Göteborg, 2025-06-19

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 the complete data set from SCAPIS is sent to the principal researcher, or when the publication is published.

The TRF:s have been updated during the spring of 2020. The TRF:s for the SCAPIS genome-wide association studies were added during the winter of 2022. The TRF:s for the SCAPIS biomarker studies were added during the spring of 2023. The TRF:s were originally composed in 2018.

Contacts

Göran Bergström
SCAPIS Director
goran.bergstrom@hjl.gu.se

Rebecca Josefson
SCAPIS Publication Support
publications@scapis.org

Table of contents

Priority 2 (1 publication)

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

EMBARGO on research hypothesis until 2025-11-04

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

1. Murray K, Godbole S, Natarajan L, Full K, Hipp JA, Glanz K, Mitchell J, Laden F, James P, Quante M, Kerr J. The relations between sleep, time of physical activity, and time outdoors among adult women. PLoS One. 2017 Sep 6;12(9):e0182013. doi: 10.1371
2. Mitchell JA, Godbole S, Moran K, Murray K, James P, Laden F, Hipp JA, Kerr J, Glanz K. No Evidence of Reciprocal Associations between Daily Sleep and Physical Activity. Med Sci Sports Exerc. 2016 Oct;48(10):1950-6.

Return to Table of contents

Priority 3 (5 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

EMBARGO on research hypothesis until 2026-06-03

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

References

1. Rawshani A, Rawshani A, Franzen S, et al. Mortality and cardiovascular disease in type 1 and type 2 diabetes. N Engl J Med 2017; 376: 1407-18.
2. Norhammar A, Tenerz A, Nilsson G, Hamsten A, Efendíc S, Rydén L, Malmberg K. Glucose metabolism in patients with acute myocardial infarction and no previous diagnosis of diabetes mellitus: a prospective study. Lancet. 2002;22;359(9324):2140-3.
3. Al Rifai M, Silverman MG, Nasir K, Budoff MJ, Blankstein R, Szklo M, Katz R, Blumenthal RS, Blaha MJ. The association of nonalcoholic fatty liver disease, obesity, and metabolic syndrome, with systemic inflammation and subclinical atherosclerosis: the Multi-Ethnic Study of Atherosclerosis (MESA). Atherosclerosis 2015;239(2):629-33
4. A Mellinger JL, Pencina KM, Massaro JM, Hoffmann U, Seshadri S, Fox CS, O'Donnell CJ, Speliotes EK., Hepatic steatosis and cardiovascular disease outcomes: An analysis of the Framingham Heart Study. J Hepatol. 2015;63(2):470-6.
5. Idilman, I.S., et al., Nonalcoholic fatty liver disease is associated with significant coronary artery disease in type 2 diabetic patients: a computed tomography angiography study 2. J Diabetes. 2015;7(2):279-86.

Return to Table of contents

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.

Return to Table of contents

K4. Association between physical activity pattern and fat depots

EMBARGO on research hypothesis until 2026-04-10

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.

References

1. Long, M.T., et al., Hepatic steatosis is associated with lower levels of physical activity measured via accelerometry. Obesity (Silver Spring), 2015. 23(6): p. 1259-66.
2. Murabito, J.M., et al., Moderate-to-vigorous physical activity with accelerometry is associated with visceral adipose tissue in adults. J Am Heart Assoc, 2015. 4(3): p. e001379.
3. Fischer, K., et al., Association of Habitual Patterns and Types of Physical Activity and Inactivity with MRI-Determined Total Volumes of Visceral and Subcutaneous Abdominal Adipose Tissue in a General White Population. PLoS One, 2015. 10(11): p. e0143925.
4. Whitaker, K.M., et al., Sedentary Behavior, Physical Activity, and Abdominal Adipose Tissue Deposition. Med Sci Sports Exerc, 2017. 49(3): p. 450-458.

Return to Table of contents

B5. Proteomics and metabolomics and ectopic fat distribution

EMBARGO on research hypothesis until 2026-02-13

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

Return to Table of contents

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

Åse Johnsson, Jenny Vikgren, Kjell Torén

References

1. https://www.cancercentrum.se/samverkan/cancerdiagnoser/lunga-och lungsack/vardprogram/
2. MacMahon H, Naidich DP, Goo JM, Lee KS, Leung AN, Mayo JR, et al. Guidelines for Management of Incidental Pulmonary Nodules Detected on CT Images: From the Fleischner Society 2017. Radiology. 2017 Jul;284(1):228-243
3. Robertson J, Nicholls S, Bardin P, Ptasznik R, Steinfort D, Miller A. Incidental Pulmonary Nodules Are Common on CT Coronary Angiogram and Have a Significant Cost Impact. Heart Lung Circ. 2019 Feb;28(2):295-301
4. Pelosof L, Ahn C, Gao A, Horn L, Madrigales A, Cox J, McGavic D, Minna JD, Gazdar AF, Schiller J. Proportion of Never-Smoker Non-Small Cell Lung Cancer Patients at Three Diverse Institutions. J Natl Cancer Inst. 2017 Jan 28;109(7)
5. Kakinuma R, Muramatsu Y, Asamura H, Watanabe SI, Kusumoto M, Tsuchida T, Kaneko M, Tsuta K, Maeshima AM, Ishii G, Nagai K, Yamaji T, Matsuda T, Moriyama N. Low-dose CT lung cancer screening in never-smokers and smokers: results of an eight-year observational study. Transl Lung Cancer Res. 2020 Feb;9(1):10-22.

