Validation of self-reported incident cardiovascular disease events in the Greek EPIC cohort study

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ABSTRACT

BACKGROUND: the aim of the study is to investigate the validity of self-reported incident cardiovascular disease in the Greek EPIC cohort during follow up.

METHODS: cardiovascular disease was considered in 4 groups: Myocardial infarction (MI), Angina, Cerebrovascular disease, and other coronary heart disease (other CHD). Validation for all reported incident cardiovascular events was sought through medical records of hospitals around the country and local death registries.

RESULTS: in total, there had been 121 self reported incident cases of angina, 683 of MI, 622 of other CHD and 855 of cerebrovascular disease. Records were searched for 926 participants with reported cardiovascular disease (CVD), and from those, medical records for the 832 (90%) were obtained from the respective hospitals. Examination of the medical records that were obtained confirmed the self report in 72% of incident strokes, 65% of MIs, 55% of other CHD cases and 32% of angina.

CONCLUSIONS: it appears that in our study self reported MI and stroke (or transient ischemic attacks) had a higher validity, compared to self reported angina and other CHD. Our results are comparable to those in other cohort studies.

Key words: Cardiovascular, Cohort, Validation, Self-reported, Myocardial infarction, Stroke

INTRODUCTION

In large prospective epidemiological studies, collection of information on outcome (disease events) during follow-up is usually implemented through linkage with hospital and/or death registers (passive follow-up). However, passive follow-up is not always possible for several reasons among which the lack of central linkage to hospital registers. In these instances, active follow-up is taking place where information on outcome event is based on self- or interviewer-administered questionnaires, and it is questionable how reliable this information is and to what extent misclassification of outcome is involved. For cardiovascular disease (CVD) the reliability of self reported cases of CVD has been investigated in several studies with variable results (1-3).
We have undertaken a validation process in order to verify incident cases of CVD which were self-reported during follow-up in the European Prospective Investigation into Cancer and nutrition (EPIC) study in Greece. The objective of the present paper is to describe the validation criteria and procedures that were used in the Greek segment of the EPIC study, as well as, to present the first results regarding the validity of the self reported information on CVD.

METHODS

The EPIC Study – EPIC Greece

The EPIC study (http://epic.iarc.fr) is a multi-centre prospective cohort study undertaken in order to examine the relationship between biological, dietary, lifestyle and environmental factors and incidence of chronic diseases, focusing on cancer but also on cardiovascular and other chronic diseases. Twenty-three centers from 10 European countries are participating in EPIC, with a total study population of over 520 000 people. The study has been coordinated by the International Agency for Research on Cancer (IARC), a World Health Organization agency. The rational and design of the study are described elsewhere (4). For Greece, the study protocol was approved by the ethics committees of IARC and the University of Athens Medical School. All participants signed informed consent forms both for their participation in the study, as well as, the right of investigators to access their medical records if needed, and all procedures were in accordance with the Helsinki Declaration of 1975 as revised in 1983.

The Greek EPIC cohort consists of 28 572 participants from different regions of Greece, covering a wide range of geographical and socioeconomic strata. During recruitment, (1994-1999), dietary and lifestyle questionnaires (including a section enquiring medical history) were administered to participants by trained interviewers. Furthermore, blood samples and body and physiological measurements were taken (height, weight, blood pressure, etc.).

Active follow-up of participants by health professionals is implemented every 3-4 years (starting at 1997) by means of a telephone interview of the participant or his/her next of kin in case the participant is unable to answer or is no longer alive. Reported information on health status (including CVD) is collected in each follow-up round and vital status of EPIC participants is ascertained. In case of participant’s death, the death certificate is obtained from the local death registries and cause and date of death are recorded. Self-reported incident cancer is subsequently verified through pathology reports, medical records, hospital discharge diagnoses or death certificates if cancer is the cause of death. Verification of reported CVD cases through medical records, hospital discharge diagnoses or death certificates started in 2005.

Coding and classification of cardiovascular disease

We focused on 4 manifestations of cardiovascular disease: myocardial infarction (MI), angina, other coronary heart disease that does not manifest in the form of angina or MI, hereafter referred to as other CHD and cerebrovascular disease (Stroke and Transient Ischemic Attacks combined).

For the classification of CVD cases we used the 10th revision of the International Statistical Classification of Diseases and Related Health Problems of the World Health Organization (ICD-10). The codes from ICD-10 that have been included in each of the above 4 major groups are shown in Table 1. It should be mentioned that coronary artery bypass graft surgery (CABG) was included in the category of MI with the reasoning that undergoing CABG is a strong indication of infarction if MI itself had not been confirmed or reported, while angioplasty and presence of other cardiac/vascular implants and grafts were included in the Other CHD group.

