PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	The influence of smoking and impaired glucose homeostasis on the outcome in patients presenting with acute coronary syndrome: a cross sectional study
AUTHORS	Odeberg, Jacob; Freitag, Michael; Forssell, Henrik; Vaara, Ivar; Persson, Marie-Louise; Odeberg, Håkan; Halling, Anders; Råstam, Lennart; Lindblad, Ulf

VERSION 1 - REVIEW

REVIEWER	Anoop Shah Farr Institute of Health Informatics Research London University College London UK
REVIEW RETURNED	09-Apr-2014

GENERAL COMMENTS	This is an interesting historical study investigating how cardiovascular risk factors are associated with the natural history of acute coronary syndrome. In view of the historic nature of the cohort, the manuscript requires more description on the study population, in particular: 1. How were patients selected? Why was the study limited to patients aged 30-74? A patient flow diagram would be helpful. 2. How were these patients treated? Please give a brief description to orientate the reader. Presumably patients were given aspirin, morphine and nitrates but not revascularisation or thrombolysis. Coronary artery bypass grafting has been performed in Sweden since the 1970s; was it not available because this is a rural area? 3. What was the final diagnosis in patients without ACS? This is crucial because some of these patients constitute the control group. A major concern is the conclusion that smoking was not associated with unstable angina. This may be true only among this population - people presenting to hospital with chest pain. It would not be true among the general population, because smoking is associated with causes of non-coronary chest pain such as gastro-oesophageal reflux disease, which may have been the final diagnosis in some of these patients. The selection of the control group is not a strength in this respect, as it does not represent the general population from which the cases arose. The definitions of acute myocardial infarction and unstable angina are different to those used nowadays, and the cardiac biomarkers used in the acute myocardial infarction definition should be stated. In

	the risk factors section, please state how ex smokers were handled. The methods should be described more precisely, e.g. what was stratified for in the 'stratified' analysis? Why were missing data handled by complete case analysis rather than multiple imputation or other methods for utilising the complete dataset? This would reduce the selection bias and increase the power of the analysis (as long as data can be assumed to be missing at random). The limitations section should mention missing data and the non-representativeness of the control group. Table 1 - misspelt 'Glucos' Missing data - perhaps better to include number of patients with data as an additional column rather than in a long footnote Tables 2 and 3. Pledase state how age was entered in the model (whether categorical or continuous), and state clearly that this is a multivariable model (as I assume it is - all variables entered in the same model and mutually adjusted). As this is a complete case analysis, state the final number of patients included in the model. Please define 'impaired glucose homeostasis' in the abstract, as this is a non-standard term (described later in methods as glucose ≥7.5 mM together with HbA1c ≥5.5)

REVIEWER	Kerstin Dudas Institute of Health and Care Science, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden
REVIEW RETURNED	06-May-2014

GENERAL COMMENTS	Thank you for allowing me to review this paper “Smoking and impaired glucose homeostasis predisposes to a more severe outcome in patients presenting with acute coronary syndrome: A cross-sectional study”. This is an interesting paper about predicted risk factors for patients diagnosed with MI compared with UA and non-ASC. However, I have a few concerns needed to be addressed. First, page 4 paragraph Strengths and limitations of the study, the second bullet; please spell out the abbreviation ER. This abbreviation ER should also be spelled out in the section Discussion in the second paragraph. In the section Materials and methods- Acute coronary syndrome patient, second paragraph; please consider if information of the criteria for a diagnosis of MI and UA is coded and according to the International Classification of Diseases (ICD) 9, which was in use from 1987 to 1996 may be inserted in text (for the reader’s information). Moreover, the method section can be improved if the authors developed the method regarding to identify patients with an impaired glucose homeostasis. In the section Risk factors, I have concerns about the smoking status, non-smoking. Many authors define non-smokers as, nonsmokers > 1months, otherwise the patients are assessed as current smokers. Do you have an appropriate reference for your smoking status classification?