Return to Table of contents

Genome-wide association studies (2 publications)

GWAS-B. A genome-wide association study of liver fat content in SCAPIS

EMBARGO on research hypothesis until 2026-05-22

Objectives

To identify genetic variants for liver fat content and steatosis and to clarify their relation to future risk of liver diseases and cardiometabolic diseases.

Description of Analysis

PROPOSED STUDY

GWAS for liver fat content and steatosis in the whole SCAPIS cohort. Analysis of genetic correlations across risk factors and hard endpoints.

BACKGROUND

Non-alcoholic fatty liver disease (NAFLD) affects as much as one quarter of adult population in the world and is defined as a condition in which the amount of fat exceeds 5% of hepatocytes in the nonappearance of secondary causes of lipid accumulation or clinically substantial alcohol intake. A growing body of evidence indicates that NAFLD is strongly associated with an increased risk of cardiovascular disease[1].

GWAS studies have revealed genetic variants in five genes that robustly associate with the susceptibility to and progression of NAFLD: PNPLA3, TM6SF2, GCKR, MBOAT7 and HSD17B13[2-5]. A GWAS in 14,440 Europeans from the UK-biobank, with MRI-based liver cT1 data, a measure of severity of steatohepatitis and liver fibrosis, identified additionally independent genetic variants in SLC30A10, SLC39A8, PCK2 and TMPRSS6 associated with liver cT1[6]. In the same study, insulin resistance, type 2 diabetes, NAFLD and BMI were causally associated with elevated cT1, whilst favorable adiposity was found to be protective using Mendelian Randomization (MR). Another GWAS study used an MRI-based machine-learning (ML) algorithm to estimate liver fat from a truth dataset of 4,511 middle-aged UK Biobank participants, enabling quantification in 32,192 additional individuals, and identified five novel variants in or near the MTARC1, ADH1B, TRIB1, GPAM, and MAST3 genes[7].

In GWAS/exome studies so far, liver steatosis has been assessed by 1H-MRS, CT or MRI, and the largest sample sizes with 1H-MRS, CT and MRI have been 2,815 (for exome-wide analyses)[5], 7,176 (for GWAS)[4] and 4,511 (GWAS)[7], respectively, and by

ML-based estimation 32,192 (GWAS)[7]. Together, the variants from references [2-5] have been estimated to explain around 10-20% of the heritability proportion of NAFLD[8].

ANALYSIS PLAN

GWAS analyses using imputed quality-control data will be performed for liver fat content in 30,000 SCAPIS participants and presented in Manhattan plots. Analyses will be adjusted for age, sex and principal components.

With the aim to determine which pathways mediate the associations between genes and liver fat content/steatosis, we will study if the associations are modified by established risk factors.

Genetic correlations and causal pathways across risk factors and hard endpoints will be investigated using co-localization analysis, disease-disease networks, and Mendelian randomization where applicable. In silico functional follow-up studies may be performed, mainly for novel loci.

MR studies will be performed with instrumental variants based on genetic variants of liver fat content on future risk of liver disease, , cardiovascular disease and type 2 diabetes including analyses in other data sets with longitudinal follow-up such as the UK Biobank and Malmö Diet and Cancer Study for association with incident events.

Significance/Rationale

Sample size has remained as the main limitation of GWAS studies of directly measured liver fat content or steatosis, and for further understanding of NAFLD biology, individual risk stratification, and drug development, larger GWAS studies are needed. The sample size of SCAPIS, with liver steatosis measured by CT in ?30,000 participants, is more than 4-fold higher compared to earlier studies and will importantly increase the statistical power compared to earlier studies. With the world-unique sample size of SCAPIS for CT data, the GWAS analyses are expected to reveal novel genetic determinants of liver fat content and providing important novel understanding of NAFLD, individual risk stratification, and drug-target identification. The data will be further used for disease prediction and Mendelian Randomization studies utilizing polygenetic risk scores of the identified genetic variants. Given the importance of NAFLD in cardiometabolic diseases, understanding of biology behind by using genetic tools is of high scientific and medical value, and in line with SCAPIS overall aim and informed consent.

Population and Required Data Variables

Study population

The entire SCAPIS population, possibly restricted to Swedish/European ancestry if needed due to population stratification

Main outcome variable

CT-data on liver fat (liver attenuation values i.e. Hounsfield units)

Demographics/medical history

- Age, gender, study site
- Country of birth, parent's country of birth
- Lipid lowering medication
- History of diabetes and CVD, family history of CVD and diabetes

Genetic variables

- Genotyping data from the Illumina GSA-MD array, quality controlled and imputed according to SCAPIS standard procedure

Potential mediators

- Risk factors: BMI, total cholesterol, LDL, HDL, triglycerides, glucose status, blood pressure, alcohol intake
- Liver markers: ALAT, GGT, ALP

Limitations and Challenges

Although this will be the largest study of its kind, the power is restricted for variants with low allele frequency and modest effect size.

