Stockholm, 210520

Topic Research Form (TRF:s) for SCAPIS core publications

Topic Research Forms

In the Topic Research Form (TRF) the planned publication is briefly described. Title, objectives, description of analysis, significance/rationale, population and required data variables, limitations and challenges as well as references are stated here.

A core publication has embargo on its research question. The embargo ends 1 year after the date complete data set from SCAPIS is sent to the principal, or when the publication is published.

The TRF:s have been updated during the spring of 2020. The TRF:s were originally composed in 2018.

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Key Publications (3 publications)

KEY 1. Prevalence and prediction of coronary artery atherosclerosis in the general population

EMBARGO on research hypothesis until 2021-05-14

Objectives

To describe frequency and distribution of coronary artery atherosclerosis in the general population
To develop models for prediction of coronary artery atherosclerosis in the general population

Rationale

Population strategies for prevention of myocardial infarction have been successful and most likely explain a substantial part of the reduction in the over-all burden of myocardial infarctions seen in recent decades (1). In contrast, high risk strategies for primary prevention of myocardial infarction is insufficient as it is applied today (2), especially considering the high occurrence of silent myocardial infarctions (3, 4), and the fact that sudden cardiac death is the presenting feature in one out of five myocardial infarctions (5).

With the advent of new imaging modalities, it is today possible to visualize coronary artery disease using low dose coronary computed tomography angiography (CCTA) (6). Direct visualization and identification of vulnerable coronary atherosclerosis may aid in developing improved high risk strategies for prevention.

Understanding the prevalence and characteristics of coronary artery atherosclerosis in the general population is key for determining the potential usefulness of screening programs for targeting preventive efforts. To identify predictors of coronary atherosclerosis is also of importance for the design of efficient screening programs. The Swedish CArdioPulmonary BioImage Study (SCAPIS) was designed for this specific purpose (7).

Population and Required Data Variables

<u>Sample</u>
Entire SCAPIS cohort

<u>Subsamples</u>

1. Subjects having performed coronary artery calcium score (CACS) / Subjects having performed CCTA
2. Subjects with / without symptoms compatible with coronary artery disease.
3. Men / women
4. Age groups 50-55 / 55-60 / 60-65

Handling of missing and ambiguous data from CCTA
Description of persons not performing CCTA (allergy, renal function etc)
Radiation burden, medication
Handling of missing information on coronary artery segment and vessel level will be described
Handling of data corrupted by calcium blooming will be described
Imputation will be performed.

Outcomes
We will tabulate and compare how the SCAPIS CCTA data can be described using the below scores. We will select three of these scores to be used in the prediction models. Preferably, the selected scores should reflect different pathophysiological disease processes and phenotypic presentations of CAD, e.g. DUKE index, SIS and CACS.

1. Clinical score - >50% stenosis in main stem or prox LAD, three vessel disease (>50% in all three vessels)
2. The DUKE risk score - weighs degree of stenosis, proximal disease and number of vessels involved (8)
3. SYNTAX CT score – similar to Duke, wide-spread and accepted ICA score adapted for CTA (9)
4. CONFIRM score – similar to Duke, developed specifically for CTA (10)
5. Leaman score - similar to Duke, adapted for CTA (11)
6. CAD-RADS score (12)
7. Segment involvement score (SIS) – CAD distribution (8, 13)
8. Non-calcified plaques – plaques in subjects with CACS =0, suggested to be vulnerable (6)
9. Coronary calcium score – level of calcification, established risk score (14)

Exposures
1. Demography (2 variables: age, gender)
2. Heredity for cardiovascular disease and its risk factors (5 variables: for myocardial infarction, stroke, diabetes, body composition)
3. Tobacco habits (13 variables: describing active and passive smoking, non-smoking tobacco)
4. Lipid-profile (6 variables)
5. Blood pressure (5 variables)
6. Diabetes Mellitus and glucose metabolism (8 variables)
7. Kidney function (s-creatinine)
8. Weight, body mass index, waist and hip circumference (6 variables)
9. Physical activity (8 variables: self-assessment, accelerometry)
10. Socioeconomic status (11 variables, education-level, income, marital stat, etc)
11. Alcohol habits (2 variables)
12. Psychosocial stress (5 variables: incl General stress-index, work-related stress index, life events index, depression index)
13. Social network (3 variables: incl. Social_network_AVSI_index and AVAT index)

14. OSAS – sleeping disorder (9 variables: incl sleep-disorder index, daytime-sleepiness-index)
15. Diet (Healthy food index, Unhealthy food index)
16. Inflammatory activity / disease (10 variables: incl. Hs-CRP, chronic inflammatory diseases)
17. Pulmonary disease/disorder (16 variables: incl. pulmonary symptoms, pulmonary diseases and results from spirometry)
18. History of cardiovascular diseases (13 variables: incl. coronary disease, heart failure, atrial fibrillation, stroke, peripheral artery disease, ABI both legs)
19. Symptoms compatible with cardiovascular disease (6 variables: chest pain-Angina (Rose-Angina-index), dyspnea, claudicatio)
20. General health perception, QoL (3 variables: SF12-physical scale, SF12-mental scale)

Description of Analysis

Initially, distributional properties of all variables will be investigated, and three primary outcome variables will be defined based on the available coronary artery disease data (CAD-outcomes, see above). Distributional properties of these variables will be described in detail, in the main sample and in defined subgroups. Feasibility data will be presented (missing data, radiation dose, side effects of medication).
An existing risk score model, SCORE (Sweden 2015), PROCAM or Framingham will be compared to outcomes and their prediction of CAD-outcomes will be tested.
The existing risk score model will be compared to optimized specific baseline model(s) to predict presence of CAD-outcomes. These baseline models will be built on “traditional” risk factors included in existing models/score such as BP, TC, smoking, age and sex. In addition, diabetes status may be added to the models.
Machine learning methods (Gradient Boosting Machines and/or Random Forest) will be used to develop optimized prediction models.
The above results will be bench-marked to Prediction models based on all available exposure data available in the SCAPIS project. Models based on easily available “home data” (weight, waist, heredity, smoking status etc) will be compared to models based on data only available after a visit to health care provider (e.g. clinical chemistry data, spirometry data).
Data will be divided into training data set (~80-90%, depending on frequency of outcomes) and validation data set. All models will be developed using the training data set and evaluated using the validation data set. Alternatively, all data will be used and prediction accuracy assessed using the optimism bootstrap. We will also involve data from the SCAPIS Pilot trial as a completely separate validation cohort (n=980 CCTA).
Relevant variables from the 20-exposure groups (i.e. having a previously reported association with CVD) will be included in the final modelling step and the 5-10 top ranked variables will be listed and described. Variables outside the “top 10” list will not bed described in detail.
Calibration curves will be produced to assess how well calibrated the predictions are.
Both traditional prediction models (ordinal regression, etc.) and machine learning models (gradient boosting machines) will be used and compared.

Limitations and Challenges

The acceptance for machine-learning methods may be limited.

TRF authors

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KEY 2. Chronic airflow limitation and emphysema – impact of different definitions and relations to symptom profiles and smoking habits

EMBARGO on research hypothesis until 2021-05-14

Objectives

• To describe the prevalence and clinical characteristics of chronic airflow limitation (CAL) and emphysema in a large general population-based sample, using different definitions.

• To compare the phenotype/clinical profile of subjects with CAL/emphysema among ever-smokers and never-smokers by using spirometry, diffusion capacity, CT imaging and symptom profile.

• To explore the impact from different exposures in terms of traditional risk factors on the prevalence of CAL and emphysema.

Description of Analysis

Prevalence

The prevalence and clinical characteristics of CAL and emphysema in the study population-based sample by using different definitions will be presented.
CAL is defined employing the spirometric definition of COPD, according to GOLD and the LLN model, and also using slow vital capacity, SVC. Emphysema is based on eCRF data where the extent of emphysema is visually estimated on a four-point scale (absent, mild, moderate or severe) in the upper, mid and lower zones of each lung.

Risk factors

Firstly, the phenotype/clinical profile of subjects with CAL/emphysema among ever-smokers and never- smokers will be presented by using spirometry, diffusion capacity, CT imaging and symptom profile. Respiratory symptoms, lung diseases and co-morbidities are based on questionnaire data and smoking is categorized as current smokers, former smokers or never-smokers, and the number of pack-years is calculated for all participants with a history of smoking. Level of education, occupation as well as “born in Sweden” are included in the analyses.
Separate analyses for males, females and never-smokers will be performed, along with sensitivity analyses excluding those with physician-diagnosed asthma at the age of <40 years. Distributional properties of these variables will be described in detail, in the main sample and in defined subgroups.

Secondly, the impact of different exposures on the prevalence of CAL and emphysema will analysed by using both traditional prediction models and machine learning models (gradient boosting machines).
Optimized specific baseline model(s) to predict presence of CAL/emphysema will be developed and compared to the existing models. These baseline models will be built

on “traditional” risk factors included in existing models/score such as smoking, age and sex. In addition, respiratory symptoms and occupation will be added to the models. Machine learning methods (Gradient Boosting Machines and Random Forest) will be used and compared to optimize models.
All data will be used and prediction accuracy assessed using the optimism bootstrap. Relevant variables from the exposure groups (i.e. having a previously reported association with CAL/emphysema) will be included in the final modelling step and the 5-10 top ranked variables will be listed. Calibration curves will be produced to assess how well calibrated the predictions are.

Significance/Rationale

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of morbidity and mortality in an adult population (1). The diagnosis of COPD is based on history, symptoms and spirometry, whereas chronic airflow limitation (CAL) is solely defined by spirometry. It has been shown that the proportion of never-smokers with CAL in an COPD population is around 20–25%. It is unknown whether CAL among never-smokers has different clinical characteristics compared to smokers and former smokers, and whether these groups differ with regard to lung architecture.

The Global Initiative for Obstructive Lung Diseases (1) recommends that diagnosis of CAL should be based on the fixed ratio of FEV1/FVC<0.7. An alternative approach is to use the lower limit of normal (LLN) as a cut-off, and the use of LLN has been jointly recommended by American Thoracic Society (ATS) and European Respiratory Society (ERS) (2, 3). However, the long-term prognosis seems to be similar regardless the definition used (4).

Recent imaging techniques have provided new ways of describing COPD and emphysema (5). Thoracic imaging provides a way to quantify airway remodeling with regards to emphysematous destruction, airway wall thickening and regional ventilation abnormalities such as air-trapping.

The strength of SCAPIS is the large size of a general population-based sample, that all subjects have undergone CT imaging, the large proportion of never-smokers and that spirometry including diffusion capacity (DLco) was performed after bronchodilation.

Population and Required Data Variables

Sample
Total SCAPIS population

Subsamples
Subjects with/without CAL/emphysema
Men/women
Smokers

Outcomes

1. Chronic airflow limitation (CAL) as defined by
    a. GOLD
    b. LLN
2. Emphysema based on CT imaging as defined by
    a. Any score > 0
    b. Total score (0-18)

Risk factors

1. Demography (age, sex) – 2 variables
2. Weight, height, BMI etc – 6 variables
3. Smoking habits – 6 variables
4. Blood pressure – 2 variables
5. Respiratory symptoms, including mMRC - 26 variables
6. History of lung disease – 15 variables
7. Comorbidities – 22 variables
8. HRCT-thorax – 13 variables
9. Socioeconomic status – 3 variables
10. Blood samples (haemoglobin, fasting blood glucose, HbAIc, creatinine, total cholesterol and hs-CRP) – 6 variables

Limitations and Challenges

The limitation of the analysis is the limited age span, 50 – 64 years, as well as the cross-sectional design. Acceptance for machine-learning may also be limited.

TRF authors

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KEY3. Patterns of arterial and pulmonary pathology in the general population: Clinical implications and etiological links

EMBARGO on research hypothesis until 2021-05-14

Objectives

Primary

To describe the prevalence and characteristics of atherosclerosis in three arterial beds in relation to comprehensive measurements of lung function, accounting for smoking

Secondary

To use proteomics to discover common pathways for atherosclerosis and impaired lung function.

Population and Required Data Variables

Sample

1. Entire SCAPIS cohort for the primary aim.
2. The 5000 with proteome analyses for the secondary aim.

Subsamples

1. Never-smokers / previous smokers / current smokers.
2. Men / women
3. Age groups 50-54 / 55-59 / 60-64

Outcomes

Coronary artery variables:

To be determined from the following:

1. Number of major coronary arteries with any >50 % stenosis
2. Number of segments with <50 % stenosis
3. Number of segments with >50% stenosis
4. Number of segments without any plaques
5. Number of segments with mixed plaques
6. Number of missing segments
7. Number of non-assessable segments
8. Coronary calcium score
9. Number of coronary stents
10. Number of coronary grafts
11. No visible coronary artery disease (0/1)
12. Stenosis in proximal left main descending artery (segment 6, 0/1)
13. Anomalous origin of any coronary artery (0/1), with free text specification

Carotid artery variables:

To be determined from the following:

1. Total number of plaques (CCA + Bulb +ICA)
2. Total plaque area (mm2)
3. Max flow velocity (m/s)

4. Intima-media thickness (mm)
5. Number of plaques >= 25 mm2 (n)
6. Stenosis > 70% (n)
7. Stenosis > 50% (n)

Peripheral artery variables:
Ankle-brachial index (ABI), measured for each ankle as the highest of the pressures in each A. Dorsalis Pedis or A. Tibialis Posterior (the numerator/ankle) over the average of the two supine brachial blood pressures in the arm with the highest blood pressures (the denominator/arm). One ABI value per ankle is obtained.5

Pulmonary variables:
To be determined from the following variables:

1. FEV1
2. VC
3. FEV1/VC >= or <0.70
4. DLCO
5. CT emphysema score

Proteomics exposures
184 proteins

Confounders
To be determined from the following, using Directed Acyclic Graphs:
Height, age , sex, diabetes (fasting glucose, questionnaire, medication), obesity (BMI, waist hip ratio), hypertension (blood pressure, medication), hyperlipidaemia (LDL, HDL and triglycerides), smoking (never, former, current), alcohol intake, SES (education), exercise habits.

Description of Analysis

All analyses will be carried out in accordance with a pre-specified statistical analysis plan, published in advance in the public space. Initially, missingness patterns will be investigated. Multiple imputation will be the main means of handling missing data. Thereafter, distributional properties of all exposure and outcome variables will be investigated, and three primary arterial (one for each vascular bed) and several secondary arterial outcome variables will be defined out of the available artery data. The three primary arterial outcomes variables will be selected to have similar properties, facilitating comparisons. Distributional patterns of all outcome variables will be described in detail, in the main sample and in defined subgroups.
All pulmonary variables will be screened for associations with all arterial outcomes, using the most appropriate models, such as circular graphs (Figure 1). Separate associations of pulmonary exposures with arterial outcomes will be modelled using restricted cubic splines with degrees of freedom allocation based on the partial apparent strength of association.
Interactions with smoking (never / former / current), age (50-54 / 55-59 / 60-64 year categories) and sex will be forced into all models; and both overall and age- and sex-specific results will be presented.

Associations of 184 proteins with pulmonary and arterial outcomes will be investigated as follows: The sample will be split into a discovery sample (2/3 of the sample) and a validation sample (1/3 of the sample). In the discovery sample, associations of the 184 proteins with the primary outcomes (each protein in a separate model) will be investigated using multivariable linear regression, adjusting for age and sex, in the three separate smoking strata. Associations significant at a false discovery rate (FDR) < 5% will be investigated in the replication sample, adjusting for the same factors. FDR will be calculated according to the original version of Benjamini and Hochberg from 1995. The rationale for this conservative significance threshold is that we want to find a reasonable balance between false positive and false negative findings. A nominal P value of <0.05 will be considered as a valid replication.

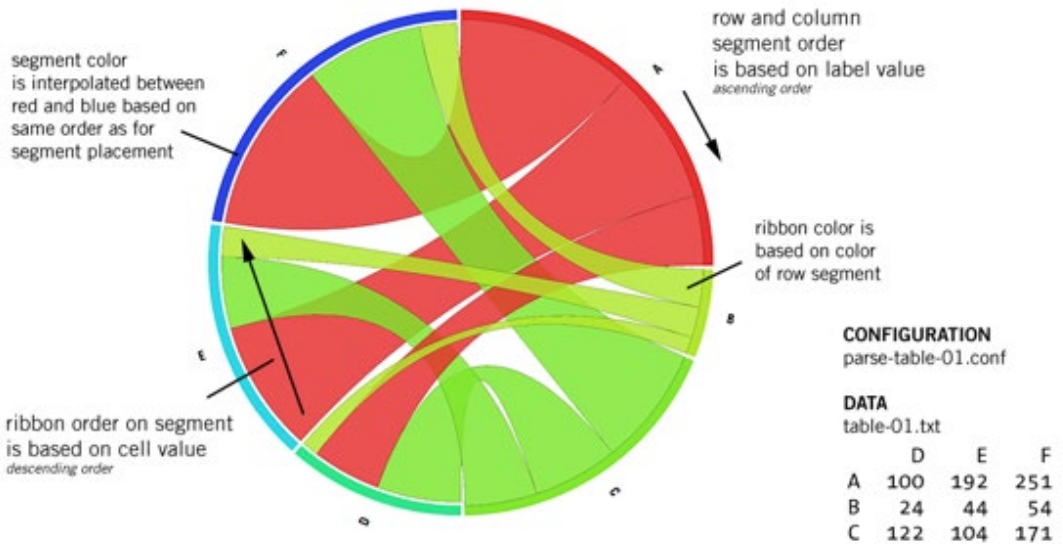

Figure 1.

Significance/Rationale

Individuals with chronic obstructive pulmonary disease (COPD)/impaired lung function are at increased risk of myocardial infarction (myocardial infarction)[1] and stroke[2], and up to one third of COPD patients die from cardiovascular disease[3]. This increased risk cannot be completely explained by smoking[4] and has been attributed to increased systemic inflammation[5].

This TRF is dealing with one of the predefined goals of SCAPIS. It will be valuable for the understanding of the link between atherosclerotic and pulmonary function and will hopefully disclose pathophysiological links that could be a starting point for the development of therapeutic interventions.

Limitations and Challenges

Finding comparable measures of atherosclerosis in three different arterial beds may be challenging.

TRF authors

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Priority 1 (24 publications)

DSO. Assessing neighbourhood-level proportions of people enrolled in the population-based Swedish Cardiopulmonary Bioimage Study (SCAPIS) – an aid to generalise findings

EMBARGO on research hypothesis until 2021-05-14

Objectives

To analyse factors associated with participation in SCAPIS using sociodemographic data at the individual and neighbourhood level, and to develop weights that can be used to generalize results from SCAPIS to various sociodemographically-defined target populations.

Background

SCAPIS is a population-based study with broad recruitment from the general population aged 50-64 years living in the areas surrounding six cities with university hospitals. Out of a random sample of 60000 invited individuals, roughly 50 percent agreed to participate in the study. It is well known that study participation tends to be lower in socioeconomically disadvantaged populations, which may limit the generalizability of findings and introduce selection bias into associational measures. We have previously demonstrated that inverse probability for participation weighting could be used to improve the validity of estimates from the pilot phase of the SCAPIS cohort.

Dependent variables

Participation in SCAPIS (Yes, No).

Independent variables

We will use sociodemographic register data at the individual and contextual level (DeSO, Demografiska Statistikområden, SCB) linked to SCAPIS participants and non-participating members of the population.

Analysis

We will model the probability for participation in SCAPIS to create propensity scores for participation. The propensity scores will then be used to calculate inverse probability for participation weights that can be used to standardize the SCAPIS cohort to the originally invited population as well as other sociodemographically-defined populations (e.g., the national population aged 50-64 years).

References

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R1. Cohort profile: The Swedish CardioPulmonary bioImage Study

EMBARGO on research hypothesis until 2021-03-19

Objectives

To provide a succinct cohort profile, including methods descriptions; data on reproducibility of key variables and strategies for statistical correction for regression dilution bias; data on site differences, and a presentation of strategies for statistical correction for these differences; and simple summary data on common risk factors, by age group and sex, and a presentation of unmet need in terms of primary and secondary prevention (proportion above current thresholds for these risk factors that are untreated).

Background

The SCAPIS study needs an early publication describing the cohort and sorting out potential site differences and reproducibility measures, and presentations of strategies for statistical correction for any such differences that need to be accounted for. A general approach for most future SCAPIS analyses may be by adding the site variable in the regression model, but there may be other differences that are better taken care of by using random effects, standardization or other procedures. This project aims to sort out these needs, as a part of quality control. There has also arisen a wish to have simple summary metrics published from these quality-controlled analyses, in order to assess unmet need for prevention.

Independent variables

Site, examination (for reproducibility analyses)

Dependent variables, cohort profile

Descriptive (median and iqr or numbers and percentages) figures per age and sex group

Clinical variables

Diabetes (Absent/Present), HbA1c, fasting glucose, BMI, waist circumference, hip circumference, hypertension (Absent/Present), brachial systolic blood pressure, brachial diastolic blood pressure, hyperlipidaemia (Absent/Present), LDL cholesterol, HDL cholesterol, triglycerides, smoking (never, former, current), alcohol intake, SES, exercise habits measured by accelerometry. Drug treatment for diabetes, hypertension and hyperlipidaemia, statin and aspirin treatment.

Unmet need for prevention

Proportion with diabetes, hypertension or hyperlipidaemia according to levels of corresponding continuous variables (according to SCAPIS definitions of the traits) that are not drug treated for the condition, stratified on previous myocardial infarction or

stroke (No/Yes). Proportion with previous myocardial infarction or stroke that is 1) not treated with aspirin or statins, or 2) is a current smoker.