	In the section Results, first paragraph, first sentence the number of patients aged 30-74 years is 2992, in the method section the number of patient aged 30-74 years was 2967. Please check up what is the correct number of patients. The interesting findings as the authors properly point out, that smoking was significantly associated with MI, but not with UA is also found by Dudas et al. 2007 in the Multi Primary Prevention Study (Dudas K et al. Predictors of coronary bypass grafting in a population of middle-aged men. Eur J Cardiovasc Prev Rehabil. 2007 Feb;14(1):122-7). Additionally, Björck et al 2009 found similar results in smoking relation among patients diagnosed with STEMI compared to NSTEMI. (Björck L. Rosengren A, Wallentin L, Stenestrand U Smoking in relation to ST-segment elevation acute myocardial infarction: findings from the Register of Information and Knowledge about Swedish Heart Intensive Care Admissions. Heart 2009;95:1006-1011 doi:10.1136/hrt.2008). Please, consider if these references can be discussed in the present study. A serious limitation is that the data are almost 2 decades old; the authors cite this as a strength but this means that the clinical applicability of the data to a modern population is limited. Also, it is a small single-centre study, which is another limitation – the only finding that sets it apart from the much larger and more current datasets offered by the RIKS-HIA is the association between impaired glucose control and ACS. The limitations of the study need to be discussed in more detail.

VERSION 1 – AUTHOR RESPONSE

Reviewer Name Anoop Shah
Institution and Country Farr Institute of Health Informatics Research London University College London UK

This is an interesting historical study investigating how cardiovascular risk factors are associated with the natural history of acute coronary syndrome. In view of the historic nature of the cohort, the manuscript requires more description on the study population, in particular:

1. How were patients selected? Why was the study limited to patients aged 30-74? A patient flow diagram would be helpful.

Reply: We have expanded the description of patient recruitment in Materials and methods, and included a new figure with a flow diagram outlining the selection of patients (figure 1). The Patient recruitment section now reads (with changes in bold):

'The Carlscrona Heart Attack Prognosis Study (CHAPS) recruited 5292 consecutive patients admitted to the coronary intensive care unit with acute chest pain (indicative of a possible ACS) at Blekinge Hospital, Karlskrona, between January 26, 1992 and January 25, 1996. Patients that presented to the Emergency Room (ER) with recent or ongoing chest pain were at this time by routine directly transferred to the coronary intensive care unit. Patients were included after written informed consent. Patients unable to give informed consent because of their medical condition were excluded. Of the total of 5292 patient admissions included, 2992 were between 30-74 years of age at admittance. In patients with multiple admittances, only the first classifying admittance was included as case in the study. The selection of patients for the current study is outlined in figure 1.'

Restricting the studied group to a certain age limit is a highly relevant discussion point made by the reviewer. However, at the time of study older patients (>75) with acute chest pain/chest discomfort and severe comorbidities (e.g. advanced dementia, cancer) could be denied admission to the coronary intensive care unit in case of limited ward resources. By choosing to limit the study to patients < 75 years old we could ensure all eligible patients had been admitted to the coronary care unit and thereby considered for inclusion or exclusion in the current study.

2. How were these patients treated? Please give a brief description to orientate the reader. Presumably patients were given aspirin, morphine and nitrates but not revascularisation or thrombolysis. Coronary artery bypass grafting has been performed in Sweden since the 1970s; was it not available because this is a rural area?

Reply: The Materials and methods section has been amended by the following text:

'Patients admitted to the coronary intensive care unit were initially treated with aspirin, and in case of on-going chest pain, also nitrates and morphine. In cases of clear diagnosis of ST elevation MI, thrombolysis with streptokinase was given (194 of 527 patients with MI). Patients with MI diagnosed by cardiac markers only were not given thrombolysis. At the time of the study, acute coronary artery intervention was not available at this hospital.'

3. What was the final diagnosis in patients without ACS? This is crucial because some of these patients constitute the control group.

Reply: We agree with the reviewer and have now expanded the description of the non-ACS group in Materials and methods. It now reads (changes in bold):

'The study population also contained 948 patients aged 30-74 (569 men and 379 women) who were admitted with suspected ACS, but were subsequently diagnosed as non-ACS and, furthermore, were not diagnosed with stable coronary artery disease (CAD). This group constitutes patients with chest discomfort or chest pain without remaining suspicion of cardiac ischemic origin, thus excluding ICD 9 codes 410-414. Patients with dyspepsia, lower airway infection or musculoskeletal origin of chest pain are found in this group, however, in many cases no specific medical condition had been established upon discharge from the coronary intensive care unit'

A major concern is the conclusion that smoking was not associated with unstable angina. This may be true only among this population - people presenting to hospital with chest pain. It would not be true among the general population, because smoking is associated with causes of non-coronary chest pain such as gastro-oesophageal reflux disease, which may have been the final diagnosis in some of these patients. The selection of the control group is not a strength in this respect, as it does not represent the general population from which the cases arose.

