Policy document for AMORIS research projects at the Institute of Environmental Medicine (IMM), Karolinska institutet, Stockholm, Sweden

Focus of AMORIS Research projects

"Metabolic abnormalities and inflammation in relation to chronic disease primarily cardiovascular diseases, kidney disease, cancer, dementia, rheumatoid arthritis and psychiatric illness – epidemiological studies based on the AMORIS cohort"

1. Background

The AMORIS (Apolipoprotein-related Mortality RISk) project has been running since 1985 with a primary focus on the importance of apolipoproteins (apo) as new lipid-related risk factors for cardiovascular (CV) diseases. Several publications from AMORIS show that high apoB (atherogenic) and low apoA-I (protective) blood levels increase the risk for myocardial infarction (MI) and stroke. During 2010-2012 the AMORIS laboratory database has been updated to include more laboratory variables and more individuals. The database has also been linked to 24 other databases/registers containing information which will enable calculations of morbidity and mortality for a broad variety of diseases. This will enable research on relations between laboratory data and their relations to chronic diseases according to the research plan (Ethical permit Dnr 2010/1047-31/1).

In a short pocket profile publication (1) and in the full AMORIS cohort profile paper (2), both published in the International Journal of Epidemiology, we present details of the AMORIS database and comment on some papers relevant to the diseases that have been studied.

1. Walldius G, Malmström H, Jungner I, de Faire U, Lambe M, Van Hemelrijck M, Hammar N, International Journal of Epidemiology, The AMORIS cohort. Pocket Profile. 2017. doi:10.1093/ije/dyw333.

2. Walldius G, Malmström H, Jungner J, de Faire U, Lambe M, Van Hemelrijck M, Hammar N. Cohort Profile: The AMORIS cohort. International Journal of Epidemiology Cohort Profile, 2017, 1–10. doi: 10.1093/ije/dyw333.

2. Summary of linkages of other registers to the AMORIS database

The AMORIS database contains 812.000 men and women aged from 10 to above 100 years. They were investigated at health check-ups from outpatient clinics and no individuals were hospitalized. They lived mainly in the Greater Stockholm area. Morbidity and mortality has been followed through various registers. All linkages were updated during 2010-2012.

Laboratory data from about 500 different laboratory tests, about 37 million analyses, have been linked to the following registers; Causes of death, In-patient care, National cancer, quality registers for prostate, breast and colo-rectal cancers, Prescribed drugs, Emmigration and Immigration, Census, Multi-generation, Education, Lisa, Ulf, Swedish Twin, WOLF, Stockholm study 60-years men and women, National Diabetes Register (NDR), Swede-Heart registers including RIKS-HIA, Sephia, SCAAR, Swedish Heart Surgery, Riks-stroke, Swedish Kidney Register (SNR), Rheumatoid arthritis registers (RA and EIRA), Sollentuna Primary Prevention study (SoPP), Swedish Mammography Cohort, SMC and Cohort of Swedish Men, COSM, PI for both Prof. Alicja Wolk. These registers are displayed in Figure 1 both regarding content and the years they assembled the data.

3. Local site and Steering group for the AMORIS project

The AMORIS-database is located at the Institute of Environmental Medicine, Unit of Epidemiology, IMM at Karolinska Institutet (KI), Stockholm, Sweden. A Steering group is overseeing the project and it consists of researchers from KI who previously have worked and published papers based on the AMORIS-project. See further section 5.