Coronary variables (in cooperation with key publication "heart")

1. Number of major coronary arteries with any >50 % stenosis
2. Number of segments with <50 % stenosis
3. Number of segments with >50% stenosis
4. Number of segments without any plaques
5. Number of segments with mixed plaques
6. Number of missing segments
7. Number of non-assessable segments
8. Coronary calcium score
9. Number of coronary stents
10. Number of coronary grafts
11. Visible coronary artery disease (No/Yes) as defined by …
12. Stenosis in proximal left main descending artery (segment 6, 0/1)
13. Anomalous origin of any coronary artery (No/Yes), with free text specification

Carotid artery variables

Absence or Presence of plaques in the carotid arteries

Peripheral artery variables

Ankle-brachial index (ABI), measured for each ankle.

Pulmonary variables (in cooperation with key publication "lung")

1. FEV1
2. VC
3. DLCO
4. CT emphysema score

Dependent variables, reproducibility study

Systolic and diastolic blood pressures, waist and hip circumferences, coronary artery calcium score (CACS), presence, location and severity of lung emphysema, tobacco habits (smoking status, smoking start age, number of cigarettes per day)

Dependent variables, site differences

Accelerometry (percent of wear time in differend physical activity classes), diabetes status, SCORE, BMI, Height, Hip, Waist, Weight, ABI (left and right), systolic and diastolic blood pressures, pulse, CACS, presence or absence of coronary stenosis (any stenosis, stenosis in 1, 2, and 3 vessels, stenosis in main stem and/or LAD), presence of cvd (angina, heart failure, mi), medication for hypertension and/or dyslipidaemia, total energy intake, intake from fat, carbohydrates, protein, salt, sugar, laboratory analyses (total cholesterol, creatinine, crp, glucose, hb, hdl, hba1c, ldl, tg), education, questions regarding cvd and pulmonary diseases, pregnancy diabetes, marital status, ethnicity.

Handling of missing data

Missing data will not be imputed but patterns of missingness will be described.

Descriptive statistics

Continuous variables will be described using medians (outer quartiles). Categorical variables will be described with frequencies and percentages. For clinical risk factors, proportions with traits diabetes (Absent/Present), hypertension (Absent/Present), hyperlipidaemia (Absent/Present), emphysema (Absent/Present and severity), COPD (Absent/Present), chronic airflow limitation (Absent/Present) will be calculated according to current guidelines and SCAPIS definitions. The proportion treated with drugs for these conditions will also be described.
Continuous variables of lipids (LDL cholesterol, HDL cholesterol, triglycerides) will be described for the whole sample, and in subsamples with and without lipid-lowering drug treatment, diabetes and previous CVD.
Continuous glucose variables (HbA1c, fasting glucose) will be described for the whole sample, and in subsamples with and without glucose-lowering drug treatment.
Continuous blood pressure variables (brachial systolic blood pressure, brachial diastolic blood pressure) will be described for the whole sample, and in subsamples with and without blood pressure-lowering drug treatment, diabetes and previous CVD.
Continuous variables FEV1, FVC, DLCO will be described for the whole population, and in subsamples based on smoking status
The unmet need for prevention will be determined as the proportion with diabetes, hypertension or hyperlipidaemia according to levels of those continuous variables that are not drug-treated for the condition, stratified on previous myocardial infarction or stroke (Absent/Present). Unmet need for secondary prevention will also be determined as the proportion with previous myocardial infarction or stroke that is 1) not treated with aspirin or statin, or 2) is a current smoker.

Analysis

Mock figure 1 presents calendar time versus the recruitment rate, overall and per site. Analyses of site differences will be carried out using multivariate tests handling variables measured on arbitrary scales as described by, e.g. Strasser and Weber (1999), Hothorn et al (2006), and Winell & Lindbäck (2018) with multiplicity adjustments taking the correlations between test statistics into account as described in Westfall and Young (1993). The results will be presented in a manhattan plot showing –log10(p-value) for all investigated variables, see mock figure 2, with the p-value taken as the smallest p-value across the sites for that variable. A large value indicates evidence against the null hypothesis of no site differences.
Reproducibility analyses will be done for a) continuous variables by considering the absolute differences between the repeated measurements, visualized by Bland-

Altman plots, see mock figure 3 and mock table 1, and for b) categorical variables by calculating Krippendorff's α or Cohen's κ. Differences between the continuous variables and cross tabulation of categorical variables will be presented, see mock table 2.

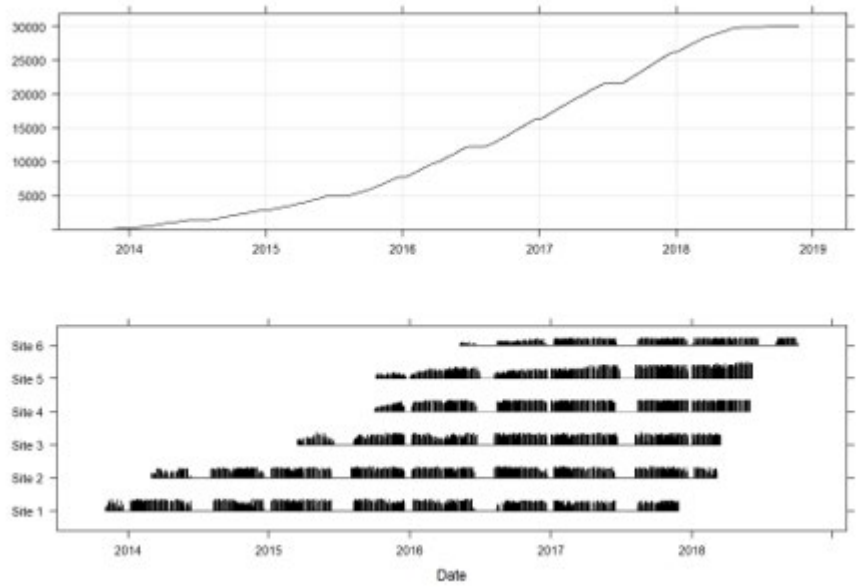
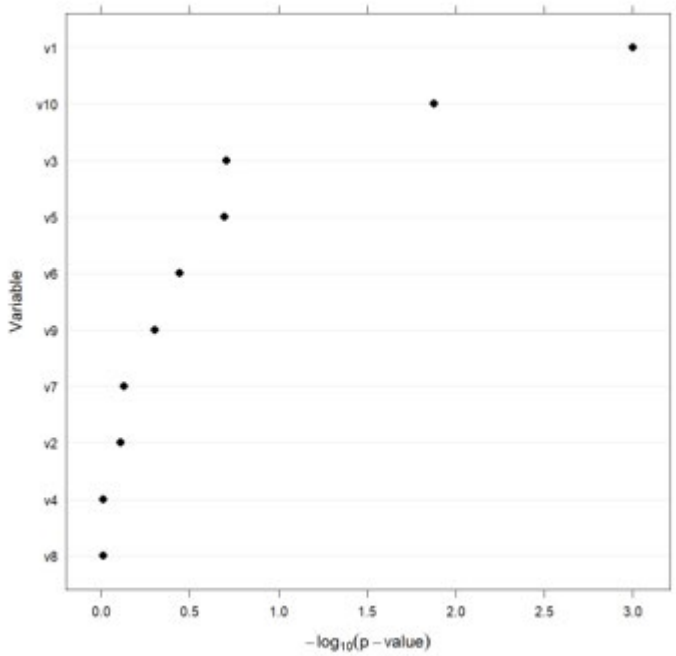
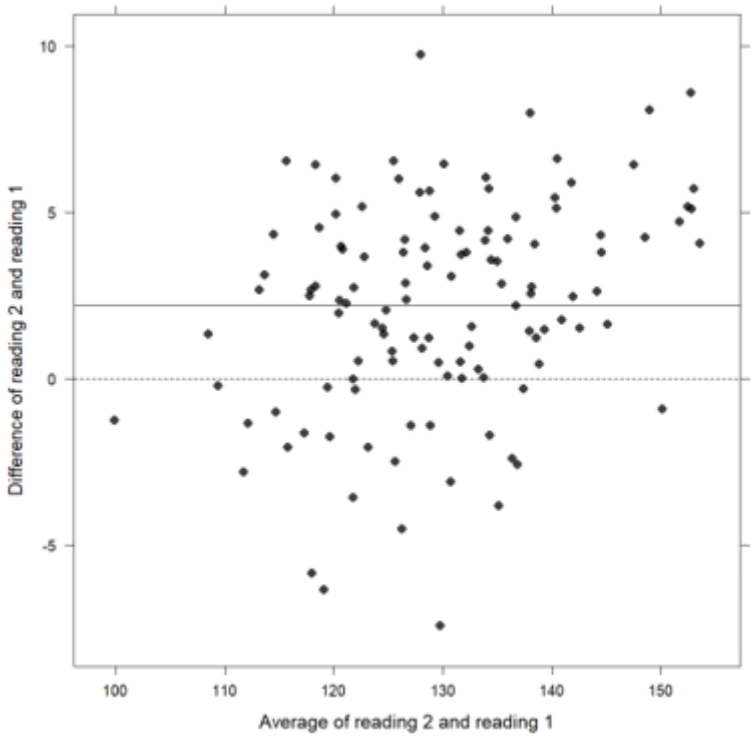


Figure 1: Date versus the cumulative number of individuals recruited (top panel) and recruitment period for each site (bottom panel).



Mock figure 2: -log10(p-value) for variables v1-v10



Mock figure 3: Bland-Altman plot of a continuous variable. The solid line is the sample mean of the pairwise differences.

Variable	Measurement	median (igr)	Absolute difference median (igr)
x	1	…	7.1 (3.4 ; 11.6)
	2	…	

Mock table 1: Summary for a continuous variable

		Measurement 2		
		Level 1	Level 2	Level 3
Measurement 1	Level 1	…	…	…
	Level 2			…
	Level 3			

Krippendorff's α = 0.85

Mock table 2: Cross tabulation of a categorical variable

Population and key variables

N/A

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K0. Accelerometer derived daily activity pattern in 30.000 middle-aged adults – the SCAPIS study

EMBARGO on research hypothesis until 2021-12-13

Objectives

The primary objective is to describe accelerometer daily activity pattern in a large sample of middle-aged men and women, including frequency, duration and distribution of low, moderate and vigorous intensity physical activity as well as sedentary behaviour and fulfilment of physical activity recommendations. Highly clinically relevant sub-group analyses will be performed across gender, age, sedentary and moderate-to-vigorous PA, region in Sweden, urban vs. rural area, socio-economic status, work/retirement, seasonal variation and weekdays variation.

Description of Analysis

In the light of new research evidence, showing an independent association between sedentary time, low intensity PA and more intense PA and metabolic status and increased CVD risk , it is highly relevant to evaluate all different aspects of the daily movement pattern (low, moderate and vigorous intensity physical activity as well as sedentary behaviour). The majority of previous studies investigating the daily activity pattern has used self-report, a method previous reported to be limited by an overestimation of physical activity and underestimation of sedentary time [1]. Previous Swedish studies using objective measurements to assess the daily activity pattern are few, including only small population samples [2, 3]. We will use accelerometer and eCRF data from the whole SCAPIS cohort (n=30.000) to describe the daily activity pattern in the total sample as well as across the above defined sub-groups, using traditionally analyses and significance testing.

Significance/Rationale

As several subcomponents of the daily activity pattern have been shown to strongly relate to metabolic health as well as the risk of fatal and non-fatal CVDs, it is highly clinically relevant to be able to detect objectively assessed variations in these variables in a large population of middle-aged men and women. Moreover, as this paper will study the variation in daily activity pattern and fulfilment of physical activity recommendations across highly relevant sub-groups, it has the potential to be a pioneer paper to identify populations at risk.

Population and Required Data Variables

Sample: All subjects with valid accelerometer data for at least 4 days.

Accelerometer variables:

- Sedentary (time in and % of wear time)
- Light intensity physical activity (time in and % of wear time)
- Moderate intensity physical activity (time in and % of wear time)
- Vigorous intensity physical activity (time in and % of wear time)
- Total wear time
- Valid days

- % weekend days
- Prolonged sedentary time

Stratification variables:
- Gender
- Age
- SCAPIS site
- Postal code (or similar to study urban vs. rural area)
- Socio-economic status (educational level, economic buffer and income)
- Working / Retirement status
- Medical history
    - Body mass @ 20 yrs
    - Chronic diseases
    - Performance
    - Parental medical history
- Visit date

Limitations and Challenges

Limitations include the inability of the accelerometer to differentiate between sitting and standing as well as the automated wear time estimation used, as low counts during 60 minutes may be common in this age-group. In addition, caution must be applied when extrapolating the presented data to men and women, outside the ages of the study participants.

TRF authors

Elin Ekblom-Bak, Mats Börjesson, Göran Bergström, Örjan Ekblom.

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I2. Body Weight in adolescence, adult weight and abdominal obesity

EMBARGO on research hypothesis until 2022-04-27

Objective

The primary objective of the study is to describe and quantify weight gain between young adulthood and middle age and to investigate the relationship between weight at age 20, weight gain/weight at middle age and abdominal obesity. Secondary objectives are to investigate which midlife characteristics are associated with having gained excessive weight from youth to adulthood and how this is modified by gender and socioeconomic factors.

Background

Elevated BMI in childhood will often persist into adolescence and from there to young adulthood [1] and weight in adolescence has distinctive relationships with type 2 diabetes and coronary heart disease [2-5]. Even mildly elevated BMI, well within the normal range, predict several cardiovascular disease outcomes.[5, 6] Questions remain to which extent these associations reflect adult weight and abdominal obesity through greater weight gain among persons with higher young adulthood weight. Weight gain during adult life is related to development of coronary heart disease, [7, 8] and to risk of the metabolic syndrome, including diabetes [9] but to which extent adolescent weight and weight gain contribute towards the development of the metabolic syndrome in a contemporary population has not yet been established.

Significance/Rationale

Weight gain over life, from adolescence to adult life, is a major problem in the Western world as well as globally. Few studies have investigated how adolescent body weight is related to weight in adult life and to the metabolic syndrome. The hypothesis of the study is that there are specific, as yet unknown, factors in early adult life that are associated with more pronounced weight gain and the development of metabolic risk factors later in life.

Description of analysis

Outcome would be adult weight, abdominal obesity measured as waist, waist/hip ratio and metabolic risk factors, including diabetes [9]. Exposures include self-reported weight at age 20. Age, sex, education and smoking will be considered as confounders. Interaction terms between BMI at age 20 and weight gain will be included in the models. Statistical models will include linear regression models and restricted cubic spline models for non-linear associations with continuous outcomes and logistic regression models for dichotomous outcomes (if applicable), multiple

imputation for missing variables, investigations of multiplicative interactions with key covariates, and two-sided hypothesis tests.

Population and required data variables

In this analysis, approximately 30,000 subjects with full anthropometry data form the basis of this investigation. We estimate that about 80% of the men will have data on adolescent weight from the conscript registry and a similar proportion of women will have data on weight in early pregnancy.

Key variables from the SCAPIS database: Weight at study visit, self-reported weight at age 20, measurement of waist, hip circumference and height, age, sex, education level, self-reported diabetes, fasting plasma glucose, HbA1c, lipids, systolic and diastolic blood pressure, self-stated prior diseases.

Limitations and Challenges

We do not recognise any major challenges with the proposed analyses. Self-reported weight at age 20 may be misreported but register data for a subset of the population will be available.

Authors

Annika Rosengren, Gothenburg University and Lars Lind and Johan Sundström, Uppsala University.

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I4. Weight Gain and Coronary Calcium

Objective

We tested the hypothesis that weight at age 20 and subsequent weight gain are positively related to coronary artery calcium score (CACS) at midlife. As a secondary objective, investigate any sex differences of the primary aim.

Background

Obesity is a well-known risk factor for future coronary artery disease, although its power as a risk factor declines with age (1). In most epidemiological studies, body mass index (BMI) or body weight is measured in adulthood, usually in midlife. Studies on weight in adolescence or early adulthood and subsequent early coronary disease typically show a markedly steep increase in risk associated with weight (2-4) but whether this is due to further weight gain during the life course, or to an effect of high early body weight, or a combination of both, is not known. This gap in knowledge is somewhat surprising since most people at middle-age or older can recall their weight in early adulthood with reasonable accuracy (5).

Both measured and self-reported weight (or BMI) in adolescence or in early adulthood have been shown to be related to future coronary heart disease (CHD) (3, 4, 6, 7). The weight gain from early adulthood to midlife is usually in the 12–16 kg range (8), and even a very moderate weight gain has been reported to relate to future myocardial infarction and coronary death (2). In the CARDIA study (9), BMI in early adulthood was related to coronary artery calcium score (CACS), which is closely related to coronary atherosclerosis as well as predictive for future CHD (10-13). Unexpectedly, weight gain from early adulthood to midlife was inversely related to CACS (9). Furthermore, BMI in early adulthood as well as weight gain until midlife have been shown to be related to midlife carotid artery intima-media thickness (IMT) (14). It is well known that cardiovascular disease develops later in women than in men, and we have previously reported that fat mass is more closely related to cardiovascular risk factors in men than in women (15). The effect of sex on the relation between early adulthood weight and weight gain on CACS has not been studied.

In the current analyses we will test the hypothesis that both weight at age 20 and subsequent weight gain were positively related to CACS at midlife, using data from subjects enrolled in the Swedish CArdioPulmonary bioImage Study (SCAPIS) (16). This large sample size will enable us to specifically address potential interactions between sex and effects of body weight in early life and subsequent weight gain on CACS.

Significance/Rationale

Weight gain over life, from early adulthood to middle age, is a major problem in the Western world. It has not previously been investigated if a high weight gain is

associated with coronary atherosclerosis. If the hypothesis is correct we need to implement weight control programs that include increased physical activity and improved food literacy in early life to reduce overweight in early adulthood.

Description of analysis

Outcome would be the CAC. Exposure would be BMI at age 20, weight gain between age 20 and weight at investigation. Age, sex and smoking will be considered as confounders. Traditional cardiovascular risk factors; diabetes, lipids and blood pressure could be regarded both as confounders and mediators in this respect.

CACS levels have a distribution in which almost half the population has zero and then values are skewed to the right. In order to treat CACS as a continuous variable, we will use a two-part model that consists of a logistic regression estimating the probability of CACS being zero or positive and a cumulative probability model (CPM), for the expected CACS value in cases where it is positive. An interaction between BMI at age 20 and weight gain will be included in the models. For the secondary objective the interaction term will also include sex.

Population and required data variables

The whole cohort will be used, approximately 30,000 subjects. Key variables see above.

Limitations and Challenges

We do not see any major challenges other than for the SEM analyses where a highly non-normally distributed variable is a problem.

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I5. The Association Between Traditional Risk Factors and Different Measures of Obesity with Subclinical Coronary Artery and Carotid Atherosclerosis

EMBARGO on research hypothesis until 2022-03-29

Objectives

To describe how the prevalence of subclinical coronary and carotid atherosclerosis is related to different measures of obesity: body mass index (BMI) and waist and hip circumferences with special reference to gender.

In multivariable analyses test whether these measures of obesity can predict the presence of subclinical atherosclerosis independently of traditional cardiovascular risk factors.

Background

Obesity defined as BMI or waist circumference is a well-stablished risk factor for insulin resistance, dyslipidaemia, diabetes and coronary heart disease in both men and women across different ethnic groups.[2] However, cross-sectional studies linking BMI to the prevalence of coronary artery disease show mixed results. Previous studies on BMI and coronary artery calcification score (CACS) have been comparably small and/or heterogeneous (n=329 to 6,814) and have in some cases demonstrated positive associations,[3-9] whereas the majority have shown neutral[10-17] or even negative[18] associations after multivariable adjustment for traditional risk factors. Data from studies linking waist circumference to CACS have in most cases failed to show an association in multivariable-adjusted models[8, 11-15] while others have seen an association.[6, 19]

An explanation for the lack of association might be that a substantial proportion of the BMI- and waist circumference-associated risk for CACS is mediated by traditional cardiovascular risk factors. Furthermore, that the impact of peripheral fat accumulation has not been considered. We have recently shown that central obesity is strongly associated with cardiovascular mortality once adjusted for peripheral obesity (Cameron 2020, JAHA).

Compared to all previously reported studies, this analysis in SCAPIS would have considerably higher power to test if there is an association between BMI and waist circumference with coronary and carotid atherosclerosis and if it is independent of traditional risk factors.

Description of Analysis

Data on coronary and carotid atherosclerosis including CACS will be tabulated and plotted after stratification for sex, BMI and waist and hip circumferences, and we will perform comparisons between relevant strata using the Kruskal-Wallis test.

Logistic regression analysis will be used to assess the relationship between BMI/waist circumference/hip circumference and the presence of a coronary and carotid

atherosclerosis including CACS; possible effect modification by sex will be evaluated. In particular, waist and hip circumferences will be modelled separately as has been done by Cameron et al (Int J Epid 2012 and JAHA 2020).

Adjustments will be performed for potential confounding factors such as age, systolic blood pressure, total cholesterol, active smoking, and use of lipid-lowering and antihypertensive therapy.

CACS will also be considered as a continuous outcome variable (natural log [coronary artery calcium score + 1]). Multivariable adjusted spline regression models can be constructed to describe the relationship linking high CACS with BMI and waist circumference.

Significance/Rationale

The study would add important information on how obesity, and abdominal obesity in particular, contributes to asymptomatic coronary and carotid artery disease. The size of the cohort will allow unprecedented resolution.

Population and Required Data Variables

The entire SCAPIS study population aged 50–64 years with data on anthropometry and with CT heart/coronary arteries and ultrasound of the carotid arteries done. Prevalent cardiovascular disease, kidney disease and diabetes will be excluded from the analysis (estimated prevalence: 1-2% with cardiovascular disease and 6-8% with diabetes).

