP was present in 36.5% of the cohort, ranging from 5.0% in Florence, Italy to 55.7% in Malmö, Sweden. Every additional LP allele was associated with a 25.5 (95%CI: 16.9, 34.2) g/day higher milk intake, but not with intake of non-milk products.
dairy products. The IV analysis showed that milk intake was not related to diabetes with an HR of 0.99 per 25 mg/day (95% CI: 0.92, 1.06).

Conclusion – This MR analysis suggests that milk intake is not causally related with diabetes, which is consistent with previous observational evidence, including from EPIC-InterAct.

P23
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Improvement of the sensitivity and sojourn time of mammographic screening: forty years of breast cancer screening in Nijmegen, the Netherlands

Introduction: Since the introduction of biennial breast cancer screening in Nijmegen, the Netherlands, in 1975, screening technology has improved and has recently changed from analogue to digital. We investigated whether these technological advancements have led to improved sensitivity of the screening examination and an elongation of the mean sojourn time.

Methods: A repeated prevalence-incidence study based on 19 biennial screening rounds from the Nijmegen program, 1975-2012, was conducted. Screening rounds were divided into five periods based on technological changes in the screening program; 1) early phase of the pilot study (1975-1982), 2) later phase of the pilot study (1983-1988), 3) introduction of nationwide breast screening (1989-2000), 4) after publication of the optimization study on the Dutch recall rate (2001-2006) and 5) after introduction of digital mammography (2007-2012). Test sensitivity of mammographic screening was calculated based on the number of screen-detected cancers divided by the sum of the number of interval cancers diagnosed in the first year after screening plus the screen-detected cancers. The mean sojourn time and underlying breast cancer incidence were estimated simultaneously using maximum likelihood estimation.

Results: Test sensitivity of the mammographic screening was 89%, 81%, 87%, 90% and 90% for periods 1 to 5, respectively. The mean sojourn time was 2.44 (2.00-2.86) years for period 1, 2.86 (2.17-3.85) for period 2, 2.86 (2.44-3.45) for period 3, 2.44 (2.00-2.94) for period 4 and 3.33 (2.86-3.85) for period 5. The underlying breast cancer incidence was 0.0026 (0.0024-0.0030), 0.0029 (0.0026-0.0034), 0.0032 (0.0029-0.0034), 0.0034 (0.0030-0.0038) and 0.0040 (0.0036-0.0044) for period 1 to 5.

Discussion: The test sensitivity of mammography has remained constant during forty years of breast cancer screening in Nijmegen. However, the underlying breast cancer incidence showed an increasing trend and the length of the mean sojourn time elongated after the introduction of digital mammography.

P24
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CALCULATION OF INTERVAL COLORECTAL CANCER in BELGIUM

Introduction: Interval colorectal cancers are colorectal cancers (CRC) that are diagnosed after a negative screening examination and before the next recommended test (Benedict, WJG, 2015). We wanted to calculate interval colorectal cancer in Belgium for the period 2002-2009 and compare different existing methods.

Methods: Most methods look back from the date of diagnosis and use the total number of individuals with cancer as the denominator. Interval cancer rate is calculated as the number of patients with interval cancer, divided by all patients with CRC. The methods differ in omitting patients with a recent colonoscopy (Bressler), in counting the patients with interval cancer in the denominator (Singh) or including all patients with CRC (colonoscopy not necessary) (LeClercq). Morris (Morris, Gut, 2014) looked forward from the date of colonoscopy, and diagnosed post colonoscopy colorectal cancer (PCCRC) as a cancer diagnosed between 6-36...
months after colonoscopy. Colonoscopies (true positive and false negatives), and not individuals, were the denominator. We calculated interval cancer in different ways for all colonoscopies performed in Belgium between 2002-2009. We used no exclusion criteria, except that 2008-2010 was omitted for the calculation of PCCRC and 2002-2004 for all the other methods.

Results:
In Belgium, 1,325,126 full colonoscopies and polypectomies were performed in 994,047 patients in 9 years. Wide variation is present between the different rates of interval cancer. PCCRC ranges from 1.26% (Bressler), to 2.38% (LeClercq), 4.46% (Cooper), and 5.21% (Singh). PCCRC rate was overall 7.26%.

Conclusions:
Different methods to calculate colorectal interval cancer give a wide variation of results. Further study are necessary to find a uniform method to calculate interval colorectal cancer or PCCRC.

Identification of Pulmonary Tuberculosis spatial clustering using surveillance data in Flanders, Belgium, 2013-2015

Introduction
Tuberculosis (TB) caused by Mycobacterium tuberculosis still pose as a major threat in both industrialized and less industrialized countries. Flanders region is a highly urbanized area in Belgium with a large population and relatively high immigration rate, which might increase the risk of contracting and developing TB. The knowledge of patients’ characteristics is important to acquire more insight about the TB transmission within the community. The aim of this study was to investigate the potential cluster of TB cases based on the birth country using geographical information system (GIS).

Methods
With a cross-sectional study using data from Orka, the surveillance system database of Flemish region, we analyzed the baseline characteristics of pulmonary TB cases from year 2013 until 2015. The incidence rate was calculated and visualized in choropleth maps at district level. The spatial autocorrelations (Global and Local Moran’s I) were used to evaluate the presence of cluster.

Results
Seven hundred and fifty five cases were included in the analysis. In general, the TB incidence rate was around 3.9 per 100,000 individuals. The highest incidence rate was found in ≥65 age group, male, residence of Antwerp province, and African or Asian-born population. The Global Moran’s I result showed significant spatial correlation in Central Africa and North Africa population (Z= 2.212, p=0.027 and Z=4.767, p<0.001, respectively). The significant cluster was found in Antwerp and Mechelen district.

Conclusion
The burden of TB in Flanders region was still low with little changes in the number and incidence rate. Different classification of TB cases provides a different perspective of the current TB epidemiology. The integration of other application such as GIS into the surveillance system will aid in preventing further TB transmission.

Pediatric Tuberculosis in Kenya (2012-2016): burden, risk factors for death and space-time clustering of case fatality

Introduction: Tuberculosis (TB) remains a high burden disease in Kenya. It is aggravated by the
presence of human immunodeficiency virus (HIV) co-infection and multidrug-resistant tuberculosis (MDR-TB). Following exposure and infection, children have a high risk of progression to TB disease. The aim of this study was to investigate the main risk factors associated with death in pediatric TB cases and to assess geographical cluster of pediatric TB in Kenya.

Methods: We performed a retrospective data analysis of all pediatric TB cases (age <15 years) registered by the Kenyan National Tuberculosis, Leprosy, and Lung Disease Program (NTLD) in 2012-2016. Data on demographics and clinical characteristics were analyzed using a multiple logistic regression model. The spatial autocorrelations analysis (Global and Local Moran’s I) and retrospective space-time analysis were used to evaluate the presence of cluster.

Results: During the 5-year period, 28601 cases of pediatric TB were notified: 13988 (48.9%) in girls and 14613 (51.1%) in boys. Most cases (47.1%) occurred in 0 to 4 years age group. The majority of cases were pulmonary TB (75.7%) and the remaining were extra pulmonary cases. HIV co-infection was present in 7633 cases (26.7%) with similar proportions in boys and girls (47.9% in boys and 57.1% in girls, p<0.001). Almost all co-infected pediatric cases received antiretroviral treatment (90.8%) and cotrimoxazole prophylaxis (99.3%). Overall, 914 cases (3.2%) were started on MDR-TB treatment empirically with only 80 children having bacteriological confirmation of resistance. In a multivariable logistic regression model, age, sex, category of TB, and HIV co-infection were the main risk factors associated with death. Significant cluster of higher case fatality rates were found around Siaya and Homa Bay districts.

Conclusion: Younger children, boys, retreatment, and HIV co-infection cases need more attention to improve treatment outcome, particularly in areas where significant cluster of higher fatality rates were found.

Long term impact of Q-fever fatigue syndrome on work status

Introduction
Understanding disease-related impact on daily functioning, including work, is relevant for person-centred care. Estimates show that 20% of acute Q-fever patients develop persistent fatigue, i.e. Q-fever fatigue syndrome (QFS). Little is known about the long term impact of this condition on work status. Aim is to compare work status with diabetes type II patients and the general population.

