

## Thinking Big: SCAPIS – The Ideal Cohort for Studies on CVD, COPD and Related Metabolic Disorders

Cardiopulmonary diseases are major causes of death worldwide, but currently recommended strategies for diagnosis and prevention are believed to be outdated because of recent changes in risk factor patterns. **In this article, Cecilia Stroe, editor of JCS, looks into Europe's largest screening study, The Swedish CardioPulmonaryBioImage Study (SCAPIS). SCAPIS will create a unique Swedish cohort for studies on CVD, COPD and related metabolic disorders at the highest international level, aiming to increase the knowledge of basal mechanisms and improve risk prediction of these diseases, and ultimately to lead to more individualised, cost-effective and better healthcare.**

Led by Professors Göran Bergström and Annika Rosengren, **The Swedish CardioPulmonaryBioImage Study (SCAPIS)** is Europe's largest screening study. It is set to create a unique Swedish cohort for studies on CVD, COPD and related metabolic disorders at the highest international level, aiming to increase the knowledge of basal mechanisms and improve risk prediction of these diseases, ultimately leading to more individualised, cost-effective and better healthcare.

According to the researchers, the risk factor patterns for myocardial infarction (MI), stroke and COPD have changed significantly during the last two decades, from an environment with high levels of cholesterol, blood pressure and smoking, to a scenario dominated by obesity, hypertriglyceridemia and diabetes.

The same period of time has also seen an unparalleled development of imaging and proteomics/metabolomics/genomics ("-omics") technologies and subsequently, the strategies for diagnosis and prevention of cardiopulmonary diseases, developed just a few decades ago, are now considered to be lacking relevance in today's healthcare.

However, these strategies have the potential to be vastly improved by using recently developed advanced imaging techniques that allow scientists to directly visualise the disease process rather than rely on the limited information provided by indirect risk factors, and by using recent developments in large-scale -omics techniques, thus facilitating the identification of new biomarkers and mechanisms for disease.

Prevention of premature CVD and COPD is a high priority worldwide, and researchers anticipate that better risk discrimination will lead to more cost-effective measures. They believe that the size and design of SCAPIS will ensure the ability to statistically account for age, sex and other confounding factors and provide the possibility to study subpopulations with high statistical power.

*The Swedish CardioPulmonary bioImage Study (SCAPIS): objectives and design* was published online by G Bergström et al. in *Journal of Internal Medicine* 2014.

Designed as a prospective observational study of a randomly-selected sample from the general population, SCAPIS is currently ongoing and approximately 40–45 participants are enrolled in it each day at six sites throughout Sweden. By the end of 2016, over 16,000 participants had been examined and the study is estimated to be completed by the end of 2018, after which quality control of collected variables will begin.

The examinations were selected on the basis of their ability to provide detailed phenotypic information on subclinical disease whilst at the same time being applicable for use in a large study population.

Completed in 2012, the pilot study of SCAPIS has already demonstrated the feasibility and financial and ethical consequences of SCAPIS.

The pilot study was performed in the city of Gothenburg, Sweden, from February to November 2012. It had as primary goals to examine the feasibility of the study design and to estimate the consequences of pathological findings identified during the examinations, on clinical resources within the public healthcare system, and on the participants, from an ethical perspective.

The only difference from the design of the main study was that the participants were recruited from areas with high versus low socio-economic status, which allowed the researchers to examine participation rates and reasons for non-participation. In total, 1111 subjects were recruited (of 2243 invited) and all main aspects of the SCAPIS design were tested. The planned time schedule was adhered to, thus verifying the feasibility of examining 5000 subjects in three years at one site.

According to the paper, the overall participation rate was 49.5% (39.9% and 67.8% in areas of low and high socio-economic status, respectively). Reasons for non-participation were given as follows: inability to make contact with the subject (37.4%), too busy (15.7%), too sick (6.6%), language difficulties (7.8%), miscellaneous (6.4%) and none given (26.1%). Lack of contact and language difficulties dominated in areas of low socio-economic status.

SCAPIS will recruit approximately 30,000 randomly selected men and women aged 50 to 65 years. The recruitment and examinations will be performed at six university hospitals (Uppsala, Umeå, Linköping, Malmö/Lund, Gothenburg and Stockholm). The study examinations are divided into core examinations, collected at all sites, and additional examinations, performed at one or more sites.

In addition to core examinations, each site can expand on its own research interests by adding additional examinations, as long as these do not interfere with the core examinations.

SCAPIS has been evaluated and approved by the ethics committee as a multi-centre study (Umeå, February 21, 2011).

One crucial objective in the recruitment process is ensuring a reasonably high participation rate. But high participation rates have been increasingly difficult to achieve in recent years, as proved by the steady decline in rates noted in the repeated studies of 50-year-old men in Gothenburg, Sweden.