Limitations and Challenges

To proper model waist and hip circumferences in order to discern the impact of abdominal obesity taken the effect of peripheral obesity into account.

Authors

Göran Bergström, Ulf Strömberg and Stefan Söderberg

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I8. Systemic Inflammation in COPD in Relation to Clinical Phenotype and Smoking History

Objectives

Overall objective is to relate systemic inflammation in chronic obstructive pulmonary disease (COPD) to self-reported clinical symptoms and smoking habits, in comparison with never-smokers and smokers with normal lung function.

Primary aim:

- To evaluate whether systemic inflammation, in terms of hs-CRP, is related to clinical phenotype and smoking habits in COPD.

Secondary aim:

- To compare systemic inflammation and clinical symptoms in smoking-induced COPD with individuals with chronic obstruction without smoking history.
- To relate the results to a simple means of emphysema classification and self-reported cardiovascular disease.

Description of Analysis

Chronic obstructive pulmonary disease (COPD) is a condition associated with inflammation in lungs and airways. However, there is a growing recognition that the inflammatory state associated with COPD is not confined to pathological mechanisms localised to the lungs, but also involves the systemic circulation and can impact non-pulmonary organs.1 Thus, COPD is considered a heterogeneous disease with a systemic chronic inflammatory process accompanied by high comorbidity and systemic manifestations linked to other systemic diseases, such as cardiovascular disease.2 The extent and severity of systemic inflammation may be partly estimated by serum measurement of several markers, including serum C-reactive protein (CRP). As an inflammatory marker, CRP can be easily and sensitively measured in a variety of clinical situations to monitor systemic inflammation, not only for diagnostic or prognostic purposes, but also for treatment evaluation in COPD.3 Several studies have reported high levels of CRP in COPD patients compared with control subjects without COPD. Also, in patients with mild COPD, in the absence of any clinical signs and/or exacerbation, and in patients with stable COPD, serum CRP may be elevated. CRP is sensitive to changes in response to variation in inflammation severity, disease exacerbation and treatment in patients with stable COPD. Furthermore, serum CRP levels have been found to be negatively associated with pulmonary function volumes, mainly FEV1.

Epidemiologic and mechanistic studies indicate that COPD is associated with a high frequency of cardiovascular disease, independent of shared risk factors. Possible pathways include complex interrelationships between chronic low-grade systemic inflammation as well as shared risk factors such as age and smoking.2

Approximately 50% of smokers will eventually develop COPD,4 and an association between CRP levels and pack-years of smoking is reported in patients with mild to moderate COPD. In contrast, no relationship could be identified between CRP levels and likelihood of survival in patients with moderate to very severe COPD.5, 6 However, following smoking cessation, it is not clear how long it may take for CRP levels to normalise, but it is suggested that a decrease in CRP after smoking cessation might be a useful indicator of a decreased risk of COPD.7

Within this SCAPIS analysis, we aim to focus on the association between systemic inflammation, clinical symptoms and smoking habits in COPD patients, in comparison with never-smokers and ex-smokers with normal lung function. Additionally, comparisons of symptoms and systemic inflammation in individuals with smoke-induced COPD and never-smokers with obstructive lung function impairment will be performed.

The study is proposed as an analysis of the Swedish CArdioPulmonary bioImage Study (SCAPIS), comprising 30,000 subjects aged 50 to 64 years.8, 9 All subjects have answered an extensive respiratory questionnaire, including items about smoking habits and respiratory symptoms. For these analyses, smoking history will be defined as never-smokers, current smokers and ex-smokers, and total cumulative smoking burden will be defined as the number of pack-years. For the purpose of this study, SCAPIS core analyses of high-sensitive CRP (hs-CRP) will be employed. Dynamic spirometry, including forced expiratory volume in one second (FEV1) and forced vital capacity (FVC), measured 15 minutes following an inhalation of 400 µg of salbutamol using a nose clamp, with the subject in sitting position. Gas diffusing capacity (DLco) has been measured using a single breath carbon monoxide diffusion test. All measurements were performed using a Jaeger Master Screen PFT, Germany.

Based on previous Swedish epidemiological data, we estimate a COPD prevalence of around 10% in the selected study population10. Recently, it has also become evident that COPD is more prevalent among never-smokers than previously known, in several studies estimated to about 20% of all COPD patients.11-13

COPD will be defined according to GOLD criteria (http://www.goldcopd.org) with a fixed ratio of FEV1/FVC <0.7 as well as employing the LLN criterion. COPD severity will be spirometrically defined according to GOLD stage 1-4 and the clinical phenotype according to GOLD A-D, based on the questionnaire and mMRC data. However, given the age interval of 50-64 years and a population-based cohort, very few individuals with GOLD 3-4 and C+D are expected.

We will assess the association between systemic inflammation, in terms of hs-CRP, in COPD patients in relation to symptoms and smoking habits, in comparison to control groups – never-smokers and smokers with normal lung function. The relative importance of symptoms and smoking history will be analysed, along with a simple estimate of CT-based diagnose of emphysema retrieved from the eCRF and self-reported cardiovascular disease.

Significance/Rationale

Whilst there is evidence for a systemic inflammation in COPD, inflammatory data from population-based studies, comprising mainly patients with mild COPD, are scarce. Hence, the size and the comprehensive protocol of the SCAPIS study will provide a unique opportunity to evaluate systemic inflammation early in the disease process and relate these findings to smoking habits in well-characterised study groups.

Population and Required Data Variables

The population will be divided into subjects with COPD and two control groups: never-smokers and smokers with normal lung function.

Key variables:

- Spirometric diagnose of COPD based on GOLD as well as LLN criteria and clinical phenotype (based on questionnaire and mMRC data)
- Smoking history
- hsCRP
- Diagnose of emphysema (CT-based variable)
- Self-reported cardiovascular disease

Limitations and Challenges

The present analyses will be performed based solemnly on data from the SCAPIS core protocol. Whilst SCAPIS is one of the largest population-based studies and will give good indications of associations, one disadvantage of SCAPIS is the narrow age-interval. Possible strengths in this case are the possibility to add the CT-based definitions of emphysema, based on the simple classifications in the eCRF, and to include self-reported data on cardiovascular disease.

TRF Authors

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K1. A novel prediction tool using traditional risk factors to predict presence of subclinical atherosclerosis

Objectives

To derivate and validate a novel prediction model to predict presence of subclinical atherosclerosis and compare it with traditional risk score, such as SCORE and Framingham risk score.

Description of Analysis

In primary prevention the use of risk assessment with the Framingham risk score or ESC SCORE is recommended. These scores assess the 10 year risk of cardiovascular death. However cardiovascular death can be due to several conditions, such as atherosclerotic disease, but also sudden death due to heart failure, cardiomyopathy, cerebral thromboembolism etc, and the reason for the underlying cause of death is often uncertain.

Thus, a score or prediction model for having subclinical atherosclerosis may be more useful and indicate the need for more specific prevention measures.

In the present study, we will use the state-of-the-art methods to develop and internally validate a prediction model/score to identify patients with subclinical atherosclerosis. The weight of each variable will be presented. We will also compare this prediction model with SCORE and Framingham risk score, although acknowledging that these scores were not developed for this purpose.

Significance/Rationale

A prediction model for having subclinical atherosclerosis may be more useful than scores for 10-year risk of cardiovascular death and indicate the need for more specific prevention measures. Such a prediction-model can then be tested in trials examining the effect of drugs, such as lipid lowering therapies.

Population and Required Data Variables

Sample
Entire SCAPIS cohort

Candidate predictors
TBD: Traditional risk factors easily obtained by practicing physician and also often available in studies and trials to test external validity.
A prediction model based on all available questionnaire data, body weight and blood pressure may also be considered.

Outcome
Presence of atherosclerotic disease: Definition: TBD
Presence of significant (at least moderate) atherosclerotic disease: Definition: TBD
Presence of coronary artery disease: Definition: TBD

Presence of significant (at least moderate) coronary artery disease: Definition: TBD

Limitations and Challenges

One of the main limitations is the lack of central core lab analyses of CCTA and carotid ultrasound.

TRF authors

Tomas Jernberg

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K5. Accelerometer derived physical activity and atherosclerosis in carotid and coronary arteries

EMBARGO on research hypothesis until 2022-03-15

Objectives

The primary objective is to explore the associations between physical activity pattern and prevalent subclinical atherosclerosis in carotids and coronary arteries. Sub-group analyses will be performed in relation to gender, age, level of sedentary behaviour, level of moderate-to-vigorous physical activity, body mass index, smoking habits and stress.

Description of Analysis

1. First, regression models with the variables indicating present carotid (binary) and coronary (ordinal and binary) atherosclerosis as dependent variables, will be performed with physical activity pattern (including sedentary, light-, moderate-, and vigorous intensity physical activity) as the independent variables. Covariates will include sex, age, visit date, SCAPIS site, socio-economic status, diet, alcohol, smoking, CVD heredity, psychosocial stress and social network.
2. By using isotemporal substitution modelling [1], the estimated effect by reallocating sedentary time to time in physical activity of different intensities on carotid and coronary plaque occurrence will be studied.
3. The above analyses will be performed in the total sample, both with and without adjustment for listed covariates. Further, the fully adjusted analyses will also be performed after stratification for sex (man/woman); age (below median age/above median age); BMI (<25, 25-30, >30); and smokers/ex-smokers/never smokers; fulfilling physical activity guidelines/not fulfilling physical activity guidelines; low time in sedentary/high time in sedentary; low stress/high stress.

Sensitivity analyses will be performed including and excluding participants with exclusion criteria (see below).

Significance/Rationale

Both regular physical activity and limited time spent in sedentary are important to maintain cardiovascular health and decrease cardiovascular disease risk, however, underlying mechanisms remain poorly understood. Previous studies have mainly investigated the association between physical activity/sedentary time and conventional cardio metabolic risk factors. A few studies have assessed measures of subclinical atherosclerosis (such as carotid intima-media thickness and/or plaque), however, with inconsistent findings [2-7]. This is mainly due to small sample sizes [2, 4, 7] and weak measurements of the physical activity pattern (through self-report) [5-7]. Moreover, relevant sub-group analyses are limited in number. No study has previously examined the association between objectively assessed physical activity and subclinical atherosclerosis assessed by coronary computed tomography angiography in a large random sample from a general population.

Understanding the association between different aspects of objectively assessed physical activity (light-, moderate-, and –vigorous intensity) and sedentary behaviour (total time and time in prolonged sedentary behaviour) with subclinical measures of atherosclerosis in the carotids and coronaries, respectively, in a large sample of middle-aged men and women, would add significant knowledge to current understanding and may have important clinical application for counselling and tailored preventive interventions in the future.

Population and Required Data Variables

Sample: All subjects with valid accelerometer data for at least 4 days, data for the atherosclerosis variables specified below and data for the covariates/stratification variables.

Exclusion criteria: Participants with previous cardiovascular disease and angina symptoms (self-reported).

Plaque variables (Dependent variables):
Coronary plaque;

- Any signs of CAD
- Duke risk score score (≥2) [8]
- Segment involvement score (SIS) [8, 9]
- CACS

Carotis plaque

- ≥1
- ≥2

Accelerometer variables:
- Sedentary (time in and % of wear time)
- Light intensity physical activity (time in and % of wear time)
- Moderate intensity physical activity (time in and % of wear time)
- Vigorous intensity physical activity (time in and % of wear time)
- Total wear time
- Valid days
- % weekend days
- Prolonged sedentary time (>20 min of uninterrupted sedentary behaviour)

Covariates and Stratification variables:
- Sex
- Age
- Visit date
- SCAPIS site
- CVD heredity
- Postal code (or similar to study urban vs. rural area)
- Socio-economic status (Educational level, income)
- Economic buffer
- Working / Retirement status

- Psychosocial stress
- Social network
- Smoking
- Diet
- Alcohol
- BMI
- Medical history (Body mass at 20 yrs, Chronic diseases, Performance, Parental medical history)

Stratification variables
- Sex (man/woman)
- Age (below median age/above median age)
- BMI (<25, 25-30, >30)
- Smokers/ex-smokers/never smokers
- Fulfilling physical activity guidelines/not fulfilling physical activity guidelines
- Low time in sedentary/high time in sedentary
- Low stress/high stress.

Limitations and Challenges

Limitations include the inability of the accelerometer to differentiate between sitting and standing as well as the automated wear time estimation used, as low counts during 60 minutes may be common in this age-group. In addition, caution must be applied when extrapolating the presented data to men and women, outside the ages of the study participants.

TRF authors

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K8:1. Atherosclerosis in individuals with prediabetes and diabetes compared to normoglycemic individuals

EMBARGO on research hypothesis until 2022-03-11

Objectives

To describe the prevalence and characteristics of atherosclerosis in three arterial beds (coronary, carotid and peripheral arteries) in individuals with prediabetes and diabetes compared to normoglycemic individuals

Description of Analysis

Primary analyses

1. Coronary artery stenoses will be compared between different categories of glycemia
2. Carotid artery plaques will be compared between different categories of glycemia
3. The ankle-brachial index will be compared between different categories of glycemia

Secondary analyses

1. Coronary artery stenoses will be compared to HbA1c
2. Carotid artery plaques will be compared to HbA1c
3. The ankle-brachial index will be compared to HbA1c
4. Coronary artery stenoses will be compared to diabetes duration
5. Carotid artery plaques will be compared to diabetes duration
6. The ankle-brachial index will be compared to diabetes duration

Sub-group analyses

1. The primary analyses described above will be compared between men and women
2. The primary analyses described above will be compared between individuals with and without known coronary artery disease/symptoms compatible with coronary artery disease

Significance/Rationale

Globally cardiovascular disease remains the leading cause of death. Patients with type 2 diabetes have two to four times greater risk of death and cardiovascular events than the general population (1). Type 2 diabetes is usually preceded by a prediabetic state, characterized by elevated levels of blood glucose i.e. impaired fasting glucose or impaired glucose tolerance, which both entail an elevated risk for cardiovascular disease (2). However, the relationship between prediabetes and asymptomatic atherosclerosis is not as well investigated. Understanding the characteristics of atherosclerosis in people with different stages of prediabetes and diabetes compared to normoglycemic individuals is potentially useful for tailored preventive interventions in the future. For type 2 diabetes patients with known

cardiovascular disease, treatment with a SGLT2 inhibitor or a GLP1 receptor agonist is recommended, because it decreases the risk for future cardiovascular events (3). It is debated if individuals without a previous cardiovascular event have the same protective effect of those drugs. We therefore aim to investigate if asymptomatic atherosclerosis is found in individuals with diabetes and prediabetes. This will help to decide which patients have the most benefit of the medications named above. A strength of our study is that we are able to investigate atherosclerosis in three arterial beds of the same subjects, e.g. the coronary, carotid and peripheral arteries.

Population and Required Data Variables

Sample and sample size consideration

All individuals from all centers will be included. From the interim analyses we anticipate that we will have 2400 subjects with type 2 diabetes and 4200 with impaired fasting glucose in the entire SCAPIS study population.¨

Outcomes

1. Coronary artery variables
    A. *Duke prognostic CAD index modified for SCAPIS*
        0. All segments healthy;
        1. <50% stenosis in one or more segments;
        2. ≥2 stenoses 1-50% (including 1 artery with proximal disease (segment 1, 5, 6 or 11) or 1 segment with 51-100% stenosis);
        3. 2 stenoses 51% to 100%;
        4. 3 stenoses 51% to 100% or 2 stenoses 51-100% with proximal left anterior descending (segment 5 or 6)
        5. 3 vessel disease 51-100% with proximal left anterior descending (segment 5 or 6);
        6. left main stenosis 51-100% (segment 5).

Patients will be assigned to the highest disease category. Calcium blooming equals 1-49% stenosis.

    B. *Segment involvement score*

The segment involvement score is calculated as the total number of coronary artery segments exhibiting plaque, irrespective of the degree of luminal stenosis within each segment (minimum 0; maximum 17 since segment 16/18 are mutually exclusive).

    C. *Coronary calcium score*

2. Carotid artery variable

Plaque in none, one carotid or two carotids.

3. Peripheral artery variable

Ankle-brachial index (ABI), measured for each ankle as the highest of the pressures in each A. dorsalis pedis or A. tibialis posterior (the numerator/ankle) over the average of the two supine brachial blood pressures in the arm with the highest blood pressures (the denominator/arm). One ABI value per ankle is obtained.

Exposures

1. Categories of glycemia
    1. Known diabetes: the study subject is diagnosed with diabetes before study start
    2. Screening detected diabetes: diabetic blood glucose levels measured in SCAPIS (either HbA1c ≥48 and/or fasting glucose ≥7.0 at both measurements)
    3. Screening detected prediabetes: impaired fasting glucose (6.1-6.9) and/or intermediate hyperglycemia (HbA1c 42-47) and not included in category 1 or 2
    4. Normoglycemia: not included in category 1–3
2. HbA1c
3. Diabetes duration

Confounders

1. Socioeconomic status (highest education, vocation)
2. Tobacco habits (current dose, pack-years, stop date if stopped)
3. History of cardiovascular diseases (coronary disease, heart failure, valvular disease, atrial fibrillation, stroke, peripheral artery disease)
4. Body mass index, waist and hip circumference
5. Systolic and diastolic blood pressures
6. Cholesterol, LDL, HDL, TG, glucose, creatinine
7. Heredity for cardiovascular diseases and its risk factors
8. Physical activity (sedentary time, LIPA, MVPA)
9. Medication

Limitations and Challenges

Prediabetes is defined as impaired fasting glucose, impaired glucose tolerance and/or intermediate hyperglycemia (=HbA1c 42-47). An oral glucose tolerance test to diagnos impaired glucose tolerance was not conducted at all study sites (only Gothenburg and Umeå). Our definition of prediabetes using impaired fasting glucose and intermediate hyperglycemia will therefore be incomplete.

TRF authors

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K8:2. Dyslipidemia, prevalence and characteristics of atherosclerosis

Objectives

To describe and compare the atherosclerotic burden in individuals with different levels of blood lipids and lipid lowering therapies. Further, to assess the lipid distribution in relation to comorbidities, lipid lowering therapies and treatment targets.

Description of Analysis

Primary analyses
Degree of coronary artery stenoses and calcification will be related to different lipid levels
Degree of carotid artery plaques will be related to different lipid levels
The ankle-brachial index will be related to different lipid levels

Secondary analyses
Degree of coronary artery stenoses and calcification will be related to lipid lowering therapy.
Degree of carotid artery plaques will be related to lipid lowering therapy.
The ankle-brachial index will be related to lipid lowering therapy.
Compare relative importance of different measures of lipids and atherosclerotic burden overall and in different patient strata (i.e. in diabetes, obesity etc.)
Investigate association between premature atherosclerotic disease in first degree relatives; i.e. the burden of atherosclerosis in relation to lipid levels.

Sub-group analyses
The primary analyses described above will be compared between men and women and in different age strata
The primary analyses described above will be compared between individuals with and without known diabetes mellitus
Of patients with lipid lowering therapy, describe coronary artery atherosclerosis composition
Of patients with indication for lipid lowering therapy, proportion of patients on treatment and at target

Exposure variables to be assessed:
LDL-strata: continuous/Z-scores, quartiles, clinical thresholds
Non-HDL: continuous/Z-scores, quartiles, clinical thresholds
Compare direct vs indirect (Friedewalds equation) LDL vs Martin/Hopkins method(1) vs SCAPIS revised Friedewald method
Statin vs non statin
Triglycerides: continuous/Z-scores, quartiles, clinical thresholds

Significance/Rationale

Cardiovascular disease is the leading cause of death. One of the causal factors for the development of cardiovascular disease in general and atherosclerotic disease in particular, is atherogenic lipid particles.(2) These particles include LDL-cholesterol. lipoprotein (a), remnant cholesterol, all characterized by the inclusion of a single protein component, the apolipoprotein B (apoB). ApoB also constitutes the means by which atherogenic particles enters the vascular wall, a process that initiates atheromatosis and atherosclerosis. In parallel with increasing levels of atherogenic lipids, there is a development of atherosclerotic and atherosclerotic diseases, such as myocardial infarction, stroke and peripheral artery disease. In the population, levels of atherogenic particles and adverse cardiovascular outcomes are well described, however, less is known on subclinical and asymptomatic atherosclerosis. In particular, the composition of atherosclerosis is not well investigated in relation to atherogenic lipids. Further, less is known on plaque transformation in individuals with ongoing lipid lowering therapy as well as lipid target achievement in the general population. Characterization of atherogenic lipids in the population in relation to atherosclerotic burden may add knowledge on future risk stratification and intensity of intervention in subclinical disease.

Population and Required Data Variables

Sample and sample size consideration

All individuals from all centers will be included.

Outcomes

1. Coronary artery variables

A. Duke prognostic CAD index modified for SCAPIS

0) All segments healthy;
1) <50% stenosis in one or more segments;
2) ≥2 stenoses 1-50% (including 1 artery with proximal disease (segment 1, 5, 6 or 11) or 1 segment with 51-100% stenosis);
3) 2 stenoses 51% to 100%;
4) 3 stenoses 51% to 100% or 2 stenoses 51-100% with proximal left anterior descending (segment 5 or 6)
5) 3 vessel disease 51-100% with proximal left anterior descending (segment 5 or 6);
6) left main stenosis 51-100% (segment 5).

Patients will be assigned to the highest disease category. Calcium blooming equals 1-49% stenosis.

B. Segment involvement score

The segment involvement score is calculated as the total number of coronary artery segments exhibiting plaque, irrespective of the degree of luminal stenosis within each segment (minimum 0; maximum 17 since segment 16/18 are mutually exclusive).