Methods
Retrospective study of patients with QFS (average 7 years after acute infection), patients with diabetes type II (average 7 years after diagnosis) and the general population. Work status (percentage unemployed, retired, incapacitated and employed), hours of paid work over the last 10 years, current need for recovery after work and current work ability were measured with a questionnaire.

Results
Percentage of current incapacitated QFS patients (44.5%) and the need for recovery of QFS patients is significantly higher and the work ability significantly reduced compared to diabetic patients and the general population (p<0.05). Following acute infection, the average number of hours that QFS patients work per week decreases every year (Fig. 1). This decrease is stronger than for diabetic patients and the general population.

Discussion
QFS patients experience high impact on work status on average 7 years after acute infection (between 1 and 10 years) compared to diabetic patients and the general population. QFS patients work less and do not return to the level of hours of paid work before infection.
Identification of barriers and facilitators for the implementation of standardized structured reporting in pathology in the Netherlands

Introduction
Standardized structured reporting (SSR) enables complete and high quality pathology reporting. This is essential for adequate discussion of patients in multidisciplinary team meetings. Although Dutch guidelines recommend using SSR-modules, a slow uptake is observed in the Netherlands. Identifying barriers and facilitators and determinants for using SSR by pathologists is necessary to develop tailored implementation tools to increase SSR uptake.

Methods
A qualitative study (focus group interview, 30 pathologists contacted) was performed to identify facilitators and barriers for using SSR-modules. These factors were classified into levels according to the theoretical framework of Flottorp, that is level of innovation (SSR), professional (pathologist), social setting, organization and (inter)national regulations and finances. To assess the importance of barriers and facilitators found, we quantified findings using a web-based survey among Dutch pathologists (approximately n=400). Descriptive analyses were used to describe the factors. Determinants related to barriers and facilitators were assessed with multivariable logistic regression analyses.

Results
Ten pathologists participated in the focus group, and 85 pathologists completed the survey. At the level of the innovation (SSR), the main barriers of the SSR-module were inability to express nuances in diagnosis (30%), and no clarity of usability (41%). Barriers within the social setting were lack of support from colleagues at the department (20%) and multidisciplinary team (34%). At organizational level, lack of support by managers (11%), priority of change (20%) and information on updates and availability of SSR-modules (22%) was mentioned. Facilitators for using SSR-module were using the SSR-module as a tool (72%), improved communication during multidisciplinary team meetings (80%). Men, specialists and pathologists in training working in academic hospitals had more barriers than others.

Discussion
Barriers and facilitators to use SSR-modules exist at different levels. These factors will be used to develop tailored implementation tools to improve the uptake of SSR in the Netherlands.

Measurement equivalence of the Belgian health interview survey auto-questionnaire: paper-based versus web-based mode

Introduction
The Belgian Health Interview Survey (BHIS) consists of a face-to-face interview and a self-completed paper-based questionnaire. Previous BHIS (2008 and 2013) showed declining participation rates for the self-completed questionnaire. To enhance participation, a web-based version of the questionnaire was developed in addition to the paper-based one. However, different modes of data-collection may generate different influences on participant’s response behavior. In this context, a pilot study was conducted to assess measurement agreement between the traditional paper-based and the web-based questionnaire.

Methods
A two-period cross-over study was organized with a convenience sample of 149 employees of two Belgian research institutes (mean age=40, 72% female). All respondents completed both the paper-based and the web-based version of an identical questionnaire comprising 19 health indicators concerning mental and psychosocial health, health behaviors and prevention. Agreement was assessed
by calculating kappas and agreement percentages for categorical indicators and intraclass correlations (ICC) for continuous indicators.

Results
Almost perfect agreement was found for 11 of 15 categorical indicators with kappas superior to 0.80. Lower but still substantial agreement was established for one prevention indicator (having done a cervix smear test) and two mental and psychosocial health indicators (lifetime problematic alcohol consumption and quality of social support) with kappas varying between 0.66 and 0.80. For the presence of a sleeping disorder (kappa= 0.50) only moderate agreement could be found. Percentages of exact agreement ranged from 77 to 100%. High measurement agreement was found for the continuous indicators (ICC coefficients exceeding 0.80) except for psychological distress (ICC= 0.71) and vitality index (ICC= 0.79).

Conclusion
Generally, high to acceptable agreement was found for all health indicators, which points to a very limited measurement effect. The results of this study have implications not only for a future BHIS but adds knowledge to the current trend towards mixed-mode data-collection in epidemiological studies.

Introduction
Drop-out from the nursing profession is increasing. Research regarding retaining nurses in their profession is scarce. The SPRING cohort follows three cohorts of third year nursing students until one year after graduation to examine the causes of drop-out from education/work. This study aims to gain insight in the determinants of (first signs of) health problems, productivity loss and drop-out and to describe the baseline characteristics of the first cohort.

Methods
For the first cohort 272 nursing students were invited to participate in a prospective cohort study (figure 1). Validated questionnaires were used for data collection, with special emphasis on mental and physical health, capacity and resilience. Content areas included: skill discretion, decision authority, psychological job demands, distress, work engagement, physical workload, musculoskeletal complaints, sickness absenteeism, presenteeism, and physical activity.

Results
Of the 272 third grade students 225 agreed to participate in the study. The mean age of the cohort was 23 years (standard deviation 4.4 ) and comprised of 198 female students (88%) of which 50% was living with their siblings. 194 students (86%) were native Dutch speakers. Even when they were ill, 68% of the students followed internships. 77 students (34%) considered at some point leaving nursing school.

Discussion
This baseline measurement of the SPRING cohort is the first step in developing an innovative validated predictive model for retaining students in the nursing profession. Intended further steps are exploring unknown reasons for drop-out through qualitative research, a systematic review of effective interventions, and testing of the most promising ones in an RCT. These steps will lead to a prediction model to prevent drop-out from nursing education and nursing profession as part of an intervention toolbox.
Maternal obesity during gestation and effects on offspring development, behavior and physical health. Systematic review of animal studies.

Context
At present, over 15% of all women are obese. Multiple observational studies show that maternal obesity during gestation may impact long-term offspring health, development and behavior: e.g. offspring may be more likely to be obese themselves, have shorter life expectancy, developmental delay and attention problems. However, observational studies in humans are hampered by confounders including heritability and postnatal environment. Therefore animal studies may provide more insight in a possible causal relationship between maternal diet during gestation and offspring health, development and behavior. A systematic review of the existing animal evidence is presently lacking, and would allow us to assess the aggregated strength and consistency of effects. We aimed to examine the effect of maternal overweight on offspring’s physical health, development and behavior.

Design
We performed a systematic literature search in EMBASE and MEDLINE. Our search yielded 1793 unique publications. Two authors independently screened the references. Data extraction was performed in two steps. In the first step, we extracted study characteristics and recorded the type of outcome measures. In the second step, we selected the most relevant outcomes to perform further (meta-)analyses, based on biological and clinical relevance. The methodological quality of the studies was assessed using the SYRCLE Risk of Bias tool. At time of presentation, the study will be still ongoing.

Impact
This systematic review will provide new perspectives on the etiology of offspring physical health problems, developmental delay and behavioral disorders. This is critical from a public health view, since the rate of obesity in women of reproductive age increases.

Discussion and conclusion
This is a large explorative review with no initial restriction in terms of outcome measures. We will discuss the study design and decisions together with results of meta-analyses on offspring development and behavior parameters.
GHGE obtained from food frequency questionnaire (FFQ) versus 24-hour recall.

Methods We analysed 1051 highly-educated men and women, aged 52 ± 12 years who participated in the NQ-Plus study in the surroundings of Wageningen. They completed a 216-item FFQ on last months’ dietary intakes and two replicates of a web-based 24-hour recalls on non-consecutive days spaced over a 5-months period. Subsequently, food consumption data were linked to data on GHGE derived from Life-Cycle-Analysis, available for 207 food products (in gram CO2-equivalents (CO2e) per 100g of edible food), to estimate GHGE of each individual diet based on FFQ versus 24-hour recall. Spearman and Kappa correlation coefficients were used to explore agreement between both methods.

