# EPIC-Heart: the cardiovascular component of a prospective study of nutritional, lifestyle and biological factors in 520,000 middle-aged participants from 10 European countries

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# EPIC-Heart: The cardiovascular component of a prospective study of nutritional, lifestyle and biological factors in 520,000 middle-aged participants from 10 European countries

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**Abstract.** EPIC-Heart is the cardiovascular component of the European Prospective Investigation into Cancer and Nutrition (EPIC), a multi-centre prospective cohort study investigating the relationship between nutrition and major chronic disease outcomes. Its objective is to advance understanding about the separate and combined influences of lifestyle (especially dietary), environmental, metabolic and genetic factors in the development of cardiovascular diseases by making best possible use of the unusually informative database and biological samples in EPIC. Between 1992 and 2000, 519,978

participants (366,521 women and 153,457 men, mostly aged 35–70 years) in 23 centres in 10 European countries commenced follow-up for cause-specific mortality, cancer incidence and major cardiovascular morbidity. Dietary information was collected with quantitative questionnaires or semi-quantitative food frequency questionnaires, including a 24-h dietary recall sub-study to help calibrate the dietary measurements. Information was collected on physical activity, tobacco smoking, alcohol consumption, occupational history, socio-economic status, and history of previous illnesses. Anthropometric measurements and blood pressure recordings were made in the majority of participants. Blood samples were taken from 385,747 individuals, from which plasma, serum, red cells, and buffy coat fractions were separated and aliquoted for long-term storage. By 2004, an estimated 10,000 incident fatal and non-fatal coronary and stroke events had been recorded. The first cycle of EPIC-Heart analyses will assess associations of coronary mortality with several prominent dietary hypotheses and with established cardiovascular risk factors. Subsequent analyses will extend this approach to non-fatal cardiovascular outcomes and to further dietary, biochemical and genetic factors.

## Introduction

EPIC-Heart is the cardiovascular component of the European Investigation into Cancer and Nutrition (EPIC), a multi-centre prospective cohort study designed to investigate the relationships of nutrition with cancer and other major chronic disease outcomes [1, 2]. The overall objective of EPIC-Heart is to make best possible use of the data and biological samples available in EPIC in order to advance understanding about the separate and combined influences of lifestyle (especially dietary), environmental, metabolic and genetic factors in the development of cardiovascular diseases, including coronary disease, stroke and other vascular diseases.

The EPIC-Heart resource differs from many previous epidemiological investigations of cardiovascular diseases in several ways that should increase its scientific value: (i) it is large, involving data on 519,978 adults, mostly aged 35–70 years thereby enabling precise estimates of the impact of suspected risk factors; (ii) it is geographically diverse, with participants recruited from 23 centres in 10 European countries, providing an opportunity to investigate the impact of contrasts in various dietary and other exposures (as well as in cardiovascular disease rates); (iii) it involves 366,521 female participants, thereby enabling detailed analyses in women; (iv) it involves prospective monitoring of participants, the great majority of whom reported no history of cardiovascular or other recorded diseases at the initial examination, thereby minimizing the influence of disease itself on the characteristics recorded at baseline (such as on dietary habits and biochemical factors); (v) it contains information on a range of lifestyle and other exposures (notably dietary intake), as well as, in about three-quarters of participants, stored biological samples, enabling biochemical and genetic analyses; and (vi) it monitors participants, after the initial examination, for cause-specific mortality and, in a large subset, for major cardiovascular morbidity. This combination of features will enable EPIC-Heart to make a substantial contribution to the prevention and understanding of cardiovascular disease by elucidating its determinants.

The present report provides a description of the aims and resources of EPIC-Heart in order to bring it to the attention of the wider scientific community, to outline certain planned analyses, and to simplify references to it in further papers reporting empirical or methodological findings. Previous reports have provided a detailed account of the individual EPIC study cohorts, their source populations, and information on samples collected at the baseline examination with particular reference to cancer outcomes [1, 2]. The present report complements those accounts by focusing chiefly on aspects relevant to EPIC-Heart.

## Methods

### *Participants*

The procedures used in the recruitment of participants into the EPIC study have been described in detail elsewhere [1]. The seven initial EPIC countries (France, Germany, Greece, Italy, the Netherlands, Spain, and UK) used a common protocol, and they were later joined by centres in Denmark, Norway, Sweden and a further centre in Italy (Naples) that were conducting broadly similar prospective studies (Figure 1 and Table 1). Between 1992 and 2000, 519,978 participants (366,521 women and 153,457 men, mostly aged 35–70 years) were recruited in 23 centres located in 10 European countries. The majority of centres invited participants (typically identified according to age, sex, and, optionally, other criteria: Table 1) from population-based registers (Denmark, Germany, certain Italian centres, the Netherlands, Norway, Sweden, the UK). In other centres, various sampling frameworks were used, including: blood donors (Spain and Turin and Ragusa in Italy); screening clinic attendees (Florence


**Figure 1.** Countries and centres involved in the EPIC study.

in Italy and Utrecht in the Netherlands); people in health insurance programmes (France); and health-conscious individuals (Oxford, UK). Participant eligibility within each cohort was mainly based on geographical or administrative boundaries. In France, Norway, Utrecht in the Netherlands and Naples in Italy, however, only women were recruited. As a rule, participants were invited to participate either by mail or in person or both (Table 1).