C. Stenosis description: mixed plaque, calcified plaque.

D. Coronary calcium score

2. Carotid artery variable

Plaque in none, one carotid or two carotids. If available, higher granularity.

3. Peripheral artery variable

Ankle-brachial index (ABI), measured for each ankle as the highest of the pressures in each A. dorsalis pedis or A. tibialis posterior (the numerator/ankle) over the average of the two supine brachial blood pressures in the arm with the highest blood pressures (the denominator/arm). One ABI value per ankle is obtained.

Confounders

Socioeconomic status (highest education)
Tobacco habits (current dose, pack-years, stop date if stopped)
History of cardiovascular diseases (coronary artery disease, heart failure, valvular disease, atrial fibrillation, stroke, peripheral artery disease)
Body mass index, waist and hip circumference
Systolic and diastolic blood pressures, a diagnosis of hypertension
Cholesterol, LDL, HDL, TG, non-HDL, HbA1c, glucose, creatinine
Heredity for cardiovascular diseases and its risk factors
Physical activity (sedentary time, LIPA, MVPA)
Medication
Diabetes mellitus

Limitations and Challenges

Lipid fractions are measured with different methods at different laboratories in the study. In standardized assessments by EQUALIS, for example LDL-C values differ up to 1 mmol/L between hospital labs in Sweden when analysing the same reference sample. This can be accounted for by including some data from EQUALIS to harmonize data. The difference in laboratory measures may also be explored as a study outcome given risk for under/overtreatment and risk for future CVD if undertreatment is common. Data on PAD and carotid atherosclerosis are not as granular as coronary atherosclerosis.
The LDL-C was measured according to the local routine at each SCAPIS site; i.e. some sites measured LDL-C directly whereas others have calculated LDL-C according to the Friedewald Formula.

TRF authors

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K9. Is metabolically healthy obesity free from atherosclerosis in the coronary and carotid arteries?

EMBARGO on research hypothesis until 2022-03-14

Objectives

The primary objective is to evaluate if metabolically healthy obese (MHO) subjects have more or similar amount of atherosclerosis compared to metabolically healthy normal-weight subjects, and if there is a difference between coronary and carotid atherosclerosis. Also the ankle-brachial index (ABI) will be evaluated in the same fashion.

Secondary objectives:

1. To evaluate if metabolically healthy overweight subjects have more or similar amount of atherosclerosis compared to metabolically healthy normal-weight subjects and if there is a difference between coronary and carotid atherosclerosis. Also the ankle-brachial index (ABI) will be evaluated in the same fashion.
2. To evaluate if metabolically abnormal normal-weight individuals have more or similar amount of atherosclerosis compared to metabolically healthy normal-weight subjects and if there is a difference between coronary and carotid atherosclerosis. Also the ankle-brachial index (ABI) will be evaluated in the same fashion.
3. To evaluate how many metabolic disturbances (and which ones) that are needed in the obese (and overweight, and normal-weight) subjects on order to see an increased atherosclerotic burden compared to metabolically healthy normal-weight subjects.
4. To evaluate if there is a sex-difference in the relationships described above.

Description of Analysis

The range of BMI could be divided into normal-weight (BMI<25), overweight (BMI 25-30) and obese (BMI>30). Any subject could also be classified as having the metabolic syndrome (MetS, based on the consensus NCEP-criteria) Thus, using a classification based on these two dimensions would identify a group of subjects being obese without MetS.

In this analysis, a composite score of atherosclerotic burden in the coronary arteries (modified Duke prognostic CAD index, ordinal 0, 1-2, >2), number of carotid arteries with plaque (ordinal; 0,1,2) and ABI<0.9 (binary) will be used as outcomes.

Analysis:

Primary analysis: Investigate if subjects with MHO have more atherosclerosis compared to normal-weight subjects without MetS. Co-variates should be age sex, LDL-cholesterol and life-style factors (alcohol intake, socioeconomic status, smoking and physical activity). Investigate if there is a difference between coronary, carotid atherosclerosis and ABI. Investigate if there is a sex-difference in these findings.

Secondary analysis:

1. Investigate if metabolically healthy subjects with overweight have more atherosclerosis compared to normal-weight subjects without MetS. Co-variates should be age sex, LDL-cholesterol and life-style factors (alcohol intake, socioeconomic status, smoking and physical activity). Investigate if there is a difference between coronary, carotid atherosclerosis and ABI. Investigate if there is a sex-difference in these findings.
2. Investigate if normal-weight subjects with MetS have more atherosclerosis compared to normal-weight subjects without MetS. Co-variates should be age sex, LDL-cholesterol and life-style factors (alcohol intake, socioeconomic status, smoking and physical activity). Investigate if there is a difference between coronary, carotid atherosclerosis and ABI. Investigate if there is a sex-difference in these findings.
3. Investigate how many and which of the 5 MetS components that has to be fulfilled in order to see an increase in coronary, carotid atherosclerosis and ABI in the obese, overweight and normal-weight groups. Investigate if there is a sex-difference in these findings.

Significance/Rationale

There is a debate in the literature if MHO (and metabolically healthy overweight) is a harmless condition or not. We have previously shown in several studies that it is not harmless, although less harmful than if being obese with MetS. It is a major health problem if physicians tell obese subjects without MetS that it is fine to be obese!

Population and Required Data Variables

Total population to be used. The variables required are given in the analysis section.

Limitations and Challenges

This is a cross-sectional study without any hard outcomes.
It might be that there are too few subjects being normal-weight and having MetS to evaluate this secondary analysis in a meaningful fashion.

TRF authors

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K11. Associations between food intake and presence of coronary artery plaques in middle-aged men and women

Objectives

To describe associations between food intake using a healthy food intake index and the presence of coronary artery plaque.

Rationale

Insufficient intake of vegetables and fruits is one of the top ten determinants of global burden of disease in Western societies (1). In longitudinal studies, Mediterranean diet has found to be associated with lower risk of cardiovascular morbidity as well as mortality (2-4). Using isotope ratio mass spectrometry, it has also been shown that diet is reflected in atherosclerotic plaque components associated with its vulnerability. Interestingly marine-derived food is associated with human carotid plaque stability (5).

Coronary artery plaque is a critical feature of cardiovascular disease risk. In the Swedish CArdioPulmonary BioImage Study (SCAPIS) data on habitual food intake has been collected by the validated MiniMeal Questionnaire, MiniMeal-Q (6, 7) and the presence of coronary artery plaques have been analysed in great detail. A pilot study of SCAPIS found an association between a healthy food index and coronary artery calcium (CAC) (8). Healthy Food Index (HFI) was associated with having no CAC. Thus, it would be important to analyse the association between food intake and coronary artery plaque in the larger SCAPIS study and identify important subgroups in which HFI can be of interest.

Population and Required Data Variables

Sample

The entire SCAPIS cohort.

Sub-sample

1. Participants with / without known coronary artery disease or symptoms compatible with coronary artery disease.
2. Men / women
3. Age groups 50-55 / 55-60 / 60-65

Main exposures

Self-reported dietary intake data from MiniMeal-Q.

Outcome

The primary outcome will be coronary artery disease.

Confounders

- Socioeconomic status (highest education, vocation)
- Tobacco habits (current dose, pack-years, stop date if stopped)
- Alcohol habits (weekly dose)
- History of cardiovascular diseases (coronary disease, heart failure, valvular disease, atrial fibrillation, stroke, peripheral artery disease)
- Known risk factors (hypertension, hyperlipidemia)
- Known diabetes
- Known other diseases (pulmonary disease, inflammatory/rheumatic disease)
- Height, weight, body mass index, waist and hip circumference
- Systolic and diastolic blood pressures
- Cholesterol, LDL, HDL, TG, glucose, creatinine.
- Symptoms compatible with coronary disease (chest pain, dyspnea)
- Heredity for cardiovascular diseases and its risk factors
- Stress level (general, work-related, traumatic life events)
- Social network
- Physical activity (sedentary time, LIPA, MVPA)
- Ongoing medications

Analysis plan

The consumption of healthy foods by the participants will be determined with a Healthy Food Index (HFI), an aggregated composite variable constructed from a priori selected food items reported in the MiniMeal-Q. The HFI encompasses the summed consumption frequencies of 17 food items, that represent the 5 food groups: vegetables, fruits, fatty fish, vegetable oil, and nuts. These groups of foods were chosen as indicators of nutritional and healthy food choices. Hence, the HFI allows rating of food intake quality by a single score, on the basis of reported intake of food groups associated with CVD risk.

Descriptive data will be provided as means (SD) or median (IQR).

The HFI will be divided into quartiles (or quintiles) with the lowest quartile (or quintile) as reference. Multivariable Hazards ratio (HR) for differences in coronary artery plaque burden (amount, location, distribution) and other composite variables of coronary artery disease adjusted for a range of variables that may affect the association between HFI and coronary artery plaque including tobacco use, alcohol consumption, socioeconomic status, physical activity level and cardiovascular- and diabetes disease related risk factors.

Limitations and Challenges

- There might be other indexes that could reflex the food intake with other perspectives, for example an unhealthy food index.
- Our analysis will only be cross-sectional and descriptive, not allowing to uncover underlying mechanisms, but only associations.
- The food intake data may suffer from general as well as specific misreporting by the participants.

• Possible selection bias of the subjects if only those caring or informed about their health participated in the study, but could be compensated for (9).
• There is a delay in time between the diet of the subjects and the formation of the plaques that can take several decades (10) patients might change their dietary patterns over time.
• Calcium score might be hard to interpret as the role of calcification in the disease is still uncertain.
• There might be an inter-site/interobserver variability in the quantification of the coronary disease, but this will be described in the SCAPIS main paper 1.

TRF authors

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K13. Social differences in relative importance of risk factor pattern for coronary artery atherosclerosis

Objectives

To analyse 1) how measures of socioeconomic position (SEP) and socioeconomic status (SES) are associated with presence/absence and pattern of coronary atherosclerosis 2) to which extent modifiable risk factors explain differences in coronary atherosclerosis between socioeconomic strata 3) the relative importance of modifiable risk factors for the presence/absence and pattern of coronary atherosclerosis in participants of different SES groups.

Significance/Rationale

Low SES has long been associated with a higher risk of coronary events (1,2), and with coronary artery disease (CAD) (3-5), but the mechanisms of this association are not fully understood and have therefore to be clarified. There is no single best indicator of SES, each indicator of SES emphasizes a particular aspect of social stratification, which may be more or less relevant to different health outcomes (6). Further, the extent to which lifestyle factors contribute to social differences in CAD has not been reliably determined. The aim of the present study, therefore, was to investigate the potential relationship between measures of SEP and coronary atherosclerosis, and to which extent this is determined by modifiable risk factors.

Population and Required Data Variables

Sample

The subsample of the entire SCAPIS cohort that has done coronary computed tomography angiography.

Subsample

Analyses will be done using the entire sample but interactions will be tested for the following sub-groups:

1. Men / women
2. Age 50-54, 55-59, 60-64 years
3. With / without known coronary artery disease/symptoms compatible with coronary artery disease

Outcomes

Coronary artery variables

1. Duke prognostic CAD index modified for SCAPIS
2. Segment involvement score
3. Coronary calcium score – level of calcification, established risk score

Exposures

1. Years of education
2. Occupational class based on longest held occupation

3. Housing conditions (owner of house, owner of apartment, rented accommodation)
4. Difficulties in raising SEK 20,000 OR difficulties in paying bills (last 12 months)

Covariates

1. Cholesterol, LDL, HDL, TG, glucose, creatinine
2. Systolic and diastolic blood pressure
3. Hypertension (known/treated or ≥140/90)
4. Tobacco use (current dose, pack-years, stop date if stopped)
5. Body mass index, waist and hip circumference
6. Diabetes (known or diagnosed at SCAPIS examination)
7. History of cardiovascular disease (coronary disease, heart failure, valvular disease, atrial fibrillation, stroke, peripheral artery disease)
8. Reproductive history (questionnaire)
9. Menopause (yes/no; menopausal age)
10. Family history of coronary heart disease (any of mother, father, sibling, any of with early disease)
11. Weight at age 20
12. Weight gain since age 20
13. Stress level (home, work-related, life events)
14. Physical activity (sedentary time, LIPA, MVPA)
15. Statins

Data analysis

Descriptive data provided as percentages (n), means (SD) or median (IQR). Outcome data will be analysed using conventional logistic regression and multivariable techniques in order to quantify the influence of major exposures.

An assessment of the relative importance of exposure variables in separate social strata will be done using machine learning (7), which is an application of artificial intelligence that provides systems with the ability to automatically learn and improve from experience without being explicitly programmed. Machine learning implies model building directly from the data, i.e by letting the data speak for themselves, with algorithms equipped with an inherent ability to capture and model complex non-linear relationships and higher-order interactions. We will use random forest (8), a machine learning algorithm that has become a standard tool in medical research, to study relationships, develop prediction models and evaluate the relative importance of various clinical predictors.

Limitations and Challenges

Occupational level (longest held occupation) requires coding of this variable according to SEI (socioeconomic index). (https://www.scb.se/Grupp/Hitta_statistik/Forsta_Statistik/Klassifikationer/_Dokument/SEI-AGG_Eng.pdf)

Traditional regression modelling from theory and subject matter knowledge is prone to bias via subjective preferences and expectations. Some of these limitations will be overcome by using machine-learning methods; however, the acceptance for machine-learning methods may be limited.

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K14. Sex and gender differences in prevalence of atherosclerosis in the coronary, carotid and peripheral arteries, and relative importance of risk factors

Objectives

1) to describe differences regarding prevalence, distribution, type and progression of atherosclerosis in the coronary, carotid and peripheral arteries 2) to examine to which extent risk factors explain differences in atherosclerosis between men and women 3) to examine the relative importance of risk factors for the presence/absence and pattern of atherosclerosis in the coronary, carotid and peripheral arteries in men and women

Significance/Rationale

Even though atherosclerosis, ultimately, is the single most important cause of death in both women and men, women have a 5 to 10 year later onset of major CVD (1). Risk factors are significantly associated with atherosclerosis in both men and women, although some risk factors, notably smoking, has been shown to have a stronger impact on women than in men (2). Differences in risk factors has been shown to explain some of the differences in CVD risk between men and women (3,4), particularly in younger women (5). Although atherosclerosis is known to be more common in men than in women of similar age, almost all information from imaging is derived from clinical populations. Additionally, differences in atherosclerotic events between men and women may be decreasing (6). Therefore, little is known about sex differences in the prevalence of atherosclerosis in the contemporary population, to which extent risk factors explain differences, and of the relative importance of risk factors separately for men and women.

Population and Required Data Variables

Sample

Men and women in the SCAPIS cohort.

Outcomes

1. Visible coronary artery disease (0/1);
2. Any major coronary artery with a >50 % stenosis
3. 1VD, 2VD, 3VD or LM
4. Different scores, such as the DUKE score, segment involvement score and CACS
5. Type of plaques (calcified, non-calcified, mixed)
6. Proximal or distal disease
7. Atherosclerotic plaques in the carotids
8. ABI<0.9

Exposures

1. Age
2. Socioeconomical status (education, income)
3. Marital status – living conditions.
4. Social support, emotional support
5. Country of birth
6. Cigarette smoking (current, prior, pack-years)
7. Alcohol habits
8. Body mass index, waist and hip circumference
9. Weight age 20, weight gain between age 20 and SCAPIS weight
10. Lipids (LDL, HDL, TG)
11. Lipid treatment
12. Plasma glucose, HbA1c
13. Diabetes (known or diagnosed at SCAPIS examination)
14. Diabetes treatment
15. Blood pressure
16. Hypertension (known or ≥140/90)
17. Antihypertensive treatment
18. Kidney function
19. Inflammatory activity (HsCRP)
20. Inflammatory disease
21. Family history of coronary heart disease (any of mother, father, sibling, any of with early disease)
22. Stress level (home, work-related, life events)
23. Physical activity (self-reported and sedentary time, LIPA, MVPA)
24. Diet habits
25. Sleeping disorders
26. Pulmonary disease/function
27. Female health, Reproductive factors

Data analysis

Descriptive data provided as percentages (n), means (SD) or median (IQR). Outcome data will be analysed using conventional logistic regression and multivariable techniques in order to quantify the influence of major exposures.

Mediation analyses will be employed to understand the underlying factors explaining the differences between men and women. An assessment of the relative importance of exposure variables will be done using machine learning (Gradient Boosting Machines and Random Forest) (7), which is an application of artificial intelligence that provides systems with the ability to automatically learn and improve from experience without being explicitly programmed.

Limitations and Challenges

Traditional regression modelling from theory and subject matter knowledge is prone to bias via subjective preferences and expectations. The acceptance for machine-learning methods may be limited.

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B2. A proteomic approach to identify systemic inflammatory changes and other biomarkers in subjects with revised definitions of chronic airflow obstruction and with different respiratory symptoms.

EMBARGO on research hypothesis until 2022-03-14

Objectives

Primary objectives

A) To use proteomics to study if systemic inflammatory changes and other biomarkers differ in subjects with chronic airflow obstruction (CAO) defined as the ratio between forced expiratory volume during the 1st second of exhalation (FEV1) divided by slow vital capacity (SVC)<0.70 as compared to CAO defined as FEV1/forced vital capacity (FVC) <0.70.

B) To analyse whether protein profiles differ between subjects with and without respiratory symptoms (breathlessness, wheezing and chronic bronchitis) when lung function is taken into account.

Description of Analysis

Chronic airflow obstruction (CAO) is usually defined as FEV1/FVC<0.70 according to the current Global Obstructive Lung Disease recommendations 1. Slow vital capacity manoeuvres are used in patients with obstructive disease as vital capacity can be underestimated during forced manoeuvres (FVC), due to dynamic compression of the peripheral airways. Based on SCAPIS pilot data, we reported a large discrepancy between the prevalence of CAO, defined as FEV1/SVC, around 15%, compared with definition by using FEV1/FVC, around 10% 2. Recent data suggest that a ratio of FEV1/SVC<0.7 might be an early sign of mild COPD 3 and it is therefore important to study if systemic inflammatory changes can be seen already in subjects with FEV1/SVC<0.7, despite a normal FEV1/FVC-ratio (>0.7).

Respiratory symptoms are common in the population. Based on interim data from the SCAPIS cohort, about 5% of the population report breathlessness defined as >2 on the mMRC scale 4 and 4.9% report chronic bronchitis (11.7% of subjects with COPD according to spirometry and 4.2% among subjects with FEV1/FVC>0.7). Breathlessness is the cardinal symptom of cardiorespiratory disease and is strongly associated with adverse health outcomes 5. The treatment goal in both asthma and COPD is to preserve lung function and abolish respiratory symptoms 6, 1. The association between lung function impairment and symptom profile is often weak and respiratory symptoms are common also in subjects without respiratory disease. However, more recently, the occurrence of respiratory symptoms in CAO has been identified as an important variable both for disease grading and prognosis 1. Furthermore, in patients with COPD according to spirometry criteria, concomitant respiratory symptoms were associated with higher pulmonary resistance and lower pulmonary reactance as measured by impulse oscillometry system (IOS)7. The

present study will give important information on whether concurrent respiratory symptoms in CAO also have an impact on systemic protein profile.

No power analysis has been performed, as we do not know what would be the expected effect size on different inflammatory proteins. In a recent study in asthmatics, proteomic profiles distinguished controlled and poorly controlled asthma with 23 and 25 subjects in each group 8. With this large cohort, we expect to identify important differences between groups. Furthermore, we do know that the groups to be studied in the main aim are large enough (both based on pilot data and interim data).

Significance/Rationale

The present study can add knowledge that might be of clinical importance if we can identify underlying inflammatory mechanisms in chronic airflow obstruction, employing these revised definitions. This would support that definitions of chronic airflow obstruction should consider slow vital capacity manoeuvres instead of forced vital capacity. If the protein profile in subjects with respiratory symptoms differ independently of lung function impairment, this is an important information on the phenotype at risk for more rapid lung function loss.

Population and Required Data Variables

Population: For objectives 1 and 2, all 5000 with proteomics. For analyses of representativeness of the selected population, data on exposure variables and confounders from the whole SCAPIS cohort (n=30,000).

The outcome variables: 184 proteins

Exposure variables:

A) Chronic airflow obstruction as defined above (spirometry data: FEV1, FVC, SVC).
B) Respiratory symptoms:
   - Wheeze
   - Breathlessness
   - Chronic Bronchitis

Confounders: age, sex, BMI, smoking (never, former, present, unknown), study site, plate, storage time.

For chronic airflow obstruction, further adjustments will also be performed for respiratory symptoms.

For respiratory symptoms, further adjustments will also be performed for lung function (chronic airflow obstruction defined as above and DLCO) and heart disease (defined as ischemic heart disease, heart failure or atrial fibrillation/flutter, Q30).

For sensitivity analyses: Questionnaire data on asthma, COPD and treatment for these diseases (Q30).

Limitations and Challenges

The cross-sectional nature of the study is a limitation.
External cohorts to confirm the findings will be needed if the present cohort would not have a large enough size to be divided into a discovery and validation cohort. If there will be another SCAPIS cohort with proteomics, it will be used as a validity cohort.

TRF authors

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B4. Associations between metabolomic and proteomic markers of CVD-risk and sub-components of the physical activity pattern.

Objectives

The general aim is to assess associations between metabolomic and proteomic markers and subcomponents of the physical activity pattern (PAP). Markers will be treated both as single makers and as clusters of markers. Time spent sedentary, in low-intensity activity (LIPA) and moderate-to-vigorous physical activity (MVPA) will calculated and related to levels of markers of importance for CVD and metabolic diseases.