Cross-sectional nature of SCAPIS and the limited age interval.

TRF authors

Marju Orho-Melander, Anders Gummesson

References

1. Targher G, Byrne CD, Tilg H: NAFLD and increased risk of cardiovascular disease: clinical associations, pathophysiological mechanisms and pharmacological implications. Gut. 2020 Apr 22. pii: gutjnl-2020-320622. doi: 10.1136/gutjnl-2020-320622
2. Romeo S, Sanyal A, Valenti L: Leveraging Human Genetics to Identify Potential New Treatments for Fatty Liver Disease. Cell Metab. 2020 31:35-45
3. Romeo S, Kozlitina J, Xing C, Pertsemlidis A, Cox D, Pennacchio LA, et al.Genetic variation in PNPLA3 confers susceptibility to nonalcoholic fatty liver disease. Nat Genet 2008 40:1461–1465.
4. Speliotes EK, Yerges-Armstrong LM, Wu J, Hernaez R, Kim LJ, Palmer CD, et al. Genome-wide association analysis identifies variants associated with nonalcoholic fatty liver disease that have distinct effects on metabolic traits. PLoS Genet 2011;7:e1001324.
5. Kozlitina J, Smagris E, Stender S, Nordestgaard BG, Zhou HH, Tybjaerg-Hansen A, et al. Exome-wide association study identifies a TM6SF2 variant that confers susceptibility to nonalcoholic fatty liver disease. Nat Genet 2014;46:352–356.
6. Parisinos CA, Wilman HR, Thomas EL, Kelly M, Nicholls RC, McGonigle J, Neubauer S, Hingorani AD, Patel RS, Hemingway H, Bell JD, Banerjee R, Yaghootkar H: Genome-wide and Mendelian randomisation studies of liver MRI yield insights into the pathogenesis of steatohepatitis. J Hepatol. 2020; 73:241-251.
7. Haas ME, Pirruccello JP, Friedman SN, Wang M, Emdin CA, Ajmera VH, Simon TG, Homburger JR, Guo X, Budoff M, Corey KE, Zhou AY, Philippakis A, Ellinor PT, Loomba R, Batra P, Khera AV:Machine learning enables new insights into genetic contributions to liver fat accumulation. Cell Genom. 2021; 1:100066.
8. Sookoian, S. & Pirola, C. J. Genetic predisposition in nonalcoholic fatty liver disease. Clin. Mol. Hepatol. 2017, 23: 1–12.

Return to Table of contents

GWAS-C. A genome-wide study of intra-abdominal and intramuscular fat

EMBARGO on research hypothesis until 2026-05-22

Objectives

To identify genetic variants for intra-abdominal (visceral and subcutaneous) and intramuscular fat distribution, to understand differences in genetic determinants of the different fat depots and to clarify their relation to future risk of cardiometabolic diseases.

Description of Analysis

PROPOSED STUDY

GWAS for visceral and subcutaneous fat and intramuscular fat in the whole SCAPIS cohort and stratified by sex. Analysis of genetic associations across the different fat depots, risk factors and hard endpoints.

BACKGROUND

Almost 40% of adults worldwide are either overweight or obese[1]. It is well established that adiposity is a risk factor for higher morbidity and mortality and that the location and distribution of excess fat provide more information than general adiposity for disease prediction. Individuals with higher central adiposity have increased risk of cardiometabolic diseases as type 2 diabetes, while individuals with higher gluteal adiposity are at lower risk, independent of BMI[2, 3].

In previous GWAS studies, fat distribution has mostly been assessed by waist-to-hip ratio (WHR) independent of overall adiposity (i.e. WHR adjusted for BMI, WHRadjBMI)[4]. Heritability estimates for body fat distribution have been estimated as ~50% in women and ~20% in men. 4 The latest meta-analysis of GWAS for WHRadjBMI in 694,649 samples identified 463 significant associations in 346 loci[5].

Several GWAS studies have investigated ectopic-fat traits

A combined multiethnic meta-analysis (n=18,332) with participants of European, African, Hispanic and Chinese ancestry, originating from 27 GWAS studies, analyzed subcutaneous and visceral fat deposits measured by CT or MRI. This study identified in total 7 new and 4 earlier described locus–trait associations[6].

More recently several studies based on the UK Biobank material (n=362,499) were performed using different methods to estimate fat depots distribution. Ninety-eight variants associated with fat distribution in the arms and trunk (29 novel and 37 sex-specific) using segmental bio-electrical impedance[7] and 14 variants (7 novel) associated with abdominal fat using MRI[8] were reported.

The genetics of intramuscular fat is largely unknown. Recently intramuscular fat has been associated with incident heart failure[9], adding a piece of information to the obesity paradox[10].

