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KORA – A Research Platform for Population Based Health Research

KORA – Eine Forschungsplattform für bevölkerungsbezogene Gesundheitsforschung

Zusammenfassung

KORA (Kooperative Gesundheitsforschung in der Region Augsburg) ist eine Forschungsplattform für bevölkerungsbasierte Gesundheitssurveys und darauf aufbauende Follow-up-Studien zu Themen der Epidemiologie, Gesundheitsökonomie und Versorgungsforschung. KORA wurde 1996 eingerichtet, um das MONICA-Projekt in Augsburg fortzusetzen und zu erweitern, einschließlich des Herzinfarktregisters. Der verfügbare Pool von Studienteilnehmern erlaubt die Durchführung von Kohorten-, Fall-Kontroll- und Familienstudien. Wir beschreiben die KORA-Infrastruktur sowie Aspekte des Datenmanagements und der Qualitätskontrolle und stellen das zentrale Kooperationskonzept vor. Die zunehmende Nutzung der MONICA/KORA-Kohorten für eine Vielzahl von Forschungsthemen, mit aktuellem Schwerpunkt im Bereich der genetischen Epidemiologie, belegt die Attraktivität dieses Konzepts.

Schlüsselwörter

Bevölkerungsbezogene Forschung · Epidemiologie · Gesundheitsökonomie · Survey · Herzinfarktregister

Abstract

KORA (Cooperative Health Research in the Region Augsburg) is a regional research platform for population-based surveys and subsequent follow-up studies in the fields of epidemiology, health economics, and health care research. KORA was established in 1996 to continue and expand the MONICA project in Augsburg, including the Acute Myocardial Infarction (AMI) Registry. The available pool of study participants allows for cohort, case-control and family studies. We present the KORA infrastructure, aspects of data management and quality control, and the concept of cooperative research. The increasing use of the MONICA/KORA cohorts for a variety of research topics, with a recent focus on genetic epidemiology, indicates the attractiveness of this concept.

Key words

Population-based research · epidemiology · health economics · survey · myocardial infarction registry

note

The KORA study group consists of H.-E. Wichmann (speaker), H. Löwel, C. Meisinger, T. Illig, R. Holle, J. John and co-workers who are responsible for the design and conduct of the KORA studies.

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bibliography

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In 1996 the GSF – National Research Center for Environment and Health initiated the research platform KORA. The acronym stands for “Kooperative Gesundheitsforschung in der Region Augsburg” (Cooperative Health Research in the Region of Augsburg) and incorporates two important characteristics: the population based research design on a regional basis and the cooperative research structure (www.gsf.de/KORA).

The choice of the target region was predetermined by the fact that the city of Augsburg and its two surrounding counties had served as study regions of the international WHO MONICA project (“Monitoring of Trends and Determinants of Cardiovascular Disease”) under local coordination by the GSF. From 1984/85 to 1994/95, three population based MONICA surveys had been conducted, and a regional myocardial infarction registry had been

established. Supported by grants from the German Federal Ministries of Research and of Health (BMBF and BMGS), the GSF decided to commit substantial resources into a continued utilization and expansion of the research infrastructure that had been created.

The aim of the KORA platform was to use new as well as existing studies with their respective data and biosamples for future research projects in epidemiology, health economics, and health care research specifically with the option of long-term follow-up of the MONICA surveys. Interdisciplinary research at this level requires a cooperative approach where expertise and resources from different institutions are combined. Thus, several institutes within the GSF as well as partners from universities and other research institutions have been collaborating closely over the years.

Study Designs

The study region of Augsburg in the southern part of Germany, about 70 km west of Munich, has a population of about 600,000 of which 430,000 inhabitants are between 25 and 74 years of age. Cross-sectional health surveys were performed in the population aged 25 to 74 with German nationality. Samples were drawn in a two-stage procedure where first Augsburg city and sixteen communities from the adjacent counties were selected by cluster sampling and then stratified random sampling was performed within each community [1]. In this way, four cross-sectional health surveys S1 to S4 have been performed at five year intervals, each comprising of an independent random sample. Fig. 1 shows a map of the study region and the 16 communities selected for one of the four surveys (S4).

