CONSTANCES COHORT

SCIENTIFIC PROTOCOL

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UMS 011 « Cohortes épidémiologiques en population »
Inserm - Université Versailles St-Quentin
Constances

Constances is a "general purpose" epidemiological cohort comprised of a representative sample of 200,000 adults aged between 18 and 69 on inclusion, consulting Social Security health clinics.

CONSTANCES ASSETS

By virtue of its population size, the quality and diversity of data and the monitoring methods, Constances is an epidemiological research tool. Constances, a platform broadly accessible to the scientific community, can be compared to the largest international cohorts.

Constances is a public health tool, designed, thanks to the particularly extensive nature of the system, along with the collection of highly diverse data from multiple sources, to support the public health objectives of the French National Health Insurance Fund for Employees (CNAMTS) and of the Government.

Constances is an epidemiological monitoring tool, implemented through a partnership with the French institute for public health surveillance and concerning several areas, such as the epidemiological surveillance of occupational hazards.

The Constances project, managed through the participation of the French local health insurance funds and health clinic, is a partnership between Inserm, Versailles Saint Quentin University, the French national health insurance fund for employees (CNAMTS), the French national old-age pension fund (Cnav) and with the support of the French Ministry of health (Directorate general for health). Constances has received French government funding for an 8-year period (CGI).
Protocol

The goal of the Constances project is to implement a large epidemiological cohort aimed at contributing to the development of epidemiological research and to provide public health information. The purpose of this cohort, created in the context of a partnership between the French national health insurance fund for employees (CNAMTS) and the French national old-age pension fund (Cnav), labelled national biology and health infrastructure by the French government's Commissariat-General for investment, is to constitute an infrastructure accessible to the research community.

Constances is a "general purpose" research infrastructure designed to help analyse a broad range of scientific problems. Constances was also designed as a public health and surveillance tool, thanks to the particularly exhaustive nature of the system for collecting and monitoring a great variety of data from a large representative sample of the adult population covered by the General Social Security scheme.

Random sampling
Subjects considered as eligible by virtue of their age and place of residence are drawn randomly by stratified sampling with unequal probabilities, over-representing individuals with a higher probability of non-volunteering according to the usual variables: age, gender and PCS. Random sampling is performed by the Cnav from the French national inter-scheme registry of health insurance beneficiaries (RNIAM), paired with the National careers management system (SNGC).

Data circuit
The Constances cohort constitutes a complex database with characteristics rendering it highly sensitive under the terms of the French data protection act, in particular due to the collection of personal data. Moreover, some data collected at the individual scale come from pairings with national databases: National inter-scheme health insurance information system (SNIIRAM), causes of death information system (CépiDc-Inserm) and the Cnav (Annual Social Security declarations, Named quarterly data, absenteeism due to illness, Active solidarity income, maternity).

Very strict data collection, organisation and management constraints are required. The procedures in place conform to legislative and regulatory texts intended to preserve high-level personal data confidentiality and security.
Health check and questionnaires

1. INVITATION

This invitation is issued at the same time as the invitation to undergo a health check-up in a health clinic. The randomly drawn individuals first receive an invitation letter presenting the project, along with a mail-back coupon enabling them to give their consent to take part in the cohort in the context of a health check-up.

2. INCLUSION

The persons having consented to participate in Constances are invited by letter to come to their health clinic, specifying the date and location of the examination. They also receive two self-questionnaires: one concerning lifestyle, along with a professional calendar to be filled in at home.

3. DATA COLLECTION

In addition to the self-questionnaire filled in at home, subjects undergo a periodical health examination used to collect health-related data: clinical examination, blood analysis, blood pressure, weight, height and waist-to-hip ratio, electrocardiogram and spirometry, sight and hearing examination. This examination is standardised by means of Standard Operating Procedures (SOPs) and permanent quality control is ensured in collaboration with the company ClinSearch and the Asqualab and Eurocell associations.

Additional questionnaires, to be filled in on-site (whole-file occupational exposures, self-questionnaire for women), are collected at the health clinic. The informed consent signature validates the collection of these data and authorises their use for research purposes.

Finally, individuals aged 45 years and over undergo a cognitive and functional check-up. This check-up is performed by a neuropsychologist and includes a series of tests. The documents pertaining to this check-up (protocol, data collection form), along with any related films, are available on request.