Reply: We agree with the reviewer that the control group is not representative of the general population, as it is enriched for people seeking medical care due chest pain, and although ACS is ruled out, other morbidities (including bronchitis, other infection, dyspepsia etc.) can be assumed to be increased in this group compared to the general population, and that these can be associated with smoking (dyspepsia, bronchitis etc). Our study does not answer if smoking is more prevalent in UA compared to a general population or not. The important observation we make is that, among patients with suspected ACS, smoking is significantly associated with MI over UA, and amongst non-MI patients presenting to the hospital with chest pain, smoking does not predispose to UA. This is in line with other publications, as also acknowledged by reviewer 2.

We have amended the discussion of limitations to more explicitly acknowledge this fact:

‘The control group is not representative of the general population, as it is enriched for individuals seeking medical attention for non-coronary conditions presenting with chest pain or discomfort, of which some may also be associated with smoking (i.e. dyspepsia, bronchitis)‘

The definitions of acute myocardial infarction and unstable angina are different to those used nowadays, and the cardiac biomarkers used in the acute myocardial infarction definition should be stated. In the risk factors section, please state how ex smokers were handled.

Reply: The Material and methods section has been modified. This section now reads (addition in bold):

’A diagnosis of acute MI was set in patients fulfilling at least two of the following criteria: (i) A history of chest pain with at least 15 min duration, (ii) an increase in activity of cardiac enzymes (aspartate amino transferase and/or creatinine kinase) to at least twice the upper limit of normality, and (iii) characteristic ECG changes for MI (typical sequence change of ST segment and/or of T-waves and/or appearance of new Q-waves). These criteria included both patients with ST-elevation MI (STEMI) and non-ST elevation MI (NSTEMI).’

The methods should be described more precisely, e.g. what was stratified for in the 'stratified' analysis? Why were missing data handled by complete case analysis rather than multiple imputation or other methods for utilising the complete dataset? This would reduce the selection bias and increase the power of the analysis (as long as data can be assumed to be missing at random).

Reply: Among all patients presenting with chest pain we stratified for final diagnosis as MI, UA, or not. We preferred to include only patients with complete information, as these analyses still seemed to return conclusive findings.

The methods section now reads:

STATA and IBM SPSS Statistics were used for data analyses. Standard methods were used for descriptive statistics. Associations between categorical variables were examined using binary logistic regression and expressed as odds ratios (OR) with 95% confidence intervals (CI). Principal analyses were made with men and women combined in one group, but were repeated where men and women were analysed separately. Age was entered into the regressions in 10-year age groups. Confounding was considered by stratification for final diagnosis (as MI, ACS or not) and by multivariate regression models forcing age group, sex, impaired glucose homeostasis, serum cholesterol, hypertension and current smoking into the same model. Individuals with a missing variable were excluded in the respective analysis. Two-way interaction terms were used to explore the association of sex and the major risk factors with ACS outcome.

The limitations section should mention missing data and the non-representativeness of the control group.

The discussion of limitations has been expanded, and now reads:

‘A number of limitations of the study should be acknowledged. Biochemical analyses were performed over a period of four years, although the hospital routine diagnostic laboratory used accredited standardised methods, providing consistency over time. Data for laboratory analyses were not complete for all patients included. The definition of MI continues to evolve as refined criteria and more sensitive and specific biomarkers are implemented. Some of the UA cases in our study would likely

have now been diagnosed as NSTEMI, using recent criteria required for MI diagnosis [5] . The control groups is not representative of the general population as it is enriched for individuals seeking medical attention for non-coronary conditions presenting with chest pain or discomfort, of which some may also be associated with smoking (i.e. dyspepsia, bronchitis). Furthermore, CHAPS is a single centre study, and treatments and risk factor profiles have also partly developed since the study was performed. The results would therefore not necessarily be generalised to a broader modern population although our results are supported by more recent studies as discussed below [4 6]. However, smoking remains a major health issue and type 2 diabetes is increasing in the western society, therefore, the results are still highly relevant for the care of patients with CAD today.'

Table 1 - misspelt 'Glucos'

Reply: This has been corrected

Missing data - perhaps better to include number of patients with data as an additional column rather than in a long footnote

Reply: A new column has been added to the right hand side in table 1.

Tables 2 and 3. Please state how age was entered in the model (whether categorical or continuous), and state clearly that this is a multivariable model (as I assume it is - all variables entered in the same model and mutually adjusted). As this is a complete case analysis, state the final number of patients included in the model.