*Dietary intake assessment*

Dietary intake was assessed using a number of different instruments that were developed and validated in various populations participating in EPIC, as described previously [3–7]. Three dietary assessment approaches were used: (i) extensive quantitative dietary questionnaires, containing at least a few hundred food items and estimating individual average portions (used in France, Germany, Italy [except in Naples], the Netherlands and Spain), involving self-administration except in Spain, Greece and Ragusa in Italy where interviewers were used; (ii) semi-quantitative food-frequency questionnaires, with the same standard portion(s) assigned to all participants (used in Denmark, Norway, Naples, and Umeå in Sweden); and (iii) combined dietary methods in the UK (where centres used a semi-quantitative food-frequency questionnaire and a 7-day food diary) and in Malmö in Sweden (where a non-quantitative food-frequency questionnaire was used together with a 14-day record on lunches and dinners). To facilitate combined analyses given the use of different dietary assessment methods across centres, additional data were collected by computer-assisted 24-h dietary recall in 36,900 EPIC participants, representing approximately 5–12% sub-samples in each centre (or about 1.5% for the UK centres). This calibration study has been described elsewhere [8–10] and a common standardized food composition database for several nutrients has been developed [11, 12].

*Other questionnaire-based data*

For the seven initial EPIC countries, a common set of questions and possible answers was agreed upon and

**Table 1.** Recruitment information and source populations

| Country | Geographical/ political area (centre) | Source population* and description | Target eligibility criteria | Initial contact | Enumeration of those invited | Total no. recruited | No. of females | Years of recruitment | No. with blood samples |
|---|---|---|---|---|---|---|---|---|---|
| *Core EPIC cohorts* | | | | | | | | | |
| Greece | Nationwide | Active recruitment of the general population | Apparently healthy men and women aged 25–82 | In person and by mail | No | 28,572 | 16,618 | 1994–1999 | 28,526 |
| Spain | Granada: province | Blood donors, general population (recruited through census, health centers) | Residents: men aged 40–64, women aged 35–64 | In person and by mail | No | 7879 | 6083 | 1992–1996 | 6892 |
| | Murcia: region | Blood donors and their partners (67% of cohort), general population of 2 towns (23%), civil servants (5%), employees of 2 companies (3%), participants in a cardiovascular risk study (2%) | Residents: men aged 40–65, women aged 35–65 | In person and by mail | No | 8516 | 5831 | 1992–1996 | 8146 |
| | Navarra: region | Blood donors | Residents: men aged 40–65, women aged 35–65 | In person and by mail | Yes | 8084 | 4176 | 1992–1995 | 7799 |
| | San Sebastian: city and Gipuzcoa province | Blood donors, employees of selected enterprises (recruited through census of selected municipalities) | Residents: men aged 40–65, women aged 35–65 | In person and by mail | Yes | 8417 | 4259 | 1992–1995 | 8325 |
| | Asturias:region | Blood donors, regional civil servants and general population | Men aged 40–64, women aged 35–64 | Mail | Yes | 8544 | 5459 | 1992–1995 | 8417 |
| Italy | Ragusa: province | Local blood donors association, population-based recruitment in 4 towns (Monterosso, Girralana, Ispica and Chiaramonte), local teachers union and other sources | Residents: men aged 35–65, women aged 35–75 | In person | Yes | 6403 | 3350 | 1993–1997 | 6396 |
| | Florence: province | Breast cancer screening participants, men and women from the general population | Residents: men aged 35–64, women aged 35–64 without prevalent cancer | In person and by mail | No | 13,597 | 10,083 | 1992–1998 | 13,597 |
| | Turin: city | Blood donors, employees, volunteers, medical test users at national health service | Residents: men aged 40–74, women aged 35–74 without prevalent cancer | In person | No | 10,604 | 4557 | 1993–1998 | 10,604 |
| | Varese: province | Volunteers from resident general population, mostly an extension of an ongoing study | Men aged 35–65, women aged 35–75 | In person | Yes | 12,083 | 9526 | 1993–1997 | 12,073 |

**Table 1.** Continued

| Country | Geographical/ political area (centre) | Source population* and description | Target eligibility criteria | Initial contact | Enumeration of those invited | Total no. recruited | No. of females | Years of recruitment | No. with blood samples |
|---|---|---|---|---|---|---|---|---|---|
| France | Nation-wide | Nationwide health insurance programme; teachers and school workers enrolled in an ongoing study prior to EPIC | Women aged 40–65 in 1990 with informed consent to obtain MGEN info on non-respondents | Mail | Yes | 72,996 | 72,996 | 1993–1997 | 20,725 |
| Germany | Heidelberg and surrounding areas | General population | Residents: men aged 40–65, women aged 35–65, completed questionnaires and examination | Mail | Yes | 25,546 | 13,617 | 1994–1998 | 24,235 |
| | Potsdam and surrounding areas | General population | Residents: men aged 40–65, women aged 35–65, completed questionnaires and examination | Mail | Yes | 27,548 | 16,644 | 1994–1998 | 26,444 |
| Netherlands | Bilthoven: Amsterdam, Doetinchem and Maastricht (three cities) | Population-based age and sex-stratified samples of the general population | Residents: men and women aged 20–59 in Amsterdam and Maastricht and aged 20–65 in Doetinchem | Mail | Yes | 22,715 | 12,435 | 1993–1997 | 19,388 |
| | Utrecht: district | Population-based breast cancer screening participants | Residents: women aged 49–70 | Mail | Yes | 17,357 | 17,357 | 1993–1997 | 16,930 |
| United Kingdom | Cambridge: Norfolk | Population-based patients of general practitioners | Listed by general practitioners: men and women aged 45–74 | Mail | Yes | 30,442 | 16,744 | 1993–1998 | 24,035 |
| | Oxford: (1) local counties; (2) "health conscious" individuals from England, Wales, Scotland & N. Ireland | (1) Population-based in collaboration with general practitioners (2) Vegetarians, vegans and other health-conscious individuals in collaboration with vegetarian societies and magazines | (1) Listed by general practitioners: men and women aged 40–65; (2) men and women aged 20+ but targeted at those aged 35+ | Mail | No | 57,498 | 44,284 | 1993–2000 | 19,103 |
| *Associated EPIC cohorts* | | | | | | | | | |
| Italy | Naples | Female volunteers from resident general population | Women aged 30–69 | In person and by mail | No | 5062 | 5062 | 1993–1997 | 5055 |
| Denmark | Aarhus | Population-based | Born in Denmark: men and women aged 50–64 without prevalent cancer | Mail | Yes | 17,154 | 8721 | 1995–1997 | 17,094 |
| | Copenhagen | Population-based | Born in Denmark: men and women aged 50–64 without prevalent cancer | Mail | Yes | 39,900 | 21,154 | 1993–1997 | 39,037 |