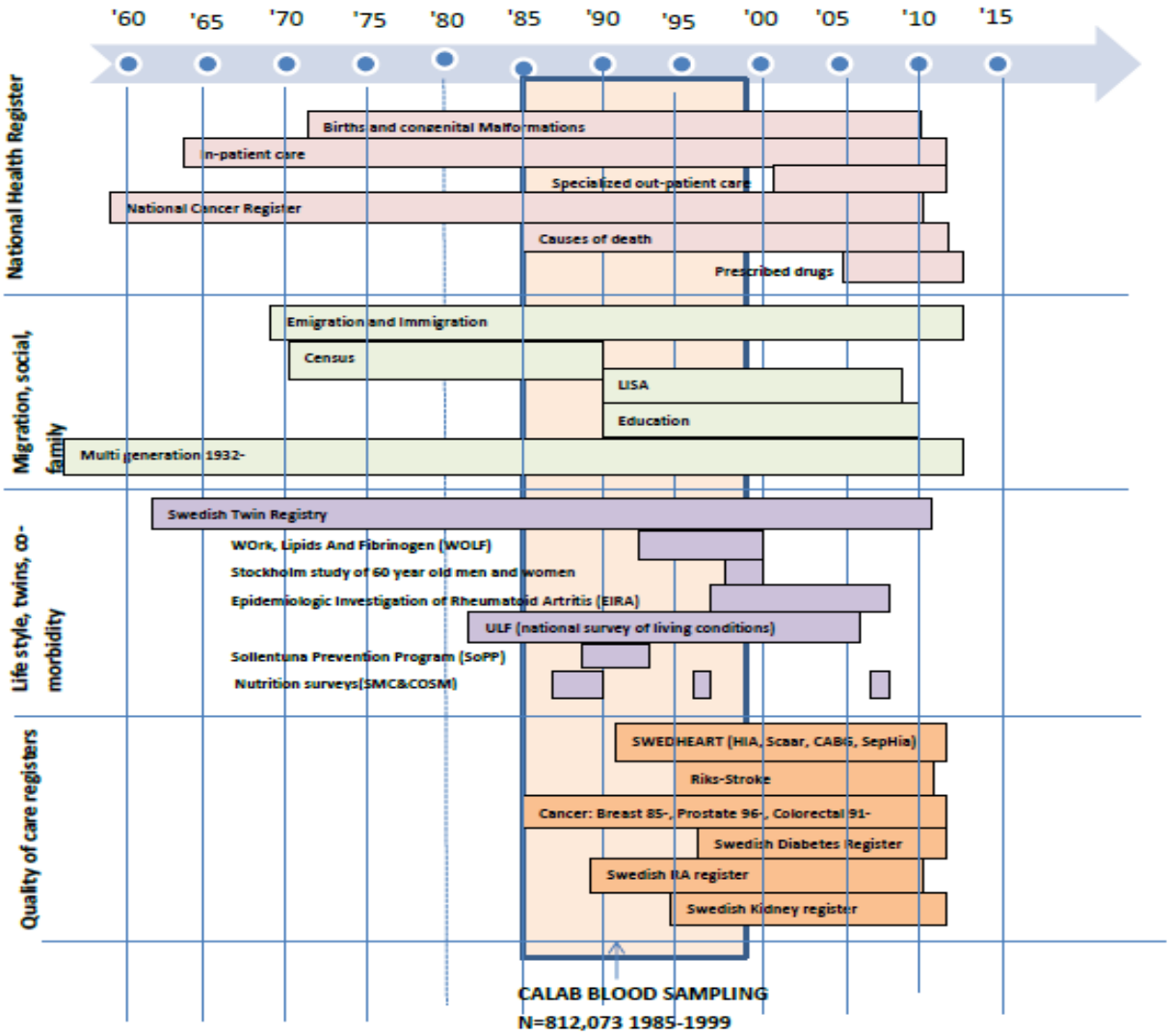
4. The AMORIS database – structure, linkages to other databases and access to the database

When this laboratory database was linked to all other registers, the ID-numbers in the overall AMORIS-database were anonymized and substituted by a unique running number for each given individual. Thus, the linked database does not contain personal identification numbers. There are three major disease areas with specific series of running numbers in each area, a) cardiovascular, b) cancer and c) rheumatoid arthritis. These three sectors of the database are stored on a separate AMORIS- server containing no other data. This server is located in IMMs fire-proof

server hall. Only three certified individuals (the principal statistician, the chairman and the vice chairman) have access to the server which is headed and serviced by the IT-responsible persons at IMM. All data runs are subjected to daily back-ups. All data runs are continuously logged on this specific AMORIS server at IMM. Certified users (guest researchers/statisticians) may have remote access to the database or segments of this through a specific safety process using passwords (SecureLan).

In the left hand part of figure 1 the overall content of registers are given. At the top of the figure the years in which data have been collected for the various registers are indicated.

