Challenges and opportunities in establishing an health examination survey

Chiara Donfrancesco (1), Luigi Palmieri (1), Cinzia Lo Noce (1), Diego Vanuzzo (2) and Simona Giampaoli (1)

(1) Istituto Superiore di Sanità, Rome, Italy
(2) Associazione Nazionale Medici Cardiologi Ospedalieri-Heart Care Foundation, Florence, Italy

CORRESPONDING AUTHOR: Chiara Donfrancesco - Istituto Superiore di Sanità - Department of cardiovascular, dysmetabolic diseases and aging-associated diseases - Viale Regina Elena, 299 - Rome, Italy - Tel 0039-(0)6-49904229, FAX 0039-(0)6-49904227 - Email: chiara.donfrancesco@iss.it

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ABSTRACT

In the last 30 years, Italy has witnessed the implementation of cross-sectional surveys providing baseline data on numerous risk factors collected from random samples of the adult general population. Some of these surveys have been followed up for all-cause mortality, fatal and non-fatal cardiovascular diseases, cancer and other chronic diseases and are part of the CUORE Project, launched in 1998 by the Italian Ministry of Health and coordinated by the Italian National Institute of Health (ISS) [1-12]. The simultaneous collection of data through different sources of information by standardized procedures and methods (population based registries, longitudinal observational studies, cross-sectional surveys) produced a global picture and time trend of the population health, identifying priority areas for treatment and prevention; this is the added value of the CUORE Project.

The objective of this paper is to describe the steps undertaken and the difficulties overcome during the surveys conducted within the CUORE Project in order to support those researchers who would like to implement a Health Examination Survey (HES).

Key words: health examination survey; epidemiologic measurements; standardization; population surveillance; quality assurance.

INTRODUCTION

In the last 30 years, Italy has witnessed the implementation of cross-sectional surveys providing baseline data on numerous risk factors collected from random samples of the adult general population. Some of these surveys have been followed up for all-cause mortality, fatal and non-fatal cardiovascular diseases, cancer and other chronic diseases and are part of the CUORE Project, launched in 1998 by the Italian Ministry of Health and coordinated by the Italian National Institute of Health (ISS) [1-12]. The simultaneous collection of data through different sources of information by standardized procedures and methods (population based registries, longitudinal observational studies, cross-sectional surveys) produced a global picture and time trend of the population health, identifying priority areas for treatment and prevention; this is the added value of the CUORE Project.

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CROSS-SECTIONAL SURVEYS OF THE CUORE PROJECT

Cross-sectional surveys represent the major source of information for cardiovascular risk factors, the prevalence of high risk conditions of cardiovascular diseases and other chronic degenerative diseases.

More specifically, in the general population, the surveys aim at:

1. describing the distribution of life-styles (diet, physical activity and smoking habits);
2. describing the distribution of common risk factors (blood pressure, body mass index-BMI, total and HDL-cholesterol, vital capacity, forced expiratory volume, waist and hip circumferences);
3. assessing the prevalence of risk conditions (hypertension, dyslipidemia, obesity and diabetes);
4. assessing the prevalence of chronic diseases (ischemic heart disease, myocardial infarction, angina pectoris, left ventricular hypertrophy, atrial fibrillation, stroke, transient ischemic attack-TIA, diabetes, chronic kidney disease, chronic obstructive pulmonary disease-COPD, cancer, osteoporosis);
5. monitoring national healthy lifestyle campaigns, evaluating in particular if salt consumption among the general population decreases over time as a result of the ‘Gaining Health’ programme;
6. identifying diseases, risk factors and other conditions in different socio-economic classes and in different groups, such as women, the elderly and migrants, who require more intensive actions in terms of prevention, diagnosis, treatment and social assistance;
7. studying time trends of risk factors and chronic diseases.

Between 1982 and 2014, 30,618 persons aged 18-84 years, randomly extracted from the general population in all Italian regions, were enrolled and examined; 5,372 were examined at least twice and 1,258 were examined at least three times. The CUORE Project cohorts are: Monitoring Cardiovascular Disease (MONICA)-Latina [6], Malattie Aterosclerotiche Istituto Superiore di Sanità (MATISS) [1-4], Finland, Italy and the Netherlands Elderly Study (FINE) [5], Osservatorio Epidemiologico Cardiovascolare (OEC) [7-10], OEC/HES [9-11], MINISIAL-GIRCSI, MENO SALE PIU’ SALUTE [12]. Surveys procedures and methods are standardized and comparable, except for the FINE-Italy cohort including men aged 65-84 years.

The CUORE project was approved by the Ethic Committees of the ISS on 11 March 2008 and on 11 November 2009, and is part of the ‘Gaining Health Programme - make healthy choices easy choices’ of the Italian Ministry of Health.

The OEC/HES survey was recognized in 2009 as part of the Joint Action of the European Health Examination Surveys (EHES – Measuring the Health of Europeans) Projects funded by DG SANCO within the Health Monitoring Programme, contributing through the collection and measurement of health determinants according to standardized procedures and method and contributing as Italy to the pilot phase of the EHES to build a surveillance system for health status monitoring at European level [13, 14, 15].

A manual of operations was developed according to the recommendations provided by the EHES Project; in turn, this manual provided recommendations to implement a HES in Italy [16].

The manual covers the entire survey process: planning, budget preparation, sampling and recruitment of participants, ethical, legal and data confidentiality issues, fieldwork staff training, selection and execution of measurements, blood sample handling, transport and storage, laboratory analyses, quality control methods, data management; some general indications on statistical analysis and dissemination.

The surveys included: blood pressure and pulse rate measurements, blood collection for lipid assays, fasting blood glucose and haemachromate, 24-hours (24h) urine collection, anthropometric measurements (height, weight, waist and hip circumference), examinations (electrocardiogram-ECG, spirometry, CO measurement, bone densitometry), questionnaire on health status, physical activity, smoking habits, personal and family history of high risk conditions (hypertension, hypercholesterolemia, diabetes) and cardiovascular diseases as well as their drug treatments; a self-reported food frequency questionnaire (EPIC questionnaire), Activities of Daily Living (ADLs) and Instrumental Activities of Daily Living (IADLs) self-reported questionnaire filled in by the participants during the survey, the Mini-Mental State examination of Folstein (MMSE) for persons aged 65 and older. Biological samples of serum, plasma, buffy coat, red cells and urine were stored and were preserved at the National Centre of Epidemiology, Surveillance and Health Promotion (CNEPS) of the ISS biobank; today they are preserved at the Department of Cardiovascular, Dysmetabolic and Aging-associated Diseases of the ISS biobank [17].