**Table 1.** Continued

| Country | Geographical/ political area (centre) | Source population* and description | Target eligibility criteria | Initial contact | Enumeration of those invited | Total no. recruited | No. of females | Years of recruitment | No. with blood samples |
|---|---|---|---|---|---|---|---|---|---|
| Sweden | Malmö: city | Population-based | Residents: men aged 50–72, women aged 46–72 | Mail | Yes | 28,098 | 17,035 | 1991–1996 | 28,023 |
| | Umeå: the Vasterbotten county | Population-based | Residents: men and women aged 30, 40, 50 or 60 | Mail | Yes | 25,732 | 13,299 | 1992–1996 | 25,732 |
| Norway | Tromsø: national sample | Population-based | Women born in Norway between 1943 and 1957 | Mail | Yes | 37,231 | 37,231 | 1998–1998 | 9197 |
| | | | | | | **519, 978** | **366, 521** | | **385, 747** |

*Under source population, the term "population-based" implies that participants were invited as a random sample of their population, while the term "general population" implies that volunteers were invited from the general population.

translated into national questionnaires to assess factors related to lifetime history of tobacco and alcohol consumption, occupational history, socio-economic status, physical activity, and history of previous illnesses (Table 2), typically involving self-completion postal questionnaires. A comprehensive system of recoding has been developed to maximize the comparability of data from these initial centres with those which joined EPIC at a later stage (i.e., Denmark, Sweden and Norway and the Naples centre in Italy) and which used different questionnaires to record information on a similar set of factors. Of particular relevance to EPIC-Heart, baseline questionnaires in most centres recorded self-reported histories of myocardial infarction, angina, stroke and hypertension (generally including the reported age at onset of such diagnoses: Table 2). In Spain, validation studies demonstrated moderately good agreement between self-reported history of hypertension and medical records about this condition [13].

*Anthropometry and blood pressure*

Height, weight, and waist and hip circumference were measured on all subjects using similar protocols (in Umea, only weight and height were measured), except in France, the Oxford centre and Norway. In France and Oxford, weight, height and waist and hip circumference were measured in only a subset of participants, but self-reported weight and height were obtained from all individuals (and, in Oxford, self-reported measurements also included waist and hip circumference). For the "health-conscious" group based in Oxford (UK), linear regression models were used to predict sex and age-specific values from participants with either measured or self-reported body measures, as previously described [14]. In Norway only self-reported height and weight are available. Systolic and diastolic blood pressure recordings were made only in Denmark, Italy, Germany, Greece, in subsets of participants in three of five centres in Spain (comprising 14% of Spanish participants), Sweden, the Netherlands and in UK centres, in a total of 322,869 individuals (or in about 62% of baseline participants). Blood pressure measurements were obtained using a variety of devices and methods, as described in detail elsewhere [15]. In most centres the measurements were taken in duplicate, from the right arm, in a sitting position, using either a mercury manometer or an oscillometric device [16–21].

*Biological samples*

Biological samples – including plasma, serum, white blood cells and erythrocytes – have been collected, separated and aliquoted for long-term storage from 385,747 of the EPIC study participants (Table 1). In the 7 initial EPIC countries and in Naples, blood samples have been aliquoted into 28 plastic straws

**Table 2.** Information about variables collected at the baseline assessment

| Characteristic | Variables collected |
|---|---|
| Socio-economic status | Marital status, occupational history, school leaving age, highest school level achieved |
| Anthropometry (measured or self-reported) | Height, weight, waist and hip circumference, weight at age 20 |
| Blood collection | Timing, fasting status, date of last smoking, drugs consumed, pulse rate, systolic and diastolic blood pressure, blood pressure measuring technique |
| Previous illnesses and age at diagnosis of each | Myocardial infarction, angina, stroke, circulatory problems in brain, hypertension, hypertension treatment, hyperlipidaemia, hyperlipidaemia treatment, elevated cholesterol, type 2 diabetes, insulin treatment for diabetes, gallstones, gallstones treatment, polyps of large bowel, cancer, hysterectomy, removal of one or both ovaries, breast surgery |
| Female reproductive history | Age at first menstrual period, age periods stopped, hormones for menopause treatment, number of live born children, age at first delivery, breast-feeding, oral contraceptive |
| Physical activity | Walking, cycling, gardening, Do-It-Yourself, housework, physical exercise according to season, vigorous physical activity, number of stairs climbed daily, occupational activity |
| Tobacco smoking | Number per day at certain ages (with/without filter), whether inhaled, age started smoking, age gave up smoking, total years not smoked, smoked occasionally during life, parents smoked in respondent's childhood, someone smokes at home/work |
| Alcohol consumption | Quantity and frequency of consumption of wine, beer/cider, fortified wine, spirit/liquor at certain ages |