Reply: The footnotes of table 2 and table 3 have been modified to clarify this.

The footnote of table 2 now reads:

'* Impaired glucose homeostasis (HbA1c≥5.5% + blood glucose ≥7.5 mM)
**Age groups: 30-39, 40-49, 50-59, 60-69, 70-74 years
Associations were estimated by binary logistic multivariate regression and expressed as odds ratios (OR) with 95% confidence intervals (CI (95%)). MI versus UA was the dependent variable and age by 10 years age groups, sex, serum cholesterol, smoking, hypertension or glucose control were entered as covariates into the same model that included 742 subjects.'

The footnote of table 3 now reads:

'* Impaired glucose homeostasis (HbA1c≥5.5% + blood glucose ≥7.5 mM)
** Age groups: 30-39, 40-49, 50-59, 60-69, 70-74 years
Associations were estimated by multivariate binary logistic regression and expressed as odds ratios (OR) with 95% confidence intervals (CI (95%)). MI and UA were the dependent variables and age by 10 year age groups, sex, serum cholesterol, smoking, hypertension or glucose control were entered as covariates into the same model. Number of patients included in final models was 680 (MI versus non-ACS), and 564 (UA versus non-ACS), respectively.'

Please define 'impaired glucose homeostasis' in the abstract, as this is a non-standard term (described later in methods as glucose ≥7.5 mM together with HbA1c ≥5.5)

Reply: The Results paragraph in the Abstract now reads:

'Current smoking (OR 2.42 (1.61-3.62)), an impaired glucose homeostasis defined as HbA1c≥5.5% + blood glucose ≥7.5 mM (OR 1.78 (1.19-2.67)) and male sex (OR 1.71 (1.21-2.40)) were significant

factors predisposing to MI over UA, in an event of an ACS. Compared to the non-ACS group, impaired glucose homeostasis, male sex, cholesterol level and age were significantly associated with development of an ACS (both MI and UA). Interestingly, smoking was significantly associated with MI (OR 2.00 (1.32-3.02)), but not UA.'

Reviewer Name Kerstin Dudas
Institution and Country Institute of Health and Care Science, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden;
Please state any competing interests or state 'None declared': None declared

Thank you for allowing me to review this paper "Smoking and impaired glucose homeostasis predisposes to a more severe outcome in patients presenting with acute coronary syndrome: A cross-sectional study". This is an interesting paper about predicted risk factors for patients diagnosed with MI compared with UA and non-ASC. However, I have a few concerns needed to be addressed.

First, page 4 paragraph Strengths and limitations of the study, the second bullet; please spell out the abbreviation ER. This abbreviation ER should also be spelled out in the section Discussion in the second paragraph.

Reply: Emergency Room (ER) has now been spelt out.

In the section Materials and methods- Acute coronary syndrome patient, second paragraph; please consider if information of the criteria for a diagnosis of MI and UA is coded and according to the International Classification of Diseases (ICD) 9, which was in use from 1987 to 1996 may be inserted in text (for the reader's information). Moreover, the method section can be improved if the authors developed the method regarding to identify patients with an impaired glucose homeostasis.

Reply:
We choose this definition as it combined two parameters for determining insufficient glucose control at the time of ACS that is independent of health records or prior diagnosis. Our reason for choosing the lab defined parameter was that data in the literature indicated that glucose levels and glucose control at the acute event influence thrombogenicity (amongst other things), and thus patients with prior diagnosis of DM, but with good blood glucose control (due to diet, medication, weight loss after diagnosis of DM) potentially could be separated from patients with DM diagnosis with less adequate glucose control with respect to risk of MI in the case of an ACS.

We have added the following text in the Materials and methods section:

'Patients with a previous diagnosis of diabetes were grouped for analysis as follows: (i) diet treated only, (ii) oral medication only, or (iii) insulin treated. In parallel, to identify patients with an impaired glucose homeostasis who had evidence of both acute and long-term insufficient glucose control, a laboratory-defined classification based on glucose ≥7.5 mM together with HbA1c ≥5.5 was used. We had previously evaluated this classification by comparing to prior diagnosis of DM, and found that 89% of those treated by diet only, 95% of those treated by oral medication only, and 100% of those treated with insulin were identified as having impaired glucose homeostasis using this classification (unpublished).'