A postal or Web-based self-questionnaire is used for active yearly follow-up at the subjects' homes, and an invitation to come to the health clinic once every 5 years is scheduled for all cohort volunteers.

Moreover, health and socio-professional data, along with causes of death, are regularly retrieved from the national health insurance, Old age pension fund and CépiDc databases.
Confidentiality and ethics

1. CONFIDENTIALITY

The Constances cohort involves long-term longitudinal monitoring of volunteer participants. It cannot therefore be strictly anonymous as the various data concerning the individuals must be linked together throughout the follow-up and the data from different sources must be paired for each subject. Moreover, it must be possible to send the various letters to the participants (questionnaires, newsletters, etc.) and to invite them to come in to their Health Clinic. It is thus essential to ensure that highly secure personal data collection and transfer procedures are followed to guarantee absolute confidentiality.

The underlying principle of these procedures is based on the assignment of multiple non-identifying numbers for each data flow, along with the implementation of independent transfer circuits between the various sources. A "trusted third party", accredited by the French national data protection commission (CNIL), acts as a pivot between the various flows and guarantees the confidentiality of all identifying data.

The data collection and management system architecture is based on processes intended to ensure that it is impossible for any person to gain (direct or indirect) access to named data other than those that he/she has provided nominatively.

The system relies on a file mapping volunteer identity to a permanent anonymity number. This file contains no other information and is stored on an independent computer. It is drawn up and managed by an organisation acting as a "trusted third party", bound to medical and statistical secrecy and independent of the team managing the Constances project.

Of course, Constances is subject to authorisation by the French national data protection commission (CNIL) and to rulings by the French national medical association and the French national advisory committee on ethics in life sciences and healthcare.

2. CODE OF CONDUCT AND ETHICS

Ethical aspects associated with the participation of multiple partners are crucial to a project of this scope. Strict rules of ethics must be enforced with the cohort participants, along with the teams and various Constances partners. The main document defining the rules of ethics that apply to epidemiological activities is "Epidemiology ethics and best practices guidelines by the association of French-speaking epidemiologists" (Adelf).

Participation in the Constances cohort relies upon the freely consented volunteering of all
consultants who accept to take part. Despite this, various ethics-related aspects apply. The Inserm ethics review board was consulted on these matters.

Information: a detailed information brochure, specifying the benefits of the project, but also its constraints in terms of data collection, management and use, is issued to participants upon inclusion. Information feedback to participants is organised with a view to ensuring better adherence of the volunteers of the Constances cohort and its various partners, throughout the follow-up period. This is also an ethical obligation with respect to participants and of code of conduct with respect to physicians and health clinic employees actively involved in the project.

The Constances cohort was granted the "Label of general interest and statistical quality" by the French national council for statistical information (CNIS).

**Biobank**

A biobank, developed through the collection of biological samples in the health clinics, will be associated with the Constances cohort. An in-depth technical analysis was conducted for the creation of a large-scale collection, including several hundred thousand distinct samples, combined with a database of clinical, paraclinical, biological, behavioural and environmental information. The aim is to develop the largest possible collection of biological samples for the future (blood: serum, plasma, urine) and to enable the storage of more specialist samples for specific research purposes.

**Diagnostic validation platform**

Investigating physicians validate certain identified health events (cancer, cardiopathy, etc.). The purpose of these investigations is to collect data or documents (examination or hospitalisation reports, etc.) used to validate the health event and to collect detailed information essential for research.
Proposing a research project in Constances

French or foreign research teams wishing to make use of the Constances cohort structure, must submit an application. This may be to use the available data or collected biological materials and/or to collect additional data for a specific purpose. Cohort data access applications are submitted in the context of calls for proposals (CFPs) issued twice yearly.

Researchers are invited to draft a protocol justifying the scientific goals of their research project. The projects are then examined by the Constances international scientific board and, where applicable, by its Ethics Review Board and authorisation are issued by the Institutional steering committee comprised of Constances partner organisations. An authorisation application must be submitted by the researchers to the French healthcare research data processing advisory board (CCTIRS) and the CNIL. Favourable rulings and the CNIL authorisation are sent to the Constances team, than then extracts the required data and sends them to the researcher in charge of the project.

To ensure that data confidentiality and security are maintained, the Constances team generates a specific study number for each participant concerned by a research project. Moreover, a log of variable requests submitted for a given project is kept to ensure that no-one has access, even after submitting multiple variable requests, to the entire Constances database.
Team

**Marie ZINS**

Marie ZINS is a physician-epidemiologist, lecturer at the Simone Veil Health Sciences Research Unit of the Versailles Saint Quentin University. She runs the Inserm - Versailles Saint Quentin "Population cohorts" mixed unit.