Procedures and methods to examine the population were deeply described in previous publications [1-13, 18-22] and are reported on the CUORE Project website; also surveys results are available on web platform called CuoreData [23].

Here we describe only the relevant information related to the organization of surveys (examination sites and selection of analytic laboratories, coordination and personnel involved, sampling and recruitment, information notice and informed consent, participation rate and non-participation bias, quality assurance and quality control, survey data, long term storage of the samples, data transfer and storage, statistical analyses, interpretation
and dissemination of results), which are usually shortly described in scientific papers, but are relevant when a HES is planned.

**EXAMINATION SITES AND SAMPLING**

Today, the sample size calculation is based on a participation rate of 70%. This minimum size relates to the requirements for statistical power when testing differences between countries for age-gender domains. It is not recommended to leave out population groups that are difficult to contact or institutionalized persons (hospitals, nursing homes, elderly homes, children homes, military barracks, jails and monasteries) or migrants.

To be eligible for participation in the survey, each centre had to meet the following requirements:

- easy access to local registry office for sample selection;
- availability of collaboration by local general practitioners who would recommend their patients to participate in the screening;
- availability of collaboration by local authorities who would support the costs of local premises (not necessarily a hospital) and laboratory blood tests;
- availability of local survey personnel, possibly nurses and secretaries, to support fieldwork activities (prepare letters of invitation, arrange telephone calls to invite recruited persons, schedule appointments, welcome participants, perform laboratory tests and interviews, enter data);
- availability of local medical personnel to read ECG, laboratory tests and other responses to be communicated to the participants;
- availability of well-equipped rooms, in particular: a big room where participants were welcomed and waited for interview/examinations; relaxation room for questionnaires administration; a quiet room with comfortable temperature to perform blood pressure measurement; a room to perform ECG, anthropometric measurements, bone densitometry, spirometry and CO measurement; a room for blood collection and laboratory tests, with a centrifuge, a -30°C or -80°C freezer for blood sample storage and containers for special waste;
- materials for blood collection: vacutainers for serum, plasma and buffy coat, needles and a small container for special waste collection.

All examination sites have their advantages and disadvantages (Table 1). CUORE cohorts were examined at temporary examination sites; only elderly and ill persons were examined at home.

The ISS provided the instruments necessary to perform measurements. The only way to be sure that the examination site is suitable to carry out physical measurements is to visit the place before selecting it. This required some time and personnel resources during survey preparation.

A local scientific responsible was nominated to actively cooperate with ISS staff and facilitate screening procedures.

Once the local authorities have given their approval, the local registry office was contacted to obtain the list of residents aged 20-79 years (age of interest for cardiovascular diseases), living in the municipality in which the centre was located; this list should be provided in electronic format. The random selection of the sample was performed at local level or by the ISS after receiving the list of residents.

The sampling frame suggested by the EHES consists of two stages: 1st stage, selection of the possible cities (primary sampling units) to carry out the survey; 2nd stage, selection of the eligible persons. In Italy, it was not possible to use a two-stage sample, since for each Region the centre was selected only if it met the general requirements reported in the study protocol and manual of operations and necessary to implement screening procedures. The survey was sustainable if there was support at local level: personnel, screening centres and laboratories. Once selected the municipality, the second stage of sampling was implemented: the sample was stratified by age and sex and was randomly selected from the list of residents, so that every eligible person had the same probability of being sampled.

The population sample was extracted from the list of residents. If the municipality covered a large area (e.g., city of Rome), the sample was extracted in the district of the screening centre. To develop the list of eligible persons, it was necessary to create a sequence of random numbers according to the number of residents for each age decade, for men and women separately; then the names of residents were listed and numbered in alphabetical order and the person corresponding to the random number was extracted. To ensure that the numerousness required was reached, irrespective of the participation rate, the numbers of persons randomly extracted from the list of residents of each centre participating in the screening were two times greater than what originally established.

**SELECTION OF ANALYTIC LABORATORIES**

Analyses were performed both at local laboratories and at the central reference laboratory. Those performed at local laboratories included total cholesterol, HDL-cholesterol, fasting plasma glucose, and complete haemachrome; determinations were given to the examined persons as result. Criteria for the selection of the local laboratory included: availability of room and materials necessary for blood collection, closeness to the screening centre, reasonable cost of determinations, and availability of a freezer for biological samples storage. For quality control, laboratories were controlled according to regional standards.
The biological material (serum, plasma, buffy coat, red cells, and urine) was collected, stored and sent according to standard methods used in several international studies. Biological samples were processed using materials resistant to low temperature, and simple, highly standardised methods allowed for multiple potential uses of the material.

**COORDINATION AND PERSONNEL INVOLVED**

The surveys were coordinated by the team of the Unit of Epidemiology of Cerebro and Cardiovascular Diseases of the CNESPS ISS; the national survey coordinator organised and coordinated the overall fieldwork of the survey:

- coordinating and supervising all fieldwork activities;
- selecting and agreeing on examination centres (municipality) in the region;
- extracting the population sample;
- sending letters of invitations;
- training the local personnel, monitoring quality control and fieldwork;
- keeping in contact with relevant regional/local administration and health services of the fieldwork sites;
- receiving and processing survey data from the fieldwork teams;
- receiving, storing and analysing blood and other samples from the fieldwork teams;

Each local team had a fieldwork team supervisor. The supervisor worked in close collaboration with the national fieldwork coordinator. The tasks of the supervisor included:

- coordinating the work of the fieldwork team, consulting, solving problems and specifying guidelines when needed;
- organizing substitutes for the fieldwork team members in case of sick leaves and other absences;
- keeping a regular contact with the ISS;
- checking daily appointment schedules, checking questionnaires (if needed and not built in computer programmes used in data collection);
- organizing and taking care of transfer of data and instruments.

The fieldwork team supervisors kept regular contact with the ISS to share up-to-date information from the centre; they also brought information from the ISS back to their teams, e.g. feedback from quality control. They were responsible for monitoring that team members carried out their tasks well on a daily basis. If there were problems that could not be solved within the team, the supervisors contacted the ISS and unclear issues were sorted out as soon as possible. It was important that the fieldwork team supervisor received support from the ISS and did not deal with problems alone.