Figure 1: AMORIS 2012 - Linkages to other information sources



5. Steering group, personnel and collaborations

In April 20, 2018 the new Steering Group was formed

- Niklas Hammar, Professor emeritus, Unit of Epidemiology, IMM, is the chairman, project leader and coordinator (NH) for the next year
- Göran Walldius, Senior professor, Unit of Epidemiology, IMM, is the vice chairman, and project leader (GW)
- Sofia Carlsson, Associate professor, Unit of Epidemiology, IMM
- Maria Feychting, Professor, Unit of Epidemiology, IMM
- Mieke van Hemelrijck, Senior lecturer, Kings college, London, UK
- Karin Leander, Associate professor, Unit of Cardiovascular Epidemiology, IMM
- Håkan Malmström, PhD, SOBI
- Mats Talbäck, statistician, Unit of Epidemiology, IMM, will be affiliated with the Steering group

- **From the previous Steering group the following changes have been made;**
- Mats Lambe, Professor at MEB, KI (ML) is retiring and will be a Senior advisor to the Steering Group
- Ulf de Faire, Senior professor at IMM (UdF) is retiring and will be a Senior advisor to the Steering Group
- Ingmar Jungner, Associate professor at IMM, representing Gunnar and Ingmar Jungner´s Foundation for Laboratory Medicine, donator of the AMORIS laboratory database to IMM (IJ), will be the Honorary advisor to the Steering group

The Steering group meets 3-4 times yearly and whenever needed to monitor the conduct and progress of the AMORIS research projects. On a daily basis, the chairman and vice chairman are responsible for conduct of the research based on the AMORIS cohort.

The Steering group may meet with the various principal investigators (PIs) and their teams to discuss specific project plans, questions and problems whenever needed.

The Steering group is responsible for prioritizations in case of project related problems occur or if financial questions need to be solved.

The Steering Group for the AMORIS-project with the Chair, co-chair and project leaders (NH and GW) in collaboration with the other Steering group members are responsible for the collaboration with researchers to ensure that regulations, secrecy, integrity and data confidentiality are followed according to standards at Karolinska Institutet. A statistician and the project leaders are partially financed by funds available specifically for the AMORIS project. The project leaders (NH and GW) are primary responsible for running the research based on the AMORIS cohort on a daily basis. They are also responsible for monitoring and reporting to the Steering group budget aspects of the AMORIS study and also to ensure that researchers in the separate studies within AMORIS regularly apply for research grants (see also section 10).

The Steering group, may also help in solving possible conflicts related to work in project groups related to the AMORIS project if this is needed.

6. Planning of research projects containing aims, methods, analytical/statistical plans, finances and publication of data

In order to be able to get access to data from the AMORIS database the researchers/groups should specify their projects according to the following headings;

1. Select a project leader
2. Define a research plan containing the main aims/question-s and focus of the research
3. Include an ethical permit in accordance with the approved research plan for the AMORIS study (if the study is not covered by previously obtained permit)
4. Propose members, collaborators, primary author and co-authors in the publication-s
5. Define which variables are needed
6. Define from which registers data should be collected
7. Propose a statistical plan
8. Propose a statistician, central to the AMORIS project or “their own statistician”
9. Propose a time frame for the project and a financial plan
10. The overall project plan could be summarized in 1-3 pages
11. The PI for the given project should write a request to the project leaders of the AMORIS study (NH, GW) to get access to the selected, defined parts of the AMORIS database according to regulations of data access, see section 7.
12. Together with the chairman of the Steering group sign a “Data access agreement” and also a “Confidentiality agreement” if data will be developed outside KI, see also section 7
13. The collaborating research group is responsible to contribute to the central AMORIS budget in order to support various administrative expenses such as

the need for discussion with the central AMORIS statistician who informs about the database structure and contents and helps in defining the relevant parts of the central database and its linkages that are needed for a given project. This can commonly be time consuming. There are also costs for various administrators and service at IMM and at the IT-data unit. Depending on time needed to start up the project as well as frequency of discussions between the PIs of the specific projects and the central statistician, the primary start-up costs and the annual costs have to be discussed separately for each project. The costs that may be needed to cover include:
a) Access to the database (fee) 10,000 SEK; b) Statistical and other consultation need per hour 750 SEK; c) Statistical analyses support per hour 750 SEK. Of these a) is mandatory and a minimal cost if no other support is needed and all work is carried out externally.

14. The research groups that have been granted access to the data-base, see section 7 below, have to develop a preliminary manuscript based on the newly calculated data within 2 years from getting data access.
15. The Chairman + vice chairman will have to review the proposed final manuscripts before submissions in order to secure that data have been developed according to good scientific standards and that it is compliant with the overall ethical permit for the AMORIS study.
16. Further information can be obtained from Niklas.hammar@ki.se and goran.walldius@ki.se and can also be found in the home page www.amoriscohort.imm.ki.se.