Her research focuses on the scientific and technical development of population cohorts (Gazel and Constances cohorts), social epidemiology (social and occupational determinations of alcohol consumption, effects of retirement on behaviour and health) and on cohort-related methodological aspects (selection effects, longitudinal data analysis, data validation).

Marie Zins is the Constances cohort scientific and technical manager.

**Marcel Goldberg**

Marcel Goldberg is a physician-epidemiologist, lecturer at the Simone Veil Health Sciences Research Unit of the Versailles Saint Quentin University. For over twenty years, he has run an Inserm research unit focusing on the epidemiology of occupational and social health determinants and was science adviser to the Occupational health department of the French health watch institute. He is a member of the Public health council and chairman of its "Information systems for public health" workgroup.

His research work focuses mainly on epidemiological studies of occupational hazards and of social determinants of health and ageing. He has created various epidemiological observation systems, in particular the Gazel cohort that has been monitored for over 25 years and for which he is co-manager with Marie Zins. He was also responsible for the Constances cohort.

Marcel Goldberg is co-manager, with Marie Zins and Lisa Berkman, of the Constances cohort.

**Lisa Berkman**

Lisa Berkman is an epidemiologist whose research work focuses mainly upon social health inequalities, social networks and health, occupational hazards and ageing.

Director of the Harvard Center for Population and Development Studies, she was chair the "Society, Human Development and Health" from 1995 to 2008. She is also the former head of the Division of Chronic Disease Epidemiology at Yale University.

In France, she is a guest professor at UVSQ and has been actively involved in the Gazel cohort since 1994.

She is co-manager of the Constances cohort, with Marie Zins and Marcel Goldberg.
**Matthieu Carton**
Matthieu Carton is a medical doctor specialising in public health.

His main research topics pertain to occupational health determinants (occupational exposure to carcinogens, asbestos, upper aerodigestive tract cancer, sinonasal cancer, musculoskeletal disorders, work hardness).

Principle investigator of the Spirale post-professional programme for monitoring workers exposed to asbestos and wood dust, he is in charge of "occupational" aspects of the Constances cohort.

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**Sébastien Czernichow**
Sébastien Czernichow is a nutritionist, professor at the UVSQ health sciences research unit. He is head of the Nutrition department, specialising in obesity medicine at the Ambroise Paré University Hospital in Boulogne-Billancourt.

His personal research work focuses on clinical or population epidemiology of obesity-related complications, with particular emphasis on metabolic and cardiovascular complications. He is involved in both the Gazel and Constances cohorts.

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**Alexis DESCATHA**
Alexis DESCATHA is a physician, professor at the UVSQ health sciences research unit, specialising in occupational diseases at the Public Hospitals of Paris, University Hospitals of the western Greater Paris area.

His research activities focus on the professional environment, health and socioprofessional disability, in particular the epidemiology of musculoskeletal disorders.

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**Joseph Henny**
Joseph Henny was, until 2009, director of the clinical biology laboratory at the Vandoeuvre lès Nancy centre for preventive medicine. In parallel to this activity he was a lecturer at Nancy University. Since then, he has been in charge of implementing a biobank applied to large-scale population studies in the context of the Constances cohort. He is also in charge of scientific coordination for the network of health clinic medical biology laboratories.

His main scientific interest concerns the effects of biological variations on laboratory examinations. Moreover, he has contributed to the development of the concept of reference values and associated topics at the French society for clinical biology (SFBC). More recently, he was actively involved in numerous studies aimed at gaining a better understanding of the components of pre-analytical and biological variation and at improving laboratory examination standardisation. He is also a regular reviewer for several scientific publications (Clinical Chemistry, Clinica Chimica Acta and Clinical Chemistry and Laboratory Medicine).
Annette Leclerc

Annette Leclerc is a director of research emeritus at Inserm. Her main areas of research are musculoskeletal disorders, social health inequalities and statistical methodology in data analysis.

She is involved in numerous scientific appraisal activities: at the international level as associate editor for the "Occupational and Environmental Medicine" periodical and scientific reviewer for various publications; at the national level on the assessment of research projects and article reviewing. She is also a member of the CCTIRS (healthcare research data processing advisory board).