The recruitment strategy used in the pilot study was designed to quantify and describe the anticipated recruitment difficulties from different social strata. As expected, researchers say, a large difference in participation rates was seen between more and less affluent areas in Swedish society (67% vs. 37%) despite an overall acceptable participation rate of 49%.

Financial restraints limit the study to those who understand written and spoken Swedish, meaning that some immigrants are excluded, thus limiting the generalisability of SCAPIS to these groups in society. However, the pilot study has clearly shown significant differences in health associated with socio-economic status in Swedish society. Furthermore, the pilot study proved that subjects at risk of disease from less affluent areas will participate in the study, albeit at a lower level than those from affluent areas. And given that SCAPIS will comprise 30,000 individuals, its size is believed to be sufficient to overcome this limitation and allow important comparisons to be made between social strata.

Despite the pilot study experience from Gothenburg showing socio-economic differences in risk factors, the researchers have chosen to recruit subjects based on a randomised selection of participants from the Swedish population register without stratification for socio-economic status.

As explained, the main reason for this decision is that smaller socio-economic gradients are anticipated at the smaller university sites (Umeå, Linköping and Uppsala) compared to the ones located in larger cities (Stockholm, Gothenburg and Malmö). The gradients will also be qualitatively different between cities, making controlled stratification impossible. In addition, the unique Swedish PIN and availability of detailed registers (with extensive records of hospitalisations, census information, education, employment, sick leave, social welfare and income) will allow scientists to quantify and statistically compensate for variations in participation rate.

In parallel with the recruitment process, virtual cohorts are going to be constructed consisting of register-based census data on hospitalisations, income, education and ethnicity in subjects aged 50–64 years in the catchment areas. The virtual cohorts will be used to gauge the representativeness of the recruited sample compared to the background population.

The examinations are performed on two or three occasions within a two-week period, dependent on logistics at each study site. Core examinations that are common for all sites are performed, as well as optional examinations at one or more sites depending on the local research interest.

Study data will be entered into a central database at the study site through electronic case report forms. Collaboration between SCAPIS and the Western Sweden Regional Image database ('BildochFunktionsregistret', Gothenburg, Sweden) will enable images generated within SCAPIS to be available both to healthcare providers for clinical follow-up and to research groups across Sweden.

For SCAPIS, all university hospitals in Sweden, backed by SwedishHeart & Lung Foundation, have chosen TrialOnline,

supplied by Replior, a Swedish IT operations and development company.

Relying on the tradition of early landmark population studies such as the Framingham Heart Study, several other large international cohort studies focusing on CVD and COPD have been completed, or are ongoing or planned. But compared with all these studies, the researchers say, SCAPIS has the advantage that it combines size with extensive and in-depth phenotyping and direct imaging of the disease process.

In a few large-scale international studies, such as the Multi-Ethnic Study of Atherosclerosis, the Dallas Heart Study and the BioImage study, extensive cardiovascular and pulmonary imaging has also been performed. However, the planned size of SCAPIS is almost three times bigger than the next largest study. Besides, SCAPIS is the only study using CCTA in the total cohort, which allows direct visualisation and quantification of plaque in the coronary arteries; the direct visualisation of disease in lung and vessels is combined with detailed metabolic imaging of fat deposits on a scale not attempted in any other study; and an unbiased and randomly selected sample is recruited from the general population. Furthermore, the Swedish identification number and registers provide advantages in selection of the cohort and follow-up. In addition, because the prevalence of smoking in Sweden is relatively low (18% in the SCAPIS pilot), it is feasible to perform subgroup analyses on never-smokers.

Therefore, SCAPIS is an ideal cohort to identify gene–metabolite–disease interactions, by combining the extensive phenotyping data with metabolomic/lipidomic, proteomic and genetic analyses.

Associations between metabolites/metabolic pathway-related metabolite patterns and the presence of severe coronary atherosclerosis at baseline will also be investigated, as well as the incidence of myocardial infarction during follow-up. In order to test whether such relationships are causal or only parallel phenomena, the findings will have to be validated by identifying genetic variants strongly associated with the plasma concentration of the particular metabolite/metabolic pathway. Such metabolite-associated gene variants will then be tested for association with the presence of coronary atherosclerosis/incidence of myocardial infarction in the entire SCAPIS population.

Gene–metabolite–disease interactions that can be validated in such a three-stage procedure are thought to imply a causal relationship between the metabolite/metabolite patterns and the presence of disease, indicating the existence of modifiable risk factors that could be potentially targeted in drug and lifestyle interventions for disease prevention.

## REFERENCES

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