Staff satisfaction was an important issue for the quality of work. The national survey coordinator and fieldwork team supervisor had an important role in creating a positive work environment since it affected the staff satisfaction.

The CUORE Project represents a system of continuous data collection and its objective was to build a permanent and greatly experienced survey staff able to carry out fieldwork activities, train local fieldwork staff and continue the collection of epidemiological data in the future.

A close cooperation between local and ISS personnel was absolutely necessary for the success of the survey. When selecting local staff, usually the preference went to young people, who were more interested in training and

**TABLE 1. Advantages and disadvantages of examination sites**

<table>
<thead>
<tr>
<th></th>
<th>Participant’s home</th>
<th>Temporary examination site</th>
<th>Mobile examination site</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Access by participants</strong></td>
<td>Easy access</td>
<td>Requires effort</td>
<td>May be easy if mobile examination site can be taken close to the participants</td>
</tr>
<tr>
<td><strong>Cost for participants</strong></td>
<td>None</td>
<td>Travel costs</td>
<td>Some travel costs</td>
</tr>
<tr>
<td><strong>Restriction to measurements</strong></td>
<td>Generally none</td>
<td>Generally none, sometimes a lack of facilities for specific measurements may come up (e.g. limited space)</td>
<td></td>
</tr>
<tr>
<td><strong>Calibration/standardization of measurements</strong></td>
<td>Difficult</td>
<td>Can be done</td>
<td>Can be done</td>
</tr>
<tr>
<td><strong>Acceptability</strong></td>
<td>Some people are not willing to let the survey team into their home</td>
<td>Generally accepted</td>
<td>Generally accepted</td>
</tr>
<tr>
<td><strong>Time and cost to set up an examination site</strong></td>
<td>Minimal</td>
<td>Time consuming</td>
<td>Time consuming and costly</td>
</tr>
</tbody>
</table>

could, in turn, train other people to carry out fieldwork activities in order to increase knowledge and expertise in the field of epidemiological data collection. However, this was not always possible, as local young staff had already a work contract and could not receive extra funds, therefore retired personnel was also engaged.

ISS personnel were responsible for training local survey personnel, verifying that all procedures were performed according to international quality standards and that equipment was properly functioning. If the survey lasted longer than foreseen, an additional visit at the screening centre was usually necessary, also to collect biological samples.

Interviewers and others in contact with the community were capable, affable and interested people, showing good manners and friendliness towards participants. An additional prerequisite for the ISS personnel was the willingness to travel around the country.

The professional team needed for most measurements consisted of physicians, nurses and other health care professionals. More specifically, including the local supervisor, the minimum personnel required in the survey were:

- a person to perform secretarial procedures, welcome participants, update the participant list on the basis of refusals and eventually select substitute participants; this person also assured that all screening phases were well developed and completed, including delivery of urine box for 24-hour collection and results printing, and checked if self-administered food questionnaires were filled out and data from instrumental and laboratory examinations entered, and printed the results for the participant;
- a professional nurse for blood pressure measurement, blood collection and questionnaire administration;
- a professional nurse to perform anthropometric measurements, electrocardiogram (ECG) at rest, bone densitometry, spirometry and CO measurement;
- a laboratory technician to separate and store blood samples and prepare urine samples.

The above personnel, except for the laboratory technician, were required to work full time over the duration of the screening procedures.

Fieldwork staff was recruited specifically for the survey. An alternative was to use personnel from the local health care organizations (e.g. primary care units or health centres or hospitals) in the selected survey sites. It was usually easier to ensure standardization of measurements, if fieldwork staff was recruited specifically for the survey. When permanent personnel of the local health services were trained to carry out the survey fieldwork, they were tempted to follow their regular practices instead of the survey protocols. This happened especially if they also had their regular tasks during the survey, and were carrying out the survey fieldwork only part time. In any case, the use of the local personnel in each survey site increased substantially the time and efforts needed for training. The use of regular health service personnel may have affected survey results, considering the differences in willingness of the survey participants to disclose their personal issues to the practitioners they were familiar with. This familiarity may have both enhanced and restricted open communication.

The personnel were motivated to strictly follow the survey protocols to ensure reliability and accuracy of the survey results.

**SAMPLE SELECTION, RECRUITMENT AND APPOINTMENT SCHEDULING**

A file with the appointment schedule was sent to the centres at the beginning of the screening: for each day of the screening, a list was provided, with the participants’ details (name, surname, place and date of birth, address) and the day and time of the appointment for the examination. The invitation letter contained the day and time of the appointment for the examination, as well as the name, the phone and time to call the nurse to confirm the appointment. This was important to take note of the number of appointments per day; for example, if the subject was unable to participate at the screening in the day scheduled, he/she could be reassigned to a more convenient date and time during the screening period. For future surveys, it might be important to keep a record of changed appointment times.

The following information and instructions for the participants should be included in the letter of invitation:

- objectives of the survey;
- importance of the survey for public health improvement;
- importance of participation and benefits for participant;
- brief description of the measurements;
- details of the appointment: date and hour of appointment; exact location of the survey centre;
- contact information: name of the person to contact, telephone number and calling hours. Contact information was important to re-schedule, confirm or cancel the appointment, or to ask for further information on the survey. Participants were asked to confirm their appointments. The opportunity to re-schedule the appointment on weekends or evenings and to obtain a certificate of absence from work was mentioned;
- indication for fasting: the minimum recommended fasting time was 12 hours (blood drawing was performed in the morning). The participant could drink water and take his/her regular medicines before the visit;
- identification: participants were recommended to
bring sanitary cards (including address and fiscal code), or any other valid identification card;
• medication: participants were asked to bring their boxes of medicines/prescriptions to the examination visit;
• participants were recommended to bring eye glasses to fill in self-administered questionnaire.

The invitation letter was sent to the participant 1.5 days prior to the beginning of screening procedures: usually, if recruited persons get the invitation too early, they may forget the date of the appointment; on the contrary, if they get it too late, they may be unable to change their previous engagements.