Self-reported data on cardiovascular disease

At enrolment

In a special section of the questionnaire participants, at enrolment, were asked whether they had ever had a medically documented diagnosis of myocardial infarction, angina, stroke or brain circulation disturbances. In case of a positive answer in any of these questions participants were also asked to report the age at diagnosis of the reported CVD and subsequently were considered as prevalent cases of one or more CVD conditions as these are indicated in Table 1.

Post enrolment

During follow-up, participants (or their next of kin if participants were unable to answer)
were asked whether they have been told by a medical doctor that they developed a myocardial infarction or stroke and, if yes, they were also asked about the date of diagnosis and the hospital they have been admitted in case of hospitalization. An additional question, namely “Are you aware of any other health problem that you would like to report with or without hospitalization” was asked, where participants could report other CVD (besides MI and stroke) for which there was not a specific question; in case of a positive answer, the date of diagnosis and hospital they may have been admitted was also recorded. All positive answers to the initial questions described above were further enquired in more detail by the Interviewer and the most suitable (for each case) ICD-10 code was selected. Any self-reported CVD condition during follow-up with a date of diagnosis/hospitalization prior to the date of recruitment was considered as prevalent CVD.

When participants reported the occurrence of a CVD event without recalling the exact date of diagnosis and/or hospitalization, an arbitrary approximate date was entered by the Interviewer that indicated the most likely year of diagnosis and/or hospitalization, e.g. 01/01/1994. This means that all participants with the same year at recruitment and year (presumed) of CVD diagnosis were considered as prevalent CVD.

Case ascertainment through hospital search

All CVD cases reported during follow-up, with a corresponding date of diagnosis/hospitalization later than the date of recruitment were considered as suspected incident CVD cases and were further examined for confirmation. Since 2005, the list of suspected cases was, on a regular basis, forwarded to medical doctors working for the Greek EPIC study in order to review the respective medical files and discharge records from the hospitals in which suspected cases have been hospitalized.

The time from reported date of onset until search of the case in the hospital varied greatly from a few weeks to several years. This happens because there is no nationwide hospital electronic database or any in place infrastructure for direct linkage with hospital archives.

The sources of information and the basis of diagnosis (diagnostic method) required for case ascertainment differed according to the type of cardiovascular disease. For angina and other CHD a discharge record with such diagnosis or the treating doctor’s notes stating the final diagnosis was

<table>
<thead>
<tr>
<th>CVD MAJOR GROUPS</th>
<th>ICD-10 CODES*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction (MI)</td>
<td>I21, I22, I23, Z95.1, I46</td>
</tr>
<tr>
<td>Angina</td>
<td>I20</td>
</tr>
<tr>
<td>Other Coronary Heart Disease</td>
<td>I24, I25, Z95.5, Z95.8, Z95.9</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td></td>
</tr>
<tr>
<td>• Ischemic</td>
<td>I63, I65, I66</td>
</tr>
<tr>
<td>• Hemorrhagic</td>
<td>I60, I61, I62, I69</td>
</tr>
<tr>
<td>• Not otherwise specified</td>
<td>I64, I67, I68,</td>
</tr>
<tr>
<td>• Transient Ischemic attack</td>
<td>645, 646</td>
</tr>
</tbody>
</table>

*Only the general code is shown – all sub-codes are included unless otherwise specified
considered adequate. For cerebrovascular disease, besides the above, description of symptoms before and on admission, as well as, findings from specific medical tests (Computerized Tomography, Magnetic Resonance Imaging, lumbar puncture, other) were considered important for the case ascertainment. For MI, specific information from the medical records was collected including symptoms, values of relevant biochemical indicators of myocardial necrosis, electrocardiographic (ECG) findings and others. For the final diagnosis and classification of cases that had reported occurrence of MI, we used diagnostic criteria based on those of the WHO MONICA project (5). These criteria were used only for non-fatal events. We have not looked at 28 days case-fatality in our study, but we rather defined CVD as fatal if a person had never reported suffering a CVD and the event was registered for the first time in a death certificate. Overall, the criteria for the diagnosis of MI required 3 elements: symptoms, ECG findings and enzymes. The classification of MI manifestations is shown in Table 2.

ECG findings were classified as Definite MI, Probable MI, Ischemic, Other, Uncodable or Insufficient data according to the WHO MONICA Project criteria and the Minnesota Code classification system for ECG findings (6). If the ECG itself was not available in order to make the classification, the medical record of the patient was examined for the description of ECG findings that could be specific and detailed enough to allow coding. In case such information was not available ECG findings were still considered diagnostic if the treating physician had stated in his notes the presence of an abnormal ECG indicative of an MI.