ANALYSIS PLAN

- Fat depots have been assessed by CT scans at the baseline in all SCAPIS study participants (n=30000)[11] and measured using previously described protocols[12, 13].
- Genomic DNA from study participants has been genotyped using Illumina Infinium Global Screening Array (GSA) and data have been imputed using Sanger imputation server.
- GWAS analyses based on an imputed quality-controlled data set will be performed for visceral-, subcutaneous fat, and for intramuscular fat in 30,000 SCAPIS participants using standard methods and software for genetic association analyses. Analyses will be performed in the whole population and stratified by gender, and adjusted for population stratification and additional confounders (age, sex when appropriate).
- GWAS results will be presented in Manhattan plots, genomic risk loci are defined around genome-wide significant variants; and significant loci will be presented in tables and regional association plots. Post-GWAS analysis will be functional in silico follow-up using the FUMA software. Analyses will be performed to investigate differences in genetics of the different fat depots by co-localization analysis[7]. To determine which pathways may mediate the associations between genes and the fat depots, analyses will be performed to investigate if the associations are modified by established risk factors or biomarkers from omic- data. Such data will be additionally used for further phenotypic characterization of identified genetic subgroups.
- Mendelian Randomization studies will be performed to investigate causal connections between the genetic variants identified as relevant to determine fat depots distribution and the risk of future risk of coronary heart disease, cardiovascular disease and type 2 diabetes.
- Validation of the results will be performed in independent populations where genetic and anthropometric data are available such as the UK Biobank and Malmö Diet and Cancer Study for association with incident events.

Significance/Rationale

- - GWAS-analyses in SCAPIS for visceral and subcutaneous fat depots will be the largest study so far and can be compared to the largest multi-ethnic meta-analysis so far of 27 studies with 18,332 participants of European, African, Hispanic and Chinese ancestry.
- - GWAS analysis for intra-muscular fat has not been performed before in human cohorts.

Population and Required Data Variables

Study population

- The entire SCAPIS population, possibly restricted to Swedish/European ancestry if needed due to population stratification.

Demographics/medical history

- Age, gender, study site
- Country of birth, parent's country of birth
- History of CVD or diabetes, family history of CVD or diabetes

Genetic variables

- Genotyping data from the Illumina GSA-MD array, quality controlled and imputed according to SCAPIS standard procedure.

Main outcome variables

- CT imaging data for subcutaneous and intra-abdominal fat and intramuscular fat

Potential mediators

- Risk factors: BMI, WHR, glucose status, blood pressure, serum lipids, physical activity level, smoking, socioeconomic factors.
- Novel/emergent biomarkers: Olink proteomics data, metabolomics data.

Power

A sample size of 30,000 individuals provides power in a GWAS to identify common variants (>10% allele frequency) with moderate effect size (β>0.1 SD-units per allele) for continuous traits.

Limitations and Challenges

Although this will be the largest study of its kind, the power is restricted for variants with low allele frequency and modest effect size.

Cross-sectional nature of SCAPIS and the limited age interval. Proteomics and metabolomics data is only available for a subgroup.

TRF authors

Bruna Gigante, Marju Orho-Melander

References

1. Piché ME, Tchernof A, Després JP. Obesity Phenotypes, Diabetes, and Cardiovascular Diseases. Circ Res 2020;126:1477-1500. doi: 10.1161/circresaha.120.316101
2. Pinnick KE, Nicholson G, Manolopoulos KN, et al. Distinct developmental profile of lower-body adipose tissue defines resistance against obesity-associated metabolic complications. Diabetes 2014;63:3785-3797. doi: 10.2337/db14-0385
3. Pramyothin P, Karastergiou K. What Can We Learn from Interventions That Change Fat Distribution? Curr Obes Rep 2016;5:271-281. doi: 10.1007/s13679-016- 0215-x
4. Shungin D, Winkler TW, Croteau-Chonka DC, et al. New genetic loci link adipose and insulin biology to body fat distribution. Nature 2015;518:187-196. doi: 10.1038/nature14132
5. Pulit SL, Stoneman C, Morris AP, et al. Meta-analysis of genome-wide association studies for body fat distribution in 694 649 individuals of European ancestry. Hum Mol Genet 2019;28:166-174. doi: 10.1093/hmg/ddy327
6. Chu A, Deng X, Fisher VA, Drong A, Y Z. Multiethnic genome-wide meta- analysis of ectopic fat depots identifies loci associated with adipocyte development and differentiation. . Nature Genetics 2017;49:125-130. doi:
7. Rask-Andersen M, Karlsson T, Ek WE, Johansson Å. Genome-wide association study of body fat distribution identifies adiposity loci and sex-specific genetic effects. Nature Communications 2019;10:339. doi: 10.1038/s41467-018- 08000-4
8. Ji Y, Yiorkas AM, Frau F, et al. Genome-Wide and Abdominal MRI Data Provide Evidence That a Genetically Determined Favorable Adiposity Phenotype Is Characterized by Lower Ectopic Liver Fat and Lower Risk of Type 2 Diabetes, Heart Disease, and Hypertension. Diabetes 2018;68:207-219. doi: 10.2337/db18-0708
9. Huynh K, Ayers C, Butler J, et al. Association Between Thigh Muscle Fat Infiltration and Incident Heart Failure: The Health ABC Study. JACC Heart Fail 2022;10:485-493. doi: 10.1016/j.jchf.2022.04.012
10. Oga EA, Eseyin OR. The Obesity Paradox and Heart Failure: A Systematic Review of a Decade of Evidence. J Obes 2016;2016:9040248. doi: 10.1155/2016/9040248
11. Bergström G, Berglund G, Blomberg A, et al. The Swedish CArdioPulmonary BioImage Study: objectives and design. J Intern Med 2015;278:645-659. doi: 10.1111/joim.12384
12. Faron A, Luetkens JA, Schmeel FC, et al. Quantification of fat and skeletal muscle tissue at abdominal computed tomography: associations between single-slice measurements and total compartment volumes. Abdom Radiol (NY) 2019;44:1907- 1916. doi: 10.1007/s00261-019-01912-9
13. Yamazaki H, Tauchi S, Wang J, et al. Longitudinal association of fatty pancreas with the incidence of type-2 diabetes in lean individuals: a 6-year computed tomography-based cohort study. J Gastroenterol 2020;55:712-721. doi: 10.1007/s00535-020-01683-x
14. Giambartolomei C, Vukcevic D, Schadt EE, et al. Bayesian test for colocalisation between pairs of genetic association studies using summary statistics. PLoS Genet 2014;10:e1004383. doi: 10.1371/journal.pgen.1004383