If the first recruiting attempt was not successful (the selected person did not show up at the scheduled appointment, the person refused the invitation, the letter did not return to sender due to addressee unknown at the address), a second letter was sent, checking accuracy and correctness of contact information. If also the second attempt failed, a telephone call was made, although reaching people by landline is difficult, as most people nowadays only have a mobile phone, and mobile phone numbers are not included in telephone directories. Telephone directories often contain alphabetical lists of households’ names; therefore it was not easy to obtain the number of married women. A personal approach through a phone call is usually more effective because allows to explain the objectives of the study, to stress the importance of participation and to schedule the appointment taking into account the requests or needs of the participant. It was important to state that all the participants were equally important for the survey, regardless of their health condition. After three failed attempts (two invitation letters and one telephone call), recruitment attempts ended. The next in the list of sampled persons was invited, in order to reach the required number. Substitution of a non-respondent with a neighbour or a person with similar characteristics was not acceptable.

INFORMATIVE NOTICE AND INFORMED CONSENT

The information notice and the letter of presentation of the project should be sent to the local general practitioners (GPs) so that they may encourage enrolled patients to participate in the survey. In small centres, it was also recommended to inform the parish priest, local pharmacies, elderly clubs, as well as local press and TV, although a widespread survey publicity could increase the request for participation from persons not enrolled in the survey.

To obtain approval for the survey, the following questions from the Ethic Committee were answered: 1) establishment and duration of maintenance of the biological bank; 2) criteria for the enrolment of people affected by serious senile dementia or mental disorders and incapable to give informed consent; 3) possibility to withdraw from the study and consequent destruction of the biological material; 4) data protection procedures; 5) procedure of patient’s health status updating, given that clinical records cannot be accessed independently; 6) possibility to use data and biological materials for future research purposes; 7) possibility to provide patients with examination results and lifestyle counselling to prevent disease occurrences; 8) destruction of identification data from participants who died during the survey period; 9) responsibilities of the survey researchers in relation to long-term storage and use of biological materials. All points were exhaustively clarified to the ISS Ethic Committee by the person responsible for the study. More precisely, the person responsible for the study highlighted that: 1) 30 years was the minimum time period required to develop a consistent number of cerebro and cardiovascular events necessary to study the association/causality between risk factors and cardiovascular and other chronic diseases and follow disease trends; 2) physically and mentally disabled people incapable to give informed consent but willing to participate in the study should undergo examinations only if accompanied by a family member who could sign the informed consent form; 3) at any point during the study, the person could withdraw from the study, asking for the destruction of his/her biological materials; 4) all data from persons who accepted to collaborate in the study and to be followed over time were kept strictly confidential. Collected data, stored in a computer database at the ISS and protected by two different passwords, could only be accessed by the researchers who have conducted the study; individual records were kept anonymized in a file separate from the one including names or other information essential to identify the participant. Biological samples were split into aliquots of small volume, paillettes that were labelled with bar codes to respect the privacy of study participants; clinical information was linked to biological samples through a secure method. A specific software kept track of all the stored samples and their location in the liquid nitrogen containers. If the person was somehow concerned about a possible violation of his/her privacy, he/she could contact the person responsible for the study, whose detailed contacts were reported in the information notes; 5, 6) the consent to a registry research in the municipality was obtained from the participant in order to realize the follow-up (vital status, total and cause-specific mortality, collection and validation of acute and chronic events); 7) at the end of the screening, examination results were collected in a folder and given to the participant. The folder contained also explanations of the exams performed and lifestyle recommendations, which represents the incentive for participating in the study; 8) identification data from participants who died during the survey period were destroyed to respect their privacy in case of future use of their clinical data, which become “irretrievably anonymized”; 9) biological samples were stored in the CNESPS biological bank at the ISS, today they are preserved at the Department of Cardiovascular,
Dysmetabolic and Aging-associated Diseases of the ISS biobank, and only the biobank personnel can be provided with patient’s name and address or any other information that can be used, if necessary, to identify him/her. The results of the study should be published or presented at scientific meetings, but the identity of the participant is protected, and data shall be always disseminated in aggregated form.

Before performing any kind of research involving humans, informed consent must be obtained, which goes beyond the mere signature of a written form by the person concerned. It is a communication process between the person and the health care professional who is conducting the survey, with the goal of ensuring that the individual fully understands the scopes of the study, the methods adopted, and how the data will be used. This communication process is both an ethical and a legal obligation. The concept of consent is relevant to both the performance of the study itself and the protection of the person’s privacy. The first step in obtaining an informed consent is to provide the study candidate with information, which must be complete and clear, given that the ultimate goal is to ensure that participants are truly informed. The way in which the information is presented could also influence the participation rate. The information is contained in the “information notice” and in the “informed consent”: both documents are important to obtain the participant’s signature.

The information notice was provided to the study candidate sometime before the informed consent form, so that the candidate had sufficient time to read and understand the information before agreeing to participate. It was provided together with the “invitation letter”, which was used as an introduction to explain in general what the study was about, its importance, and how and when the candidate could be contacted. The invitation was short and “appealing”.

The information notice was given to the enrolled person to make him/her truly informed about the objectives of the survey, the importance of the survey for public health improvement, information on sample selection, a brief description of instrumental and laboratory examinations, information on delivery of examination results, storage of biological samples, personal data treatment, ethical approval, personal data protection and future follow up with collection of morbidity and mortality data. The most common question from participants was: “why was I selected, can you take a member of my family who needs a health examination?” and the usually reply was: “this is a random sample, sorry we cannot take others”.

Fieldwork staff members were recommended to illustrate in simple words the key points of the consent to the participant, and check if he/she had well understood the contents of the information notice, giving the possibility to ask questions or express doubts before signing the consent form.

The participant was asked to sign three copies of the informed consent form: one was given to the participant together with the results of instrumental and laboratory examinations, one is stored at local level and one is stored at the ISS.

### PARTICIPATION RATE

A high participation rate is extremely important for the reliability and validity of the survey and depends directly on the success of recruitment. Since non-respondents tend to have different health characteristics from the rest of the sample, their omission often results in bias: some subjects refuse to come for examination, because they feel healthy and do not find it useful to be examined, or because they feel sick and are afraid to come for a screening. The amount of bias introduced depends on the frequency of the high risk condition (i.e. hypertension, obesity, dyslipidaemia) in the sample as a whole, the proportion of non-respondents, and the extent to which the non-respondents are atypical.

Since the likelihood of bias depends on the cause of non-response, the investigator numbered those who fell into various categories were reported – for example, removed since census, on holiday, ill, dead, or refused to take part.

Personal contact (by nurse, physician or other local health professionals), convenient appointment and arrangements for time off from work were of help to elicit cooperation and overcome resistance to response.