Lastly, the enzymes used for the diagnosis of MI were Creatine Phosphokinase, Creatine Kinase MB and Troponin. Any other enzyme mentioned in the medical record (e.g. LDH) was also noted. The classification was based on the range of normal values given by the lab that performed the analysis in each case and, if these were not available, values should be at least twice over the following suggested upper normal values: 2 ng/ml for troponin, 24 U/l or 5 ng/ml for CK-MB (CKMBm) and 190 U/l for CPK. Enzyme levels were classified as Normal, 1. typical

When chest pain is present and characterized by (a) duration of more than 20 minutes and (b) no definite non-cardiac or cardiac non-atherosclerotic cause. If symptom duration is not stated, then the pain is considered as inadequately described. The duration can be assumed to be 20 minutes if the history implies that the pain lasted while something else was going on, or until something else happened.

2. Atypical

If symptoms were not typical but there was (a) one or more of: atypical pain, acute left ventricular failure, shock, and syncope and (b) absence of cardiac disease other than ischemic heart disease and (c) no definite non-cardiac or cardiac non-atherosclerotic cause.

3. Other

When symptoms are well described but do not meet the criteria for typical or atypical. Symptoms due to a definite non-cardiac cause or to a definite non-atherosclerotic cardiac cause (e.g., pericarditis).

4. None

In nonfatal cases if the patient reported no symptoms in the attack and in fatal cases if the eyewitnesses of the fatal collapse state that the individual was completely normal and uncomplaining before the moment of death.

5. Inadequately described

For cases otherwise satisfying criteria for typical pain but in which the duration of the pain is not described, so that it is not possible to classify the symptoms as typical.

6. Insufficient data

If information on the presence or character of symptoms is inadequate.

Source of information: WHO MONICA
Abnormal (when at least one measurement was twice over the upper normal value within 3 days of onset or admission) and Equivocal (when levels are risen but less than twice the upper normal value). When values were not available but there was a note in the medical record that a relevant biomarker was abnormal, enzymes were still considered as abnormal. Generally, a subject was considered as having abnormal enzymes if values in any of the abovementioned enzymes were in the abnormal range.

For the validation of stroke cases we used the World Health Organization (WHO) definition of stroke: “rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than of vascular origin” (5). Additionally, although they do not fall into the definition of stroke above because their duration is less than 24 hours, Transient Ischemic Attacks (TIA) were also considered as part of the cerebrovascular diseases group.

A large proportion of medical records were incomplete, and therefore it was not possible to apply the WHO criteria for the classification of cases of MI and stroke. Nevertheless, if there was clear affirmation from the treating doctors in the medical record, the case was considered confirmed.

Case ascertainment through Death registries search

For the ascertainment of CVD cases through the search of death certificates in local death registries we considered all deaths for which a relevant ICD code (as indicated in Table 1) was included in either the preceding, underlying or contributing cause of death of the death certificate.

In mortality analyses, CVD is counted as cause of death only if CVD is mentioned as preceding or underlying cause or if it is mentioned as immediate cause of death without any mention of a preceding or underlying cause of death. If CVD is mentioned only as co-existing condition it is not considered as cause of death in the particular case (unless if as underlying cause of death a “mechanism”, like arrhythmia or syncope is indicated, so that the co-existing condition can be inferred to actually have been the underlying cause of death).

In morbidity analyses, when CVD is mentioned as preceding or underlying cause of death it is of course considered an incident event (assuming that, for the same person, there is no earlier similar CVD event from, say, a hospital discharge). However, this person is counted as incident CVD even if this is mentioned ONLY as co-existing condition in the death certificate (the rationale being that the certifying physician had some knowledge to that effect). The time of occurrence of this incident event (first discovered through mention in the death certificate) was arbitrarily assigned at the midpoint between the last follow-up at the date of death.

Definition of confirmed self-reported CVD cases

We considered as confirmed CVD cases those subjects who had reported a CVD that was classified in a specific major group according to Table 1 and who were subsequently confirmed through hospital search as cases of the same major group of CVDs (“self reported and confirmed”). Subjects who reported a CVD and they subsequently died without having been searched through hospital search were considered as confirmed cases only if their self-reported diagnosis was verified through death certificates as cases of the same major group of CVD (“self reported and confirmed”). We also considered confirmed CVD, cases which were accidentally found during hospital search either for another condition (usually cancer) or for a CVD classified in a different major group, and cases that CVD was not reported but was confirmed by the death certificate (”not self reported but confirmed”).