In explorative analyses, we aim to assess the relation between PAP and CAC score (Agaston score) using identified markers as potential mediators. We will also assess the potential moderating effect of high CAC score on the relations between PAP and markers.

Description of Analysis

Metabolomics: We will use data of 230 metabolites, with emphasis on lipoproteins and fatty acids, analyzed by magnetic resonance spectroscopy by Nightingale Health, Helsingfors, Finland. Proteomics: From Olink the CVD panels II and III (184 unique proteins) are analyzed at SciLifeLab, Solna, Sweden.
Linear regression regression models using the False Discovery Rate to control for multiple testing in discovery will be performed using PAP-components (continuous data) as dependent variable adjusted for age, gender, antropometrics and education to identify influence of potential confounders. After that, cluster analyses will be performed to study relations between subcomponents of PAP and potential pathways, either as principal component analyses or identification of latent classes. Manhattan plots of metabolite associations with PAP-components will be produced, based on the classification of metabolites.

Significance/Rationale

Omics are powerful tools to comprehensively evaluate global metabolic and proteomic signature associated with physical activity and helps to pinpoint the pathways that mediate the health effects of physical activity.

Data from the SCAPIS pilot study [1, 2], showed that time spent sedentary, in low-intensity activity and moderate-to-vigorous activity all affected the risk of having the metabolic syndrome and variables related to glucose regulation. Data is currently lacking in the field of explaining these findings. As physical activity pattern acts via a long range of mechanisms, assessing single potentially important markers may not be sufficient to describe the active pathways.

The use of proteomic and metabolomics markers together with objectively assessed physical activity is very unusual. A few studies have used self-reports [3-5]. Results show physical activity and sedentary leisure time were associated to a long range of markers, but the degree of resolution and details in the activity assessment was very low. One previous study [6] on a limited sample (n=277), based on technically assessed activity data showed that 11 metabolites were related to total activity duration. The relation to time spent sedentary or in MVPA seemed more complex. However, due to the sample size, detailed subgroups analyses could not be performed. There is an urgent need for more detailed knowledge on the specific relations between PAP, proteomic and metabolomics markers.

As the relation between physical activity and mortality seems to be vastly different between individuals with and without manifest CVD and also varying with increasing predicted risk [7], it would be of interest to study relations between PAP and metabolomics and proteomic markers stratified for degree of subclinical vascular disease, such as CAC-score.

Detailing the above mentioned relations will give the possibility to recommend specific physical activity for the prevention and perhaps adjuvant treatment. SCAPIS is one of the few studies able to answer these questions.

Population and Required Data Variables

Variables needed are:

- Sociodemographics (detailed list to follow)
- Medical history
- Atropometrics and blood pressure data
- Laboratory data
- PAP-components
- Olink CVD II and III panel data
- Nightingale chip data
- CAC score

Limitations and Challenges

As data are cross-sectional, no causal relations can be identified. Data on proteomic and metabolomics markers has not previously been performed in such large cohorts and therefore the analytic procedure is not fully known.

TRF authors

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B9. Plasma proteomic and metabolomic profiling of coronary and carotid atherosclerosis

EMBARGO on research hypothesis until 2022-03-15

Objectives

The overall aim of this study is to identify circulating metabolomic and proteomic biomarkers of coronary and carotid atherosclerosis to a) elucidate mechanisms and to b) improve prediction models. A secondary aim is to assess whether the proteomic and metabolomic profile differs between coronary and carotid atherosclerosis.

Background

The underlying pathophysiology of atherosclerosis is still not completely understood. Carotid and coronary atherosclerosis share common risk factors such as diabetes mellitus, hypertension, smoking, older age, high triglyceride levels and low high-density lipoprotein cholesterol levels.(1) Identification of changes of the molecular profile of asymptomatic atherosclerosis in different vascular beds can aid in the understanding of the pathophysiology and contribute to prediction. Novel technologies have enabled the measurement of a large number of molecules in biological samples, such as proteins and metabolites. A recent study among 3,867 participants from the Multi-Ethnic Study of Atherosclerosis (MESA), with replication among 3,569 participants from the Rotterdam and LOLIPOP studies used nuclear magnetic resonance spectroscopy (NMR) to study the metabolomic profile of coronary artery calcium and intima media thickness.(2) Overall, 30 metabolites were found associated with atherosclerosis in either or both arterial beds. These associations were substantially attenuated after adjustment for conventional cardiovascular risk factors. Metabolite associations with atherosclerosis were largely consistent between the two arterial beds.

In SCAPIS-OMICS, 5,000 plasma samples from the six different centers have been analysed using NMR by Nightingale Health in Finland providing ~220 metabolites. Plasma samples have also been analysed with the Olink Proseek CVD panel II and III, comprising 184 cardiovascular candidate proteins. These measurements allows for a detailed investigation of the differences and similarities of the plasma proteomic and metabolomics profile of coronary and carotid atherosclerosis.

Data

We will perform the main analysis in the subpopulation of 5,000 individuals (SCAPIS-Omics) with proteomics/metabolomics measurements. We will validate our findings in the SCAPIS-Pilot study (n=1,000).

Outcome definition

Coronary atherosclerosis

In the initial analysis, coronary atherosclerosis will be defined as a binary variable (presence/absence). In follow-up analysis, levels of metabolites and proteins will be

described across the different categories of the modified Duke index as described in (3).

Carotid atherosclerosis

In the initial analysis, carotid atherosclerosis will be defined as a binary variable (presence/absence). In follow-up analysis, levels of metabolites and proteins will be described across the different levels of carotid atherosclerosis such as number of vessels affected (0-2).

Biomarkers

184 cardiovascular candidate proteins (Olink CVD II+III) undergoing standard quality control (per-protein missingness <15% samples, per-individual <5% of proteins). Normalized for plate. Use on log2scale.

Around 220 metabolites and metabolite ratios from NMR analysis undergoing quality control. Normalized for batch. Use on log2scale.

Description of Analysis

I. Identification of biomarkers for potential causal pathways

Table 1. Analytical dataset setup

ID	Atherosc l	Location	Biomarker_1	Biomarker_n	Age	Sex	Study_ Center
1	1	Carotid	2.5	6.7	51	F	Sthlm
1	1	Coronary	2.5	6.7	51	F	Sthlm
2	0	Carotid	5.9	1.2	60	M	Gbg
2	1	Coronary	5.9	1.2	60	M	Gbg
3	0	Carotid	3.3	5.4	64	F	Malmö
3	0	Coronary	3.3	5.4	64	F	Malmö

We will assess the association of each protein/metabolite with coronary atherosclerosis and carotid atherosclerosis jointly in a series of logistic regression models, one for each biomarker. We will set up the dataset as described in Table 1. Logistic regression with the binary atherosclerosis variable as the dependent variable, and the location (coronary/carotid), biomarker, sex, age and study center as independent variables, adding a correction for multiple rows per individual with a cluster robust sandwich estimator will be assessed. Importantly, an interaction variable for biomarker x location will be included.

The command line for the first candidate biomarker in the Table 1 (Stata):

logit Atherosclerosis Biomarker_1 Location Biomarker_1# Location age sex study_center, vce(cluster ID)

From this model we will be able to extract a) Association (odds ratio, OR, per doubling of biomarker) with coronary atherosclerosis b) Association with carotid atherosclerosis c) Test if there is difference in effect size for coronary and carotid atherosclerosis d) Association of each biomarker on presence of atherosclerosis in any location if c) is non-significant. We will use a 5% FDR to correct for multiple testing.

In follow-up analysis we will add

1. further covariate adjustment (BMI, diabetes, LDL-cholesterol, smoking, blood pressure, kidney function, alcohol intake)
2. more refined outcome phenotype (e.g. modified Duke index)
3. test of linearity (spline models)
4. interaction tests for age and sex
5. validation in SCAPIS-Pilot

II. Prediction of coronary and carotid atherosclerosis from plasma proteomics and metabolomics.

Here we will apply suitable machine learning methods such as the LASSO ((least absolute shrinkage and selection operator) method to select those proteins and metabolites that together provides the best prediction of presence or absence of atherosclerosis in the two vascular beds. We will include the variables from the Framingham Risk Score as well as the study center in the basic model. Thereafter the LASSO model with cross-validation will be used to select the best combination of variables to include in the prediction model. We will validate the model in SCAPIS Pilot and present the C-statistics (AUC) and calibration metrics for detecting atherosclerosis for the basic model and for the new model and also for detecting severe coronary atherosclerosis (more than 50% stenosis of at least one segment).

TRF authors

Tove Fall, Anders Gummesson, Gunnar Engström

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L5. Insomnia, sleep duration and cardiometabolic risk in a middle-aged population (SCAPIS)

Objectives

Primary objective: To investigate the influence of insomnia with or without short sleep duration on cardiovascular/metabolic risk in the SCAPIS cohort

Secondary objectives: To investigate the association between sleep duration and cardiovascular/metabolic risk in the SCAPIS cohort

Description of Analysis

In adults, 7 or more hours of sleep per night on a regular basis is important to promote optimal health.(1) Short sleep time has a substantial influence on cardiovascular, metabolic, mental and immunologic health as well as human performance. Short sleep time can be a consequence of lifestyle habits, environmental factors, or the presence of a sleep disorder, such as insomnia. Regardless of the underlying cause, short duration of sleep seems to be associated with increased morbidity and mortality.(2)

In the current protocol, we plan to run a cross-sectional analysis on all participants from the SCAPIS main cohort. Self-reported insomnia and sleep length (Covered in Core Sleep Questionnaire) will be used to quantify insomnia and habitual sleep time. The parameters will be used as either a continuous variable or a categorical variable. Furthermore, Self-reported sleep apnea, snoring and witnessed apnea will be used to classify sleep disordered breathing. The frequency of insomnia/short sleep time will be analysed according to anthropometric variables and comorbidities. Factors to be probed in the analysis include age, gender, ethnicity, body composition (BMI, waist hip ratio), education level/socio-economic status, life style factors (smoking, alcohol intake, exercise habits), daytime sleepiness and comorbidities (e.g. mental disorders). The association between short sleep time/insomnia and cardiovascular/metabolic risk factors (e.g. hypertension, coronary, carotid and peripheral artery disease, diabetes mellitus, metabolic syndrome, blood pressure, lipids, HbA1c, reduced lung function, metabolomic and proteomic markers) data will be systematically analysed controlling various confounders.

Significance/Rationale

Regardless of the underlying cause, short duration of sleep seems to be associated with increased morbidity and mortality(2). Although emerging evidence suggests a link between short sleep times and diabetes mellitus, obesity, and cardiovascular disorders, a causal relationship between short sleep duration and cardiovascular/metabolic risk is not confirmed (3).

Insomnia is the most prevalent sleep disorder and is associated with impaired quality of life, occupational dissatisfaction, and other healthcare-related outcomes. Approximately, 20%–30% of the general population experience insomnia symptoms, while 8%–15% experience chronic insomnia.(4) Few studies have addressed the

association between insomnia and cardiometabolic health. A causal relationship between insomnia disorder and cardiovascular/metabolic risk is not fully established.(5)

Accumulating evidence has suggested that insomnia with short sleep duration may represent a more biologically severe phenotype associated with significant morbidity and mortality (6). However, large population-based studies with adequately controlled comorbid conditions are lacking. The SCAPIS cohort with its large sample size including a complete mapping of cardiovascular/metabolic risk factors including markers of subclinical atherosclerosis provides a unique opportunity for this purpose (7). In the current analysis, we aim to investigate relationships between short sleep duration, insomnia symptoms and subclinical atherosclerosis as well as atherosclerosis risk factors in a middle aged population.

Population and Required Data Variables

Population:
All SCAPIS participants from six study sites.

Required variables:
Core sleep questionnaire (136-144)
Anthropometric data (age, sex, ethnicity, BMI, waist/hip circumference, education, marital status)
Life style factors (smoking, daily exercise [accelerometer assessed time spent sedentary, moderate-to-vigorous intensity physical activity], dietary, living conditions)
Cardio-metabolic comorbidities (core questionnaire nr 30 and sub questions)
Psychiatric comorbidities (question 116 and sub questions)
Blood pressure including ABI
Accellerometric data
Biochemistry variables
Variables denoting imaging of carotid and coronary arteries (and fat if available)
Metabolomics data
Proteomics data

Limitations and Challenges

The current analysis will not provide a causal link between short sleep time/insomnia and cardiovascular/metabolic risks. Narrow age range of the population may limit the interpretation of age influence on sleep. Sleep duration question does not separate week days and weekend.

TRF authors

Lead authors: Viktor Hamrefors (Malmö), Ding Zou (Göteborg), Anders Blomberg (Umeå), Eva Lindberg (Uppsala), Jan Hedner (Göteborg), Kenneth Caidahl (Stockholm) and the SÖMN SCAPIS group (Franklin K, Grote L, Jansson C, Sahlin C, Theorell Haglöw J)

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L7. The prevalence of pulmonary nodules in a general population, data from the Swedish CArdioPulmonary bioImage Study (SCAPIS)

Objectives

The primary objective is to investigate the prevalence of solid and sub-solid pulmonary nodules in the Swedish population. The secondary objective is to investigate the dependency on participant characteristics for presence and type of pulmonary nodule.

Description of Analysis

Detection of pulmonary nodules has been amplified by an increased use of computed tomography (CT), although a reported stable incidence of cancerous nodules suggests that more frequent use of diagnostic imaging does not identify more cases of lung cancer (1). Today, prevalence and incidence data on pulmonary nodules are scarce, especially in the general population (2). To the knowledge of the authors there are no screening studies on the prevalence of pulmonary nodules in a general population not being referred for diagnostic imaging.

Data from chest CT-scans will be explored in order to assess the prevalence of pulmonary nodules and additional analyses on symptoms, risk factors, co-morbidities, lung function and concurrent CT findings will be performed.

Logistic regression models will be used in order to assess if there is an association between pulmonary nodules and participant characteristics exploring respiratory symptoms, risk factors (nicotine use, other exposures), comorbidities, pulmonary function as well as background characteristics of the participants. Separate analyses will be performed for males, females and never-smokers.

Significance/Rationale

The large population sample including a significant proportion of never-smokers in SCAPIS will provide novel in depth knowledge on the prevalence of pulmonary nodules and the dependency on associated risk factors, offering new insights to today's knowledge mainly based on data from lung cancer screening studies.

Population and Required Data Variables

Population: Total SCAPIS population (30 000 individuals).

Outcome variable: Presence of pulmonary nodules (nodule type and size)

Associated factors/confounders: Sex, age, height, weight, BMI, background characteristics, highest education, occupational exposures, nicotine use including detailed smoking habits and pack-years, data on lung diseases (Asthma/COPD/Emphysema/other lung disease), rheumatic diseases, comorbidities

(diabetes, tuberculosis, cancer), airway symptoms; cough (whether it is chronic, productive) and breathlessness, heredity of lung cancer. Spirometry (FEV1, FVC, VC, DlCO), blood test (hsCRP), Pulmonary CT variables from eCRF.

Limitations and Challenges

The main limitations of the analysis are the inclusion of participants between 50 to 64 years of age and the cross-sectional study design.

TRF authors

Åse Johnsson, Jenny Vikgren, Karen Sörensen, Anders Blomberg, Kjell Torén, Annelie Behndig

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L8. Risk factors for restrictive spirometric pattern (RSP) – a Swedish general population study (SCAPIS)

Objectives

1. To establish the prevalence restrictive spirometric pattern (RSP) in a middle-aged population, especially among never-smokers.
2. To evaluate whether RSP is associated with affected diffusion capacity, emphysema, fibrosis or other signs of respiratory diseases
3. To evaluate whether occupational exposures, smoking and other socioeconomic factors are associated with RSP
4. To evaluate prevalence and associations separately in men and women

Description of Analysis

Restrictive spirometry pattern (RSP) will be defined using two approaches. First as FEV1/FVC≥0.7 and FVC<80% and secondly as FEV1/FVC≥LLN and FVC<LLN. An additional approach will to include the subgroup FEV1/FVC≥0.7 and FEV1<80% and secondly as FEV1/FVC≥LLN and FEV1<LLN. This latter group is frequently included in the group RSP.

Potential contributing causes will be identified from the literature and pilot data, and their inter-relations and the required set of adjustment variables (confounders) will be defined using a Directed Acyclical Graph (DAG; www.dagitty.net). Associations to explore will include respiratory symptoms and diseases, diffusion capacity (CO-diff), body mass index (BMI), diabetes and glucose in blood as well as other markers of diabetes and cardiovascular disease including coronary plaques (CTA data). Pulmonary CT findings will also be explored. Further, the impact of smoking habits and occupational exposures will be investigated, as well as other socioeconomic factors like education and income.

The main analyses will be based on logistic regression models with proper adjustments for confounders.

Significance/Rationale

It has been suggested that low vital capacity in the absence of airflow limitation could be used as a proxy for true restrictive lung function impairment. Hence, the proxy restrictive spirometry pattern (RSP) has been defined as FEV1/FVC≥0.7 and FVC<80% predicted, but it seems to have a low validity in relation to true pulmonary restriction (1, 2). However, the phenotype RSP, seems to be more prevalent than expected and has emerged as a phenotype of its own (1). RSP has been associated with diabetes, metabolic syndrome, respiratory morbidity and increased mortality. In population-based studies RSP have been associated with poverty and low income. However, there is a lack of estimates of prevalence from general population samples with never-smokers. There is also a lack of studies where RSP is based on spirometry after bronchodilation, as well as such studies investigating the importance of smoking and occupational exposures (3).

Population and Required Data Variables

Population: Total SCAPIS population.

Outcome variable: RSP defined based on spirometry (FEV1, FVC)

Associated factors/confounders: Diffusion capacity, respiratory and cardio-vascular symptoms, diagnosed diseases, diabetes, heart disease, heart rhythm (ECG), measured coronary plaques (from CTA data); blood tests (fasting glucose, hsCRP, Hb, CRP, HbA1c, eGFR and creatinine, age, sex, highest education, occupational history (two occupations), blood pressure, blood lipids, detailed smoking status, height, weight, waist circumference, waist-hip ratio and self-reported comorbidities. Finally pulmonary CT variables from eCRF.

Limitations and Challenges

The main limitation of the proposed analysis is the cross-sectional character of the study.
The main strengths are that RSP will be defined after bronchodilatation, and that SCAPIS comprise a large proportion of life-long never-smokers

TRF authors

Kjell Torén, Per Wollmer, Gunnar Engström, Anna-Carin Olin, Magnus Sköld

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L10. The prevalence of interstitial lung abnormalities and its association with symptoms, lung function risk factors and comorbidities

EMBARGO on research hypothesis until 2022-04-27

Objectives

To study the prevalence of interstitial lung abnormalities (ILA) in the Swedish population and its association to risk factors, symptoms lung function and comorbidities.

Description of Analysis

Idiopathic pulmonary fibrosis (IPF) is a chronic fibrotic disease affecting the lung. IPF has a poor prognosis and is most often diagnosed in an advanced stage. Many risk factors for IPF are identified, including male sex and smoking [1]. Interstitial lung abnormalities (ILA) are interstitial changes described as ground-glass opacities, reticular pattern, centrilobular nodules, non-emphysematous cysts, honeycombing and traction bronchiectasis [2, 3]. These lung abnormalities are often clinically silent findings in high resolution computed tomography (HRCT) but can be a pre-stage for IPF and other pulmonary diseases. Smoking and age have been considered as risk factors for ILAs [4, 5]. It has been proposed that patients with ILA have deteriorated lung function, especially total lung capacity (TLC) and diffusing capacity of carbon monoxide (DlCO) [4, 5]. Based on population-based observational studies, the prevalence of ILAs has been estimated to 7 – 10.5% in smaller study populations [4-6]. However, the prevalence, characteristics and associations to functional impairment and co-morbidities is unknown.

In this descriptive cross-sectional analysis, we will explore data from chest CT-scans in order to assess the prevalence of ILAs in the Swedish population. Further analyses on lung function symptoms, risk factors co-morbidities and how it correlates with the ILA will be made.

The occurence of HRCT findings from eCRF data from SCAPIS will be compiled and logistic regression models will be used in order to assess if there is an association between ILAs (reported as binomial variable) and lung function (reported as continuous variables). Symptoms, such as dyspnoea, chronic bronchitis will be included as well as risk factors (i.e. smoking, other exposures) and comorbidities.

Since this is a descriptive study, we will use all available data (30 000) in order to make a good estimation on prevalence as possible. Thus, no power calculation is made. As far as we know, this is the largest cohort analysed involving the described research questions.

Significance/Rationale

In order to make an earlier diagnosis and affect the risk factors for IPF we need to find new diagnostic methods and increase the knowledge of IPF. This includes ILAs

since they are known to be a pre-stage for lung diseases in some cases. With the knowledge of the prevalence of ILAs we can estimate our possibilities to assess these findings and if e.g. screening risk groups could be possible in the future.

Population and Required Data Variables

Total SCAPIS population (30 000 individuals). Sex, age, BMI, smoking status (current, former, never and passive smoker), pack-years, data on lung diseases (Asthma/COPD/Emphysema/other lung disease than asthma and COPD), rheumatic diseases comorbidities (cardiovascular diseases, hypertension, diabetes, tuberculosis, obstructive sleep apnea, cancer), airway symptoms; cough (whether it is chronic, productive) and breathlessness, heredity of lung cancer, gastroesophageal reflux symptoms. FEV1, FVC, VC, DlCO, eCRFdata from chest CT-scans (Emphysema (yes or no, whether there are bullae, located centrilobular, panlobular or paraseptal) and categorized data (none, mild, moderate, severe) in three different parts (upper, middle, lower) of right and left lung, respectively. Binary variables (yes or no) on bronchial wall thickening, bronchiectasis, consolidation, cysts, ground glass, honeycombing, linear scars or atelectasis, mosaic attenuation and reticular abnormality).