Results Standardised to 2,000 kcal using residual method, mean diet-associated GHGE was 3.33 ± 0.67 kg CO2e/day when using FFQ, and 3.58 ± 1.28 kg CO2e/day when using 24-hour recall, with animal-based products being responsible for about 50% to daily GHGE irrespective of the method of dietary assessment. Agreement between both methods was poor, with a Spearman correlation coefficient of 0.31 and a Kappa coefficient of 0.21 (95% CI: 0.16; 0.26) based on correct ranking of subjects into tertiles. This discrepancy could be attributed to differences in reference time and in the possibility of assessing episodically-consumed foods.

Discussion Estimates of diet-associated GHGE are dependent on the dietary assessment method used. This may have implications for relative risk estimates, because of the poor ranking agreement. Further research is needed to quantify the level of precision of the diet-associated GHGE from the different dietary assessment methods.

Heterogeneity of EU diets

Introduction Europe has a wide variety of foods available on the market, and food consumption patterns differ across countries. We aimed to describe the European heterogeneity in dietary intake at the level of foods and nutrients using four countries, thereby capturing the geographical diversity of dietary intake across Europe.

Methods Individual-level dietary intake data in adults were obtained from nationally representative dietary surveys from Denmark (Scandinavia) and France (Western Europe) using a 7-day diet record, Italy (Mediterranean region) using a 3-day diet record, and Czech Republic (Central East Europe) using two replicates of a 1-day recall. Energy-standardised intakes were calculated for each subject from the mean of two randomly selected days, and were evaluated against reference intakes that were derived for food groups from different European food-based dietary guidelines, and for nutrients from the Dietary Reference Values of EFSA.

Results For foods, standardised mean daily intakes of fruit, vegetables, fish, dairy products, sugar-sweetened beverages and alcohol varied most between countries, with a between-country range for fruit from 118 to 215 g/day, for vegetables from 95 to 258 g/day, and for fish from 12 to 48 g/day, representing lower intakes in Czech Republic, moderate intakes in Denmark and France, and higher intakes for Italy. Conversely, mean dairy intake ranged from 136 to 302 g/day with higher intakes in Denmark and lower intakes in Czech Republic, and mean sugar-sweetened beverage intake ranged from 23 to 224 ml/day and alcohol from 8.9 to 14.6 g/d with higher intakes in Denmark, moderate intakes in Czech Republic and France, and lower intakes in Italy. In all countries, low mean daily intakes were observed for legumes (< 20 g), and nuts and seeds (< 5 g), but high intakes for red and processed meat (>80g). For nutrients, intakes were relatively low for vitamin D, dietary fibre in all countries, and for potassium and magnesium except for Denmark, for vitamin E in Denmark and France, and folate in Czech Republic.

Discussion Adherence to food-based dietary guidelines and fulfilling nutritional requirements varies between these four countries, which is important to consider for EU-wide health policy. Generalisability to the EU at large remains to be addressed.
Focus group interviews: Knowledge, beliefs and attitudes towards dementia risk assessment and reduction

Context: Individuals with a parental history of dementia have a higher risk to develop dementia in the future, as they do not only have the same genetic makeup but also share their psychosocial behavior. This study will evaluate the knowledge, beliefs and attitudes towards dementia risk assessment and dementia risk reduction by changing health behavior among middle-aged descendants of people with recently diagnosed Alzheimer’s Disease (AD) or vascular dementia (VD).

Design: Three focus groups will be conducted in March 2017. Participants consist of middle-aged (40 to 70 years) descendants of recently diagnosed people with AD or VD at the memory clinic of the University Medical Center Groningen. The medical specialists (n=2) of the parents will approach eligible individuals during face-to-face during consultation with the individuals’ parent. Focus group discussions will be audio recorded and transcribed. Subsequently, transcripts will be analyzed thematically using Atlas-TM 8.1.

Impact: The results of the focus groups will be presented at the conference. These results will be used to inform individuals about dementia and the advantages and disadvantages of dementia risk assessment and how to reduce their dementia risk. This will support potential participants to make a well-informed decision about participating in the Dementia Risk Reduction (DRR) Program. This program, consists of a two-step dementia risk assessment and a tailor-made computerized lifestyle advice for dementia risk reduction. By providing knowledge on dementia and describing all possible advantages and disadvantages of dementia risk assessment, attrition bias within the DRR Program will be reduced.

Discussion: Knowledge, beliefs and attitudes towards dementia risk assessment and dementia risk reduction by changing health behavior among middle-aged descendants of people with recently diagnosed AD or VD have the potential to influence the decision to participate in the DRR Program.
Women had an average total calcium intake of 878.7 mg/day (SD 467.5 mg) and median calcium intake was 819.1 mg/day. Dietary calcium intake was on average 789.8 mg/day (SD 445.0 mg) and the mean calcium content from supplement use among users was 137.5 mg/day (SD 148.2 mg). Multivitamins for pregnant women were the most used supplements, with an average calcium content of 124.4 mg per day among users [range 60 to 326 mg].

Discussion: Our results indicate that almost two thirds of Dutch pregnant women have an inadequate calcium intake. Most used supplements contain restricted amounts of elementary calcium. We therefore recommend extra calcium supplementation by use of separate calcium tablets of 1000 mg per day for all pregnant women.

Introduction: According to Dutch guidelines, active-surveillance (AS) is recommended for prostate cancer patients with the lowest risk of cancer progression. However, a proportion of these patients still undergo immediate treatment with curative intent. Variation in the uptake of AS between hospitals might be explained by heterogeneity in patient and tumour characteristics but also hospital-related factors may play a role. The aim of this study is to provide insight in the treatment variation of very-low-risk prostate cancer patients in the Netherlands and to assess the role of hospital-related factors.

Methods: All patients diagnosed with very-low-risk prostate cancer (cT1c-cT2a, PSA<10 ng/mL, Gleason score<7 and <3 positive cores) between Oct 2015 – Apr 15th 2016 were identified through the population-based Netherlands Cancer Registry. Multilevel logistic regression analyses were performed to examine the crude and case-mix adjusted probability of undergoing immediate treatment versus AS according to hospital of diagnosis and to evaluate the effect of hospital-related factors.

Results: In total 564 (86.8%) of the 650 patients with very-low-risk prostate cancer were managed with AS. The crude proportion of patients with AS varied from 50-100% between hospitals. After adjusting for patient and tumour characteristics, this range decreased to 71-97%. Multivariable multilevel logistic regression analyses showed that cT2a vs. cT1c (OR=2.0, 95%CI:1.1-3.6), two vs. one positive core (OR=2.8, 95%CI:1.6-4.7), diagnostic MRI (OR=2.8, 95%CI:1.5-5.2), discussion of a patient in a multidisciplinary team (OR=2.2, 95%CI:1.1-4.5) and discussion of treatment options with the patient (OR=3.3 95%CI:1.5-7.4) were all factors associated with immediate treatment. In addition, patients diagnosed in a non-university referral hospital were less often treated immediately compared to patients diagnosed in a community hospital (OR=0.5, 95%CI:0.2-0.9).

Conclusion: The vast majority of Dutch very-low-risk prostate cancer patients are managed with AS but variation between hospitals exists. Part of the variation is explained by patient- and tumour characteristics but also hospital-related factors play a role. This implies that clinical practice could be improved.

Active treatment instead of active surveillance in low-risk prostate cancer: the role of hospital or physician-related factors.
Effectiveness of a multifaceted intervention aimed at improving management of low back pain by healthcare professionals in primary care

Introduction
Low back pain is a highly prevalent and costly healthcare problem worldwide, and a variety of healthcare professionals are involved in its management. The current study evaluates the effectiveness of a multifaceted implementation strategy for the implementation of the Dutch multidisciplinary guideline for low back pain. This study aimed to reduce referrals for diagnostic imaging and medical specialist care, and improving collaboration and communication between healthcare professionals in Dutch primary health care setting.

Methods
Performance indicators were used to measure changes in number of referrals for various diagnostic imaging and medical specialists. Questionnaires were used to measure professionals’ attitudes towards the guideline, low back pain management in general, and collaboration and communication with other professionals. Questionnaires also included knowledge of the guideline, and levels of perceived self-efficacy on multidisciplinary communication and collaboration. Generalized Estimating Equation modelling was used in SPSS to analyse data.