In all surveys, baseline information on sociodemographic variables, risk factors (smoking, alcohol consumption, physical activity, etc.), medical history and family history of chronic diseases, medication use, and more was gathered by trained medical staff during an extensive standardized face to face interview. In addition, all participants underwent a standardized medical examination including blood pressure measurements and anthropometric measurements. Additional modules (e.g. ECG) were added in only some of the surveys.

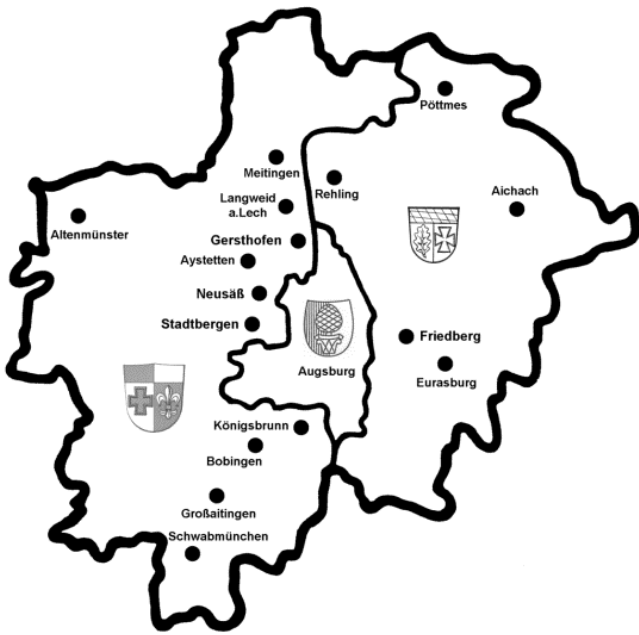


Fig. 1 Study region Augsburg.

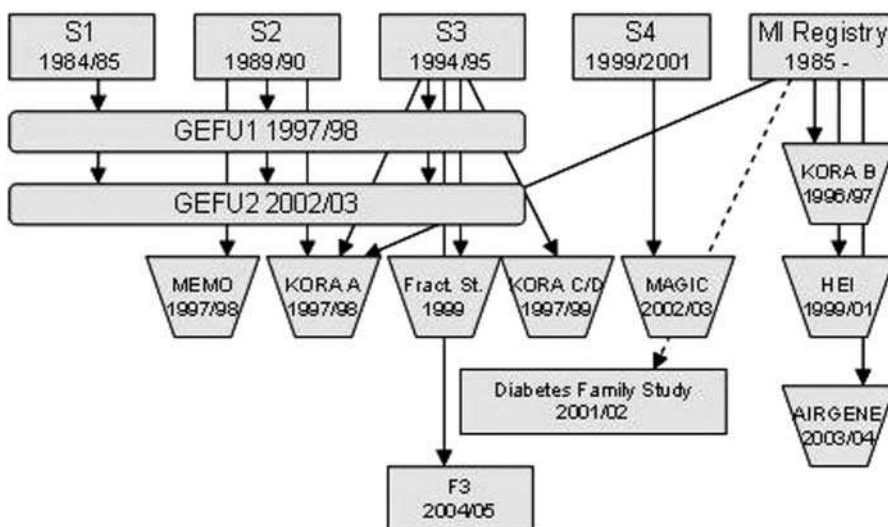


Fig. 2 Overview of MONICA and KORA studies (for details see table).

The four cross-sectional surveys serve as cohorts for long term follow-up studies and as a pool for nested case-control and case-cohort studies [2]. This pool consists of approximately 18,000 participants with a follow-up duration between 4 and 20 years. Follow-up activities include address inquiry for all participants (incl. assessment of vital status and cause of death), postal questionnaires focusing on chronic diseases, and complete follow-up studies with interviews and physical examination. Therefore, changes in base line variables (e.g. risk factors) as well as morbidity and mortality endpoints can be analyzed over a long observational period.