To obtain a high participation rate, the first contact attempt was crucial. The invitation letter was easy to understand, even by participants with slight linguistic or cognitive impairment; it stated that the examination was free and refusal to participate did not compromise any future health assistance.

The number of persons invited to participate were recorded, as they represent the participation rate denominator. To calculate participation rate, the following categories were excluded from the denominator: persons who died between recruitment and invitation; persons who moved out of the sampling area; persons whose invitation letter returned to sender for unknown address. The enrolled populations were followed over time for total and cause-specific mortality; to achieve the objectives of mortality registration, the following information was collected and stored also for non-respondents: name, surname, date of birth and residence. This allowed linkage with total and cause-specific deaths and comparison between respondents and non-respondents.

The participation rate is essential to generalize results yielded from the sample to the general population. Participation rates vary significantly across places: usually, they are higher in small towns and suburban areas than in metropolitan areas.

Recruitment efforts were done towards obtaining the highest possible participation rate to be representative of the general population. The ideal participation rate is at least 70%, although a higher rate was preferable. However, during the last few years, only a few surveys
have reached such a high participation rate (today we reach a mean of 55%, with some regions i.e. Lazio) that get 40% participation rate and other regions (i.e. Valle d’Aosta) that get 85% participation rate). This is why special attention was given to increase participation rate.

Competent and motivated survey personnel played an important role during the recruitment process. They were trained to make enrolled persons feel valued and appreciated, feel they were part of the study and aware that their contribution to future research on chronic disease prevention was important. They were professional, friendly and respectful people; they showed caring manners towards participants. A proper training to manage telephone calls was also important: they received training on the correct answers to frequently asked questions; on how to persuade uncertain participants in an acceptable manner; on the options that could be offered in case of difficulties in scheduling a visit (weekends, evening hours); and on how to ask reasons for non-participation.

During the recruitment process, there were several important issues that influenced the motivation to participate, such as multiple contact attempts, a communication plan involving local press, local General Practitioners’ and other health operators, possibility to schedule appointments on weekend, possibility to re-schedule an appointment and to withdraw from the study at any time and for any reason, prolonged opening hours, delivery of examinations’ results to participants, as well as absence from work certification.

In addition, the letter of invitation was structured to favour participation in the study. The sample included resident immigrants, defined as those persons born outside Italy. In the last survey, they represented 5% of the whole examined population (4.3% men and 5.8% women). To facilitate participation of resident migrants showing language difficulties, they were assured that one member of the family (usually a younger component) or other migrants could help them to understand questions if necessary.

No monetary incentives were used to encourage attendance, but participants received the results of instrumental and laboratory examinations and also detailed lifestyle recommendations (tips for healthy eating, smoking cessation and physical activity).

In addition to the recruitment process, motivation of the personnel was also important during the fieldwork. Issues that increased motivation at the examination site were:

- a friendly atmosphere, so that participants felt welcome and appreciated;
- examination site near participants’ home;
- comfortable facilities, e.g. room privacy is important;
- no waiting times or minimal waiting between measurements;
- possibility to interrupt visit and re-schedule it in a later time;
- possibility to be accompanied by a family member or a proxy, if needed.

Partnership and collaboration with local organizations, professionals and communities helped to raise awareness about the importance of the survey, and to arrange easy access to examinations.

**NON-PARTICIPATION BIAS**

In order to assess the non-participation bias, information on non-participants was collected, to evaluate potential biases in estimates. Vital status follow-up was updated until December 2014, for both participants and non-participants.

It is known that non-participant are more often young men from lower socio-economic classes; non-participants have also worse health profile or more psychological disorders; they are more often smokers and have a higher total and cause-specific mortality than participants.

Some key information, such as age, sex, and some aspects of social status, can be obtained from the sampling frame.

For each person invited to participate, the number and type of contact attempts were recorded; it was also recorded if the person refused participation or dropped out after having agreed to participate, and if examinations were completed or not completed. Reasons behind refusals were recorded as follows:

- Refused: no reason given
- Refused: lack of time
- Refused: personal principle
- Refused: health problem (e.g. disability restricting access to the examination site, or participant was hospitalised)
- Refused: feeling healthy (therefore participant thought there was no reason to participate)
- Not contacted: not reached (no address/phone number available, outdated information)
- Not eligible: moved abroad (not known at the address; the letter was returned to sender)
- Not eligible: age out of survey range
- Temporarily unavailable: e.g. holiday, work outside the area
- Language problems
- Not eligible: died
- Impossible to examine for other reason (this reason had to be specified, if possible).

**TRAINING OF PERSONNEL**

Training is the key element of standardization and quality assurance. All members of the national survey team, both those working at the ISS and all fieldwork staff members, received a training programme. This training was essential for the quality of the survey: secretaries and assistants working at the central survey office, those who...
contacted the selected persons, sent the invitations and scheduled the visits, data managers, statisticians and all field work staff members understood the aims of the survey and the whole data collection process.

All survey staff members were recommended to read the manual before participating in training sessions and eventually update it at the end of the screening on the basis of suggestions arisen during fieldwork procedures.

The ISS was responsible for training fieldwork staff members. The training sessions took place in each selected centre during the first week of the screening, although their duration varied depending on the previous survey experience of the selected staff members and the distribution of tasks among fieldwork members. Each team member was trained to handle several measurements, to allow substitution with other fieldwork members when needed, and to rotate tasks. If the screening lasted longer than planned, refresh training sessions were foreseen.

The training included general issues for all staff members, general fieldwork skills and practices for the fieldwork staff, and specific training for each selected measurement. Practical measurement sessions were needed also for experienced staff members to ensure that standards were followed correctly.

The training for all survey members included the following topics:

- purpose and aims of the survey: it was important that all staff members understood the importance of the survey and were able to describe its aims and purpose to the participants in a standard way;
- ethical issues and confidentiality: a clear definition of what data confidentiality meant and how it was assured by all staff members; the reason why an informed consent was needed, and what this informed consent meant;
- random samples and the importance of high participation rates: how people were selected, and why all selected persons were equally important regardless of their health status or other characteristics; how participation could be encouraged and motivated;
- the importance of standardization and quality assurance: understanding the aims of audit visits and quality assurance, the role of survey manuals, the importance of consulting supervisors when needed;
- survey organization: roles and responsibilities of each staff member at the central office and in the fieldwork teams;
- working with the local health care professionals, that is, building and maintaining good collaboration, so that they could encourage their patients to participate in the survey; referring participants with abnormal measurement results to their GPs or other local health care professionals;
- how the survey results were reported and published; publicity rules and rules to apply when working with local media during the fieldwork;
- data management system and IT skills for data entry, handling and reporting.