containing 0.5 ml each (12 plasma with sodium citrate, 8 serum, 4 erythrocytes, 4 buffy coat for DNA). To ensure standardization, the same materials (syringes, straws, etc) were purchased centrally and distributed to the centres. The samples were then split into 2 halves of 14 aliquots each, 1 stored locally and 1 transported to the International Agency for Research on Cancer (IARC) in Lyon, France, to be stored in liquid nitrogen (at −196 °C) in a central repository with computerized sample tracking capabilities. Samples in Norway were collected into twenty 0.5 ml plastic straws, a subset of which was shipped to IARC for storage. In Sweden and Denmark, blood samples were collected into tubes and have been kept solely in local freezers at −80 and −150 °C, respectively.

*Biochemical and genetic analytes*

Measurements of established biochemical risk factors and emerging biomarkers have so far been done only in subsets of participants in some EPIC centres, typically involving local sample aliquots and sometimes using different assay methods. For example, a number of reports have emerged from individual EPIC centres in relation to associations of coronary disease or stroke (or carotid thickening) with established cardiovascular risk factors, dietary factors, novel lipid markers, glycated haemoglobin, growth factors, haemostatic factors, and markers of insulin resistance, oxidation status and iron metabolism [22–37]. EPIC-Heart intends to measure a range of established risk factors (e.g., concentrations of serum lipids and their sub-fractions) and various emerging risk markers (e.g., concentrations of novel lipid and apolipoprotein markers, markers of inflammation and haemostasis and metabolic characteristics) in subsets of the entire collection, using standardized assays according to a common protocol. A few of the individual EPIC centres have reported on genetic factors in relation to cardiovascular diseases [38–40]. EPIC-Heart plans to conduct genotyping studies on subsets of the entire collection, particularly in relation to hypotheses related to lipid, inflammatory, haemostatic and metabolic pathways.

*Cardiovascular outcomes*

Data on cause-specific mortality, including cardiovascular causes, have been collected in all EPIC study centres through mortality registries or active follow-up and death-record collection. By April 2004, a total of 15,619 deaths had been recorded, of which 3663 were attributed to circulatory causes (including approximately 1544 coronary deaths: Table 3). Additionally, a further approximately 5000 non-fatal myocardial infarctions and a further approximately 3700 non-fatal strokes have been recorded by April 2004 across all centres (data available on request). Different centres have used different methods to ascertain incident non-fatal coronary and stroke events, depending on the follow-up procedures used (e.g., active versus passive follow-up). These methods

**Table 3.** Approximate numbers of fatal coronary heart disease cases reported to the coordinating centre by the latest available follow-up (April 2004), grouped by age and sex

| Age at recruitment (years) | Sex | | |
|---|---|---|---|
| | Men | Women | Both |
| < 55 | 200 | 47 | 247 |
| 55–69 | 166 | 47 | 213 |
| 60–64 | 273 | 87 | 360 |
| 65–69 | 192 | 93 | 285 |
| 70–74 | 191 | 95 | 286 |
| 75–80 | 71 | 33 | 104 |
| 80 + | 26 | 23 | 49 |
| All ages | 1119 | 425 | 1544 |

have included self-report questionnaires, queries of medical records linkage with hospital morbidity registers, MONICA registries or combinations of these methods (Tables 4 and 5). For example, in relation to non-fatal coronary outcomes, record linkage systems have been used in Cambridge in the UK, Denmark, Italy, the Netherlands, Spain and in Swedish centres (including the Umeå centre, which involves a MONICA registry for myocardial infarction and stroke); in the case of the Italian centres, record linkage is routinely supplemented by information from medical records. In Potsdam in Germany, in Greece and in Spain, self-report questionnaires about cardiovascular outcomes are checked against medical records by physicians and/or hospital discharge information. In Norway and in Oxford in the UK, so far only self-report questionnaires have been used to record coronary outcomes.

This variation in ascertainment methods has resulted in some differences in definitions used (and in the detail of classification available) for non-fatal myocardial infarction and for non-fatal stroke events. To help judge the validity and comparability of such diagnoses, validation studies for non-fatal coronary outcomes have been conducted, are in progress or planned in 10 centres (Table 6). Such studies assess in sub-samples of participants the concordance of diagnoses based on a centre's routine ascertainment method(s) with those based on an internationally agreed criteria (such as MONICA criteria). Overall, 1955 to 2207 (89%) of suspected non-fatal coronary outcomes were confirmed against MONICA (or similar) criteria, with the successful validation rate varying from 82% in Denmark (which employed particularly broad diagnoses at ascertainment) to in excess of 95% in Cambridge in the UK, Italy, and Navarra and Murcia in Spain. These findings suggest that the non-fatal coronary outcomes already recorded in most EPIC centres should be sufficiently accurate for use in epidemiological studies. Nonetheless, EPIC-Heart is planning further validation studies of non-fatal cardiovascular outcomes to optimise comparability of outcomes across centres (and an update will soon take place for cause-specific mortality recorded after April, 2004, in the central database) in order to enhance the numbers of fatal and non-fatal cardiovascular outcomes available for analyses.