Limitations and Challenges

Cross-sectional nature of SCAPIS and a limited age interval. Since the CT-scans are analysed by different radiologists, there may be differences in the interpretation of the radiology. Furthermore, the definition of ILAs used in the literature prescribed above will not be used, instead, we will only describe whether there are any abnormal, preclinical findings in the CT-scan or not. However, this will be a unique start in describing this new, internationally currently highly investigated, issue.

TRF authors

Magnus Sköld, Ida Pesonen

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L13. Physical activity and its association with respiratory symptoms and spirometry

Objectives

To explore the association between: A) physical activity pattern and lung function; and B) physical activity pattern and prevalent respiratory symptoms, after adjusting for lung function, in a general population-based cohort (SCAPIS)

Description of Analysis

Respiratory symptoms are common in the population, with approximately 15% of the SCAPIS cohort reporting breathlessness defined as ≥2 on the mMRC scale (1). Furthermore, 4.9% report chronic bronchitis (11.7% of subjects with COPD according to spirometry and 4.2% among subjects with FEV1/FVC>0.7). As the cardinal symptom of cardiorespiratory disease, breathlessness is strongly associated with adverse health outcomes (2), and the treatment goal in airway disease is to preserve lung function and abolish respiratory symptoms (3,4). The associations between lung function impairment and symptom profile are often weak and respiratory symptoms are common also in subjects with normal lung function.

Daily physical activity has widely documented cardioprotective effects (5) and is also related to improved quality of life and beneficial health effects in COPD (6). However, its association with lung function and symptoms has rarely been studied. In a recent study, the association of accelerometer-based physical activity with spirometric indices was investigated. Although the effects were small, active subjects showed better lung function and the observed associations were more pronounced among ever smokers, suggesting a higher benefit of physical activity for subjects at risk for chronic lung diseases (7). It has also been shown that older nicotine-dependent adults are less engaged in less physical activity and have a more sedentary behaviour than controls (8).

Furthermore, a restrictive spirometric pattern is common in asymptomatic adults and is a risk factor for cardiovascular disease, especially hypertension. Smoking and physical inactivity were directly associated with a restrictive pattern, even when the analysis was adjusted for cardiorespiratory fitness (9).

Data on respiratory symptoms and association with physical activity are scarce. In a preschool-age population, decreased physical activity was observed among children with a history of asthma or wheezing (10).

Significance/Rationale

Understanding the association between physical activity pattern, respiratory symptoms and lung function in a large population-based cohort of mainly non-smokers, is potentially useful for improvement of risk prediction and tailored preventive interventions, as positive effects of physical activity have been shown in many diseases.

Population and Required Data Variables

Sample

Population: All subjects with questionnaire data on wheeze, breathlessness (mMRC) and chronic bronchitis, accelerometry and spirometry data are included.

General analysis

Primary analyses will be performed in all subjects, using spirometry data as continuous variables

Stratified analyses

1. Individuals with/without impaired lung function, divided into COPD (FEV_1/FVC<0.7, according to GOLD) and restrictive spirometric pattern (FEV_1/FVC>0.7 and FVC<80%)
2. Men/women

Other covariates and Stratification variables:

- Age
- SCAPIS site
- Postal code (or similar to study urban vs. rural area)
- Socio-economic status (educational level and income)
- Working / Retirement status
- Visit date

Lung outcomes (dependent variables)

1. Spirometry (FEV_1, FVC, FEV_1/FVC and DLco)
2. Questions about wheezing, chronic bronchitis and breathlessness, after adjusting for lung function

Exposure variables

1. Physical activity, by accelerometry:
   - Sedentary (time in and % of wear time)
   - Light intensity physical activity (time in and % of wear time)
   - Moderate intensity physical activity (time in and % of wear time)
   - Vigorous intensity physical activity (time in and % of wear time)
   - Total wear time
   - Valid days
   - % weekend days
   - Prolonged sedentary time (>20 min of uninterrupted sedentary behaviour)
2. Tobacco habits (current dose, pack-years, stop date if stopped)
3. History of cardiovascular diseases (coronary disease, heart failure, valvular disease, atrial fibrillation, stroke, peripheral artery disease)
4. Body mass index, waist and hip circumference

No proper power analysis has been performed, but given the full study population of n=30 000, the study is implied to have enough power to detect changes.

Limitations and Challenges

Data on symptoms are based on the questionnaire. The inability of the accelerometer to differentiate between sitting and standing as well as the automated wear time estimation used, as low counts during 60 minutes may be common in this age-group, are other limitations.

TRF authors

Anders Blomberg, Kjell Torén, Örjan Ekblom, Elin Ekblom-Bak, Lowie Vanfleteren, Magnus Sköld, Eva Lindberg, Mats Börjesson.

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L15. Reference values for pulmonary function tests in SCAPIS

EMBARGO on research hypothesis until 220113

Objectives

1. Define SCAPIS reference values for spirometry and $D_{L,CO}$
2. Study the differences between SCAPIS and Global Lung Function Initiative (GLI)-generated lower limit of normal (LLN) for spirometry in SCAPIS and its relation to respiratory burden
3. Study the relation between impaired spirometry and/or $D_{L,CO}$ in relation to respiratory burden

Description of Analysis

We have previously shown [1] in the SCAPIS interim analyses that the newly proposed GLI reference values [2] for D_{LCO} underestimate the lower limit of normal (LLN) in health, middle-aged Swedish adults. We could find that even the same was true for the LLN of the ratio between forced expiratory volume during the first second of exhalation and forced vital capacity (FEV1/FVC-ratio) when GLI 2012 reference values were used [3]. However this was not part of the aim of our study and therefore the clinical importance of underestimating LLN has not been studied in SCAPIS. This will be studied with regard to respiratory burden (respiratory symptoms, physician-diagnosed respiratory disease and CT-assessed emphysema).

Generally it is recommended to use reference values that are relevant for the specific population and ideally are coming from the same population [4]. Therefore there is a need of generating reference values for pulmonary function tests within SCAPIS for future analyses. We will use the lambda-mu-sigma (LMS) method, a mathematical approach that originally was applied for nonlinear growth charts, that has also been used by GLI [2].

Moreover, usually the information from D_{LCO} and spirometry are not analysed per se, but together, when both are available [4]. Therefore we want to analyse the clinical value of abnormal spirometry and D_{LCO}, based on our own reference values, in the SCAPIS population. This will be studied with regard to respiratory burden (respiratory symptoms, physician-diagnosed respiratory disease and CT-assessed emphysema).

Significance/Rationale

The clinical discussion regarding implementing GLI reference values in Sweden is continuing. Therefore it is important to increase the knowledge regarding eventual risk of underdiagnosing obstruction if the LLN for FEV_1/FVC-ratio is underestimated.

The SCAPIS-generated reference values in healthy, never-smoking individuals are important for future analyses in SCAPIS involving lung function.

Finally, the clinical importance of having impaired spirometry and/or diffusing capacity in a large population been limitedly studied.

Population and Required Data Variables

Population – entire SCAPIS.

Required variables: anthropometric variables, respiratory symptoms, smoking history, physician-diagnosed diseases and use of medication for respective disease, pulmonary function tests and CT findings are key variables.

Limitations and Challenges

Lack of variables describing quality of spirometry in the database at the present moment.

TRF authors

Andrei Malinovschi, Per Wollmer, Jan Engvall

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Priority 2 (14 publications)

K6. The association between mild to moderate renal dysfunction and extent and distribution of subclinical coronary artery disease, coronary calcification and type of coronary plaques

Objectives

To examine the association between mild to moderate renal dysfunction and extent and distribution of subclinical coronary artery disease, coronary calcification and type of coronary plaques.

Description of Analysis

Chronic kidney disease (CKD) is an important risk factor for the coronary artery disease (CAD). When the CAD is established, patients with simultaneous CKD have a worse prognosis with less effect of evidence-based treatment, indicating a partly different pathophysiology. The CAD is different in patients with CKD. The atheromatous plaques are more calcified and medial calcification is more common. However, the association between mild to moderate renal dysfunction and extent and distribution of early subclinical coronary artery disease, coronary calcification and type of coronary plaques has not been well described and most studies have been from clinical populations, examined because of suspected or already confirmed disease. There are no studies examining the association between mild to moderate renal dysfunction and findings on coronary angiography in a large random sample of a general population.

In the present study we will examine the association between renal function measured as eGFR from s-creatinine and
- extent of CAD
- distribution of CAD
- coronary calcification
- type of coronary plaques

We will compare the CAD anatomy in individuals with mild to moderate renal dysfunction with that in individuals with normal renal function.

Significance/Rationale

By examining the association between mild to moderate renal dysfunction and extent and distribution of subclinical coronary artery disease, coronary calcification and type of coronary plaques, we will increase the understanding of underlying mechanisms and how coronary artery disease differ between those with and without CKD.

Population and Required Data Variables

Sample
Entire SCAPIS cohort

Exposure
eGFR calculated from S-creatinine, using the CKD-EPI formula

Other covariates
TBD: mostly traditional risk factors, such as SeS (education, income), lipids levels and lipid treatment, smoking, hypertension, blood pressure, BP-treatment, diabetes, glucose-level, HbA1c, diabetes-treatment, BMI, waist and hip circumference, psychosocial stress, physical activity, Family history, diet, alcohol. Hs-CRP

Outcome
Degree of coronary artery disease: Definition: TBD consider both degree and number of stenoses.
Degree of coronary calcification: Definition: TBD: CACS, number of non-calcified, calcified and mixed plaques
Degree of coronary calcification in relation to degree of coronary artery disease

Limitations and Challenges

One of the main limitations is the lack of central core lab analyses of CCTA.

TRF authors

Tomas Jernberg

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K10. Inter-arm blood pressure differences (IABPD) – a marker of subclinical atherosclerosis?

Objectives

1. To explore factors associated with IABPD.
2. To explore whether IABPD is associated with subclinical atherosclerosis.

Description of Analysis

Inter arm blood pressure differences (IABPD) are calculated as absolute value of blood pressure in right arm minus left arm. This is calculated for systolic and diastolic blood pressures. IABPD is analysed as continuous variable and categorised in >=10 mmHg and <10 mmHg. Other cut-off limits for IABPD are also explored. The relationships between IABPD and risk factors (lipids, blood pressure, age, sex, anthropometry, smoking, diabetes, FEV1, FVC, CRP, HbA1c) are explored in linear or logistic regression analyses. The relationships with CACS, CTA and carotid plaque are examined.

Significance/Rationale

In clinical practice, it is recommended that blood pressure is measured in both arms. Substantial IABPD could indicate stenosis of the subclavian artery, and could therefore be a marker of severe atherosclerosis. Some studies have reported that IABPD >=10 mmHg or >=15 mmHg is associated with increased mortality or cardiovascular disease (Cao et al, 2015; Clark et al 2012). A study of 1120 patients reported that ankle-brachial index <0.9, high brachial ankle pulse wave velocity, and high left ventricular mass were independently associated with an inter arm SBP difference of 10 mmHg or more (Su et al 2012). In a study of 261 patients with >=3 risk factors, an increased inter-arm SBP difference (≥6 mm Hg) was associated with coronary atherosclerotic disease burden using CACS (Her et al 2017). However, most studies have been performed in older subjects or in studies of patients with CVD (e.g., as part of ankle-arm blood pressure measurement). Also, many studies have performed the blood pressure readings sequentially (instead of simultaneously), used only one BP reading or used manual instead automatic readings, all of which could affect the IABPD (Verberk et al, 2011).
The SCAPIS cohort could answer several important questions in relation to IABPD. Is IABPD associated with subclinical atherosclerosis in a middle-aged general population sample? What cut-off for IABPD is reasonable in this group? Does IABPD add information on top of traditional risk factors? What are the main determinants of IABPD in the general population?

Population and Required Data Variables

The whole SCAPIS cohort. Lab (Lipids, CRP, HbA1c, glucose, eGFR) blood pressure, age, sex, anthropometry, smoking, diabetes, antihypertensive and lipid-lowering

drugs, FEV1, FVC, CTA, coronary calcium score, ultrasound of the carotid arteries (from eCRF), Ankle-brachial index.

Limitations and Challenges

Possible differences between sites with respect to measurement of blood pressure and measurement of carotid plaque. Assessment of subclavian atherosclerosis from CT examinations in a subgroup would improve the study.

TRF authors

Gunnar Engström, Viktor Hamrefors

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K15. Comparative associations of blood pressure with atherosclerosis patterns in coronary, carotid and peripheral arteries

Objectives

To study the comparative associations of blood pressure with atherosclerosis patterns in coronary, carotid and peripheral arteries.

Description of Analysis

All analyses will be carried out in accordance with a pre-specified statistical analysis plan. Initially, missingness patterns will be investigated. We will restrict the analyses to persons that have complete data on systolic and diastolic blood pressures.

The distributional properties of all exposure and outcome variables will be investigated, and three primary (one for each vascular bed) and several secondary outcome variables will be defined out of the available artery data. The three primary outcomes variables will be selected to have similar properties, facilitating comparisons. Distributional patterns of all exposure variables and the primary outcome variables will be described in detail, in the main sample and in defined subgroups.

The blood pressure variables will be screened for associations with the primary outcomes, using the most appropriate models. Blood pressures will be modelled using restricted cubic splines with degrees of freedom allocation based on the partial apparent strength of association. Confounders will be identified using directed acyclic graphs. Interactions with age (50-55 / 55-60 / 60-65 year categories) and sex will be forced into all models; and both overall and age- and sex-specific results will be presented.

Significance/Rationale

High blood pressure is the leading risk factor for premature deaths worldwide[1] and accounts for more than 10% of all health care costs in some developed countries.[2] Less than half of those who have high blood pressure are aware of it, and in spite of widely available low-cost drugs to treat it, only a small minority are treated to target blood pressure levels.[3] Hence, the immense public health effects of high blood pressure are not likely to go away anytime soon, and its detrimental effects need better understanding for better prioritization of public health measures.

High blood pressure accelerates atherosclerosis in multiple arterial beds. Blood pressure-lowering treatment reduces atherosclerotic events in coronary and carotid arteries, as well as renal events. Blood pressure-lowering treatment is more effective in reducing strokes than myocardial infarctions;[4] comparative effectiveness in reducing peripheral vascular disease events is uncertain.

The present study proposal aims at investigating the comparative associations of blood pressure phenotypes with atherosclerosis patterns in three different arterial

beds: coronary, carotid and peripheral arteries. The SCAPIS study is uniquely suited to such comparisons as it encompasses state-of-the-art examinations of all those arterial beds.

Population and Required Data Variables

Sample
Entire SCAPIS cohort.

Subsamples

1. Persons with / without blood pressure-lowering drugs.
2. Men / women
3. Age groups 50-55 / 55-60 / 60-65

Outcomes
Coronary artery outcomes:

1. Coronary calcium score
2. Coronary atherosclerosis (CTA), variables TBD
3. Anomalous origin of any coronary artery (0/1), with free text specification

Carotid artery outcomes:
Carotid plaque and carotid IMT (if available).

Peripheral artery outcomes:
Ankle-brachial index (ABI), measured for each ankle as the highest of the pressures in each A. Dorsalis Pedis or A. Tibialis Posterior (the numerator/ankle) over the average of the two supine brachial blood pressures in the arm with the highest blood pressures (the denominator/arm). One ABI value per ankle is obtained.[5]

Exposures
Brachial systolic and diastolic blood pressures, measured according to a standardized protocol, in accordance with current European guidelines.[6] The average of two supine brachial blood pressures in the arm with the highest blood pressures will be used. If data are available: year of start of blood pressure-lowering drugs; number and type of current blood pressure-lowering drugs.

Limitations and Challenges

Finding three comparable outcome measures may be challenging.

TRF authors

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B1. Relationships between lung function, proteomic and metabolomic biomarkers

Objectives

The primary aim is to explore the relationships between proteomic and metabolomic biomarkers and measures of lung function.
As a secondary objective we will identify proteomic and metabolomic biomarkers with significant relationships both with lung function and coronary heart disease, as measured by the calcium score.

Description of Analysis

It is now widely acknowledged that moderately reduced lung function, as measured by VC or FEV1, is a major risk factor for cardiovascular disease. Even if common risk factors such as smoking may partly explain this relationship, a significant proportion of this relationship remains unknown. In addition, low FVC is also associated with adverse metabolic profile, such as the metabolic syndrome. Several prospective cohort studies have shown that incidence of diabetes is increased in individual with poor FVC or FEV1. Hence, it could be hypothesized that reduced FVC is associated with adverse metabolic profile, even in apparently healthy individuals.
Raised levels of various plasma proteins have repeatedly been linked to incidence and prevalence of cardiovascular diseases. Two proteomic panels (CVD-II and CVD-III) have been developed with the purpose to assess the risk of cardiovascular disease. To what extent plasma proteins associated with CVD also are associated with reduced lung function has not been extensively studied.

Primary analysis will be using an -omic approach with linear regression of FVC (dependent) with biomarker, adjusted for 1) age, height and sex 2)+ waist and smoking 3) other potential confounding factors. Significant results will be further explored in never smokers.
Secondary analyses will include analysis of FEV1, FEV1/VC<0.7, diffusion capacity for CO (DLCO) and restrictive pulmonary pattern.
Biomarkers with significant relationships with FVC will be explored in relation to coronary calcium score.
Due to the large number of highly correlated metabolites, a false discovery rate correction (corrected p values <0.05) will be used. The SCAPIS pilot study will be used for replication of significant results.

Significance/Rationale

The proposal adheres well to the general aims of SCAPIS. It will not be one of the key publications of SCAPIS, but the study will provide new data that clarify the relationships between biomarkers and lung function on one hand and cardio-metabolic diseases on the other.

Population and Required Data Variables

Individuals with diabetes or treatment with lipid lowering drugs will be excluded. The metabolites from the analysis at Nightingale laboratories will be used, together with HbA1c, CRP, plasma lipids from the core protocol. Proteomics data from OLINK panel CVD-II and CVD-III will be used. Smoking, lipid-lowering drugs, diabetes, anthropometry, spirometry results (from eCRF), blood pressure, blood pressure drugs, coronary calcium score, ultrasound of the carotid arteries (from eCRF). Individuals with diabetes or treatment with lipid lowering drugs will be excluded in sensitivity analysis.

Limitations and Challenges

Many biomarkers and several lung function measures could cause problems with multiplicity. False discovery rate and replication in SCAPIS pilot will be used.

TRF authors

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B7. Identification of novel pro-atherogenic plasma lipid patterns in middle-aged adults with different stages of dysglycemia

Objectives

To describe the association between the plasma lipid profile and prevalent subclinical atherosclerosis in subjects with type 2 diabetes (T2DM), impaired fasting glucose (IFG) and in normoglycemic subjects.

Description of Analysis

From the interim analyses we anticipate that we will have 400 T2DM and 700 IFG-subjects in the SCAPIS study population of 5000 subjects with available data on metabolomics. The dysglycemic categories, T2DM and IFG, will be compared with each other and with non-diabetic subjects. Different manifestations of coronary artery disease (CAD) will be used as outcome variables.

We will determine the absolute concentrations and fractions of nine amino acids, three apolipoproteins, nine types of cholesterol, 16 fatty acids, creatinine, albumin, nine glycerophospholipids, five glycolysis metabolites, total glycoprotein acetyls, three ketone bodies, and >160 lipoproteins by magnetic resonance spectroscopy (MRS) by Nightingale Health (Helsingfors, Finland; nightingalehealth.com/).

First, logistic regression models will be used to identify metabolites (focused on lipid fractions) significantly associated with dysglycemic categories with adjustment for age and sex. For each individual, the levels for these metabolites will define a position in a n-dimensional space so the distance between individuals can be calculated. This allows for clustering of individuals and identification of novel subgroups of dysglycemia. To identify potential biomarker candidates, we will for each IFG/T2DM subject calculate the distance from the average non-diabetic metabolomics/lipid profile and use it as a single continuous variable to study correlations with CAD and IFG/T2DM-related metabolic risk factors.

Secondly, multivariable regression models (with proper adjustments) will be performed for potential biomarker candidates discovered above using CAD as the dependent variable. In addition, we will address potential mediation of the biomarker between dysglycemia and CAD. For the biomarker to be considered a potential mediator between IFG/T2DM and CAD, the regression model must show that i) the biomarker remains associated with CAD while controlling for IFG/T2DM, and ii) that biomarker significantly reduces the association between IFG/T2DM and CAD.

Results will be validated in the SCAPIS pilot study with a total of 1,100 subjects with similar MRS based metabolomics data.

Significance/Rationale

Cardiovascular diseases have remained the leading causes of death globally in the last 15 years. Patients with type 2 diabetes have risks of death and cardiovascular events that are 2 to 4 times as great as the risks in the general population [1]. Type 2 diabetes is usually preceded by a “pre-diabetic” state, characterized by elevated levels of blood glucose i.e. IFG or impaired glucose tolerance, which also entails an elevated risk for CVD [2].

Type 2 diabetes is associated with atherogenic dyslipidemia, including elevated levels of plasma triglycerides (TG), very-low density lipoprotein (VLDL) particles, post-prandial triglyceride rich lipoprotein remnants and apoliporotein B (apoB), and low evels of high density lipoprotein cholesterol (HDL-C) [3]. These atherogenic changes precede type 2 diabetes by several years and are associated with high risk of cardiovascular events in type 2 diabetes [4,5]. We will investigate the various lipoprotein and apolipoprotein traits and their ratios as predictors for subclinical atherosclerosis in people with different stages of dysglycemia compared to normoglycemic persons. Our findings may provide tools to improve precision medicine to patients in routine clinical settings.