The training for the fieldwork team members who carried out the measurements included the following topics:

- specific procedures for each interview module or instrument;
- specific measurements: rationale for the measurement, measurement methods, including practical training;
- how to provide a feedback to participants concerning measurement results;
- information to physicians and local health care professionals when needed;
- safety of the fieldwork team members (e.g., actions needed in case of needle stick injuries, violently acting and aggressive participants).

For example, the personnel responsible for collecting blood samples were trained following the part of the protocol that pertains to blood collection, and the safety instructions to protect the participant and the nurse or technician during the blood sample collection. Similarly, those who carried out the blood pressure measurements needed specific information on why standardized blood pressure measurements were needed, what the key steps were in the measurement protocol, how the results were recorded and how the results were explained to participants. The practical training included an adequate number of measurements observed by supervisors, and feedback sessions. The double stethoscope was used to check the readings of blood pressure measurement. Differences exceeding 2 mmHg between the trainer and the nurses were not allowed.

Trainers participated in the training seminars organized by the EHES; they were encouraged to read the survey manuals before the training sessions, during and/or after them. The manuals of operation, continuously updated until 2011, formed the basis for all training.

Open discussions between all fieldwork members and other survey staff members were encouraged during the training sessions. During the fieldwork, meetings with supervisors, audit visits and feedback sessions supported learning and pointed out the importance of standardization.

The best time for training was the first week of the screening: in this way, trainees had the possibility to observe trainers and progressively replace them in performing measurements as they gain expertise. To allow substitution of fieldwork team members when needed, and to allow task rotation, each team member was trained to handle several measurements. A retraining was organized during fieldwork if the fieldwork lasts for more than two or three months; this was done to ensure that standards are kept. In our case, retraining was essential also if effects or non-adherence to survey standards were observed during audit visits or
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SURVEY DATA

When the participant was welcomed to the screening centre, and before signing the informed consent, the following information was recorded:

- serial number assigned to every participant: this is a unique number and was included in all paper documents, laboratory tests and other exams of the participant (ECG, questionnaire on health status, nutrition questionnaire, ADL-IADL questionnaire, spirometry, bone densitometry);
- registry data (surname, name, married surname), checking that the registry data reported in the appointment list were correct;
- fiscal code;
- sex;
- date and place of birth;
- country of birth (used as a proxy to evaluate immigration);
- home address and landline or mobile phone number (work, relative’s phone number, etc.);
- self-reported weight and height, flu vaccination.

The procedures used to record survey measurements and to get data from different examination sites included:

- self-administered questionnaires: ADL-IADL was self-administered and results were later inserted in the database software, usually in the afternoon following the screening;
- interview: this was a computer-assisted data collection; this methodology reduced the number of manually transferred data and facilitates to check data at an early stage;
- physical values measured: vital capacity and forced expiratory volume in one second through spirometry; information present on the result sheet and referred to stiffness, t-score and z-score from bone densitometry was inserted in the database, usually in the afternoon following the screening;
- laboratory tests assessed at local level: total and HDL-cholesterol, fasting blood glucose and haemachrome were assessed at local level; these laboratory tests were inserted in the database software usually in the afternoon following the screening; these tests were not used for statistical data analysis, but they were important as result of clinical examination;
- the number of the pallettes of serum, plasma, buffy coat, red cells, prepared in the laboratory, and the identification number of the biological samples; this number is different from the participant’s serial number and corresponds to the serial number of the biological bank specimen;
- the quantity of 24h urine collection; when the participant came back to the screening centre to deliver the urine container, the nurse controlled the quantity of urine, inserted the data in the database and stored 4 tubes in the freezer.

Every participant in the survey was identified using a serial number, which included a code identifying the region, a code identifying the centre, and a code identifying the subject.

The inclusion of the biological/physical measurements in the database software allowed to prepare the result-sheet for the participant. All the important results (blood pressure, height, weight, hip, waist, body mass index, spirometry, bone densitometry, the CUORE Project cardiovascular risk score, total and HDL cholesterol, fasting blood glucose and haemachrome) were printed and given to the participant when he/she came back to the screening centre with the 24h urine collection and food frequency questionnaire.

Usually, every 3-months, the centralized laboratory sent the tests results (lipids-total and HDL cholesterol, triglycerides and fasting blood glucose) to the ISS; these results were labelled with a serial number that univocally identified the screened person, were inserted in the database and were considered in the statistical analysis.

The self-reported diet questionnaire was coded at central level and transformed into an electronic file through an optical reading.

The staff prevented errors and incompleteness of records by routinely checking forms and data. A specific code was used for relevant data not obtained by the subject (missing data). To prevent loss of records, the subject identification code was recorded at all stages, and also laboratory samples were labelled with bar codes bearing a reference to the subject identification code.

LONG TERM STORAGE OF THE SAMPLES

The biological samples were packaged on dry ice for transfer to the CNESPS-ISS biobank. Long term storage
was foreseen, for additional measurements and future use; therefore the samples were frozen at -80°C or stored in liquid nitrogen at -196°C.

After performing the required determinations, each centre was then required to send data, in electronic format, to ISS.

INTERNAL QUALITY CONTROL

The examination procedure was carefully planned and a routine retraining of all personnel doing examinations was performed.

To comply with EHES recommendations, some changes were introduced with respect to the previous surveys. For example, two consecutive blood pressure measurements were performed in the 1998-2002 survey; three were performed in the 2008-2012 survey, although the participant’s position and the methodology used were the same (blood pressure measurements in supine position at the end of the clinical examination within FINE-Italy Study). To study temporal trends, the mean values of 1st and 2nd measurements were considered; while the mean values of 2nd and 3rd measurements were considered to make comparisons with EHES partner countries.

Some internal quality controls were carried out during the screening. In the case of blood pressure, these controls included:

- proportion of identical blood pressure values in the two/three measurements performed;
- frequency of the last digit: 0, 2, 4, 6, 8 (the same chance of occurring is expected - 20% each).