*Statistical approach*

A methodology guideline statement has been developed to achieve a harmonized approach to data analyses (http://phpc.cam.ac.uk/EPIC-Heart/). Data will be analysed using Cox's proportional hazards models, with age as the primary time variable, and stratified by sex, centre and age at baseline. Main exposure variables will, where possible, be treated as continuous variables (following logarithmic or other transformation, if required) or as indicator variables (e.g., quantiles). Calibration of dietary exposures using information from the 24-h dietary recall substudy will be performed where appropriate. Tests for linear trend will involve data on the continuous scale (or, where appropriate, use of a score variable for categories of exposure). Sub-group analyses will be done sparingly for pre-specified hypotheses (which will be specific to exposures).

*Study organization*

Since 2005 the activities of EPIC-Heart have been organized by a secretariat (coordinated by Professor J Danesh at the University of Cambridge) comprised largely of members from several different EPIC centres. In addition to leading the drafting of the present report, the secretariat has prepared a strategy document to help the planning of the EPIC-Heart working group and a methodology guideline statement including statistical and epidemiological approaches that can be used in publications that will emerge from EPIC-Heart (http://phpc.cam.ac.uk/EPIC-Heart/). Like all EPIC working groups, EPIC-Heart is directed by and responsible to the EPIC steering committee (which is comprised of principal investigators from all 10 participating countries and led by Professor Elio Riboli at Imperial College, London).

*Concluding remarks*

EPIC-Heart involves almost 520,000 middle-aged participants from 10 European countries and has already recorded an estimated 10,000 incident fatal and non-fatal cardiovascular outcomes. It will become increasingly informative as the numbers of cardiovascular outcomes recorded continue to increase and as further efforts are made to improve the characterization of outcomes. Although the EPIC study was initially set up to investigate nutrition and cancer, its data and biological resources provide an excellent

**Table 4.** Non-fatal coronary endpoints: definition and classification

| Country | Region(s) | Ascertainment method | Definition of endpoints | | | Classification of endpoints | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | Clinical features | ECG | Cardiac enzymes | Definite | Possible | Silent | Unspecified |
| *Core EPIC cohorts* | | | | | | | | | |
| Greece | Nationwide | Self-report questionnaire followed by validation through hospital discharge data and medical records | ■ | ■ | ■ | ■ | ■ | □ | □ |
| Spain | Granada | Self-report questionnaire and record linkage followed by validation with hospital notes | ■ | ■ | ■ | ■ | ■ | ■ | ■ |
| | Murcia | As above | | | | | | | |
| | Navarra | As above | | | | | | | |
| | San Sebastian | As above | | | | | | | |
| | Asturias | As above | | | | | | | |
| Italy | Ragusa | Record linkage followed by validation with hospital notes | ■ | ■ | ■ | ■ | ■ | ■ | □ |
| | Florence | As above | ■ | ■ | ■ | ■ | ■ | ■ | □ |
| | Turin | As above | ■ | ■ | ■ | ■ | ■ | ■ | ■ |
| | Varese | Record linkage followed by validation with hospital notes | ■ | ■ | ■ | ■ | ■ | ■ | □ |
| France | Nationwide | Contact with GPs and hospitals after self-report | ■ | ■ | ■ | ■[b] | ■[b] | ■[b] | ■[b] |
| Germany | Heidelberg | Self-report questionnaire, partly record linkage and review of medical records | □ | □ | □ | □ | □ | □ | □ |
| | Potsdam | Self-report questionnaire followed by validation by treating physician or clinics, | ■[a] | ■[a] | ■[a] | ■ | ■ | □ | □ |
| Netherlands | Bilthoven: Amsterdam, Doetinchem, Maastricht | Record linkage, self-report questionnaire | □ | □ | □ | ■ | ■ | ■ | ■ |
| | Utrecht | As above | □ | □ | □ | ■ | ■ | ■ | ■ |
| UK | Cambridge: Norfolk | Record linkage | ■ | ■ | ■ | □ | □ | □ | ■ |
| | Oxford: (1) local counties; (2) "health conscious" from UK | Self-report questionnaire | □ | □ | □ | □ | □ | □ | □ |
| *Associated EPIC cohorts* | | | | | | | | | |
| Italy | Naples | Record linkage followed by validation with hospital notes | ■ | ■ | ■ | ■ | ■ | ■ | □ |
| Denmark | Aarhus | Record linkage | ■ | ■ | ■ | ■ | ■ | ■ | □ |
| | Copenhagen | | | | | | | | |
| Sweden | Malmö | Record linkage (by epidemiologic centre with the National Board of Health and Welfare) | ■ | ■ | ■ | ■ | □ | □ | □ |
| | Umeå | Record linkage (by registration with the MONICA centre) | ■ | ■ | ■ | ■ | ■ | □ | □ |
| Norway | Tromsø | | | | | | | | |

□ = Criterion not used.
■ = Criterion specifically used.
[a]Whole range of diagnostic tools used.
[b]Determined by ad hoc committee.