Nested case-control studies have been performed using information on specific diseases of the participants, e.g. diabetes and allergies. With the growing interest in genetic epidemiology in recent years, KORA has repeatedly provided a pool of population controls for genetic case-control studies performed in various clinics. Moreover, data on family history and family structure of KORA participants have proved useful for recruiting participants for family studies on myocardial infarction and diabetes in genetic epidemiology.

The Augsburg myocardial infarction registry was an integral part of the MONICA study and was continued under KORA. All myocardial infarctions and coronary deaths occurring in subjects from the Augsburg region up to an age of 74 years are registered. Besides being a valuable data source for the Federal Health Reporting System (www.herzschlag-info.de/start.html and www.gbe-bund.de), it supplies information on morbidity and mortality endpoints of survey participants, and provides a patient pool for specific studies on survivors of an acute myocardial infarction.

For all KORA studies approval is sought from the Ethics Committee of the Bavarian Medical Association (Bayerische Landesärztekammer) and the Bavarian commissioner for data protection and privacy (Bayerischer Datenschutzbeauftragter). All study participants provide written consent after being informed about the study. All subjects have the option to restrict their consent to specific procedures, e.g. by denying storage of biosamples.

Research Areas and Topics

Due to its origin in the WHO-MONICA project, epidemiological research in KORA still mainly focuses on risk factors of cardiovascular disease [e.g. 3, 4]. With growing knowledge about associated diseases (diabetes, metabolic syndrome) and new potential pathological mechanisms (e.g. endothelial dysfunction, role of inflammation, [5, 6]) research topics in KORA have been broadened. Gender differences in risk factors and outcome of cardiovascular and metabolic diseases, the study of psycho-social risk factors [7], and environmental variables which may trigger cardiac events [8] are only three examples of new topics which are being studied in KORA.

The most prominent change in epidemiologic research within the last decade is the advancement of genetic epidemiology as a result of the technological progress in genetics and molecular medicine. Several population based case-control studies as well

as family studies have been performed on the KORA platform in order to study genetic markers which may have a role in the development of diabetes [9], myocardial infarction, obesity, or other polygenetic chronic diseases.

Health care research and health economics are other facets of public health research for which the population based approach of KORA can provide data. Issues of equity in health care and on the role of socioeconomic status on health, health attitudes, and health behaviour have been analysed from different perspectives [10]. Recent changes in the health system have motivated population based studies on attitudes towards health insurance [11] and disease management programs [12].

Economic research in KORA has been focused on cost of illness studies, e.g. for obesity [13], and on using population based data for health economic models as in the case of diabetes screening [14]. Data from the myocardial infarction registry are being used to describe changes in health care technologies and to estimate their economic impact.

KORA Infrastructure

The organizational structure in KORA consists of a network of boards and working units as shown in Fig. 3. Its central element is the Executive Board, which is composed of the heads of the participating GSF institutes, research groups, and management representatives of GSF. Its responsibility is to coordinate and manage the KORA platform. The speaker of the Executive Board acts as the representative of KORA.

In order to communicate research plans to local partners from the Augsburg hospital and local health authorities, quarterly meetings of the Augsburg Information Circle are held. On a broader platform, the KORA Regional Forum convenes annually with a range of representatives from local health care institutions, research and media. An important panel for KORA is the Scientific Advisory Board whose members are renowned representatives from health research and health care management.