Return to Table of contents

Prospective studies – Incident cases of myocardial infarctions (5 publications)

PMI-B. Chronic airflow limitation and incident ischemic heart disease

TRF authors

Andrei Malinovschi, Per Liv (statistician), Anders Blomberg

Objectives

To examine in a longitudinal approach whether CAL increases the risk of coronary heart disease and myocardial infarction

Description of Analysis

CAL will be defined as postbronchodilatory FEV_1/FVC, either as <lower limit of normal (LLN) or <0.7 as main analysius. As secondary analysis we will also study the value of FEV_1/FVC as continuous variable.

As an additional aim we will look at the additive value of emphysema and reduced diffusing capacity for carbon monoxide on the risk of incident MI.

Individuals with normal spirometry (FEV_1/FVC, FEV_1, FVC and $D_{L,CO}$ all above LLN) and no emphysema will be used as reference group.

We will use the local SCAPIS equations to calculate LLN for the different pulmonary function testing indices.

Potential contributing causes and confounders and their inter-relations will be identified from the literature, and the required set of adjustment variables (confounders) will be defined using a Directed Acyclical Graph (DAG; www.dagitty.net).

The main outcome will be incident coronary heart disease. Possible co-variates will include age, sex, BMI, respiratory symptoms, smoking habits, socioeconomic factors, comorbidities, diffusing capacity for carbon monoxide, emphysema (in the primary analysis) (the last two named in the first analysis),

Associations between incident angina (I20) and myocardial infarction (I21) will be analyzed using Cox proportional hazards models, adjusting for covariates. Individuals with normal spirometry (see description before) and no emphysema will be a comparison group. The results will be expressed as hazard ratios (HR) with 95% CI. Interactions with smoking, sex, age group and CACS score (for example >100) at baseline will also be performed. The analyses will also be stratified for smoking and sex. Incident coronary heart disease is new-onset disease from the year of inclusion

and until end of follow-up. Persons with existing coronary heart disease at baseline will be excluded.

Significance/Rationale

The association between established COPD disease and cardiovascular morbidity, including myocardial infarction, is relatively well studied. However, the association between CAL and cardiovascular morbidity is less studied and few studies have looked longitudinally if CAL can precede and increase the risk of myocardial infarction.

Population and Required Data Variables

Population: Total SCAPIS population.

Outcome variable: Incident angina (I20) or coronary heart disease (I21)

Main predictors: CAL (and FEV_1/FVC ratio) and for subanalyses combination with impaired $D_{L,CO}$ and emphysema

Associated factors: self-reported respiratory and cardiovascular symptoms, self-reported comorbidities, coronary plaques (from CACS data), blood tests (fasting glucose, hsCRP, Hb, CRP, HbA1c, eGFR and creatinine), age, sex, highest education, blood pressure, blood lipids, smoking status, height, weight, waist circumference, waist-hip ratio, pulmonary CT variables from eCRF (with emphasis on emphysema), diffusing capacity for carbon monoxide ($D_{L,CO}$).

Limitations and Challenges

A possible limitation could be lack of power and a narrow age span (50-64 years) in the SCAPIS population. Stratified analyses (for sex, smoking habits and CACS) might be underpowered and therefore we choose to primarily study interactions.