Results
In total, 129 healthcare professionals participated in this study, of which 53 general practitioners, 47 physiotherapists, and 29 occupational physicians. The intervention reduced the number of referrals to neurologists significantly (p=0.008). Furthermore, HCPS attitude towards inquiries for X-rays and MRIs for LBP improved (p=0.004), as did their belief that the guideline will help them improve their advice, treatment or counselling of patients with LBP (p=0.002).

Discussion (conclusion)
This study led to small changes in various outcomes. However, these changes need to be interpreted with caution. Changing healthcare professionals’ behaviour remains a challenging task and future research should focus on developing effective methods for changing professional practice in the management of low back pain. Also, system and societal expectations need to be changed in order to improve guideline adherence by professionals. Future interventions, guidelines, and policies should take into account the political, organisational, and cultural context of the health care system in which professionals operate.

Active-surveillance; for patients with intermediate-risk prostate cancer in the Netherlands: a population-based study

Introduction:
According to the current guidelines, active-surveillance (AS) is recommended for patients with low-risk prostate cancer (PCa), but also part of the patients with intermediate-risk PCa might be appropriate candidates for AS. Knowledge on which part of the patients with intermediate-risk PCa are managed with AS in the Netherlands is limited. Furthermore, little is known about which tumour-, patient-, and hospital-related factors are associated with AS in these patients.

Objective:
To investigate the use of AS for patients with intermediate-risk PCa in the Netherlands and to determine which patient-, tumour-, and hospital-related factors are associated with AS.

Methods:
All patients diagnosed with intermediate-risk PCa (T2b-c, or Gleason score 7, or iPSA 10-20ng/mL) between Oct 2015–Apr 15th 2016 were selected from the Netherlands Cancer Registry. Descriptive analyses were performed to determine the proportion of patients with AS and immediate treatment. Univariable and multivariable multilevel logistic regression analyses were used to examine the association between patient-, tumour-, and hospital-related factors and the initiation of AS.

Results:
Of all patients with intermediate-risk PCa, 212 (24%) were managed with AS. Multivariable multilevel logistic regression analyses showed that age older than 75 year vs. younger (OR=1.98 95%CIs 1.07-3.68), PSA level higher(continuous) (OR=0.9 95%CIs 0.81-0.99), cT2c vs. cT1c (OR=0.23 95%CIs 0.09-0.58) and more than four vs. one-two positive core (OR=0.21 95%CIs 0.1-0.42), and a higher volume percentage tumour (OR=0.98 95%CIs 0.97-
0.99) were all associated with the AS as treatment choice. We found no association between hospital-related factors and initiation of AS.

Conclusion: In the Netherlands a substantial part of the patients with intermediate-risk are managed with AS. Mainly clinical factors are associated with the choice for AS as management strategy.

Effects of physical exercise on markers of inflammation in breast cancer patients during adjuvant chemotherapy

Introduction — Physical exercise has proven to be an effective intervention to prevent and diminish levels of fatigue in breast cancer patients during adjuvant cancer treatment. These beneficial effects are hypothesized to be mediated by changes in inflammatory markers. Several inflammatory markers, such as interleukin-6 (IL-6) and interleukin-1-receptor antagonist (IL-1ra), have indeed been correlated with fatigue. Effects of physical exercise during chemotherapy for breast cancer on inflammatory markers so far are unknown.

Methods — We combined data of two randomized controlled trials on exercise effects in breast cancer patients during adjuvant chemotherapy: the BEATE study (‘Bewegung und Entspannung als Therapie gegen Erschöpfung’) and PACT study (‘Physical Activity during Cancer Treatment’). The BEATE study was conducted in Heidelberg, Germany, and the PACT study in seven Dutch hospitals. Exercise comprised a 12-week resistance training (BEATE) or an 18-week combined resistance and aerobic training (PACT). Both studies suggested a beneficial impact of exercise during chemotherapy on (physical) fatigue. At baseline, mid-intervention, post-intervention (13 to 18 weeks post-baseline), and long-term follow-up (6 to 9 months post-baseline), blood samples were taken. Serum IL-6 and IL-1ra were quantified by use of Quantikine Immunoassay kits and the IL-6/IL-1ra ratio was calculated. Mixed effect models, adjusted for baseline inflammatory marker levels, were used to determine between-group changes in (log-transformed) inflammatory markers.

Results — Inflammatory markers were measured in 66 patients randomized to an exercise program, and 64 patients randomized to control. Post-intervention, no exercise effects were found on IL-6 (treatment effect ratio (TER) 1.3, 95%CI 0.8; 2.2), IL-1ra (TER 1.0, 95%CI 0.8; 1.3) or IL-6/IL-1ra ratio (TER 1.3, 95%CI 0.8; 2.3) No significant between-group changes were observed at mid-intervention and long-term follow-up either.

Discussion (conclusion) — Combined results from two randomized controlled trials did not indicate effects of physical exercise during adjuvant chemotherapy for breast cancer on inflammatory markers.

The impact of cardiovascular events on physical activity characteristics

Introduction:
Physical activity (PA) is an effective strategy to lower the risk of primary and secondary cardiovascular events. Hence, patients with cardiovascular risk factors (CVRF) and diseases (CVD) are encouraged to perform PA. This study investigated whether a diagnosis of CVRF/CVD changed PA patterns and explored which individual factors may influence PA characteristics.

Methods:
Participants of the Nijmegen Exercise Study with a diagnosis of CVRF/CVD were eligible for participation. Demographic information, lifestyle characteristics and lifelong exercise volume (average MET-min/wk) were collected from an online questionnaire. Based on PA volumes pre-CVRF/CVD diagnosis, subjects were allocated to an inactive (<675 MET-min/wk), moderately active (675-1350 MET-min/wk) or highly active group.
Linear regression was applied to study the factors which may relate to changes in PA.

Results:
1973 participants (60±8 years, 72.2% males) with diagnosis of CVRF (n=1541, 68.4% males) or CVD (n=432, 85.9% males) were included. Unadjusted analysis revealed no significant difference in PA before and after diagnosis (1117±1200 vs. 1104±1020 MET-min/wk, P=0.59). Nevertheless, PA of inactive (297±218 vs. 629±625 MET-min/wk) and moderately active patients (989±200 vs. 1137±736 MET-min/wk) significantly increased after diagnosis (both P<0.0001). In contrast, the most active individuals demonstrated a significant decrease in PA following diagnosis (2585±1384 vs. 1843±1307 MET-min/wk; P<0.0001). Adjusted analysis revealed that especially females (β=164.9, P=0.002) and smokers (light: β=117.5, P=0.024 and heavy: β=223.4, P=0.000) increased their PA after diagnosis. PA patterns were not influenced by age of CVRF/CVD diagnosis (β=0.7, P=0.80), type of diagnosis (CVRF vs. CVD: β=9.3, P=0.87), education level (middle and high/academic education level respectively: β=−5.2, P=0.94 and β=53.5, P=0.44) or family history with CVRF /CVD (β=83.2, P=0.14).

Conclusion:
These findings suggest that a diagnosis of CVRF/CVD could trigger inactive and moderately active individuals to become physically active, whereas highly active individuals may reduce their PA levels.

**Context:**
Approximately 60% of breast cancer patients treated with chemotherapy experience cognitive problems, which can persist up to 10 years after treatment. Further, imaging studies documented brain changes associated with chemotherapy. Cognitive problems may reduce quality of life, daily functioning and work performance. In elderly and in patients with neurological diseases, studies showed positive effects of exercise on cognition. Hence, a promising non-pharmacological option for cognitive problems in breast cancer patients is physical exercise. We will investigate the effects of exercise on cognition, brain structure and function in breast cancer patients with cognitive problems after treatment with chemotherapy.

**Design:**
In the Physical Activity and Memory (PAM) study, breast cancer patients are randomised to an exercise group (n=90) or a waiting list control group (n=90). Inclusion criteria are: curative treatment for breast cancer, use of chemotherapy, 2-4 years after diagnosis, aged 30-75 years, no indication of relapse or metastases, self-reported cognitive problems confirmed by neuropsychological tests and physically inactive. The 6-month intervention programme consists of aerobic and strength exercises supervised by a physiotherapist (2hrs/w) and Nordic/Power Walking (2hrs/w). Controls will be asked to retain their usual physical activity level.