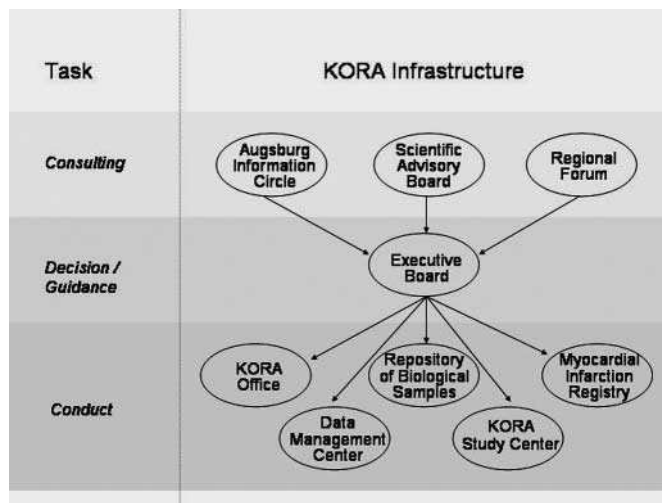


Fig. 3 KORA organizational structure.

Its task is to give scientific guidance for present and future KORA research projects.

Important for the operation of the KORA platform are the working units which are responsible for the daily routine and the support of all scientific projects. These include the KORA Study Center, the Myocardial Infarction Registry, the Repository of Biological Samples, the Data Management Center, and the KORA office. The KORA Study Center in the center of Augsburg is responsible for the recruitment and examination of the KORA study participants. Its facilities allow about 15 participants per day to be examined though the interview and physical examination of each subject requires three hours. A laboratory is also available for initial processing of blood samples. To assist recruitment, additional regional study centers for the communities outside the city of Augsburg were opened for short time periods. A local partner organisation assisted in recruitment and study logistics.

Similarly, the Myocardial Infarction Registry located at Klinikum Augsburg fulfills the task of continuous registration of all incident myocardial infarctions in the region of Augsburg up to the age of 74 years. All hospitalized cases of acute myocardial infarction are documented extensively. In addition, data is collected on all deceased persons with a suspected coronary cause of death in cooperation with three regional health departments as well as with physicians and coroners.

The Repository of Biological Samples is located in the GSF and its tasks are the storage and distribution of biological samples. It is closely linked with the Genome Analysis Center of the GSF which has high-throughput genotyping facilities. The Repository of Biological Samples stores DNA and blood samples from about 18,000 MONICA/KORA participants.

The Data Management Center at the GSF is responsible for data transfer from the study center to the GSF and for central data management. Since it coordinates all relevant information across studies it also serves as a Method Center consulting external partners and the Executive Board in questions concerning study design. Recently, the tasks of data management and statistical consulting are shared with another working unit, called KORA-gen, which is responsible for all aspects involving genetic data. Finally, the KORA Office is concerned with the administration of all KORA activities and assisting the Executive Board.

An important substructure within each KORA study is the project conference, which consists of all involved project partners and members of the KORA team and meets every one or two months to discuss the progress of the study. It acts as a steering committee of the specific study.

Cooperation in KORA and Use of KORA Data

Cooperation is an integral part of KORA research. The internal cooperation of different GSF institutes has been mentioned in the context of the KORA infrastructure. Right from the start, KORA was designed as a research platform which would also be open for external project partners. Sharing the study costs and making

efficient use of the KORA infrastructure are only two aspects from the economic point of view. Of equal importance is the added value gained by combining the expertise of researchers and the data collected in their respective sub studies.

For external partners to join the KORA study group, they must be approved by the Executive Board based on a scientific protocol describing their research questions. The second step is a written cooperation contract between the GSF and its partner institution which fixes the financing of the project specific costs, the rights and responsibilities regarding study execution and data analysis, and the acceptance of the KORA approach to make project data available to other partners.

KORA is also willing to share the available resource with other researchers from universities and public research institutes retrospectively for relevant research questions. KORA project partners and external scientists may apply for data sets for specific analyses. The regulations for data ownership in KORA and for applications for access to KORA data are described in detail in documents which are available via the KORA website. In order to protect the rights of the data owners, a written and signed cooperation agreement is required.