References

1. Laurien Goedemans, Jeroen J. Bax, Victoria Delgado COPD and acute myocardial infarction. European Respiratory Review 2020
29: 190139; DOI: 10.1183/16000617.0139-2019

Return to Table of contents

PMI-C. Imaging based Ectopic Fat as an Independent Predictor of Myocardial Infarction in the General Population

EMBARGO on research hypothesis until 2025-11-22

TRF authors

Carl-Johan Carlhäll, Carl Johan Östgren

Objectives

To longitudinally investigate whether imaging based adipose tissue depots

can predict hospitalization and mortality due to coronary artery disease.

Description of Analysis

Adipose tissue depots will be based on computed tomography (CT) data:

- Visceral: area (cm^2) and attenuation in a CT slice
- Intrahepatic: attenuation in a CT slice (HU)
- Intramuscular (thigh): area (cm^2) and attenuation (HU) in a CT slice

- Subcutaneous (abdominal): area (cm^2) and attenuation (HU) in a CT slice

Potential contributing causes and confounders and their inter-relations will be identified from the literature, and the required set of adjustment variables (confounders) will be defined using a Directed Acyclical Graph (DAG; www.dagitty.net).

The main outcome will be incident coronary artery disease.

Possible covariates/cofactor variables (confounders, mediators, moderators) will include for instance: age, sex, smoking, metabolic disease, alcohol, diet, stress, socio-economic status, SCAPIS site.

Descriptive data will be presented: for categorical variables including numbers and percentages, and for continuous variables mean values and standard deviations (SD).

Relationships between time to coronary event and fat depots (perhaps separate/combined) will be analyzed using Cox proportional hazards models, adjusting for covariates. The results will be expressed as hazard ratios (HR) with 95% CI. The analyses will also be stratified for sex.

Incident coronary artery disease is new-onset disease from the year of inclusion and until end of follow-up. Persons with existing coronary artery disease at baseline will be excluded.

Significance/Rationale

Visceral adipose tissue is an established risk factor for cardiometabolic disease. Moreover, fat infiltration in the liver and skeletal muscle has also been associated to increased cardiovascular risk.

However, there is a lack of knowledge of the risk for incident myocardial infarction in a large cohort of individuals from general population samples using a comprehensive assessment of CT based adipose tissue depots including both ectopic, visceral and subcutaneous fat.

Population and Required Data Variables

Population: Total SCAPIS population.

Outcome variable: Incident coronary artery disease, either defined as new-onset hospital-care or cause-of-death defined by ICD-codes I20 – I25.

Main predictors: Fat depots: visceral, intrahepatic, intramuscular and subcutaneous.

Associated factors/confounders:

For instance, age, sex, height, weight, waist circumference, waist-hip ratio,

BMI, smoking status, SES, blood tests, self-reported comorbidities.

Limitations and Challenges

A possible limitation could be lack of power due to few events and narrow age span (50 – 64 years) in the SCAPIS population.

The main strengths are assessment of several different fat depots (both metrics of amount and quality) using high-quality CT imaging in a large sample from the general population.

References

5. Hiuge-Shimizu A, Kishida K, Funahashi T, et al. Absolute value of visceral fat area measured on computed tomography scans and obesity-related cardiovascular risk factors in large-scale Japanese general population (the VACATION-J study). Ann Med 2012;44:82–92.
6. Lee JJ, Pedley A, Hoffmann U, et al. Visceral and Intrahepatic Fat Are Associated with Cardiometabolic Risk Factors Above Other Ectopic Fat Depots: The Framingham Heart Study. Am J Med 2018;131:684-692.
7. Adams LA, Anstee QM, Tilg H, et al. Non-Alcoholic fatty liver disease and its relationship with cardiovascular disease and other extrahepatic diseases. Gut 2017;66:1138–53.
8. Yoshida T, Shibata A, Tanihata A, et al. Thigh Intramuscular Fat on Prognosis of Patients With Nonischemic Cardiomyopathy. Am J Cardiol 2022;169:113-119

Return to Table of contents

PMI-D. Socioeconomic differences in risk of coronary events in Sweden. The SCAPIS study

EMBARGO on research hypothesis until 2025-12-09

TRF authors

First author: ***Annika Rosengren***

Last author: ***Carl Johan Östgren***

Objectives

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

Description of Analysis

All analyses will be carried out in accordance with the statistical analysis plan. Initially, missingness patterns will be investigated. Missingness in disease history and treatments based on questionaries will be imputed as “NO”.

Thereafter, distributional properties of all exposure and outcome variables will be investigated. The study population will be described with total number and percent, mean and 95% C.I. or median and interquartile range (IQR).

Conventional methods for the prospective analyses will be applied.

Significance/Rationale

Cardiovascular disease (CVD) remains the leading single cause of death globally and in Sweden. Atherosclerotic coronary artery disease (CAD), the disorder underlying acute myocardial infarction and coronary death, is a major manifestation of CVD. While coronary atherosclerosis may be present early in life (1) symptomatic disease does usually not appear before middle age. Based on autopsy studies in US soldiers, the prevalence of coronary atherosclerosis has decreased markedly over the last 60 years, but was still evident in 11% of US soldiers aged 25-29, and 22% aged 30-39 years in 2001-2011 (2).