Finally, we considered as not confirmed those self-reported CVDs which were not verified as CVD cases by hospital search or by death certificate (“self reported but not confirmed”).

Self-reported CVDs which were not further enquired through hospital search, and were alive as of December 2009 were considered as “self reported to be searched”. The rest of the EPIC participants who had not declared at any time post recruitment that they had been diagnosed with CVD, who were not accidentally found to have been hospitalized for CVD, and who had not died as of December 2009 from a CVD (reported as preceding or underlying cause of death or co-existing condition in the death certificate) were considered as “not self-reported, not confirmed”.

RESULTS

Up to December 2009, the median follow-up time for the Greek EPIC cohort was 10.7 years, and the third follow-up round was ongoing. From the initial 28 572 participants 1 061 (3.7%) were
lost to follow-up. The total number of prevalent CVD cases, reported at baseline, retrospectively during follow up, or both, was 1,071 for angina, 825 for MI, 445 for other CHD, and 907 for cerebrovascular disease. Some participants had more than one prevalent CVD, thus there is some degree of overlap in the indicated figures.

Table 3 shows the number of CVD cases reported as incident, during the three follow-up rounds, the number of medical records actually obtained from the hospitals and the number of cases confirmed. A total of 121 self-reported incident cases of angina, 683 of MI, 622 of other CHD, and 855 of cerebrovascular disease have been reported until December 2009. These numbers denote the earliest report of each of the indicated conditions and are not mutually exclusive, i.e., a participant might be counted in more than one conditions. From the self-reported CVDs, 40 cases of angina, 389 of MI, 226 of other CHD, and 346 of cerebrovascular disease were further investigated. The rest of the self-reported cases were not further enquired for one or more of the following reasons: some patients refused access to their medical files; access to hospitals in remote areas of Greece was difficult; in few cases hospitalization was done abroad; many participants were not hospitalized or did not recall the place of hospitalization and thus, several patients had not been searched as of the time of this analysis. In total, records were searched for 926 participants with reported CVD, and from those, medical records for the 832 (90%) were obtained from the respective hospitals. Because of multiple distinct outcomes, the sum of records searched in Table 3 is greater than 926 (1,001) and those obtained greater than 832 (893). Reasons for not obtaining records of the enquired subjects included inaccurate information for hospitalization (80 cases), incomplete medical records (4 cases) and lack of cooperation with the responsible hospital authorities (10 cases). Examination of the medical records obtained confirmed the self-reported information in 72% of incident cerebrovascular disease, 65% of incident MI, 55% other CHD cases and 32% of angina.

In Table 4 the classification of incident CVD cases according to the source of information used is shown. In total, 239 MIs, 51 angina cases, 158 other CHD cases, and 219 cerebrovascular disease were confirmed through hospital search. From these, the majority had been self-reported (as indicated in Table 3), but a smaller fraction was identified “by chance”, that is, when searching patients’ medical records for another medical condition (e.g., for another CVD or cancer). This “by chance” confirmation was evident mostly with respect to angina (40/51 cases, 78%), and to a lesser extend with respect to other CHD (44/158, 27.8%) and was minimum among MI and Stroke (8/239, 3.3% and 6/219, 2.7% respectively). Another 215 MIs, 1 angina case, 269 other CHD cases, and 257 strokes were identified as incident cases based solely on the death certificate (i.e., had not reported a CVD before nor were confirmed by hospital search). Finally, an additional number of 452 MIs, 508 other CHDs, 642 strokes, and 110 angina incident cases were self-reported during follow-up but were not yet searched for in the respective hospitals. However, 7 of these self-reported cases of MI, 25 of the self-reported cases of stroke, and 8 of the self-reported other CHD cases were dead as of December 2009 and their conditions were confirmed by the death certificates.

**Table 3**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Number of Cases Reported During Follow-up</th>
<th>Number of Cases Searched</th>
<th>Number of Medical Records Obtained</th>
<th>Case Diagnosis Confirmed (from Obtained Medical Records)</th>
<th>% Confirmed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angina</td>
<td>121</td>
<td>40</td>
<td>34</td>
<td>11</td>
<td>11/34=32%</td>
</tr>
<tr>
<td>MI</td>
<td>683</td>
<td>389</td>
<td>355</td>
<td>231</td>
<td>231/355=65%</td>
</tr>
<tr>
<td>Other CHD</td>
<td>622</td>
<td>226</td>
<td>208</td>
<td>114</td>
<td>114/208=55%</td>
</tr>
<tr>
<td>Stroke/TIA</td>
<td>855</td>
<td>346</td>
<td>296</td>
<td>213</td>
<td>213/296=72%</td>
</tr>
</tbody>
</table>