Population and Required Data Variables

Sample

The 5 000 subjects in the SCAPIS cohort and 1100 subjects in the SCAPIS Pilot trial where data on metabolomics are available.

Subsamples

1. Persons with / without known coronary artery disease or symptoms compatible with coronary artery disease.
2. Men / women

Outcomes

Primary

Duke prognostic CAD score (integrated score of coronary atherosclerosis)

Secondary

Total number of plaques in the carotid arteries.
Segment involvement score (SIS, number of coronary segments with disease)
Coronary calcium score
Combination of carotid and coronary plaques

Exposures

1. T2DM/IFG/Normoglycemic subjects
2. The absolute concentrations and fractions of 230 metabolites, with emphasis on lipoproteins.
3. Physical activity (sedentary time, LIPA, MVPA)
4. Socioeconomic status (highest education, vocation)
5. Tobacco habits (current dose, pack-years, stop date if stopped)

6. History of cardiovascular diseases (coronary disease, heart failure, valvular disease, atrial fibrillation, stroke, peripheral artery disease)
7. Body mass index, waist and hip circumference
8. Systolic and diastolic blood pressures
9. Glucose, creatinine.
10. Heredity for cardiovascular diseases and its risk factors

TRF authors

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L1. Isolated, reduced diffusing capacity for carbon monoxide ($D_{L,CO}$) – relation to symptoms, smoking habits, spirometry, metabolomics and computed tomography (CT)

Objectives

To identify risk factors for isolated, reduced $D_{L,CO}$.

Description of Analysis

Patents referred for pulmonary function testing may show normal spirometry and static lung volumes, but significantly reduced $D_{L,CO}$. $D_{L,CO}$ reflects gas transfer from the alveoli to pulmonary capillary blood. The underlying pathology may vary considerably. In the presence of an obstructive ventilatory defect, low $D_{L,CO}$ often indicates emphysema, whereas in combination with a restrictive ventilatory defect, it often reflects interstitial inflammation or fibrosis. $D_{L,CO}$ is however not specific to pulmonary pathology an can also be reduced in heart failure, for example.

The finding of isolated, reduced $D_{L,CO}$ is therefore difficult to interpret. There are few studies on this problem in the literature. Small, retrospective studies in patient materials have shown that CT indicates either mild emphysema or mild interstitial disease as the cause (1). This study reported a low prevalence of isolated DL,CO (about 0.5%), but probably the prevalence is higher as a population-based sample (2) reported that more than 10% can have isolated, reduced DL,CO. Independent risk factors for isolated, reduced DL,CO were sex and a history of smoking. No CT was performed in this study.

We will explore associations between isolated, reduced $D_{L,CO}$ and symptoms, smoking habits, spirometry, proteomics, metabolomics and CT variables with regression analysis. Risk factors for isolated, reduced $D_{L,CO}$ will be identifies by logistic regression.

Significance/Rationale

The interpretation of isolated, reduced $D_{L,CO}$ is a clinical problem. Knowledge about associations with symptoms, smoking habits, metabolomics, proteomics and CT findings will be of value for determination of possible further diagnostic measures.

Population and Required Data Variables

Population – entire SCAPIS. Required variables: symptoms, smoking history, pulmonary function tests, proteomics, metabolomics and CT findings are key variables. Information about other diagnoses and medication are needed to account for confounders.

Limitations and Challenges

SCAPIS is the largest population-based material in which this problem has been explored.

A low number of subjects with isolated, reduced $D_{L,CO}$ might be an issue, but interim data suggests that this is not the case.

TRF authors

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Revised by Andrei Malinovschi and Per Wollmer.

References

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L2. What are the important risk factors for daytime sleepiness as measured by Epworth sleepiness scale in a population-based sample?

Objectives

To study which variables in the population that affect daytime sleepiness defined by Epworths sleepiness score.

Description of Analysis

The diagnosis and treatment decisions in obstructive sleep apnea syndrome is based on whole-night sleep recordings in combination with evaluation of daytime symptoms, most importantly daytime sleepiness 1. Both in research and in clinical settings, Epworth sleepiness scale (ESS) 2, a generic scale that measures the risk of falling asleep during daily activities, is extensively used to measure daytime sleepiness. Interventional studies in sleep apnea patients do repeatedly show a decline in ESS score 3,4. The usefulness of ESS for diagnostic purposes is less valid as many other factors influence daytime sleepiness.

The outcome variables: ESS score (continuous variable) and excessive daytime sleepiness (ESS>10).

Exposure variables: age, sex, obesity (BMI, waist hip ratio), somatic disease, depression, pressure, smoking (never, former, current), sleeping habits, sleep disturbances, alcohol intake, SES, exercise habits.

If there is a significant difference in ESS score between men and women, the analyses will be stratified by sex.

Significance/Rationale

Several case-control studies have reported increased ESS scores in specific patient groups. Less is known about risk factors for increased ESS scores in the population. The SCAPIS cohort will be much larger and include significantly more life-style factors than previous studies within the field 5.

The study will give important information life-style variables and somatic diseases that have to be taken into account when evaluating ESS scores. The results will be of significant value to clinicians evaluating symptom profile in patients undergoing investigation for suspect obstructive sleep apnea.

Population and Required Data Variables

In the analyses we will include all subjects in SCAPIS.

Variables: Height, weight, waist and hip circumferences. Questionnaire data for ESS (Q141) and all variables mentioned above.

Limitations and Challenges

A limitation is the narrow age span as daytime sleepiness differ by age. Another limitation is the cross-sectional nature of the study.

TRF authors

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6. ion with adverse events. Sleep Breath. 2018.

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L3. Frequency of sleep apnoea diagnosis in relation to symptoms and risk factors – a population-based analysis

Objectives

Primary objective: Frequency of self-reported diagnosis of obstructive sleep apnoea (OSA) in a population-based cohort stratified for age, gender, BMI classes according to WHO criteria, socio-economic status, and the number of cardio- metabolic diseases

Secondary objectives:

- Frequency of self-reported sleep apnoea diagnosis in relation to the likelihood of OSA according to the STOP BANG questionnaire criteria stratified for anthropometric factors, comorbidities and degree of daytime sleepiness;
- Frequency of self-reported OSA treatment by CPAP and oral devices in relation to age, gender, degree of obesity and cardio-metabolic comorbidity
- Influence of daytime sleepiness (assessed by the Epworth Sleepiness Scale) on the likelihood of a self-reported OSA diagnosis and treatment in a population-based cohort

Description of Analysis

All available patients from the entire SCAPIS cohort (all University sites) will be included. A sleep apnoea likelihood score will be computed based on the information about witnessed apnoea (question 143), frequent snoring (question 144) and the Epworth Sleepiness Scale (question 141), Body Mass Index, and the existence of comorbid hypertension. Additional risk factors include current smoking and other cardiovascular disease.

The actual frequency of self-reported sleep apnoea diagnosis will be stratified for several anthropometric data and the occurrence of comorbidities. In addition, the actual frequency of OSA diagnosis will be compared to the proportion of individuals with a high likelihood of OSA according to the classification stated above. In adjusted analysis we will address the factors which actually increases the probability for a medical diagnosis of OSA in a middle aged population sample. Factors to be probed in the statistical analysis include age, gender, socio-economic status (highest education level), degree of daytime sleepiness, comorbidities like hypertension/diabetes, and marital status.

Significance/Rationale

The prevalence of sleep apnoea is very high, we estimate that approximately 1.8 Million Swedish adult citizen fulfil the criteria of sleep apnoea with an apnoea hypopnea index of 5/hour. At least 600 000 adults are expected to suffer from moderate to severe sleep apnoea with at least 15 breathing pauses/hour of sleep. We therefore need to identify the selection factors which bring a patient to the diagnosis of sleep apnea in specialised care (sleep centers). In addition, we need to identify those individuals which may have less chances for a diagnosis or adequate

treatment despite a strong risk factor profile. This knowledge may affect clinical sleep apnoea management inside and outside of Sweden.

Population and Required Data Variables

Population:
All SCAPIS participants with complete dataset.

Required variables:
Anthropometric data
Cardio-metabolic comorbidities
Psychiatric comorbidity
Core questionnaire (questions 141-146)
- Self-reported sleep apnoea diagnosis
- Self-reported sleep apnoea treatment
- Witnessed frequent snoring
- Witnessed apnoea during sleep

Socio-economic status, education level, marital status

Limitations and Challenges

Limitations: Limited questionnaire data about key sleep apnoea symptoms
Cross sectional data, incomplete phenotyping of different sleep apnoea-subtypes
Self-reported data on sleep apnoea diagnosis and –treatment.
The questions applied in the SCAPIS Core questionnaire do not fully cover all items of the best validated sleep apnea risk assessment questionnaire (STOP-BANG).

Challenges: Handling of missed data in the analysis
Verification of the self-reported sleep apnoea diagnosis

TRF authors

Lead authors: Ludger Grote, Franklin K, Theorell Haglöw J, Zou D and the SCAPIS Sleep Group (Blomberg A, Hedner J, Janson C, Lindberg E, Sahlin C)

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L4. Lung function association with sleep time and insomnia symptoms

Objectives

To study the association between lung function (VC, FVC, FEV1, FEV1/VC, FEV1/FVC and DLco) and insomnia symptoms and sleep length.

Description of Analysis

Previous studies have shown that subjects that sleep less than 6 hours per night are more obese and have higher prevalence of cardiometabolic morbidity (1). We have also shown that being a short sleeper is associated with a higher prevalence of respiratory symptoms (2). Subjects with asthma have an increased prevalence of insomnia symptoms (3) and having insomnia has a large effect on quality of life in asthma (4). Preliminary analyses from the European Community Respiratory Health Survey (ECRHS) III have shown that insomnia is related to both respiratory symptoms and lower lung function. The direction of this association could be twofold: having low lung function may impair sleep. The opposite is, however, also possible as having insomnia is related to a higher risk of developing asthma (5). We have also preliminary data indicating that subjects with insomnia have a higher risk of developing chronic rhinosinusitis. The mechanism for such an association is not clear but it is known that insomnia symptoms are linked to chronic inflammation and associated with changes in the production of pro-inflammatory cytokines. This could have a negative effect on lung function as an association between lower lung function and systemic inflammation has benne found in many studies (6)

In this investigation we will
A: Study lung function in short sleepers: < 6 hours/night, normal sleepers 6-9 hours per night and long sleepers > 9 hours/night
B: Study lung function in association to the presence of insomnia symptoms: difficulty initiating sleep, difficulty maintaining sleep and early morning awakenings.

Linear regressions will be used with the various lung function variables as dependent variables and the sleep related variables as independent variables. In the adjusted analyses we will include potential confounders such as sex, age, BMI and smoking history.

We have made no formal power calculation but this study is by far the largest study investigating this association. As an example the study is 6 times larger than ECRHS III where we previously investigated association between lung function and insomnia symptoms.

Significance/Rationale

This study may detect an important additional factor that influences lung function. Interventions aiming at improving sleep may in the future be an important part also for preserving lung function.

Population and Required Data Variables

Sex and age, Spirometry variables: VC, FVC, FEV1 and VC. Questionnaire data on sleep: Q 137-140. Information on smoking history, physical activity and data on height and weight. In this analyses we will include all subjects in SCAPIS.

Limitations and Challenges

The data will be based on self-reported sleep which is a limitation. As thus is a cross-sectional analyses we cannot say anything for certain about cause and effect.

TRF authors

Christer Janson (Uppsala), Anders Blomberg (Umeå), Ludger Grote (Göteborg), Eva Lindberg (Uppsala), and the SCAPIS Sleep Group (Ding Z, Franklin K, Hedner J, Sahlin C, Theorell Haglöw J)

References

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L6. Occupational exposures and chronic obstructive pulmonary disease, chronic airflow limitation and emphysema

Objectives

The primary aim of this paper will be to investigate whether occupational exposure to gas, dust and fumes increase the risk of chronic airflow limitation (CAL), chronic obstructive pulmonary disease (COPD) and emphysema.

The secondary aim will be to analyze the risk patterns separately among men, women and never-smokers.

Description of Analysis

COPD and CAL will be defined according to GOLD and the LLN model and emphysema will be based on eCRF data, where the extent of emphysema will be visually estimated on a four point scale (absent, mild, moderate or severe) in the upper, mid and lower zones of each lung. Symptoms based on questionnaire items, like dyspnea, wheezing and cough will be included additional outcome definitions. In the questionnaire there is also information about physician-diagnosed asthma and year of diagnosis.

The occupational exposure will be based on two items about current occupation and the longest held occupation. These occupations will be classified according to standard classifications and the exposure to gas; dust and fumes will be assessed using established job-exposure matrices.

Smoking will be categorized as current smokers, former smokers or never-smokers, and pack-years will be calculated for all participants with a history of smoking. Socioeconomic status (SES) will be defined as according to the highest education into three groups, university education (high), high school (medium) and elementary school or not completed school (low).

Categorical variables will be compared using $\chi 2$-test to identify significant associations and we will apply multivariate adjusted logistic regression models calculating odds ratios as approximations of the relative risk. We will perform separate analysis for males, females and never-smokers.

Significance/Rationale

A number of studies show an increased risk for COPD or CAL among groups with occupational exposures to gas, dust and fumes (1). However, there are several important gaps of knowledge. One major weakness is the lack of separate risk estimates regarding occupational exposures and COPD for men and women. This is probably due to lack of power, as many studies have been too small to stratify for gender. Another knowledge gap is the importance of occupational exposures among never-smokers, especially never-smoking women. The impact of occupational exposure and risk for emphysema in a general population context is not at all studied,

with exception of a small analysis of SCAPIS Pilot (2). In addition, there is a lack of studies using operational definitions of COPD/CAL based on spirometry after bronchodilation, and there is no studies defining COPD as a combination of chronic airflow limitation and symptoms.

The strength of SCAPIS is the large size of a general population sample of which all have undergone CT imaging, the large proportion of never-smokers, and that the spirometry is performed after bronchodilation.

Population and Required Data Variables

Population: Total SCAPIS population.

Outcome variable: CAL, COPD and emphysema based on spirometry and CT imaging

Associated factors/confounders: Diffusion capacity, SVC, self-reported respiratory symptoms, blood tests (hsCRP and Hb), age, sex, highest education, detailed smoking habits including pack-years, height, weight, and self-reported comorbidities. Occupations from three items. Pulmonary CT variables from eCRF.

Limitations and Challenges

The limitation of the analysis is the limited age span, 50 – 65 years, as well as the cross-sectional design

TRF authors

Kjell Torén, Mathias Holm, Anna-Carin Olin, John Brandberg and Magnus Sköld

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L9. Causes of activity-related breathlessness in the population

Objective

Primary: To establish the contributing factors to activity-related breathlessness in the middle-aged population, with a focus on respiratory and cardiovascular disease.

Secondary:

1. To evaluate the causes of breathlessness in people with no self-reported known cardiorespiratory disease
2. To evaluate the contributing causes separately in men and women
3. To evaluate contribution from cardiovascular disease in the subgroup (n=5000) with data on NT-proBNP

Description of Analysis

Activity-related breathlessness is measured using the validated modified Medical Research Council (mMRC) 0–4 ordinal scale.

Potential contributing causes will be identified from the literature and pilot data, and their inter-relations and the required set of adjustment variables (confounders) will be defined using a Directed Acyclical Graph (DAG; www.dagitty.net). Causes to explore will include respiratory disease (self-report; symptoms; spirometry), body mass index (BMI), anaemia and cardiovascular disease including coronary plaques (CTA data) and data on NT-proBNP in the sub group with laboratory data. Confounders to explore will include age, sex, smoking, highest education, anxiety, depression and level of physical exercise/activity.

Associations with breathlessness (mMRC) will be analysed using ordinal logistic regression models. Planned analyses:

For the primary objective: Prevalence (%) of the contributing causes and crude and adjusted associations with breathlessness in all participants.

Sub groups for secondary objectives,

1. The analyses will be performed in people without known cardiorespiratory disease;
2. Men and women, separately;
3. People (n=5000) with data on NT-proBNP.

Significance/Rationale

Activity-related breathlessness in daily life is common in the community, affecting about 10% of the middle-aged population.[1, 2] Contributing causes of breathlessness have been established in laboratory studies.[3] No published study has measured and evaluated the contributing causes of breathlessness in the population. The only study in this field interviewed 268 breathless people, of whom about 70% reported that the symptom was caused by respiratory disease.[4] An analysis of the SCAPIS pilot is underway. That analysis includes only about 100 people

with breathlessness and will explore the prevalence of the major groups of factors (respiratory disease, self-reported heart disease, obesity and low physical activity).

The current proposal would be the first large-scale analysis of contributing causes of breathlessness in the population. Advantages and unique features include detailed physiological data including of coronary plaques and blood tests (NT-proBNP) in a subgroup. The large sample size would enable analyses in important groups including of causes in men and women separately, and in people with no known cardiorespiratory disease. This would be a landmark study in the epidemiology of breathlessness and help to take forward improved evaluation of breathlessness.

Population and Required Data Variables

Population: Total population for primary and secondary objectives. For the third secondary objective, people with data on NT-proBNP will be analysed.

Outcome variable: mMRC scale

Contributing causes: lung function (spirometry values); self-reported respiratory and chest symptoms, heart disease; heart rhythm (ECG); measured coronary plaques (from CTA data); blood tests (NT-proBNP and Hb) for the sub group with available data.

Confounders: age, sex, highest education, profession, hypertension (blood pressure); diabetes (fasting glucose); hyperlipidaemia (LDL, HDL and triglycerides); smoking status and pack-years; obesity (height, weight, waist circumference, waist-hip ratio); self-reported comorbidities, anxiety and depression, and physical activity.

Limitations and Challenges

A limitation is the cross-sectional nature of the data.

TRF authors

Magnus Ekström, Josefin Sundh, Eva Lindberg

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L11. Chronic rhinosinusitis (CRS) – prevalence and associated comorbidities

Objectives

Primary:
To study the prevalence of the CRS phenotype, especially in relation to co-morbidities

Description of Analysis

CRS is diagnosed on answers from items 145-152. Occupational exposures, smoking habits and socioeconomic factors are based on items 1 – 28 and 95 - 104. Co-morbidities and respiratory disease are based on items 29 -51. Used medications item 53. Sleep 136 – 144. Lung function FEV1 and FVC will be based on eCRF data.

The outcome, CRS, will be defined according to certain items, and cross-sectional associations with smoking and obstructive airways disease will be analyzed using multiple logistic regression models. Potential confounders will be identified from the literature.

Significance/Rationale

Chronic rhinosinusitis (CRS) is a chronic upper airway inflammatory disease closely related to nasal polyps, asthma and COPD. According the international consensus definition (EPOS), CRS is defined symptoms of nasal obstruction and/or nasal discharge for more than 3 months with additional facial pain and loss of their sense of smell (Fokkens 2012). One study has estimated CRS to 11% of the population, but otherwise data are lacking (Hastan 2011). The patients with more severe CRS are subject to repeated sinonasal surgery procedures in general anesthesia associated with risk for intracranial complications and high treatment costs. The etiology behind CRS remains unclear, but factors associated with chronic rhinitis, such as obstructive airways disease, and smoking are probably of importance (Bergqvist 2016).

The planned project in SCAPIS will increase the knowledge whether occupational exposures and co-morbidities are associated with CRS. The SCAPIS cohort is unique in size and geographical spread and the study will be the first to investigate the importance of certain co-morbidities in relation to CRS.

Population and Required Data Variables

Total population for primary and secondary objectives.
CRS is diagnosed on answers from items 145-152. Smoking habits and socioeconomic factors are based on items 1 – 28 and 95 - 104. Co-morbidities and respiratory disease are based on items 29 -51. Used medications item 53. Sleep 136 – 144. Lung function FEV1 and FVC will be based on eCRF data.

Limitations and Challenges

The limitation of the proposed studies is the cross-sectional design

TRF authors

Johan Hellgren, Ulrika Clarhed, Eva Lindberg, Kjell Torén

References

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L12. Lung manifestations in subjects with Rheumatoid Arthritis

Objectives

To study the prevalence and characteristics of lung function impairments in patients with Rheumatoid Arthritis.

Description of Analysis

Rheumatoid Arthritis (RA) is a common disease with lung changes known to be an important cause of morbidity and mortality. The reported incidence of lung involvement varies largely between studies from 5 to over 50 percent, with a clinically significant portion according to latest reports being about 10%. This include interstitial lung disease, but also an increased risk of bronchiectasis and COPD.

Population

In this investigation we will use data from lung function measurements from SCAPIS for a comparative, cross-sectional analysis of those with RA in comparison to those without. The prevalence of RA is 0.5-1% in European populations with an incidence maximum around 50 years of age. We estimate that we will identify approximately 150-300 cases. This should provide sufficient data for comparing the lung function in the RA group with those without, including identifying subgroups within first group; i.e. those with obstructive and restrictive signs. Also, interstitial lung abnormalities on computed tomography may be evaluated through eCRF.

Statistical analyses

We will compare the mean values and distribution of various lung function variables between the group with and without RA. We will perform both unadjusted and adjusted analyses. In the adjusted analyses we will include potential confounders such as sex, age, BMI and smoking history. We will also do sex stratified analyses. In the RA group we will analyse correlation between various lung function variables and known and suspected risk factors (smoking, occupational exposure etc)

We have made no formal power calculation but this study is one of the largest studies investigating this association.

Significance/Rationale

The SCAPIS study provides a unique opportunity to investigate the prevalence and characteristics of lung impairment in RA as well as an opportunity of identify risk factors for lung involvement within this group. This can affect how we screen RA patients for lung changes and potentially affect their treatment with early identification of lung impairment.