Access to KORA biosamples is restricted to special laboratory analysis and has to take into account that the material is limited. The research question and the requested amount of biosamples are checked, a written and signed sample transfer agreement is required, and the requestor has to share the costs depending on the number of samples and the amount of material. For genetic research the biobank KORA-gen is being established, and the rules for access are described on the homepage www.gsf.de/KORA-gen [20]. It has to be kept in mind, that extended research using data and biosamples from MONICA/KORA retrospectively is only possible based on the informed consent of the study participants and permission of the responsible committees for ethics and data confidentiality.

A further aspect of cooperation concerns the exchange of expertise with other population based study groups like the SHIP study in Greifswald [15] and the Heinz Nixdorf RECALL study in Essen [16]. In order to achieve comparability and a general high level of quality in population based epidemiologic research in Germany, study materials like manuals, questionnaires, quality control procedures, and data entry software were made available to these study groups. As an example, specific software for generating computer-assisted patient interviews [17] and for documentation of medical drugs [18] was developed in the GSF. After its first routine use in the S4 survey, the software was released and used in several large population based studies.

Quality Assurance and Data Management

KORA had the advantage to build upon the experiences from ten years of MONICA research and field work and to further develop the acquired standards. Making use of established standard operating procedures (SOPs) and employing experienced personnel lead to a high level of quality and efficiency in the conduct of studies. Nevertheless, constant efforts are needed to guarantee

smooth and flawless study performance. According to the German guidelines for Good Epidemiological Practice [19], quality assurance (guideline 5) and data management (guideline 6) are essential features which deserve special attention in large epidemiological studies.

Basic elements which ensure high quality of KORA studies are extensive operations manuals, training and certification of interviewer and examination personnel, and a pilot study well in advance of the main study. The pilot study checks the feasibility of all study elements and the overall time schedule. Extensive revision of the study protocol has been necessary after each pilot study showing the relevance and usefulness of this measure.

During a KORA study, internal quality control concentrates on regular monitoring of all relevant aspects. Weekly transfer of all study data into the central data base allows timely data access for study monitoring. For each element of the study protocol there is one person responsible for quality control. Control procedures include application of control charts for laboratory values, intra- and inter-reader comparisons for specific imaging procedures (e. g. ECG, retinal image), and statistical analysis of interviewer and examiner effects.

All patient interviews are taped and stored until the end of the field phase, unless the subject denies permission. These tapes serve as a back up for plausibility checks, and a random sample is used to control interviewer performance. In regular intervals of about three months, all researchers participating in a KORA study are required to provide a written internal quality control report about the protocol elements for which they are responsible. These reports are of particular importance in the first months of a study when observed quality problems can still be counteracted.

An independent external quality control board is established for each KORA study consisting of three to five experts with experience in health survey field work. Besides checking the operation manuals and the internal quality reports, the external quality board performs site visits to audit the routine procedures in the study center.

Data management in KORA requires a high degree of standardization and quality assurance. KORA is a research platform with many studies which partially overlap with respect to participants. As a consequence, an integrated data base includes information from more than 20,000 study participants which belong to one or more of over 15 studies. The survey data base is kept in the GSF by the KORA data management center and it has more than 100 tables with a total of over 10,000 variables.

Basic principles of the central data management in KORA include a comprehensive concept for variable and table names, extensive documentation of data and procedures in the GSF intranet, password controlled data access via ODBC, and daily data back-up by the GSF computer center.

In the Augsburg Study Center and in the Myocardial Infarction Registry, the respective contact data bases with address data are strictly separated from the scientific data base. They serve as or-

ganizational tools to assist the recruitment process. Data acquisition in Augsburg is nowadays mainly paperless, with computer assisted personal interview (CAPI) software storing the data locally on the personal computer as well as on the central server of the Study Center. From there the data are transferred weekly via a constant data line to the GSF.

According to the rules for cooperation stated above, the data management center will generate analysis data sets and distribute them on the basis of written cooperation agreements. These data sets will be archived for at least ten years after publication.