Primary outcome parameters are: cognitive functioning (HVLT-R) and self-reported cognitive complaints (MDASI-MM module). Secondary outcomes include brain structure and function (brain MRI), anthropometrics, physical fitness, quality of life, fatigue, anxiety and depressive symptoms and work performance.

**Impact:**
If effective, breast cancer patients with cognitive problems will have access to an evidence-based treatment.

**Discussion:**
If exercise shows to improve cognition in breast cancer patients, the results may be extrapolated to other chemotherapy-exposed patients confronted with cognitive problems. The study is currently recruiting patients and first experiences will be presented.
Towards diagnosis-specific lifetime risks for total hip arthroplasty revision surgery.

Background
Information on lifetime revision risks is needed to guide decision making for individual patients regarding timing of primary surgery. Our aim was to provide the 7th year cumulative percentages for revision surgery stratified for diagnosis, sex, type of fixation and age at which primary total hip or knee arthroplasty (THA/TKA) was performed.

Methods
Data was available from the Dutch Arthroplasty Register (LROI). All patients receiving a primary THA or TKA between 2007-2015 were included except for patients with a metal-on-metal prosthesis, patients with a hybrid/reversed hybrid fixation type or without primary surgery registered. Revision surgery was defined as any change of one or more components of the prosthesis. The 7th cumulative revision percentages risks were calculated stratified according to, THA/TKA, the underlying diagnosis (osteoarthritis/other), sex, age at primary arthroplasty and fixation type (cemented/uncemented). Furthermore we estimated the percentage of avoided OA revisions by assuming that all OA patients received their primary arthroplasty 5 years later (in all age groups < 85 yrs) and that the revision risks remained the same in all age categories.

Results
In total 134463 primary THA and 120807 TKA patients were included of whom 89% and 95% had OA and 34% and 94% of the THAs/TKAs were cemented. The uncemented-other-diagnosis TKA groups were too small to calculate cumulative risk percentages. The 7th year cumulative risk percentage varied between 0 and 12.5% (Table 1). Overall cumulative revision percentages were higher in younger age categories (Table 1). We estimated that by delaying for 5 years, 197 THA revision surgeries (4.4% of all THA revisions) and 1321 TKA revision (20.8%) could be avoided. This could result in a yearly cost reduction of approximately 30 million euros.

Conclusions
Cumulative 7th year risk percentages decreased by age in all different categories. By delaying the primary THA/TKA surgery, revisions might be avoided thereby resulting in cost reduction.
Three cohorts were included: the Nijmegen Bladder Cancer Study (NBCS, Nijmegen, The Netherlands), the Toronto Biobank (TB, Toronto, Canada), and the Bladder Cancer Prognosis Programme (BCPP, Birmingham, UK). We genotyped common single nucleotide variants (SNVs) using GWAS arrays and performed imputation using the 1000 Genomes phase1 v3 and GoNL4 reference panels. After quality control, we included 1,799, 1,105, and 845 samples from the NBCS, TB and BCPP, respectively. Cohort-specific GWAS for recurrence-free (RFS) and progression-free survival (PFS) adjusted for 10 multidimensional scaling components were performed. Results were combined in a fixed-effects inverse-variance weighted meta-analysis (total N 2,574) applying genomic control to the GWAS results and including only SNVs with a minor allele frequency >1% in all three cohorts.

Results
Three SNVs showed genome-wide significant association with RFS ($p<5\times10^{-8}$), but none with PFS (smallest $p$-value $9.2\times10^{-8}$). Bio-informatic follow-up analyses for prioritization of top findings are currently ongoing, including in silico annotation, eQTL analysis using data from The Cancer Genome Atlas (TCGA), and study of SNV function with regard to e.g. transcription binding sites and chromatin interactions. Prioritized results will be tested for association in additional replication cohorts.

Discussion (conclusion)
Results of our study will increase insight into the mechanisms of prognosis in NMIBC and may point the way to biomarkers that add to the currently used prediction models in the clinic.

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Fluid intake and the risk of recurrence in patients with non-muscle invasive bladder cancer: a prospective cohort study

Introduction: Increased fluid intake has been associated with a reduced risk of developing bladder cancer. The impact of fluid intake on bladder cancer recurrence is less established.

Objective: To investigate the role of fluid intake in relation to the risk of developing recurrence of bladder cancer in a prospective cohort study.

Methods: 754 patients with non-muscle invasive bladder cancer (NMIBC) included in the West Midlands Bladder Cancer Prognosis Programme (BCPP), and who received transurethral resection of a primary bladder tumour (TURBT), self-reported on fluid intake pre-diagnosis (1 year before diagnosis) and post-diagnosis (1 year after diagnosis). Multivariable Cox regression was used to calculate hazard ratios (HRs) of developing recurrent bladder cancer in relation to the intake of fluid (total fluid/total alcohol/coffee/tea/milk/water).

Results: During 2141 person-years of follow-up, 232 (30.8%) NMIBC patients developed a recurrence from bladder cancer. Total fluid intake (lowest versus highest tertile) was not associated with recurrence of bladder cancer (HRpre-diagnosis intake= 1.05; 95% CI 0.74-1.48, $p=0.79$, HRpost-diagnosis intake= 0.87; 95% CI 0.46-1.67, $p=0.68$). Intakes of alcohol (lowest versus highest tertile) were also not related to bladder cancer recurrence (HRpre-diagnosis intake= 0.90; 95% CI 0.63-1.29, $p=0.85$, HRpost-diagnosis intake= 1.20; 95% CI 0.62-2.30, $p=0.59$).

Conclusion: Results from this study among NMIBC patients did not indicate a relationship between fluid intake and recurrence of bladder cancer.

P45
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Application of MSKCC and IMDC models in sunitinib-treated metastatic renal cell cancer patients - a European multi-center study.

Introduction: The MSKCC and IMDC risk group models are the two most commonly used prognostic models in metastatic renal cell cancer (mRCC). Here, we evaluate their performance for
sunitinib-treated mRCC patients in a European multi-center observational study: EuroTARGET. Methods: A total of 713 mRCC patients who received sunitinib as first-line targeted treatment were included in this study (median follow-up time 17.0 months (interquartile range 9.0-33.4)). Clinical data, collected from medical files, were extracted from the EuroTARGET database. Patients were classified into MSKCC and IMDC risk groups, where possible, using literature-based as well as center-specific cut-off values for biochemical variables. Survival analysis and bootstrapped Harrell’s Concordance statistics were used to evaluate the models’ performance for overall survival (OS) and progression-free survival (PFS). Results: For 396 (56%) and 387 (54%) patients, complete information on all five MSKCC and six IMDC model variables, respectively, were available and 375 (53%) had complete information for both. C-statistics for MSKCC (n=387) were 0.639 for OS and 0.584 for PFS, while for IMDC (n=396) these were 0.639 and 0.593, respectively (see Table 1). An additional 117 (16%) and 135 (19%) patients had ≥1 missing MSKCC and IMDC model variable but could still be unambiguously classified. Inclusion of these patients and the use of center-specific cut-off values had only minor impact on the prognostic performance. Conclusion: Reliance on medical file data for MSKCC and IMDC risk classification in an observational study setting leads to ~30% unclassifiable patients. Prognostic performance of both models in terms of C-statistic was poor and similar to that reported in other (observational and clinical) studies.

P46
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Association of Single Nucleotide Polymorphisms (SNPs) and mortality in breast cancer patients

Introduction: Hereditary genetic variation is likely to be an important factor in breast cancer prognosis. Since the effect of SNPs on mortality in breast cancer patients is expected to be small, the hypothesis is that SNPs affecting survival are more likely to be identified in subgroups of patients that are homogeneous with respect to stronger prognostic factors. The aim of the study is to investigate the association of SNPs with mortality in breast cancer patients overall and in specific tumor and treatment subgroups. Methods: The analyses are based on the Breast Cancer Association Consortium clinico-pathological and genetic database (n=110,000). To deal with missing values in the clinico-pathological variables, a multiple imputation approach was applied to a relevant subset of those variables, resulting in ten imputed datasets. Pilot statistical analyses were performed to compare the effects of selected subsets of SNPs on mortality in the imputed versus the complete-case datasets. Univariate Cox models were performed in subgroups based on the Estrogen Receptor status and grade of the tumors and multivariate Cox models were performed overall, adjusting for age, treatment and tumor characteristics.