Low SES has long been associated with a higher risk of coronary events (3,4), and with coronary artery disease (CAD) (5-7). 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 (8).

To which extent the relation between SES and CAD can be explained by the distribution of cardiovascular risk factors, with low SES associated with a higher prevalence of risk factors, is not entirely clear. A recent Mendelian randomization study based on data from the UK Biobank (9) found that body mass index (BMI), systolic blood pressure, and smoking mediated a large proportion of the protective

effect of education on the risk of cardiovascular outcomes but also that more than half of the protective effect of education was unexplained. In the Prospective Urban Rural Epidemiologic (PURE) study, low education was associated with higher levels of risk factors in high-income countries, whereas the reverse was true in low-income countries (9). Despite this, low education was associated with higher risk of CVD across high-, middle- and low-income countries. While education and income currently are widely used measures of SES in Sweden (10), low occupational class was the first indicator shown to be a risk factor for CAD in Sweden (11) but to which extent this is still valid has not been evaluated. Accordingly, there is a need of further study on to which extent an uneven distribution of risk factors might impact socioeconomic differences in risk of coronary atherosclerosis, but also to investigate which indicator might carry the most pertinent information on SES in contemporary Sweden.

Population and Required Data Variables

Sample

The subsample of the entire SCAPIS cohort with data on non-contrast and contrast-enhanced cardiac coronary computed tomography angiography.

Subsamples

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

1. Men / women
2. Age 50-54, 55-59, 60-65 years
3. Without known CAD defined as history or registered diagnosis of MI/coronary procedure/angiographic evidence of procedure (eg. presence of stent)

Outcomes

Coronary events defined as myocardial infarction, any coronary revascularization procedure, or death due to coronary heart disease

Exposures

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

Covariates

1. Age
2. Sex
3. Cholesterol, LDL, HDL, TG, glucose, creatinine
4. Systolic and diastolic blood pressure
5. Hypertension (known/treated or ≥140/90)
6. Tobacco use (current dose, pack-years, stop date if stopped)
7. Alcohol intake
8. Body mass index, waist and hip circumferences

9. Diabetes (known or diagnosed at SCAPIS examination)
10. History of cardiovascular disease (myocardial infarction, heart failure, valvular disease, atrial fibrillation, stroke, peripheral artery disease)
11. Other comorbidities (renal disease, cancer, respiratory disease, autoimmune/inflammatory disease)
12. Reproductive history (women; questionnaire)
13. Menopause (women; yes/no; menopausal age)
14. Family history of myocardial infarction (any of mother, father, sibling, any of with early disease)
15. Family history of diabetes (any of mother, father, sibling, any of with early disease)
16. Weight at age 20
17. Weight gain since age 20
18. Stress level (home, work-related, life events)
19. Physical activity (sedentary time, LIPA, MVPA)
20. Statin usage, yes/no
21. Ongoing medications

Limitations and Challenges

Outcome data not yet in place, validation of outcome procedures not yet initiated.

References

1. Dalen JE, Alpert JS, Goldberg RJ, Weinstein RS. The epidemic of the 20th century: coronary heart disease. Am J Med. 2014;127:807-812.
2. Webber BJ, Seguin PG, Burnett DG, Clark LL, Otto JL. Prevalence of and risk factors for autopsy-determined atherosclerosis among US service members, 2001-2011. *JAMA.* 2012;308:2577–2583.
3. Havranek EP, Mujahid MS, Barr DA, et al. Social determinants of risk and outcomes for cardiovascular disease: a scientific statement from the American Heart Association. Circulation 2015; 132: 873–898.
4. Kaplan GA and Keil JE. Socioeconomic factors and cardiovascular disease: a review of the literature. Circulation 1993; 88: 1973–1998.
5. Djekic D, Angerås O, Lappas G, Fagman E, Fagerberg B, Bergström G, Rosengren Impact of socioeconomic status on coronary artery calcification. Eur J Prev Cardiol. 2018;25:1756-1764.
6. Steptoe A, Hamer M, O'Donnell K, Venuraju S, Marmot MG, Lahiri A. Socioeconomic status and subclinical coronary disease in the Whitehall II epidemiological study. PLoS One 2010;5(1):e8874.
7. Dragano N, Verde PE, Moebus S, et al. Subclinical coronary atherosclerosis is more pronounced in men and women with lower socio-economic status: associations in a population-based study. Coronary atherosclerosis and social status. Eur J Cardiovasc Prev Rehabil 2007; 14: 568–574.
8. Braveman PA, Cubbin C, Egerter S, et al. Socioeconomic status in health research: one size does not fit all. JAMA 2005;294:2879–88.
9. Carter AR, Gill D, Davies NM, et al. Understanding the consequences of education inequality on cardiovascular disease: mendelian randomisation study. BMJ. 2019;365:l1855.