Number of CVD cases of interest reported during follow up, number of reported cases searched and found in hospitals, and percentage of suspected diagnosis confirmed over those cases found in the hospitals.
Table 5 shows the classification of all subjects that comprise the Greek EPIC database with respect to incidence of CVD. From the 683 reported incident MIs confirmation by means of either medical records from hospital search or death certificate was successful in 238 (34.8%) whereas the proportions for stroke, other CHD and angina were 27.8%, 19.6% and 9% respectively. An additional 223 MI, 41 angina, 313 other CHD and 263 stroke cases were confirmed either incidentally through hospital search of by the death certificate.

DISCUSSION

We have undertaken an arduous validation process in order to confirm self-reported incident cases of CVD in the Greek EPIC cohort. Validation procedures included verification of CVD cases reported during follow-up through the search of official sources of information in hospitals, as well as death registries.

Confirmation of the self-reported cases based on the medical records obtained was high for cerebrovascular disease (72%) and lower for MI (65%) and other CHD conditions (55%). In our study we observed a low percentage of self-reported angina cases that were further confirmed. Perhaps, the fact that specific questions were posed by the interviewers for MI and stroke whilst information on angina and other CHD was collected through an open ended question (reporting any other health problem the participant had over the past years) could have led to more precise reporting for the former. Furthermore, it is possible that the reporting validity is higher for the diseases which are more life-threatening.

From the confirmed CVD cases through hospital search a quite small percentage (7.3%)
were not reported during follow-up. However, this percentage was very high (78%) for angina. One possible reason for this could be that participants when asked about other heart problems, except myocardial infarction and stroke, do not precisely mention the term ‘Angina’ but rather a general ischemic heart problem which is classified by the interviewers under ‘Other CHD’. There are also many CVD cases that were only confirmed through death certificates and were not reported during follow-up. This is probably due to two facts: participants that really had not symptomatic CVD and their first CVD event was fatal and participants that had developed CVD before dying from it but did not had the chance to report it because of the long time interval between follow-up rounds (especially if participants have missed a round).

The percentage of confirmation for MI and stroke is quite similar with the percentage found in other relevant studies. In the Nurses’ Health study, the levels of confirmation for self reported myocardial infarction and stroke through medical records review were 68% and 66% respectively (3). In the Australian Diabetes, Obesity and Lifestyle (AusDiab) study of the 276 self-reported CVD events, 188 (68.1%) were verified by adjudication of medical records (7). Another study by Okura et al showed that self report of disease showed 90% specificity for MI and stroke and substantial agreement between self report and medical records. Factors associated with high total agreement were age below 65 years, female sex, high education (>12 years) and no co-morbidities (8). For angina however, confirmation in our study was lower compared to the respective results from the British Regional Heart where 70% of men who reported angina diagnosis had confirmation of this from the record review (9). In the Japan Public Health Center–based prospective Study (JPHC Study) cohort (n = 91 186), sensitivity of self-reported incident stroke was 73%, and that for MI was 82%. Positive predictive values were 57% for stroke and 43% for MI (1). In a study by Reitz and colleagues, sensitivity of self-reported stroke for a diagnosis of stroke on MRI was 32.4% and accuracy of self-report was influenced by age, presence of vascular disease, and cognitive function (2). Data from the Minnesota heart survey registry (presenting results on the validity of self-reported history of previous acute myocardial infarction among 3 703 patients admitted to a coronary care unit with suspicion of acute myocardial infarction) substantiated the history of a prior event for 60% of those who reported one (629 of 1 053) and found 40% to be false-positive histories. Much of the false-positive reporting was related to previous cardiac hospitalizations, predominantly for unstable angina (10). Although there are differences in the methodology, the sample and the criteria used, these results may suggest that this type of misclassification is inevitable in cohort studies and that a certain percentage of reported cases will not be confirmed.

Among the limitations of our study is that sensitivity and specificity of the self reports to accurately indicate CVD cases could not be estimated since it is unknown whether those who had not reported CVD in the entire cohort had actually developed or not the respective diseases. Also, a large proportion of medical records were incomplete and therefore it was not possible to apply the WHO criteria for the classification of cases of MI and stroke in all hospitalised cases.

Overall, it appears that our validation results are comparable to those in other cohort studies. From our study it appears that self-reported MI and stroke (or TIA) have a higher validity, while self-reported angina and other CHD have a lower one.

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