Results: The analyses of the association of SNPs with survival suggest that there is no substantial gain in performing the tumor subgroup analyses using imputed data. However, in the overall multivariate analysis the gain in terms of precision is high, with a reduction of 40% in the standard errors of the estimates for 80% of the SNPs analyzed. Therefore, associations become stronger in the imputed data analysis compared to the complete-case analysis.

Discussion: Based on the results of the pilot analyses, survival analysis at a genome-wide level will be performed within specific tumor and treatment subgroups on the complete-case data, while overall multivariate analyses will be performed on the imputed datasets.

P47
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Dietary patterns and risk of recurrence and progression in non-muscle invasive bladder cancer

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Awareness of, adherence to, and interest in lifestyle recommendations for cancer prevention among bladder cancer patients

Introduction: A healthy lifestyle is associated with decreased cancer risk, a better quality of life and could also possibly reduce risk of bladder cancer recurrences. This emphasizes the importance of physicians discussing lifestyle with their patients. We investigated whether Dutch non-muscle-invasive bladder cancer (NMIBC) patients are aware of possible risk factors for (bladder) cancer, adhere to lifestyle recommendations for cancer prevention, and do and/or would like to receive lifestyle advice after diagnosis.

Methods: A subset of 594 NMIBC patients participating in the prospective cohort study UroLife filled out questionnaires at six weeks and three months after diagnosis. Frequencies were calculated and McNemar’s test was used to investigate differences in adherence between the two time points.

Results: Only 45% of patients were aware that smoking is a risk factor for bladder cancer. Alcohol consumption, overweight, and insufficient physical activity were mentioned as risk factors for cancer by only 42-68%. Adherence to cancer prevention guidelines at baseline was poor for body weight (35%) and alcohol consumption (41%), but better for physical activity (85%), smoking cigarettes (76%) and use of dietary supplements (65%). Three months after diagnosis, a higher percentage of patients were physically inactive, but the percentage of patients smoking cigarettes, consuming alcohol or using dietary supplements decreased. Of the smokers, 76% were advised to quit, while only 23% of all respondents received lifestyle advice. More than 80% of respondents had a positive attitude towards receiving lifestyle advice from their physician.

Discussion: Most cancer risk factors were relatively unknown among NMIBC patients and the degree of adherence to cancer prevention guidelines varied widely. Although patients have a positive attitude towards receiving lifestyle advice, they were not routinely informed about this by their physician. Since lifestyle factors may possibly prevent (recurrence of) bladder cancer, information provision by physicians should be improved.

Risk factors associated with post-marketing changes in specific obligations of conditionally authorised products in the EU

Introduction: The Conditional Marketing Authorisation (CMA) in Europe aims to provide timely access to medicines for which immediate availability outweighs the risk of less comprehensive data than normally required. To minimise post-marketing uncertainties for these products, specific obligations are imposed as a condition to the marketing authorisation (MA). Yearly follow-up of these requirements and assessment of study results during annual renewal (AR) may lead to changes in descriptions and due dates of obligations when results are not as expected. This study aims to characterise these changes, and identify procedural and drug-related factors associated with them.

Methods: We performed a retrospective cohort study of obligations imposed on the CMA of products licensed since 2006 (excluding vaccines) with at least one year follow-up or one AR (until 31/12/16). Changes in wording or due date of obligations were identified by comparing the MAs of products at granting, AR(s) and conversion of the CMA. Unconditional logistic regression was performed to calculate odds ratios and 95% confidence intervals for the association between
Factors extracted from documentation of the European Medicines Agency and post-marketing changes in completed obligations.

Results: For 26 CMA products 79 obligations were requested (median: 2, interquartile range [IQR]: 1-3.75) with a median follow-up of 2 ARs (IQR: 1-3). 67 were imposed at time of MA and 12 during AR. In total, 31 changes were observed in 25 obligations (32% of all obligations). Changes concerned a change (delay) of due date (n=19, 61%), description (n=4, 13%) or both (n=8, 26%). Six factors for changes in 61 completed obligations were identified (Table 1).

Discussion: In almost one-third of obligations, at least one change in initial wording or planning was identified. We found six factors associated with risk of change that can inform strategies for better prospective planning of post-marketing studies to reduce uncertainties.

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Smoking habits and the chance of reaching longevity in men and women: the Netherlands Cohort Study

Introduction
Even though it is well-known that smoking decreases the chance of reaching longevity, little is known about how specific smoking habits relate to this chance. We examined how specific smoking habits relate to the chance of reaching 90 years of age, in men and women separately.

Methods
We conducted a prospective cohort study among the oldest birth cohorts (1916-1917) of the Netherlands Cohort Study, who completed a baseline questionnaire in 1986 (at age 68-70), and had complete vital status information until the age of 90 years (n=7,807). A total of 6,642 men and women with complete exposure and co-variable data were included, of which 16.0 and 34.3 percent survived to the age of 90, respectively.

Multivariable Cox regression analyses with fixed person-times were used to calculate risk ratios (RR).

Results
Never smokers had a significantly higher chance of reaching 90 years compared to former and current smokers of any tobacco product. However, the relationship of smoking with longevity seemed stronger in men than in women (current vs. never smokers; RR 0.44, 95% confidence interval 0.34-0.56, and RR 0.67, 95% CI 0.57-0.79, respectively).

We found a significantly inverse association between cigarette smoking quantity and reaching longevity in current smokers, and to lesser extent in ex-smokers. Moreover, we found a significantly inverse association between cigarette smoking duration and longevity. Finally, quitting smoking significantly increased the chance of reaching longevity, even quitting after 60 years of age.

Discussion
Our findings confirm that smoking decreases the chance of reaching longevity in both sexes. Furthermore, increasing cigarette smoking quantity and duration strengthen the inverse association between smoking and reaching longevity, especially in current smokers. While never smokers had the highest chance of reaching longevity, quitting smoking increased the chance of reaching longevity compared to current smokers at baseline, even after the age of 60.

P50
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Determinants of selective citation: a citation network analysis on the effect of industrially produced trans fatty acid on LDL- and HDL-cholesterol in humans

Background: Balanced citations are a necessary condition for a sound development of scientific knowledge. Selective citations might result in biased scientific consensus. Especially systematic reviews and meta-analyses, which are used by practitioners and policy makers in decision-making processes, should give a correct overview of all available literature. To prevent biased knowledge development due to selective citations, insight should be gained into determinants of selective citation behaviour.
Objective: Assess which determinants influenced the likelihood of being cited in the literature on trans fatty acids and cholesterol. In addition, we wanted to assess the effect of citations on the development of knowledge in this research area.

Design: We conducted a citation network analysis of the literature concerning industrially produced trans fats and LDL- and HDL-cholesterol. Each publication was scored on various potential determinants of citation, among which are study outcome, study design, sample size, journal impact factor, funding source and affiliation of the corresponding author. Random effect logistic regression was applied to identify determinants of citation.

Results: A network of 108 publications was identified, containing 5041 potential citations and 669 performed citations. Reporting of statistically significant results was found to be a strong predictor of citation, as well as sample size, journal impact factor and authority of the authors. Even after adjusting for study design and sample size, statistically significant results increased the likelihood of being cited by approximately three times.

Conclusion: Within the literature of trans fat intake and cholesterol, citations are selected on several grounds. Especially the effect of study outcome on citation requires special attention. Disproportionate attention goes to the publications suggesting a harmful effect of trans fat intake on cholesterol, potentially leading to an artificially strong scientific consensus in this area.

DNA methylation mediates the association between occupational exposures and lung function

Introduction: Occupational exposures, such as biological dust, mineral dust and gases/fumes, are associated with lower lung function levels and attribute to 15-20% of all Chronic Obstructive Pulmonary Disease (COPD) cases. Epigenetic mechanisms such as DNA methylation have been suggested to play a role in these associations. We therefore aimed to assess if the association between occupational exposures and lung function (FEV1/FVC) is mediated by DNA methylation.

Methods: We included 1,561 subjects of the LifeLines cohort with either no, low, or high occupational exposure to biological dust, mineral dust and gases/fumes, based on the current or last held job. Associations between the three exposures and 420,938 blood DNA methylation sites (CpGs, Illumina 450K array) were assessed using robust linear regression adjusted for appropriate confounders. Differentially methylated regions (DMRs) were identified using comb-p in python. Mediation of the top site per region was assessed using bootstrapping in R.