**Table 5.** Non-fatal stroke endpoints: definition and classification

| Country | Region(s) | Ascertainment method | Definition of endpoints | | Classification of endpoints | | |
|---|---|---|---|---|---|---|---|
| | | | Clinical Features | CT/MRI imaging | Ischaemic vs. haemorrhagic | Transient ischaemic attacks | Unspecified |
| *Core EPIC cohorts* | | | | | | | |
| Greece | Nationwide | Self-report questionnaire followed by validation through hospital discharge data and medical records | ■ | ■ | ■ | ■ | ■ |
| Spain | Granada | Self-report questionnaire | □ | □ | □ | □ | □ |
| | Murcia | Self-report questionnaire and hospital discharge record | □ | □ | □ | □ | □ |
| | Navarra | Self-report questionnaire and record linkage followed by validation with hospital notes | ■ | ■ | ■ | ■ | ■ |
| | San Sebastian | As above | ■ | ■ | ■ | ■ | ■ |
| | Asturias | Self-report questionnaire | □ | □ | □ | □ | □ |
| Italy | Ragusa | Record linkage followed by validation with hospital notes | ■ | ■ | ■ | □ | □ |
| | Florence | As above | | | ■ | □ | □ |
| | Turin | As above | ■ | ■ | ■ | □ | ■ |
| | Varese | As above | ■ | ■ | ■ | □ | □ |
| France | Nationwide | Unavailable | Unavailable | Unavailable | Unavailable | Unavailable | Unavailable |
| Germany | Heidelberg | Self-report questionnaire, partly record linkage and review of medical records | □ | □ | ■ | | |
| | Potsdam | Self-report questionnaire followed by validation by treating physician or clinics | ■[a] | ■[a] | ■ | ■ | ■ |
| Netherlands | Bilthoven: Amsterdam, Doetinchem, Maastricht | Record linkage, self-report questionnaire | ■ | ■ | ■ | ■ | |
| | Utrecht | As above | ■ | ■ | ■ | ■ | □ |
| UK | Cambridge: Norfolk | Record linkage | ■ | ■ | □ | □ | ■ |
| | Oxford: (1) local counties; (2) "health conscious" from UK | Self-report questionnaire | □ | □ | □ | □ | □ |
| *Associated EPIC cohorts* | | | | | | | |
| Italy | Naples | Record linkage followed by validation with hospital notes | ■ | ■ | ■ | □ | □ |
| Denmark | Aarhus Copenhagen | Record linkage | ■ | ■ | ■ | ■ | ■ |
| Sweden | Malmö | Record linkage with STROMA (Stroke Register of Malmö) | ■ | ■ | ■ | □ | □ |
| | Umeå | Record linkage (by registration with the MONICA centre) | ■ | ■ | ■ | Unavailable | Unavailable |
| Norway | Tromsø | | | | | | |

□ = Criterion not used.
■ = Criterion specifically used.
[a]Whole range of diagnostic tools used.

**Table 6.** Description of non-fatal coronary disease validation sub-studies already completed or in progress in EPIC

| Centre | Method of coronary disease case ascertainment | Method of case validation/criteria | No. successfully validated/ No. ascertained |
|---|---|---|---|
| Cambridge, UK | Hospital discharge records involving ICD-9 codes 410–414 | Review of medical records/MONICA criteria | 38/39 (97%) |
| Denmark | Hospital discharge records involving incident ICD-8 codes 410 and ICD-10 codes I21 | Review of medical records/AHA, WHF, ESC, CDC, and NHLBI criteria | 878/1074 (81.8%)[a] |
| Greece | Hospital discharge data and in patient medical records involving ICD-10 codes I20–I25 | Review of medical records/MONICA criteria and/or treating physician diagnosis | Ongoing |
| Italy | Hospital discharge records involving ICD-9 codes 410 and 412 | Review of medical records/MONICA criteria | 385/405 (95%)[b] |
| Malmö, Sweden | Hospital discharge records of ICD-9 code 410 | Review of medical records/WHO criteria | 275/293 (93%) |
| Umea, Sweden | MONICA criteria | Review by MONICA registration group | Highest quality MONICA registration score achieved |
| Bilthoven (Maastricht only), the Netherlands | Hospital discharge records involving ICD-9 codes 410–414 | Validation case ascertainment through systematic review of medical records | Ongoing |
| San Sebastian, Spain | Telephone questionnaires 3 years after recruitment, supplemented by postal questionnaire and hospital discharge records involving ICD-9 codes 410–414 | Review of medical records/MONICA criteria | 128/143 (90%)[c] |
| Navarra, Spain | Telephone questionnaires 3 years after recruitment, supplemented by postal questionnaire and hospital discharge records involving ICD-9 codes 410–414 during 1996–2004 | Review of medical records/MONICA criteria | 153/153 (100%) |
| Murcia, Spain | Telephone questionnaire 3 years after recruitment, supplemented by postal questionnaire and hospital discharge records involving ICD-9 codes 410–414 during 1996–2004 | Review of medical records/MONICA criteria | 98/100 (98%) |

ICD = International Classification of Disease; MONICA = Multinational MONItoring of trends and determinants in CArdiovascular disease Project; AHA = American Heart Association; WHF = World Heart Federation; ESC = European Society of Cardiology; CDC = Centres for Disease Control and Prevention; NHLBI = National Heart Lung and Blood Institute; WHO = World Health Organization.

[a]The validation rate in the Danish centres may be somewhat lower than those in other EPIC centres owing to the pragmatic approach used in identifying patients in hospital discharge registries, i.e., all patients with the discharge diagnoses listed in the table were included, irrespective of where the diagnosis had been made (emergency room and outpatient clinics were also included) and whether or not it was a primary or secondary diagnosis. A paper is in preparation that discusses the Danish validation study in more detail.

