Anaemia and the development of depression following acute coronary syndrome: Longitudinal clinical observational study

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Anaemia and the development of depression following acute coronary syndrome

Longitudinal clinical observational study

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Keywords: Myocardial infarction; Depression; Anaemia

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Article summary

Article focus

- Depressive symptoms are common among survivors of acute myocardial infarction and other acute coronary syndromes, and predict a poor long-term outcome.
- Depressive symptoms appear to be independent of clinical disease severity.
- However, anaemia is common in acute coronary syndrome patients, and has not previously been examined as a predictor of depressive symptoms.

Key messages

- Anaemia on admission with acute coronary syndrome predicted depressive symptoms three weeks later, independently of covariates.
- Anaemia also predicted major adverse cardiac events over the next 12 months.
- Anaemia and haemoglobin levels should be considered as biological determinants of depressive symptoms following myocardial infarction and other acute coronary syndromes.

Strengths and limitations

- This is the first study to investigate anaemia and subsequent depression in acute coronary syndrome patients using a prospective design.
- The study was small scale, and was not powered to investigate the impact of depression on long-term cardiac outcomes.

Abstract

Objective: Depressive symptoms are common following acute coronary syndrome and predict subsequent cardiovascular morbidity. Depression in acute cardiac patients appears to be independent of clinical disease severity and other cardiovascular measures. One factor that has not been considered previously is anaemia, which is associated with fatigue and adverse cardiac outcomes. This study assessed the relationship between anaemia on admission and depressive symptoms following acute coronary syndrome.

Design: Longitudinal clinical observational study

Setting: Coronary care unit

Patients: 223 patients with documented acute coronary syndrome

Main outcome measures: Depressive symptoms measured with the Beck Depression Inventory (BDI) 3 weeks after admission

Results: Anaemia was defined with World Health Organization criteria, and was present in 30 (13.5%) of patients. Anaemia predicted raised depression scores 3 weeks later independently of age, gender, marital status, educational attainment, smoking, Global Registry of Acute Cardiac Events (Grace) risk scores, negative mood in hospital and history of depression (P = 0.003). The odds of a BDI score ≥10 among anaemic patients were 4.03 (95% confidence intervals 1.48 – 11.00), adjusted for covariates. Sensitivity analyses indicated that effects were also present when haemoglobin was analysed as a continuous measure. Anaemia also predicted major adverse cardiac events over the subsequent 12 months.

Conclusions: Anaemia appears to contribute to depression following ACS, and is associated with future cardiac morbidity. Studies evaluating the effects of anaemia management will help delineate the role of this pathway more precisely.

Keywords: Myocardial infarction; Depression; Anaemia

Introduction

Depression is common in the weeks following an ACS, with around 20% of patients fulfilling the criteria for major depressive disorder, while a substantial number report symptoms of subclinical dysphoria.[1] Clinical depression and depressed mood are predictors of future cardiac mortality and morbidity,[2] and this has led to intensive efforts to understand the biology linking depression with CHD, and to manage depression effectively.

One possibility is that depression following ACS is related to the extent of underlying coronary artery disease or to the severity of the cardiac event. Although the evidence is inconsistent [3], a number of studies have demonstrated that depression among cardiac patients is not related to left ejection fraction, Killip class, previous myocardial infarction (MI) and other indices of disease severity.[4 5] The association between depression future morbidity and mortality has also been shown to be independent of cardiovascular risk factors and aggregate measures of post-MI risk such as the Global Registry of Acute Cardiac Events (Grace) risk score.[2 6] Nevertheless, other biological factors present during ACS that are only weakly associated with the extent of underlying coronary disease or severity of the cardiac event may be relevant. Acute inflammation is one such mechanism,[7] but a factor that has received less attention is anaemia.

Anaemia is relatively common in acute cardiac patients, with rates ranging from 12 – 16%.[8 9] An association between anaemia on admission for ACS and adverse cardiac outcomes is now well documented, with significant effects on 30 day and longer-term mortality.[8-10] Anaemia is also associated with fatigue and impaired quality of life in various patient groups,[11 12] and two population studies of men and women aged 50 and over have documented positive relationships between anaemia and depressive symptoms.[13 14] We therefore tested the hypothesis that mild anaemia on admission with an ACS would be associated with greater symptoms of depression three weeks after the ACS, and with the occurrence of major adverse cardiac events over the following 12 months. In these analyses we also examined previous history of depression and negative moods during hospitalization in order to examine the possibility that anaemia is related to longer standing depressed mood.

Methods

Patients

Participants were 223 ACS patients admitted to St. George's Hospital in South London between June 2007 and October 2008 as part of a larger study of psychobiological aspects of ACS.[15] Inclusion criteria were a diagnosis of ACS based on the presence of chest pain plus verification by diagnostic EKG changes, troponin T or troponin I ≥ 99th percentile of the upper reference limit. Patients were required to be aged 18 or over, not to have comorbid conditions that might influence either symptom presentation or mood, and ability to complete interviews and questionnaires in English. Patients with severe anaemia (haematocrit <25%) were eligible for blood transfusion and were excluded from the study.[16] 666 potentially eligible patients were admitted on the days of recruitment. Of these, 125 patients (19%) had been discharged or transferred to a different hospital before they could be recruited into the study, 90 (14%) were too clinically fragile (e.g. critical ischemia, ventricular tachyarrhythmia) to take part, 58 patients (9%) declined to participate, 75 (11%) did not complete measures of depression 3 weeks after hospitalization, 27 (4%) could not speak English, 23 (3%) were in confusional states, 7 (1%) patients died in hospital, and a further 38 (6%) were excluded for other reasons. The study was approved by the Wandsworth Research Ethics Committee, and written consent was obtained.