Results: Using p<10^{-5}, 4, 5 and 6 single CpGs were associated with biological dust, mineral dust and gases/fumes, respectively, but none were genome-wide significant. In total 7, 8, and 30 genome-wide significant DMRs were identified, respectively. The CpG cg06462684 in the promoter of YWHAH, which binds to the glucocorticoid receptor, significantly mediated the association of FEV1/FVC with mineral dust. In addition, cg14870271 in the promoter of LGALS3BP, known to play a role in immune responses, mediated the association of FEV1/FVC with gases/fumes.

Discussion: We show that the association between lung function levels and occupational exposure to mineral dust and gases/fumes is mediated by DNA methylation.
Contribution of chronic conditions to gender disparities in life expectancy and health expectancies in Belgium, 1997-2013

Introduction
The aim of this study was to investigate the contribution of selected chronic conditions to gender differences in life expectancy (LE), disability-free LE (DFLE) and LE with disability (LED) in Belgium, 1997-2013.

Methods
Data on disability and chronic diseases from individuals aged 15 years or older who participated in the 1997, 2001, 2004, or 2008 Belgian Health Interview Surveys (N = 36,451) and a mortality follow-up until 2013 of survey participants were used (number of deaths = 5,905). Deaths were classified by underlying cause of death. The attribution method was used to estimate the disability prevalence by cause. The Sullivan method was used to estimate partial LE, DFLE and LED (age 15-89 years). The contribution of causes of death and disability to gender differences in LE, DFLE, and LED was assessed using decomposition methods.

Results
The partial LE in women was larger than in men (67 vs 62.6 years). The DLFE advantage of 0.4 years for women (56.1 years) compared to men (55.7 years) was the result of lower mortality (+2.7 years) and higher disability (-2.3 years). Women also showed higher LED than men (10.9 vs 6.9 years). Of the 4 additional years with disability, 1.7 years reflect lower mortality while the remaining 2.3 years reflect higher disability prevalence compared to men. Less mortality from other diseases, ischaemic heart diseases, and cancer of larynx, trachea or lung increased DFLE and LED in women relative to men, while higher disability from musculoskeletal conditions, diabetes, and depression reduced DFLE and increased LED in women (Table 1).

Conclusion
The mortality advantage in women is counterbalanced by their disability disadvantage for DFLE but not for LED in Belgium. Our findings indicate that public health policies should consider both fatal and non-fatal diseases to reduce the gender gap in LED in the country.

P53
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Associations of health status with donation cessation and intensity — an alternative perspective on the Healthy Donor Effect from Donor InSight

Introduction: In donor health research, the ‘Healthy Donor Effect’ (HDE) often hampers study results and their interpretation. This refers to the fact that donors are a selected ‘healthier’ subset of a population due to both donor selection procedures and self-selection. Donors with long versus short donor careers, or with high versus low donation intensities are often compared to avoid this HDE, but underlying health differences might also cause these different behaviours. Our aim was to estimate to what extent a donor’s health status associates with donation cessation and intensity.

Methods: All active whole blood donors participating in Donor InSight (2007-2009; 11,107 male, 12,616 female) were included in this prospective cohort study. We performed Cox survival and linear regression analyses to assess whether self-reported health status, medication use, disease diagnosed by a physician and recent visits to a general practitioner (GP) or specialist were associated with (time to) donation cessation and donation intensity.
Results: At the end of 2013, 44% of the donors had stopped donating. Donors in self-rated good health had a lower risk to stop donating compared to donors in poor or neutral health. Medication use, disease diagnoses and visits to a GP were associated with an increased risk to stop donating, even after adjusting for age, smoking and number of donations. Both men and women reporting good health were more likely to donate with a higher intensity. 

Conclusion: Donors with a “good” health status were less likely to stop donating blood and tended to donate blood more often than donors with a worse health status. This implies that the HDE is an important source of selection bias in studies on donor health and this includes studies where comparisons within donors are made. This HDE should be adjusted for appropriately when assessing health effects of donation.

Methods: We conducted a cross-sectional study using the baseline data of the Lifelines cohort study, a large prospective study of more than 167,000 individuals. We calculated the Root Mean Square of Successive Differences (RMSSD) between adjacent inter-beat intervals as an index of cardiac parasympathetic nervous system activity using ECG measurements of 10 seconds. RMSSD was corrected to take into account for its dependency on mean heart rate level and RMSSD was transformed to a natural logarithm (ln) to achieve approximate normality. To assess the relationship of determinant factors with RMSSD, multiple linear regression models were performed. Adjusted R2 was calculated to estimate the total variance explained by determinant variables.

Results: A total of 149,205 individuals were included in the analysis. From this total study population, 58.7% of participants were female and over one third were in age group 40-50 years. Men and women differed markedly in HRV value where mean lnRMSSD was significantly higher in females (p<0.001). After controlling for potential confounders (medication use and disease), demographic factors explained almost one quarter of the variance (R2=0.24) of HRV. Adding lifestyle and psychosocial factors to demographic variables hardly increase (~1%) the variance estimation.

Conclusions: In this study age and sex were the most important determinants to explain the individual difference of HRV in which one quarter of the variation was attributed to demographic factors. Further research needs to consider genetic information to better estimate individual differences in HRV.

Demographic, Lifestyle and Psychosocial Determinants of Heart Rate Variability in the General Population: A Study from the Lifelines Cohort and Biobank Study.

Introduction: Heart rate variability (HRV) is an important marker of heart health with low values reflecting (sub) clinical target organ damage of heart. Given that many studies have reported substantial individual differences for HRV, the overall aim of this study was to estimate to what extent demographic, psychosocial and lifestyle factors explain individual differences in HRV in the general population.
Risk Factors for Incident Heart Failure in a Population-Based cohort using linked Electronic Health Records (CALIBER)

Heart failure is one of the leading causes of mortality and morbidity among patients aged 55 years and older. Several risk factors for incident heart failure have been identified, however Linked electronic health records (EHR), that capture clinical data across healthcare settings, may provide the opportunity to discover and examine previously unknown risk factors across different subgroups from the general population at high-risk for development of heart failure.

We used linked EHR data from 2000 to 2010 as part of the UK based CALIBER resource, in which clinical data from primary care, hospital admissions and mortality registry are linked for research purposes. We assembled a cohort of individuals 55 years or older and free of heart failure at baseline. Informed by literature, potential risk factors included: ethnicity, social deprivation, BMI, lifestyle factors, blood pressure, lipid levels, comorbidities such as hypertension and diabetes mellitus, and several other potential risk factors that may have a role in modifying heart failure outcomes. The primary endpoint was the first record of heart failure from primary care or secondary care. Multivariable Cox regression analysis will be used to estimate hazard ratios for associations between risk factors and incident heart failure, separately for men and women and by age category: 55–64 years, 65 – 74 years, and > 75 years.

We identified 871,687 individuals and during a median follow up of 5.7 years a total of 47,987 incident heart failure events were recorded. Of the 23,314 (48.6%) males with incident heart failure events, 23.2% were between 55-64 years, 34.5% between 65-74 years, 42.3% were 75 years or older. Of the 24,673 (51.4%) women with incident heart failure events, 11.7% were between 55-64 years, 26.8% between 75-74 years and 61.5% were 75 years or older. Main findings will be presented at the conference.

Marja Veugen

MUMC+

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NT-proBNP and TNT are independently associated with MRI brain abnormalities in both older and younger individuals, but with cognitive performance only in older individuals - The Maastricht Study

Introduction

Brain natriuretic peptide (NTproBNP) and troponin-T (TNT) are associated with lower cognitive performance (CP) in older individuals. It is unclear if this extends to younger individuals (<60 years). We therefore investigated if age modified the associations between NTproBNP and TNT, and, not only CP, but also abnormalities on brain MRI.

Methods

In the Maastricht Study (n=3011; age 60±8; women:49%) NTproBNP- and TNT levels were determined, in addition to CP (domains: memory (M), information processing speed (IPS) and, executive functioning (ExF)). Furthermore, MRI white matter hyperintensities (WMH), grey matter (GM) and white matter (WM) volumes were quantified. We used regression analyses with adjustments for sex, age, education, (pre)diabetes, BMI, smoking, alcohol, lipid profile- and modifying medication, eGFR and intracranial volume and MRI lagtime, in addition to adjustments for systolic pressure, antihypertensive medication and albuminuria.