[b]Most of the few "non-validated" cases actually had a previous history of myocardial infarction prior to the study's baseline examination, and, therefore, did not fulfill this centre's criterion of first myocardial infarction.

[c]The validation rate in San Sebastian may be somewhat lower since all patients with the discharge diagnosis listed in the table were included irrespective of whether it was a primary or secondary diagnosis.

opportunity to study the determinants of cardiovascular diseases in order to help advance scientific understanding and disease prevention strategies. The first cycle of EPIC-Heart analyses will assess associations between coronary mortality and several prominent dietary hypotheses (e.g., fish, meat, nut, fruit and vegetable consumption) and established cardiovascular risk factors (e.g., anthropometric indices, blood pressure). Subsequent analyses will extend this approach to non-fatal cardiovascular outcomes as well as to further dietary, biochemical and genetic factors.

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## References

1. Riboli E, Hunt KJ, Slimani N, et al. European Prospective Investigation into Cancer and Nutrition (EPIC): Study populations and data collection. Public Health Nutr 2002; 5(6B): 1113–1124.
2. Bingham S, Riboli E. Diet and cancer – the European Prospective Investigation into Cancer and Nutrition. Nat Rev Cancer 2004; 4(3): 206–215.
3. Overvad K, Tjonneland A, Haraldsdottir J, Bang S, Ewertz M, Moller-Jensen O. Development of a semi quantitative food frequency questionnaire to assess food, energy and nutrient intake in Denmark. Int J Epidemiol 1991; 20: 906–912.
4. Bingham SA, Gill C, Welch A, et al. Comparison of dietary assessment methods in nutritional epidemiology: Weighed records v. 24 h recalls, food-frequency questionnaires and estimated-diet records. Br J Nutr 1994; 72(4): 619–643.
5. Margetts BM, Pietinen P. European Prospective Investigation into Cancer and Nutrition: Validity studies on dietary assessment methods. Int J Epidemiol 1997; 26(Suppl 1): S1–S5.
6. Riboli E, Elmstahl S, Saracci R, Gullberg B, Lindgarde F. The Malmö Food Study: Validity of two dietary assessment methods for measuring nutrient intake. Int J Epidemiol 1997; 26(Suppl 1): S161–S173.
7. Kroke A, Klipstein-Grobusch K, Voss S, et al. Validation of a self-administered food-frequency questionnaire administered in the European Prospective Investigation into Cancer and Nutrition (EPIC) Study: Comparison of energy, protein, and macronutrient intakes estimated with the doubly labeled water, urinary nitrogen, and repeated 24-h dietary recall methods. Am J Clin Nutr 1999; 70(4): 439–447.
8. Slimani N, Deharveng G, Charrondiere RU, et al. Structure of the standardized computerized 24-h diet recall interview used as reference method in the 22 centers participating in the EPIC project. European Prospective Investigation into Cancer and Nutrition. Comput Methods Programs Biomed 1999; 58(3): 251–266.
9. Slimani N, Ferrari P, Ocke M, et al. Standardization of the 24-hour diet recall calibration method used in the European Prospective Investigation into Cancer and Nutrition (EPIC): General concepts and preliminary results. Eur J Clin Nutr 2000; 54(12): 900–917.
10. Slimani N, Kaaks R, Ferrari P, et al. European Prospective Investigation into Cancer and Nutrition (EPIC) calibration study: Rationale, design and population characteristics. Public Health Nutr 2002; 5(6B): 1125–1145.
11. Charrondiere R, Vignat J, Moller A, et al. The European Nutrient Database (ENDB) for nutritional epidemiology. J Food Comp Anal 2002; 15: 435–451.
12. Slimani N, Charrondiere R, Van Staveren WA, Riboli E. Standardisation of food composition databases for the European Prospective Investigaion into Cancer and Nutrition (EPIC); general theoretical concept. J Food Comp Anal 2000; 13: 567–584.
13. Tormo MJ, Navarro C, Chirlaque MD, Barber X. Validation of self diagnosis of high blood pressure in a sample of the Spanish EPIC cohort: Overall agreement and predictive values. EPIC Group of Spain. J Epidemiol Community Health 2000; 54(3): 221–226.
14. Haftenberger M, Lahmann PH, Panico S, et al. Overweight, obesity and fat distribution in 50- to 64-year-old participants in the European Prospective Investigation into Cancer and Nutrition (EPIC). Public Health Nutr 2002; 5(6B): 1147–1162.
15. Schulze MB, Kroke A, Saracci R, Boeing H. The effect of differences in measurement procedure on the comparability of blood pressure estimates in multi-centre studies. Blood Press Monit 2002; 7(2): 95–104.
16. Appleby PN, Davey GK, Key TJ. Hypertension and blood pressure among meat eaters, fish eaters, vegetarians and vegans in EPIC-Oxford. Public Health Nutr 2002; 5(5): 645–654.
17. Canoy D, Luben R, Welch A, et al. Fat distribution, body mass index and blood pressure in 22,090 men and women in the Norfolk cohort of the European Prospective Investigation into Cancer and Nutrition (EPIC-Norfolk) study. J Hypertens 2004; 22(11): 2067–2074.
18. Khaw KT, Bingham S, Welch A, et al. Blood pressure and urinary sodium in men and women: The Norfolk Cohort of the European Prospective Investigation into Cancer (EPIC-Norfolk). Am J Clin Nutr 2004; 80(5): 1397–1403.
19. Psaltopoulou T, Orfanos P, Naska A, Lenas D, Trichopoulos D, Trichopoulou A. Prevalence, awareness, treatment and control of hypertension in a general population sample of 26,913 adults in the Greek EPIC study. Int J Epidemiol 2004; 33(6): 1345–1352.
20. Schulze MB, Kroke A, Bergmann MM, Boeing H. Differences of blood pressure estimates between