Perspectives

The advantages and strengths of the KORA research platform are its 20 years of continuity in recruiting and maintaining cohorts for population based research thereby providing research options without parallel in Germany. With increasing follow-up duration, the KORA platform becomes more and more valuable, and the growing utilization of MONICA/KORA data and publication activities confirm this trend. The availability of biosamples has made KORA a much sought-after partner for genetic research projects in the National Genome Research Network (NGFN). The recent conduct of comparable studies in other regions of Germany is not viewed as a potential competition but as a chance for transregional comparisons.

To take further advantage of the availability of the population-based KORA cohorts, follow-up studies are being conducted and planned for the future. The current F3 study provides a ten year follow-up of the S3 survey. The main focus is to repeat the echocardiography for all participants of the sub study on left ventricular hypertrophy. This is also one of the major projects within the Competence Network Herzinsuffizienz (Chronic Heart Failure).

A seven year follow-up of the S4 survey is now being planned for the years 2006/07. In cooperation with the German Diabetes Center in Düsseldorf, this study will focus on determinants of incident diabetes in the older age groups. Other partners still have the chance to participate in this follow-up study.

Several recent studies with international funding were based on patients from the KORA myocardial infarction registry. They have shown its potential for genetic, socio-economic, and environmental health research, including gene-environment interaction, especially with the newly established GSF particle measurement center located in the city of Augsburg.

It has to be discussed whether in the future the KORA platform, which has always been restricted to observational research, may also be used to perform intervention studies. From the pool of participants and from the information about their relatives, specific risk populations could be defined and invited to take part in tailored prevention schemes. Risk assessment and subsequent prevention strategies could be assessed from an epidemiological and economical point of view.

Table 1 List of MONICA/KORA Studies in chronological order

study	year	topics	participants
MI registry	since 1984	acute myocardial infarction and sudden cardiac death	about 1,000 cases per year, only up to age 75
1-year follow-up of MI patients	1985–94	post infarction course of disease	postal questionnaires
survey S1	1984/85	cardiovascular diseases	age 25–64 years, n = 4,022
follow up of S1 participants	1987/88	cardiovascular diseases	n = 3,753 participants of S1
survey S2	1989/90	cardiovascular diseases	age 24–74 years, n = 4,940
survey S3	1994/95	cardiovascular diseases, allergies, lung diseases	age 24–74 years, n = 4,856
“A22-Study”	1994/95	long term survival after MI	n = 832 MI patients, interviews only
KORA-B “MI family study”	1996/97	myocardial infarction	MI registry cases and their relatives
KORA-A “Diabetes study”	1997/98	diabetes	n = 1,013 cases and controls from MI registry, S2 and S3
KORA-C/D “Asthma & Allergy study”	1997–99	asthma and allergies: risk factors and costs	n = 1,537 participants from S3
health questionnaire GEFU1 and mortality follow-up	1997/98	cardiovascular diseases	n = 9,631 participants from S1, S2 and S3, postal questionnaires
“Seniors Study” (MEMO-Study)	1997/98	neurologic problems in the elderly	n = 385 participants from S2, age 65–83 years
“Fractures Study”	1999	fractures in the elderly	n = 458 participants from S3 (age > 58 years)
alternative therapies for allergic patients	1999–2000	allergies	subsample of KORA C, telephone interview
survey S4 (S2000)	1999–2001	cardiovascular diseases, diabetes, obesity, dermatology, allergy	age 25–74 years, n = 4,261
HEI-study	1999–2001	MI and air pollution	n = 906 MI survivors
HEAPPS-study	1995–2000	MI-follow-up and air pollution	n = 1,565 MI survivors
diabetes family study	2001/02	diabetes and genetics	n = 1,800 participants (600 families)
MAGIC-controls study	2002/03	cardiovascular diseases and genetics	n = 880 participants from S4
health questionnaire GEFU2 and mortality follow-up	2002/03	cardiovascular diseases, diabetes	n = 9,145 participants from S1, S2 and S3, postal questionnaires
AIRGENE	2003/04	MI and air pollution	n = 220 MI patients
F3: follow-up study of S3	2004/05	cardiovascular diseases, diabetes	about 4,000 participants from S3

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