Results

In individuals ≥60 years, after adjustment, higher NTproBNP-levels were associated with lower M (β (95% CI); -0.10 (-0.22; 0.01)), IPS (-0.10 (-0.19; -0.01)), and ExF (-0.11 (-0.21; -0.02)); and smaller GM (-5.52 (-10.22; -0.82)). In addition, higher TNT-levels were associated with lower M (-0.31 (-0.52; -0.11)) and IPS (-0.14 (-0.30; 0.02)); and smaller GM (-14.16 (-22.98; -5.34)) and greater WMH (0.28 (0.07; 0.48)). In individuals <60 years, after adjustment, neither NTproBNP nor TNT was associated with CP (Pinteraction<.10). However, higher NTproBNP-levels were associated with smaller GM (-6.94 (-11.22; -2.66)) and greater WMH (0.12 (-0.00; 0.24);
Pinteraction>.10). Higher TNT-levels were associated with greater WMH (0.15 (-0.05;0.34); Pinteraction>.10), but were not associated with GM (1.35 (-5.59;8.29); Pinteraction<.10).

Discussion
Our study shows that NTproBNP and TNT are associated with abnormalities on brain MRI in older and younger individuals, but poorer CP only in older individuals. Thereby NTproBNP and TNT are, age-independent, promising tools to identify individuals at risk of developing poor(er) CP.

P57
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Dyslipidemia and risk of renal replacement therapy or death in pre-dialysis patients: PREPARE-2 study

Introduction: Though dyslipidemia is associated with a higher cardiovascular mortality in the general population, in dialysis patients dyslipidemia confers a paradoxical survival benefit. Little is known about the effect of dyslipidemia in CKD stage 4-5 pre-dialysis patients. The aim of this study is to assess the association between dyslipidemia and risk of renal replacement therapy (RRT) or death among incident pre-dialysis patients with CKD stage 4-5 receiving specialized pre-dialysis care.

Methods: The PREPARE-2 study included incident pre-dialysis patients (>18y) referred during 2004-2011 to any of 25 participating Dutch outpatient clinics, and prospectively followed until start of renal replacement therapy, death or October 2016 (end of follow-up). Baseline levels of serum total cholesterol, LDL cholesterol, HDL cholesterol, HDL/LDL ratio, and TG were categorized according to the target goals of pre-dialysis guidelines, being <5.00 mmol/L, <2.50 mmol/L, ≥1.00 mmol/L, ≥0.4, and <2.25 mmol/L, respectively. Cox models were used to estimate the hazard ratio (HR) for the combined endpoint RRT or death, with multivariable adjustment for confounding.

Results: Of all 502 patients 68% were men, mean age was 69y, and 54% used lipid lowering drugs. Lipid levels were available in 284 patients and imputed for the other patients. Mean (SD) total cholesterol was 4.45 mmol/L (1.20), LDL 2.49 mmol/L (0.93), HDL 1.28 mmol/L (0.45), and median (interquartile range [IQR]) triglyceride was 1.52 mmol/L (1.1-2.2). During follow up 376 (75%) patients started RRT and 47 (9%) patients died. After multivariable adjustment the HR (95% CI) for the combined endpoint for high total cholesterol was 1.02 (0.75-1.38), for high LDL 1.17 (0.89-1.52), for high HDL 1.05 (0.68-1.42), for high HDL/LDL ratio 0.98 (0.68-1.29), and for high TG 0.89 (0.62-1.29).

Conclusion: We did not find an association between serum lipid levels and RRT or death in incident pre-dialysis patients on specialized pre-dialysis care.

P58
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Blood Pressure Variability In Individuals With And Without (Pre)diabetes – The Maastricht Study

Introduction: The mechanisms underlying the associations between (pre)diabetes and cardiovascular disease (CVD) are incompletely understood. We hypothesize that greater blood pressure variability (BPV) may underlie this
association, as greater BPV is associated with (incident) CVD. Therefore, we investigated the association between (pre)diabetes and within-visit, 24-hour and 7-day BPV.

Methods: Cross-sectional data from The Maastricht Study (N=3451, 1924 with normal glucose metabolism [NGM], 511 with prediabetes, 975 with type 2 diabetes [T2D], 51% men, aged 60±8 years). As BPV-indices, we determined standard deviation for within-visit BPV (n=3244), average real variability for 24-hour BPV (n=2699), and standard deviation for 7-day BPV (n=2259). Additionally, 24-hour BPV was divided into day (09:00h – 21:00h) and night (01:00h – 06:00h). Differences in BPV as compared to NGM were assessed with multiple linear regression, adjusted for age, sex, mean systolic/diastolic blood pressure, smoking status, alcohol use, BMI, prior CVD, lipid profile, use of lipid-modifying and antihypertensive medication, and eGFR.

Results: In T2D, the average systolic/diastolic values of within-visit, 24-hour and 7-day BPV were: 4.8/2.6, 10.5/7.3 and 10.4/6.5mmHg, respectively and in prediabetes 5.0/2.6, 10.3/7.0 and 9.4/5.9mmHg, respectively. Adjusted analyses showed that T2D was associated with greater nocturnal systolic BPV (0.42mmHg [95%CI: 0.05 – 0.80]) and greater 7-day systolic BPV (0.76mmHg [0.32 – 1.19]) as compared to NGM. Prediabetes was associated with greater within-visit systolic BPV only (0.35mmHg [0.06 – 0.65]) as compared to NGM.

Discussion: Both prediabetes and T2D are associated with greater very-short to mid-term BPV. Nevertheless, the slightly greater BPV seen in (pre)diabetes as compared to NGM suggest that very-short to mid-term BPV may explain not more than a small part of the increased CVD risk associated with glucose metabolism status. These findings do not detract from the fact that very-short to mid-term BPV is substantial and important in individuals with and without (pre)diabetes.

Matrix Gla Protein, plaque characteristics and cardiovascular events

Objective: Observational studies demonstrated that uncarboxylated matrix-Gla protein (MGP) is associated with coronary calcification. However, the relation between different uncarboxylated MGP (ucMGP) species and cardiovascular events is not clear yet. Moreover, it is unknown whether plasma MGP levels represent plaque MGP levels, or other plaque characteristics.

Methods: This study included 100 participants from the AtheroExpress cohort, a longitudinal vascular biobank study including biomaterials from patients undergoing carotid endarterectomy. At baseline, plaque characteristics and plaque ucMGP were measured, as well as plasma total uncarboxylated MGP (t-ucMGP) and desphospho-uncarboxylated MGP (dp-ucMGP). Weighted kappa statistics were calculated to assess whether plaque ucMGP represents plasma dp-ucMGP and t-ucMGP levels. During a yearly-follow up, vascular events were registered (fatal and non-fatal). We fitted cox proportional hazard regression models assessing the association between t-ucMGP and dp-ucMGP and cardiovascular events, adjusted for cardiovascular risk factors.

Results: Weighted Kappa statistics between ucMGP levels in plaque and plasma dp-ucMGP and t-ucMGP, were 0.08 (-0.15-0.30) and 0.14 (-0.06-0.34), respectively. Patients with increased plasma dp-ucMGP levels more often had plaque calcification, less often had intraplaque hemorrhage, less plaque smooth muscle cells and less plaque macrophages. Patients with increased plasma t-ucMGP levels had lower plaque fat content. During a mean follow up of 2.6 years, 20 cardiovascular events occurred. Dp-ucMGP was not associated with cardiovascular events. Higher levels
of t-ucMGP were associated with a reduced CVD risk with a hazard ratio of 0.95 (0.91-0.99) per 100 nM increase in t-ucMGP; the hazard ratio was 0.28 (0.07-1.06) for the highest versus the lowest tertile of t-ucMGP in a multivariable adjusted model. Conclusion: Plasma dp-ucMGP and t-ucMGP levels were not related to plaque ucMGP levels. Dp-ucMGP levels were not associated with cardiovascular risk, but increased levels of plasma t-ucMGP were associated with a reduced cardiovascular risk.