It was useful to check minimum, maximum, mean value and standard deviation of single parameters measured after the first day of the survey. Data errors could depend on: instruments not perfectly functioning, incorrect procedure and method used for the measurement, incorrect reporting of measured value in the electronic form. If minimum and maximum values are not plausible or mean, and especially when the standard deviation was too much different from the value assessed in other teams, the procedure for blood pressure, weight/height, circumference and other measurement were checked and, if necessary, instruments were calibrated again and personnel was trained again.

Personal data, as well as education, lifestyles, pathological history, family history, drug treatment, MMSE, were collected by means of an electronic questionnaire that automatically considered the answer options and did not allow continuation if the answer was not entered. It was recommended to check these data during the screening, so to confirm that the electronic questionnaire was working properly. Data collected by ADL-IADL self-reported questionnaire were manually entered in the electronic form during the screening and were checked for completeness and consistency.

EXTERNAL QUALITY ASSESSMENT

Data obtained from the CUORE Project were assessed by the EHES Reference Centre (RC). The EHES Reference Centre was responsible for reviewing national manual and assessing survey and quality control procedures through site visits. The quality performance of external laboratories was also assessed by the RC.

The evaluation of the OEC/HES procedures used, the data generated in the surveys and the data and information generated through external controls were evaluated by the RC, with the help of the national survey coordinator and organizers. The site visit was carried out by the EHES –RC at Brescia on May 24-25, 2011. The complete report of this visit can be found on the CUORE Project web site [23]; here below we present the conclusion and recommendations of the Italian site visit report:

<<The Italian OEC/HES has been built since the 1990s. It is based on collaboration with regional authorities and the methods have been adapted to what is feasible in each region. A specific characteristic of the Italian survey is that separate local fieldwork teams are recruited for each centre (region). This is challenging for the training. Therefore, particular attention during the site visit was paid to the training procedures and the performance of the fieldwork staff. Our observations were positive, and the team was very dedicated to the work. Future surveys can no doubt be built on this excellent work.

The main challenge in Italy is the participation. The impression was that rural areas are easier for recruitment and largest cities most challenging, but not much can be done to motivate people to show up. Perhaps one solution could be to increase the awareness of the population about the survey, so they will recognize it when they receive the invitation. So far the participation rates have varied in the Centres from 40 to 78 %.>>

As always, it was possible to further enhance standardization and quality control. Specific issues of our OEC/HES on this are summarized below:

- More attention should be given to the position of the measuring tape for waist circumference measurements;
- Attention should be paid to sufficient resting time before and between blood pressure measurements;
- Quietness of the room during blood pressure measurement should be ensured. During the site visit, the window was open and noise from the traffic could disturb the auscultation;
- We did not get a good record of the tubes used in blood drawing, for the centralised blood measures and preservation in the CNESPS/ISS biobank. 1 blood collection tube of serum of 10cc and 2 blood collection tubes of 4.5 cc with EDTA are recommended; these quantity
allow to preserve 6 paillettes of serum (2 sent to Campobasso for the centralised tests) 6 of plasma, 2 of buffy coat and 2 of red cells; for local blood analysis (to be given to the participant) 1 tube of serum and 1 tube of 4.5cc with EDTA. All the blood collection kit is available at local level and differs from centre to centre;

- It is strongly recommended that a routine back-up of the data entry system is taken several times each day;
- The relative centrifugal force should be calculated using the formula in the EHES manual. If it is less than 2000g, the centrifuging speed should be increased.>>

Data management planning was part of the general planning of the survey from the beginning. Well-planned data management facilitates good quality and availability of data for analysis. Data management ensured that the data recorded during the fieldwork were available for analyses, and that the available data were complete (no data collected from the participants were lost), correct and verifiable. In this way, data analyses were done using properly documented, correct and error-free data, so that the whole analysis could be repeated later. Data management included also data storage security.

A detailed data management plan including all phases of the survey (sample selection and recruitment; appointment scheduling; survey data collection; recording the laboratory and exams; error checking, corrections, and documentation of the data; data transfer and storage) was elaborated at the beginning of each surveys.

A central database was developed, to separately store personal data and data on measurements; these data are kept at the ISS.

FEEDBACK TO PARTICIPANTS

The feedback to participants was an important part of the fieldwork procedures. For many participants, this was one of the main reasons to participate in the HES. The feedback on anthropometric measurements and blood pressure was provided to the participant right after the measurements. Results of blood analysis usually needed more time and could not be provided during the same visit when blood samples were collected.

Examination results were collected in a folder and given to the participant at the end of the examination visit (or later mailed to the participant). The folder also contained explanations on the examinations and lifestyle recommendations, including healthy diet, smoking cessation, and physical activity suggestions. For those participants who had both total cholesterol and HDL assessments, the individual risk score of the CUORE Project for persons aged 35-69 years and free from previous cardiovascular event was printed; for those participants who had total cholesterol only, the Progetto CUORE risk chart for persons aged 40-69 years was printed. It was possible to print results of measurements, examinations and blood tests for all participants.

The folder also contained laboratory blood results, ECG, spirometry and bone densitometry printouts, and a copy of the signed informed consent.

Results were provided when the participant came back to the centre, the day after the visit, to hand in the 24-hour urine collection.

ERROR CHECKING AND DATA CORRECTION AND DOCUMENTATION

At the end of each survey, data were checked for completeness and consistency. The number of missing values was assessed for all variables; for every continuous variable we calculated the mean, standard deviation, minimum, maximum and frequency distribution; these data were compared with standard values. The frequency distribution of every categorical variable was calculated and compared with standard values as well. The paper form was checked if a value in the electronic form was found to be out of the standard interval or internal to the standard interval but close to the lower bound or upper bound. If the variable was not included in the paper form, the plausibility of the value was checked by evaluating linked variables, e.g. weight was checked by evaluating height, waist and hip circumference. When the evaluation regarded laboratory determinations, the centralized laboratory was contacted. When the value was recognized as not acceptable and the original source of data was not available, value was recorded as missing.

Related variables were cross checked, e.g., number of cigarettes smoked per day were reported only for persons who answered yes to the question “do you smoke?”; if incongruities were found and the original source of data was not available and the cross assessment of variables did not allow to understand which variable was incorrect, values were recorded as missing.

Getting data from different survey to the common database was an essential part of data management. Both the original and the corrected databases were kept and stored. All corrections of original databases as well as the motivation of each correction and the rationale of the intervention were recorded in a SAS software language (syntax of operations made using the SAS software to check and correct data). The SAS syntax allows to check and modify corrections at any time.