We have amended the Materials and methods section accordingly to clarify that patients with MI correspond to ICD 9 code 410, patients with UA correspond to ICD9 code 411, and furthermore that

the control group constitute patients with chest discomfort or chest pain without remaining suspicion of cardiac ischemic origin, thus excluding ICD 9 codes 410-414.

In the section Risk factors, I have concerns about the smoking status, non-smoking. Many authors define non-smokers as, nonsmokers > 1months, otherwise the patients are assessed as current smokers. Do you have an appropriate reference for your smoking status classification?

Reply: The section about risk factors has been clarified to read:

'Smoking status was defined as current- or non-smoker. Non-smoker included patients who quit smoking >1 month before admission.'

In the section Results, first paragraph, first sentence the number of patients aged 30-74 years is 2992, in the method section the number of patient aged 30-74 years was 2967. Please check up what is the correct number of patients.

Reply: Thank you for pointing out this error. The correct number is 2992 and the Results section has been corrected accordingly.

The interesting findings as the authors properly point out, that smoking was significantly associated with MI, but not with UA is also found by Dudas et al. 2007 in the Multi Primary Prevention Study (Dudas K et al. Predictors of coronary bypass grafting in a population of middle-aged men. Eur J Cardiovasc Prev Rehabil. 2007 Feb;14(1):122-7). Additionally, Björck et al 2009 found similar results in smoking relation among patients diagnosed with STEMI compared to NSTEMI. (Björck L. Rosengren A, Wallentin L, Stenestrand U Smoking in relation to ST-segment elevation acute myocardial infarction: findings from the Register of Information and Knowledge about Swedish Heart Intensive Care Admissions. Heart 2009;95:1006-1011 doi:10.1136/hrt.2008). Please, consider if these references can be discussed in the present study.

Reply: We thank the reviewer for pointing out these relevant publications and a discussion of these have been included in the Discussion section (in bold):

'Interestingly, our finding that smoking was associated with MI, but not UA, when compared to the non-ACS patients, shows that smoking has a significant effect mainly in the acute event, possibly through modulation of thrombogenicity at the site of a ruptured plaque [12]. This is supported by the finding of Dudas et al. that smoking was associated with MI but not with extensive CAD in need of a coronary bypass grafting [13]. Furthermore, Björck et al. found smoking to be an independent determinant for presenting with STEMI compared with non-STEMI in 93 416 consecutive patients aged 25 to 84 years and admitted to hospital between 1996 and 2004 with a first AMI. ([14]. Previous reports show that the increased risk for MI associated with smoking decreases rapidly after cessation [12 15 16], supporting the idea that smoking is a critical risk factor in the acute stages of ACS, rather than in all clinical manifestations of CAD.'

A serious limitation is that the data are almost 2 decades old; the authors cite this as a strength but this means that the clinical applicability of the data to a modern population is limited. Also, it is a small single-centre study, which is another limitation – the only finding that sets it apart from the much larger and more current datasets offered by the RIKS-HIA is the association between impaired glucose control and ACS. The limitations of the study need to be discussed in more detail.

Reply: We agree with the reviewer the limitations of the single centre design and the historical character of the study needs to be discussed more in detail. The 4th paragraph in the discussion has been updated and now reads (additions in bold):

‘A number of limitations of the study should be acknowledged. Biochemical analyses were performed over a period of four years, although the hospital routine diagnostic laboratory used accredited standardised methods, providing consistency over time. Data for laboratory analyses were not complete for all patients. The definition of MI continues to evolve as refined criteria and more sensitive and specific biomarkers are implemented. Some of the UA cases in our study would likely have now been diagnosed as NSTEMI, using recent criteria required for MI diagnosis [5]. The control group is not representative of the general population as it is enriched for individuals seeking medical attention for non-coronary conditions presenting with chest pain or discomfort of which some may also be associated with smoking (i.e. dyspepsia, bronchitis). Furthermore, CHAPS is a single centre study, and treatments and risk factor profiles have also partly developed since the study was performed. The results would therefore not necessarily be generalisable to a broader modern population, although our results are supported by more recent studies as discussed below [4 6]. However, smoking remains a major health issue and type 2 diabetes is increasing in the western society, therefore, the results are still highly relevant for the care of patients with CAD today. ‘

Furthermore, we have added a sentence to the listing of limitations in the beginning of the manuscript:

• Some of the UA cases would likely have been diagnosed as NSTEMI using the most recent criteria of MI.
• The control group is not representative of the general population
• Treatments and risk factor profiles have partly evolved since the study was performed.