consecutive measurements on one occasion: Implications for inter-study comparability of epidemiologic studies. Eur J Epidemiol 2000; 16(10): 891–898.
21. Tormo MJ, Navarro C, Chirlaque MD, Barber X. Is there a different dietetic pattern depending on self-knowledge of high blood pressure? Eur J Epidemiol 2000; 16(10): 963–971.
22. Berglund G, Elmstahl S, Janzon L, Larsson SA. The Malmö diet and cancer study. Design and feasibility. J Intern Med 1993; 233(1): 45–51.
23. Boekholdt SM, Kuivenhoven JA, Wareham NJ, et al. Plasma levels of cholesteryl ester transfer protein and the risk of future coronary artery disease in apparently healthy men and women: The prospective EPIC (European Prospective Investigation into Cancer and nutrition)-Norfolk population study. Circulation 2004; 110(11): 1418–1423.
24. Hedblad B, Nilsson P, Janzon L, Berglund G. Relation between insulin resistance and carotid intima-media thickness and stenosis in non-diabetic subjects. Diabet Med 2000; 17(4): 299–307.
25. Hoffmann K, Heidemann C, Weikert C, Schulze MB, Boeing H. Estimating the proportion of disease due to classes of sufficient causes. Am J Epidemiol 2006; 163(1): 76–83.
26. Jansson JH, Olofsson BO, Nilsson TK. Predictive value of tissue plasminogen activator mass concentration on long-term mortality in patients with coronary artery disease. Circulation 1993; 88(5 Pt 1): 2030–2034.
27. Johnsen SP, Hundborg HH, Sorensen HT, et al. Insulin-like growth factor (IGF) I, -II, and IGF binding protein-3 and risk of ischemic stroke. J Clin Endocrinol Metab 2005; 90(11): 5937–5941.
28. Key TJ, Appleby PN, Davey GK, Allen NE, Spencer EA, Travis RC. Mortality in British vegetarians: Review and preliminary results from EPIC-Oxford. Am J Clin Nutr 2003; 78(3 Suppl): 533S–538S.
29. Khaw KT, Wareham N, Bingham S, Luben R, Welch A, Day N. Association of hemoglobin A1c with cardiovascular disease and mortality in adults: The European prospective investigation into cancer in Norfolk. Ann Intern Med 2004; 141(6): 413–420.
30. Kok HS, van Asselt KM, van der Schouw YT, et al. Heart disease risk determines menopausal age rather than the reverse. J Am Coll Cardiol 2006; 47(10): 1976–1983.
31. Mann JI, Appleby PN, Key TJ, Thorogood M. Dietary determinants of ischaemic heart disease in health conscious individuals. Heart 1997; 78(5): 450–455.
32. Panico S, Celentano E, Galasso R, et al. Dietary Pattern and Ischemic heart disease incidents in female population of a mediterranean country; findings from EPIC-Italy Collaboration. Circulation 2003; 108(Supp IV): 737.
33. Rubba P, Panico S, Bond MG, et al. Site-specific atherosclerotic plaques in the carotid arteries of middle-aged women from southern Italy: Associations with traditional risk factors and oxidation markers. Stroke 2001; 32(9): 1953–1959.
34. Thogersen AM, Jansson JH, Boman K, et al. High plasminogen activator inhibitor and tissue plasminogen activator levels in plasma precede a first acute myocardial infarction in both men and women: Evidence for the fibrinolytic system as an independent primary risk factor. Circulation 1998; 98(21): 2241–2247.
35. Tolstrup J, Jensen MK, Tjonneland A, Overvad K, Mukamal KJ, Gronbaek M. Prospective study of alcohol drinking patterns and coronary heart disease in women and men. Br Med J 2006; 332(7552): 1244–1248.
36. van der A DL, Marx JJ, Grobbee DE, et al. Non-transferrin-bound iron and risk of coronary heart disease in postmenopausal women. Circulation 2006; 113(16): 1942–1949.
37. Weikert C, Hoffmann K, Dierkes J, et al. A homocysteine metabolism-related dietary pattern and the risk of coronary heart disease in two independent German study populations. J Nutr 2005; 135(8): 1981–1988.
38. Vaessen SF, Schaap FG, Kuivenhoven JA, et al. Apolipoprotein A–V, triglycerides and risk of coronary artery disease: The prospective EPIC-Norfolk Population Study. J Lipid Res 2006; 47(9): 2064–2070.
39. Boekholdt SM, Sandhu MS, Wareham NJ, Luben R, Reitsma PH, Khaw KT. Fibrinogen plasma levels modify the association between the factor XIII Val34-Leu variant and risk of coronary artery disease: The EPIC-Norfolk prospective population study. J Thromb Haemost 2006; 4(10): 2204–2209.
40. van der A DL, Peeters PH, Grobbee DE, et al. HFE mutations and risk of coronary heart disease in middle-aged women. Eur J Clin Invest 2006; 36(10): 682–690.

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