DATA TRANSFER AND STORAGE

Computerized data were stored on an external hard
drive, from which data were further transferred into the central CUORE database. Collected data, protected by two different passwords, can only be accessed by the researcher responsible for the database, in order to prevent disclosure of information to unauthorized individuals. The access to information is allowed only through a proper identification and authentication of the user. The database does not include personal data, but only the personal identification number.

Participant sensitive information was recorded in a separate file (Anagrafe) that contained also registry data of non-respondents. Due to its sensitive data (name, surname, data of birth, sex, address), the Anagrafe file is available only in one computer, accessible to one person only, protected by a password. A copy of that file is available at the storage backup device; that file contains the participation status (respondent or non-respondent) and eventually the reason for non-participation.

STATISTICAL ANALYSES AND INTERPRETATION OF RESULTS

Those who analyse the data and interpret the results need to know the quality and the specific characteristics of the data.

In order to assess population health conditions, efficacy of assistance and preventive actions, it could be interesting to compare risk factors distribution, high risk conditions and diseases prevalence between sexes, periods and geographical areas.

In order to plan assistance and preventive actions, stakeholders could be interested to know how many persons are affected by diseases or high risk conditions in the target population.

In the survey data analysis and interpretation of results, particular attention was paid to the age distribution. A sampling of all regional samples, stratified by sex and age-classes, allows to compare data by sex, different geographical areas and period, knowing that comparisons are not affected by different age distributions, but means, standard deviation levels and prevalence depend on the age distribution planned for the sampling. These statistics, then, are not representative of target population values.

In order to take into account the real age distribution of the population, means and standard deviation levels and prevalence were age-adjusted. The survey data of the CUORE Project were age-adjusted using the Italian age distribution according to sex and screening period.

The age-adjustment done by using the age distribution of the Italian population allows to assess risk factors and prevalence distribution and their trends; it takes into account the real Italian age distribution of the population and its modification over time, and estimates the number of persons affected by diseases or high risk conditions in the target population.

To maximize the comparability of published statistics at international level, survey data were also age-standardized using the age distribution of the European population.

DISSEMINATION OF RESULTS

The purpose of the CUORE Project is to provide processed information to health policy planners and decision makers, health professionals, the general public, and researchers. It is important that the survey results are reported at national and international level. The distributions of lifestyles, risk factors and high risk conditions, and cardiovascular diseases prevalence were published in Italian by age-adjusting data using the Italian age distribution, and in English by standardizing data using the European age distribution [9, 10]. A section on the CUORE surveys is available, both in English and in Italian, on the website of the CUORE Project and provides basic information on the study. Information is kept updated with the project progress, and data about risk factors and health conditions of the population are published as soon as available. This means of communication provides an easy solution to communicate information to different target audiences. A communication expert helps survey staff to ensure that web pages are simple to understand while providing an effective message.

Part of the CUORE Project database is available on a web platform called CuoreData [23]. Through personalized queries (by period, geographical area, gender, age groups and level of education), CuoreData provides main statistics on the health status of the Italian adult population, concerning:

- distribution of measured cardiovascular risk factors (blood pressure, total, HDL and LDL cholesterol, triglycerides, blood glucose, weight, height, BMI, waist circumference, waist circumference, number of cigarettes for smokers, salt and potassium consumption);
- distribution of absolute cardiovascular risk assessments by the CUORE Project score, to assess the likelihood of developing a major cardiovascular event (myocardial infarction or stroke) in the following 10 years;
- prevalence of high risk conditions (hypertension, hypercholesterolemia, smoking habit, physical inactivity, obesity, diabetes);
- awareness of being in a high risk condition prevalence;
- prevalence of drug treatment adequacy for high risk conditions;
- prevalence of cardiovascular diseases of arteriosclerotic origin, such as myocardial infarction, stroke, angina pectoris, TIA, intermittent claudication, left ventricular hypertrophy and atrial fibrillation.
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COMMENTS

The Italian CUORE surveys represent a system of periodical data collection: the surveys lasted three-four years, and between one survey and the following there was a five-six years break. In the Italian experience, a four-year period is the minimum time to examine 10,000 adult people using two sets of standard instruments, with one team travelling across the country to involve local personnel, provide training and assess quality control. Collected data are used to monitor time trends of risk factors distribution, and prevalence of lifestyles, high risk conditions and chronic diseases. This system has allowed to build a permanent survey team at the ISS, with great expertise on organizing surveys, training local fieldwork staff and conducting surveys, analysing and disseminating data. The EHES recommendation is to repeat the HES core measurements about every five years, while some additional measurements may be repeated less frequently (e.g. every 10 years). More frequent surveys usually do not reveal interpretable measurement changes. They can be considered only if there is a need to closely follow trends related to potential effects of specific health promotion activities.

The HES key messages are:

- health surveys are vital to understand the health situation and the behaviours of the population, and they provide an evidence-base for health policies;
- the identification of health differences between population groups is a prerequisite in the work to narrow down health inequalities;
- to support healthy aging, we need to know the current state of health of adults and children;
- the national survey is conducted by a reliable public health authority, the methods are secure and science-based, and the results do not serve any other interests than public benefit;
- the participation in the survey gives participants a free-of-charge opportunity to receive up-to-date information on their own health;
- information about people’s health is vital to build an efficient health care system geared to our health needs and those of our families. Each individual’s contribution is important in making the study representative;
- data collected within a HES is a source of valuable information not only for stakeholders at national level but also for local healthcare professionals who, based on the findings highlighted in the surveys, can deepen some aspects through further studies on their geographical area;
- the health examination survey will verify and complement data collected through other health questionnaires and registries.

The HES could become a periodical sustainable system for national health, providing nationally representative, high quality and comparable information to support the planning and evaluation of health policies and prevention activities.

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Statement

The findings and conclusions in this paper are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of European Commission/DG Santé or the Italian Ministry of Health or the Istituto Superiore di Sanità. Therefore, no statement in this report should be construed as an official position of European Commission/DG Santé or the Italian Ministry of Health or the Istituto Superiore di Sanità.

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CuoreData shows data based on the same age distribution for both sexes, all periods and all geographic areas, thus allowing a comparison between data free from the effect produced by different age distributions for the various groups. Age-adjusted statistics will be available.


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