7. Requests from various researchers for access to and output of data from the AMORIS database at the central AMORIS server at IMM

Researchers from KI and external to KI can apply for access to the AMORIS database as long as their projects and requests containing selected and well defined data from adequate linkages/registers and are in line with the overall research plan (ethically granted) for the AMORIS research project. If a study does not fall under the ethical permit of the general AMORIS research plan an ethical approval must be obtained separately for the proposed study. Permits shall also have been given by the Steering group, and formal agreements have been signed, see details in section 6.

The chairman + vice chairman will for a specified study and time period give formal permits/rights for named researchers to access sectors of the AMORIS database. The database is stored at IMM and accessed through the SecureLan technology. Through this well protected, encrypted and safe remote data access system the researcher has access to statistical programs and can create analysis datasets, tables, figures and the text/manuscript. All data and resulting files are stored inside

SecureLan without any files leaving IMM. Tables, figures, text and other files that do not include any sensitive information can be transferred out from SecureLan only by users that are associated to IMM and have been given access to that feature by the head of the unit. All non-privileged users must have their files reviewed by a privileged user before they can get it transferred out of SecureLan. Files that contain sensitive information or are too large will need to be accepted for transfer on a per-time basis by the head of the unit. All transfers of data in to - and out from the central server will be logged in order to be able to check the handling and use of data. The user of data has to sign an agreement that certain types of data, under no circumstances, will be allowed to be transferred out from the central server. Access will only be granted for a specific project to the data needed to complete the project. To define this the researcher, need to supply a research plan with a list of variables needed for the project.

8.Documentation of ongoing plans for projects based on the central AMORIS database

The Steering group through the Chair and the co-chair will enlist all projects and project plans that are underway according to “Study track of projects”.

9. Publication strategies

Project leaders/researchers who propose studies should early discuss with the Chair and the co-chair and if relevant the general Steering group which of the members from this group should be coauthors of the individual projects. To be a coauthor you have to actively participate in the project discussion, planning, and contribute to the writing and review of the manuscript. These principles are also valid when discussing other coauthors and their contributions to published materials according to the Vancouver-rules for publications.

Many researchers have contributed with important data from their own registers to the overall AMORIS database. If these data are used to highlight the primary aims and questions (exposure and outcome) in a project/publication these researchers /groups should be actively invited to participate as coauthors. On the other hand, if the data from researchers are mainly used for confounding control or only in multivariate adjustments these researchers will be informed of development of a publication and acknowledged for their contribution of data at the end of the publication, see an example in Appendix 1.

10. Economy, budget review and summary of publications

The Steering group through primarily the Chair and the co-chair for the AMORIS project will oversee and is responsible for the total budget resources allocated from various funds. Expenses for meetings, travel expenses to congresses, educational meetings, invitations of external scientists and /or lecturers to participate in certain projects/symposia related to or based on the AMORIS database, data equipment and other expenses will be monitored and acted upon by the Chair and the co-chair with consultation with the Steering group on an as needed basis.

All PIs for different AMORIS projects are asked to apply for research grants for their specific projects but also to support funding to the AMORIS cohort for linkages, administrative and maintenance reasons, see also section 6.13.

The budget for the AMORIS cohort will be repeatedly monitored by the Steering group via the Chair and the co-chair.

Steering group for the AMORIS research projects

IMM, KI 2018-04

Niklas Hammar (chairman), Göran Walldius (vice-chairman), Maria Feychting, Sofia Carlsson, Karin Leander, Mieke van Hemelrijck, Håkan Malmström Mats Talbäck (affiliated),

Appendix 1.

Acknowledgement, an example

Information about tobacco smoking, blood pressure/hypertension and body mass index have been generously provided for this study by record linkage to the WOLF (Work Lipids and Fibrinogen) study (PI Professor Lars Alfredsson, Karolinska Institutet, Stockholm, Sweden and Professor Peter Westerholm, Uppsala University, Sweden), from the Investigation of 60 year old subjects in Stockholm (PI Professor Ulf de Faire, Karolinska Institutet, Stockholm, Sweden), from the Sollentuna Prevention Project (SoPP; PI Professor Mai-Lis Hellenius), from the Swedish Swedish Mammography Cohort, SMC and Cohort of Swedish Men, COSM, (PI for both Prof. Alicja Wolk, Karolinska Institutet, Stockholm, Sweden) and from the National Diabetes Register (PI Soffia Gudbjörnsdottir, Gothenburg University, Sweden).