10. Rosengren A, Smyth A, Rangarajan S, et al. Socioeconomic status and risk of cardiovascular disease in 20 low-income, middle-income, and high-income countries: the Prospective Urban Rural Epidemiologic (PURE) study. Lancet Glob Health. 2019;7(6):e748-e760.
11. Rosengren A, Wedel H, Wilhelmsen L. Coronary heart disease and mortality in middle aged men from different occupational classes in Sweden. BMJ. 1988;297(6662):1497-1500.

Return to Table of contents

PMI-E. Restrictive spirometric pattern and preserved ratio impaired spirometry and incidence of ischemic heart disease

EMBARGO on research hypothesis until 2025-11-11

TRF authors

Kjell Torén, Magnus Sköld

Objectives

To examine in a longitudinal approach whether Restrictive spirometric pattern (RSP) and Preserved Ratio Impaired Spirometry (PRISm) increase the risk of coronary heart disease and myocardial infarction

Description of Analysis

Restrictive spirometry pattern (RSP) will be defined using two approaches. First as $FEV_1/FVC \geq 0.7$ and $FVC < 80\%$ and secondly as $FEV_1/FVC \geq LLN$ and $FVC < LLN$. PRISm will be defined as $FEV_1/FVC \geq 0.7$ and $FEV_1 < 80\%$ and secondly as $FEV_1/FVC \geq LLN$ and $FEV_1 < LLN$. Obstructive spirometry will be defined as $FEV_1/FVC < LLN$ or as $FEV_1/FVC < 0.70$. Normal spirometry will be defined as $FEV_1/FVC \geq 0.70$ and $FEV_1 \geq 80\%$ or as $FEV_1/FVC \geq LLN$ and $FEV_1 \geq LLN$. We will use the local SCAPIS equations as reference values.

Potential contributing causes and confounders and their inter-relations will be identified from the literature, and the required set of adjustment variables (confounders) will be defined using a Directed Acyclical Graph (DAG; www.dagitty.net).

The main outcome will be incident coronary heart disease. Possible co-variates will include respiratory symptoms, comorbidities, diffusion capacity for carbon monoxide (D_{LCO}), body mass index (BMI), and blood tests. Further, the confounding impact of smoking habits and other socioeconomic factors such as education and income will also be assessed.

The prevalences of RSP, PRISm, RSP without PRISm, PRISm without RSP and Overlap between RSP and PRISm with 95% confidence intervals (CI) will be presented, as well as descriptive data for categorical variables including numbers and percentages, and for continuous variables mean values and standard deviations (SD).

Associations between incident coronary heart disease and myocardial infarction will be analyzed using Cox proportional hazards models, adjusting for covariates. The group with normal spirometry will be the comparison group. The results will be expressed as hazard ratios (HR) with 95% CI. The analyses will also be stratified for smoking and gender. Especially findings among never-smokers will be of highly relevance. Incident coronary heart disease is new-onset disease from the year of inclusion and until end of follow-up. Persons with existing coronary heart disease at baseline will be excluded.

Significance/Rationale

RSP and PRISm have emerged as separate phenotypes, and have recently been associated with diabetes, metabolic syndrome, respiratory morbidity and increased mortality. However, there is a lack of estimates of the risk for coronary heart disease from general population samples where definitions of RSP and PRISm are based on spirometry after bronchodilation.

Population and Required Data Variables

Population: Total SCAPIS population.

Outcome variable: Incident coronary heart disease, either defined as new-onset hospital-care or cause-of-death. The broad definition is ICD-codes I20 – I25 with acute myocardial infarction (I21) as a subgroup.

Main predictors: RSP and PRISm based on spirometry (FEV_1, FVC)

Associated factors/confounders: Diffusion capacity for carbon monoxide ((D_{LCO}), respiratory and cardio-vascular symptoms, comorbidities, heart rhythm (ECG), measured coronary plaques (from CTA data); blood tests (fasting glucose, hsCRP, Hb, CRP, HbA1c, eGFR and creatinine, age, sex, highest education, blood pressure, blood lipids, smoking status, height, weight, waist circumference, waist-hip ratio and self-reported comorbidities, and finally pulmonary CT variables from eCRF.

Limitations and Challenges

A possible limitation could be lack of power anda narrow age span (50 – 64 years) in the SCAPIS population.

The main strengths are that RSP and PRISm will be defined after bronchodilatation, and that SCAPIS comprise a approximately 50% life-long never-smokers

References

1. Godfrey MS, Jankowich MD. The vital capacity is vital. Epidemiological and clinical significance of the restrictive spirometry pattern. Chest 2016;149:238-251.

2. Torén K, Blomberg A, Schiöler L, Malininovschi A, Backman H, Caidahl K, Carlhäll C-J, et al. Restrictive spirometric pattern and preserved ratio impaired spirometry in a population 50 – 64 years. Ann Am Thorac Soc 2024;[E-pub ahead of print].

3. Wan ES, Balte P, Schwartz JE, Bhatt SP, Cassano PA, Couper D, et al. Association between preserved ratio impaired spirometry and clinical outcomes in US adults. JAMA 2021;326:2287-2298.

Return to Table of contents