Population and Required Data Variables

• Lung function data in the form of FEV1, FVC; FEV1/FVC ratio before and after bronchodilation, DLCO and variables from the IOS measurements (from centres where this has been done).

• Questionnaire data for whether they have RA including year of diagnosis and treatment for connective tissue disease, smoking status including pack years, socioeconomic status including profession, environmental exposures, respiratory and allergic symptoms, level of physical activity, comorbidities including other known lung diseases.
• Anthropometric data: Height, weight, BMI.
• eCRF data from computed tomography on interstitial lung abnormalities

Limitations and Challenges

The data will be based on self-reported RA which is a limitation. As this is a cross-sectional analyses we cannot say anything for certain about cause and effect.

TRF authors

Emil Ekbom, Christer Jansson and Eva Lindberg, Uppsala, Magnus Sköld, Ida Pesonen, Stockholm

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L14. Physical activity – an independent risk factor for sleep disorders – a population-based analysis

Objectives

Primary objective:

- To determine the influence of physical activity on occurrence of sleep complaints in a population-based cohort stratified for traditional risk factors including gender, body composition, socio-economic status, educational level, and psychiatric comorbidity

Secondary objectives:

- To study the association between physical activity and the degree of daytime sleepiness in relation to anthropometric factors and comorbidities
- To study the influence of the degree of physical activity on the increased likelihood of obstructive sleep apnea (snoring, witnessed apneas, and excessive daytime sleepiness)

Description of Analysis

All available patients from the six SCAPIS centers with SCAPIS CORE questionnaire data together with accelerometer data (at least 600 minutes of accelerometer wear-time per day for at least 4 days) will be included. According to well established standards, sleep complaints will be defined as follows: Short sleep (question 137, less than 6 hours), difficulties initiating sleep (question 138, ≥3 nights/week), difficulties maintaining sleep and early morning awakening (questions 139 and 140; ≥3 nights/week), insomnia like sleep disorder (questions 138, 139 and 140, all sleep complaints ≥3 nights/week, plus habitual sleep <6 hours, plus general sleep quality “bad” or “very bad” (question 136)). The likelihood of obstructive sleep apnea will be defined by questions 143 and 144 (snoring often or very often plus witnessed apnea plus excessive daytime sleepiness (Epworth Sleepiness Score 11 and above)).

Various activity-related markers determined by accelerometer during wakefulness are determined (time spent sedentary, light-intensity physical activity, moderate to vigorous intensity physical activity) and subdivided into sections of morning, afternoon and evening. Multivariate models will be constructed with the sleep complaints listed above as the main outcome variables. Confounding factors to be probed in the statistical analyses include age, gender, socio-economic status (highest education level), comorbidities like depression/anxiety, hypertension/diabetes, and marital status.

A separate analysis will address the influence of physical activity on daytime sleepiness assessed with the Epworth Sleepiness Scale (cut off for ESS score 11 and above).

Significance/Rationale

Sleep disorders like insomnia, shortened habitual sleep time, hypersomnia and sleep apnea are highly frequent in modern society with increasing prevalence. Sedentary lifestyle, increased stress levels, high exposure to light and intake of alcohol, caffeine, and nicotine have been identified as potential causes for the high prevalence of sleep disorders. Non-pharmacological management of sleep disorders include increased physical activity and the reduced intake of stimulants like caffeine and nicotine. In fact, recent accelerometer data indicate a strong positive association between physical activity and sleep length and sleep efficacy. However, data are collected in small selected groups of individuals or preselected cohorts of patients with an increased number of comorbidities.

Previous data suggests that low degree of physical activity is an independent predictor for development of sleep apnea, insomnia and hypersomnia independent of traditional risk factors like obesity, age and gender. Particularly moderate evening activity assessed by actigraphy may be particularly protective against overnight OSA and vigorous exercise in the morning but not in the evening has shown beneficial effects on sleep efficacy and daytime well-being.

Population and Required Data Variables

Population:
All SCAPIS participants with complete dataset including accelerometric data and sleep variables (question 137-144).

Required variables:
Percentage time spent sedentary
Percentage time of light-intensity physical activity
Percentage time of moderate to vigorous intensity physical activity
Mean physical activity (cpm) from the accelerometer recording
Full polygraphic recording during sleep if applicable
Anthropometric data
Cardio-metabolic comorbidities
Psychiatric comorbidity
Core questionnaire (question 30)
• Self-reported sleep apnoea diagnosis
• Self-reported sleep apnoea treatment
Socio-economic status, education level, marital status

Limitations and Challenges

Limitations:
Incomplete data in any aspect regarding accelerometer recordings
Cross-sectional data, incomplete phenotyping of different sleep apnoea-subtypes

Challenges:
Handling of missing data in the analysis

Exact pattern of time spent sedentary/ light-intensity/ moderate to vigorous physical activity to be determined in a large population based sample
Verification of the self-reported insomnia and sleep apnoea diagnosis

TRF authors

Lead authors: Zou D and the SCAPIS Sleep Group (Blomberg A, Franklin K, Grote L, Hedner J, Jansson C, Lindberg E, Sahlin C, Theorell Haglöw J)

References

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Priority 3 (7 publications)

K2. The association between nonalcoholic fatty liver disease (NAFLD), visceral fat distribution, low grade inflammation and subclinical atherosclerotic burden in middle-aged adults in people with different stages of dysglycemia compared to normoglycemic persons

Objectives

To explore the association between NAFLD and visceral fat distribution, low grade inflammation and prevalent subclinical atherosclerosis in patients with type 2 diabetes (T2DM), prediabetes and in normoglycemic people.

Description of Analysis

From the interim analyses we anticipate that we will have 2400 T2DM and 4200 IFG-subjects in the entire SCAPIS study population. The dysglycemic categories, T2DM and prediabetes, will be compared with each other and with normoglycemic subjects.

Significance/Rationale

Cardiovascular diseases have remained the leading causes of death globally in the last 15 years. Patients with type 2 diabetes have risks of death and cardiovascular events that are 2 to 4 times as great as the risks in the general population [1]. Type 2 diabetes is usually preceded by a “pre-diabetic” state, characterized by elevated levels of blood glucose i.e. IFG or impaired glucose tolerance, which also entails an elevated risk for CVD [2]. Obesity and dysglycemia are major risk factors for NAFLD [3] and it is a significant association of hepatic steatosis with subclinical CVD outcomes [4,5]. Further understanding of the association between NAFLD the prevalence and characteristics of atherosclerosis in the coronary and carotid arteries in people with different stages of dysglycemia compared to normoglycemic persons is potentially useful for improvement of risk prediction and tailored preventive interventions in the future.

Population and Required Data Variables

Sample

All study participants with T2DM, pre-diabetes, and normoglycemic subjects.

Subsamples

1. Persons with / without known coronary artery disease or symptoms compatible with coronary artery disease.
2. Men / women

Outcomes

To be determined from the following variables, all continuous or ordinal variables from the eCRF:

1. Assessment of hepatic steatosis and visceral adiposity (when available)
2. Total number of plaques in the carotid arteries.
3. Number of major coronary arteries with any >50 % stenosis
4. Number of segments with <50 % stenosis
5. Number of segments with >50% stenosis
6. Number of segments without any plaques
7. Number of segments with mixed plaques
8. Number of missing segments
9. Number of non-assessable segments
10. Coronary calcium score
11. Number of coronary stents
12. Number of coronary grafts
13. No visible coronary artery disease (0/1)
14. DUKE risk score
15. Stenosis in proximal left main descending artery (segment 6, 0/1)
16. Anomalous origin of any coronary artery (0/1), with free text specification

Exposures

1. T2DM/IFG/Normoglycemic subjects
2. Physical activity (sedentary time, LIPA, MVPA)
3. Socioeconomic status (highest education, vocation)
4. Tobacco habits (current dose, pack-years, stop date if stopped)
5. History of cardiovascular diseases (coronary disease, heart failure, valvular disease, atrial fibrillation, stroke, peripheral artery disease)
6. Body mass index, waist and hip circumference
7. Systolic and diastolic blood pressures
8. Cholesterol, LDL, HDL, TG, glucose, creatinine, hs-CRP.
9. Heredity for cardiovascular diseases and its risk factors

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K3. Differences between coronary and carotid atherosclerosis in terms of ectopic fat distribution

Objectives

The primary objective is to see if ectopic fat distribution, liver fat and visceral fat (pericardial fat?) differs between coronary and carotid atherosclerosis.

Description of Analysis

In the total population:

1. Evaluate ectopic fat distribution, liver fat and visceral fat (pericardial fat?) in those without coronary or carotid atherosclerosis (referent), coronary or carotid atherosclerosis only and both conditions. Co-variates should be age sex, total fat mass/BMI/SAT, traditional CV risk factors and some life-style factors, such as alcohol intake, SES, smoking and exercise habits.

Significance/Rationale

The present study will be the first comprehensive evaluation of the differences in ectopic fat distribution between coronary or carotid atherosclerosis.
It could identify/validate new pathways leading to atherosclerosis.

Population and Required Data Variables

The total population (excluding those with disabling disorders)

Limitations and Challenges

This is a cross-sectional study without any hard outcomes.
It is possible that the combination of coronary or carotid atherosclerosis is too infrequent to have a good statistical power in the evaluation.

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K4. Association between physical activity pattern and fat depots

Objectives

The primary objective is to increase our knowledge about the cross-sectional association between sub-components of the physical activity pattern (PAP, i.e. the frequency, pattern and duration of low, moderate and vigorous intensity activity as well as sedentary behaviour over a period of time) and fat depots (assessed as intra-muscular, hepatic, visceral and epicardial fat). Sub-group analyses will be performed for age, gender, smoking-status, diabetics/pre-/non-diabetics, BMI-status and waist-hip ratio. In stratified analyses, using non-linear analyses (spline regressions), we will analysis relations between PAP and depots in search for thresholds, which then can be used for the development of PAP recommendations in specific subgroups.

Description of Analysis

Only a limited number of studies exist on the relation between PAP and fat depots, based on objective measurements [1, 2], i.e not using traditional self-reported PAP through questionnaires. Previous studies [1-4] have indicated some gender differences, however, with limited power (size of population) to make further analyses across important subgroups. Also, the latest imaging techniques for detection of epicardial fat has not been fully used. We will use accelerometer data and CT-data on fat depots, together with other eCRF in the whole SCAPIS cohort as potential confounders. We will use regressions and general/linear mixed models or linear models for analyses. PAP-data will be analysed traditionally and composite data analysis (CoDA) and/or isotemporal substitution will be applied. Long et al [1] found correlation between visceral fat, liver fat and MVPA among 1060 subjects and Murabito et al [2] found the same in 1249 subjects. This would allow detailed analyses in subgroups down to approximately 1000-1200 individuals, with the additional advantage of the latest accelerometry algorhithms, providing the highest quality PA-data, to match the advantages of high quality imaging and large cohort.

Significance/Rationale

As several subcomponents of the PAP have been shown to drastically affect the risk for fatal and non-fatal CVDs, the detailed relations between these factors should be identified. This paper will present the relation between PAP and fat depots, and will be a base for future clinical advice and preventive work. As several subgroups are analysed separately, more specified advice can be generated from these analyses. Also, this will be a pioneer paper in trying to create PA recommendations for CVD prevention based on objective data, which is urgently needed. The chosen methodology is unique in size and quality measures for both exposure and outcome.

Limitations and Challenges

A main limitation in the coming analyses is the cross-sectional nature of data. However, given the size of the cohort, which allows for detailed sub-group analyses, the results will be of great clinical importance. The statistical analyses are complex and during the work with establishing the statistical analyses plan (SAP), additional analyses may prove useful and important.

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K7. Clinical consequences of a screening program using coronary computed tomography angiography (CCTA) and carotid ultrasound in a random sample of middle age men and women

Objectives

To determine the clinical consequences of a screening program using CCTA and carotid ultrasound in middle age men and women.

Description of Analysis

In primary prevention the use of risk assessment with the Framingham risk score or ESC SCORE is recommended.

CCTA has now been available in the clinical routine for more than a decade. There has been a continuous improvement regarding image quality and radiation exposure with doses clearly lower than from a traditional invasive coronary angiography, and CCTA has been suggested as useful for screening also in asymptomatic individuals. So far there are no large studies examining the clinical consequences of using CCTA together with carotid ultrasound for screening purposes.

In the present study, we will examine the association between findings on CCTA and carotid ultrasound and subsequent results of non-invasive and invasive examinations, revascularization (PCI and coronary artery by-pass grafting (CABG)), and pharmacological treatment (Aspirin, P2Y12-rec blockers, lipid-lowering and antihypertensive treatments).

Some chart reviewing will be necessary to get information about non-invasive tests. Regarding coronary angiography and revascularization data will be obtained by linking to Swedeheart. Regarding medical treatment data will be retrieved from the drug prescription registry.

Significance/Rationale

CCTA is an easily available method and its use for screening purposes is appealing. It´s important to describe the clinical consequences of such program.

Population and Required Data Variables

Sample
Entire SCAPIS cohort

Exposure
Findings on CCTA and carotid ultrasound.

Outcome

• Non-invasive (Exercise-ECG, stress-echocardiography, nuclear imaging) and invasive (coronary angiography) examinations
• Revascularization (PCI or CABG)
• Pharmacological treatment (Aspirin, P2Y12-rec blockers, lipid-lowering and antihypertensive treatments).

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K17. Pregnancy complications, fetal outcomes, and coronary atherosclerosis in Swedish women

Objectives

To analyse the effect of metabolic and vascular pregnancy complications, fetal outcomes and pattern of coronary atherosclerosis in women.

Population and Required Data Variables

Sample

Parous women in the SCAPIS cohort without clinical coronary artery disease (prior MI, coronary interventions) or heart failure, valvular disease, atrial fibrillation, stroke, peripheral artery disease who are also registered in the Medical Birth Registry.

Outcomes

1. Visible coronary artery disease (0/1);
2. Any major coronary artery with a >50 % stenosis
3. >50% stenosis in ≥2 major coronary arteries

Main exposures

- Small for gestational age
- Heavy for gestational age
- Premature child (created from MBR variables)
- Stillborn child
- History of infertility
- Hypertension in pregnancy
- Preeclampsia
- Diabetes in pregnancy
- Height and weight at first antenatal visit

Potential confounders

1. Years of education
2. Social support, emotional support
3. Marital status
4. Country of birth
5. Cigarette smoking (current, prior, pack-years)
6. Body mass index, waist and hip circumference
7. Weight gain between antenatal visit and SCAPIS weight
8. Lipids (LDL, HDL, TG)
9. Lipid treatment
10. Blood pressure
11. Hypertension (known or ≥140/90)
12. Antihypertensive treatment
13. Hypertension (prior to pregnancy according to the MBR)
14. Diabetes (prior to pregnancy according to the MBR)
15. Tobacco use during pregnancy

16. Diabetes (known or diagnosed at SCAPIS examination)
17. Reproductive history (questionnaire)
18. Menopause (yes/no; menopausal age)
19. Family history of coronary heart disease (any of mother, father, sibling, any of with early disease)
20. Stress level (home, work-related, life events)
21. Physical activity (sedentary time, LIPA, MVPA)

Data analysis

Descriptive data provided as percentages (n), means (SD) or median (IQR). Outcome data will be analysed using conventional logistic regression and multivariable techniques in order to quantify the influence of major exposures.

Rationale

Pregnancy requires an extensive and coordinated maternal response and substantial cardiovascular and metabolic adaptation. Pregnancy complications such as preeclampsia, gestational hypertension, gestational diabetes mellitus, and delivery of a preterm or intrauterine growth-retarded infant may signal maladaption, with links to cardiovascular disease (CVD) decades later (1,2). In a study from California, over one third of mothers experienced at least one of these complications, and any one of these signalled increased risk of subsequent CVD death over a 5-decade of follow-up (3). Still, mechanisms remain unclear, and imaging studies of vascular beds in relation to these complications are rare. One recent study found that 30% of women aged 45 to 55 years, with a history of preeclampsia had signs of atherosclerosis estimated as coronary artery calcification (CACS) compared to 18% of controls from the Multi-Ethnic Study of Atherosclerosis (MESA) (4). Data on coronary plaques was only available in women with a history of preeclampsia and showed that 47% had at least one plaque. Coronary angiography data from SCAPIS combined with data from the Medical Birth Registry provide unique opportunities to investigate these issues in parous women.

Limitations and Challenges

Traditional regression modelling from theory and subject matter knowledge is prone to bias via subjective preferences and expectations. The project requires collaboration with external partners (reproductive epidemiology/obstetrician).

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B5. Proteomics and metabolomics and ectopic fat distribution

Objectives

The primary objective is to evaluate if how ectopic fat distribution, here measured as liver fat and visceral fat, is associated with the proteomic and metabolomic profile independently of general obesity. Do ectopic fat depots relate to different proteomic and metabolomic profiles compared to the profiles associated with subcutaneous fat and compared to each other?

Description of Analysis

In conditions with excess caloric intake comparted to energy expenditure, fat can be deposited either in subcutaneous adipose tissue (SAT) or in ectopic depots, such as the liver and visceral adipose tissue (VAT). To date, there is only a limited knowledge on which mechanisms that determines the site of fat storage. A GWAS on this matter have only disclosed a few genes related to ectopic fat distribution. Two recent studies in 300 obese subjects have shown that the protein and metabolome profiles might be different for liver fat and visceral fat. In SCAPIS, this could be evaluated in a much larger population-based sample.

In the SCAPIS omics subcohort (n=5000)

Analyses:

1. Regress proteins/metabolites one by one vs liver fat, SAT and VAT (as well as the VAT/SAT ratio). Co-variates should be age sex, BMI (to account for general obesity), and some life-style factors, such as alcohol intake, SES, smoking and exercise habits.
2. Include a sex-interaction in all models, and if significant, stratify the material by sex.
3. Evaluate the overlap /non-overlap between the proteomic and metabolomic profiles between liver fat, SAT and VAT (as well as the VAT/SAT ratio).
4. Two-way Mendelian Randomization could be used for causal estimations of interesting proteins/metabolites vs fat distribution using already published GWASes.

Significance/Rationale

It is not known if different ectopic fat depots are linked to different proteomic and metabolomic profiles. This analysis might disclose some of these mechanisms or disclose mechanisms whereby ectopic fat could cause CVD.

Population and Required Data Variables

SCAPIS omics subcohort. The variables required are given in the analysis section.

Limitations and Challenges

This is a cross-sectional study without any hard outcomes.

TRF authors

Lars Lind and others

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L16. Risk for lung cancer in pulmonary nodules detected in a general population, data from the Swedish CArdioPulmonary bioImage Study (SCAPIS)

Objectives

The primary objective is to investigate the risk for lung cancer in relation to presence and characteristics of pulmonary nodules in the general population-based cohort SCAPIS. The secondary objective is to use the information gained to suggest follow-up guidelines for incidental nodules among individuals with low risk of developing lung cancer.

Description of Analysis

Background: A pulmonary nodule can correspond to an early-stage lung cancer. The increased use of computed tomography (CT) has amplified nodule detection. Current guidelines (1,2) are based on lung cancer screening studies performed in populations of smokers and former smokers. However, incidental pulmonary nodules are commonly found in never-smokers (3), a field where scientific evidence regarding management of nodules is scarce. On the other hand, there are data indicating that that the actual incidence of lung cancer in never smokers is increasing (4). A recent study from Japan including 12,114 subjects of which 49.70% were never-smokers reported that the odds ratio (OR) of lung cancer detection in smokers with <30 pack-years of smoking was the same as that in the never-smokers (5). The SCAPIS population could provide new knowledge regarding the risk of lung cancer in never-smokers with pulmonary nodules.

Analysis: Follow-up of participants in SCAPIS will be performed by matching the study population with Swedish Registers. The dependency of nodule characteristics, participant characteristics and concurrent parenchymal findings will be analysed by multiple regression analyses. Based on the results from pilotSCAPIS, an estimated 10 000 subjects will have nodules, with 4500 subjects qualifying for surveillance. Assuming that the presence of nodules requiring follow-up doubles the risk of lung cancer, the probability is 0.98 to get a statistically significant difference between the groups five years after nodule detection.

Significance/Rationale

Although not included in the overall aim of SCAPIS, it is of fundamental importance to investigate the value of surveillance or work-up of incidental nodules in the general population and from these data design an evidence-based algorithm for nodule follow-up. A reduction of the numeral follow-up examinations recommended in current guidelines would have a great impact on the use of the limited health care resources of the society, and result in a reduced radiation burden to the population, thereby decreasing the risk for radiation induced cancers. The analysis could also provide information on other risk factors for lung cancer in never smokers.

Population and Required Data Variables

Population: Total SCAPIS population (30 000 individuals).

Outcome variable: Presence of lung cancer in pulmonary nodules.

Associated factors/confounders: Sex, age, height, weight, BMI, background characteristics, highest education, occupational exposures, nicotine use including detailed smoking habits and pack-years, data on lung diseases (Asthma/COPD/Emphysema/other lung disease), rheumatic diseases, comorbidities (diabetes, tuberculosis, cancer), airway symptoms; cough (whether it is chronic, productive) and breathlessness, heredity of lung cancer. Spirometry (FEV1, FVC, VC, DlCO), blood test (hsCRP), Pulmonary CT variables from eCRF.

Limitations and Challenges

The main challenge of the study is the relative low incidence of lung cancer (1). However, our calculations indicate sufficient power of the study. Another limitation is the inclusion of participants between 50 to 64 years of age only, as this impacts generalizability of the results. On the other hand, during this period lung cancer tumor incidence increases significantly.

TRF authors

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