Clinical measures

Admission ECGs were reviewed for presentation as STEMI or non-STEMI / unstable angina (NSTEMI/UA). Cardiovascular history, clinical factors during admission and management were obtained from clinical notes, and the extent of significant stenosis of coronary arteries from angiography records. Clinical risk was assessed using the Grace risk score.[17] Creatine kinase was measured in 210 patients. Anaemia on admission was defined according to WHO criteria as <13 g/dL for men and <12 g/dL for women. Major adverse cardiac events over the

12 months following ACS were defined as cardiovascular death, readmission with reinfarction or UA, coronary artery bypass surgery, or angioplasty.

Assessment of depressive symptoms

Patients were interviewed in their own homes an average 21.6 days following admission to hospital, and the BDI was administered.[18] This consists of 21 items rated on a scale of 0-3, so maximum scores can range from 0 - 63. In addition to the standard scoring of the BDI, we also computed the somatic/affective and cognitive/affective subscales identified by De Jonge et al [19]. The somatic/affective subscale comprised 13 items (e.g. crying, irritability, fatigue, pessimism), while the cognitive/affective subscale included 12 items (e.g. sense of failure, guilt indecisiveness). The Cronbach α was 0.86 for the complete scale, and 0.80 and 0.83 for the somatic/affective and cognitive/affective components respectively.

Other measures

Patients' emotional state in hospital was assessed with a shortened version of the Profile of Mood States (POMS), as used previously.[20] Six high-loading items were taken from each of the original POMS scales (vigour, tension–anxiety, depression–dejection, confusion, anger-hostility, and fatigue). Current feelings on each item were rated on a 5-point scale ranging from 0 = *not at all* to 4 = *extremely*. Negative mood was indicated by summarizing the five negative scales. SES was measured in terms of educational attainment, and participants were classified on whether they had secondary (high school) and college qualifications or less than this (primary education only). Marital and smoking status were assessed by self-report.

Statistical analysis

Comparisons between patients with and without anaemia were made using t-tests for continuous variables and X^2 tests for categorical variables. The relationship between anaemia on hospital admission and depression 3 weeks later was assessed using analysis of covariance on BDI scores, with age, gender, marital status, smoking, educational attainment,

Grace risk score, negative mood in hospital and history of depression as covariates. Similar methods were used to analyse the association between anaemia and somatic and cognitive symptoms of depression. Additionally, we computed the proportion of patients with BDI scores ≥ 10, the recognized threshold for possible depression. Logistic regression computed the odds of elevated depression in patients with anaemia compared with no anaemia, and odds ratios with 95% confidence intervals adjusted for the same covariates were calculated. In order to test whether associations depended on the diagnosis of anaemia or persisted across the entire spectrum of haemoglobin concentrations, linear regression of haemoglobin on depression scores was also carried out. The association of anaemia and future cardiac morbidity was investigated by regressing anaemia onto major adverse cardiac events recorded over the 12 months following ACS, controlling for age, gender, marital status, smoking, educational attainment, Grace risk score, maximum creatine kinase and history of depression.

Results

Haemoglobin levels ranged from 8.3 to 19.0 g/dL, and 30 patients (13.5%) were defined as anaemic according to WHO criteria. There were no differences between the anaemia and no anaemia groups in gender distribution, age, ethnicity, educational attainment or marital status (table 1). There were also no differences in history of depression or in negative mood assessed during hospitalization, though 30% of patients had a history of depression. There was a tendency for Grace risk scores to be higher in patients with anaemia, but the differences was not significant. However, creatine kinase levels were lower among patients with anaemia ($P = 0.028$). The groups did not differ in extent of coronary disease, history of MI, or in presentation with STEMI or NSTEMI/UA. There were also no differences in preadmission rates of diabetes (15.2%), hypertension (44%) or raised cholesterol (74%). Percutaneous coronary intervention (PCI) was performed on 164 patients, 48 were managed medically, and 11 were referred for coronary artery bypass surgery. Treatment plans did not differ in patients with and without anaemia.

Anaemia and depression following ACS

The mean score on the BDI measured 3 weeks following admission for ACS was 6.70 ± 6.7, and 43 patients (19.3%) had BDI scores ≥ 10. BDI scores were significantly higher in patients with anaemia (mean 9.35 ± 8.7) than no anaemia (mean 6.28 ± 6.3) after controlling for age, gender ($P = 0.017$), and the difference was maintained after additional adjustment for marital status, educational attainment, smoking, Grace risk score, negative mood in hospital, and history of depression (means 9.73 ± 8.7 and 6.23 ± 6.3 respectively, $P = 0.003$). A higher proportion of patients with anaemia had BDI scores ≥ 10 compared with the no anaemia groups (33.3% and 17.1% respectively). The odds of a high depression score in patients with anaemia were 4.03 (95% C.I. 1.48 to 11.00, $P = 0.006$) after adjustment for age, gender, marital status, educational attainment, smoking, Grace risk score, negative mood and history of depression (Table 2). Other independent predictors in the model were negative mood in hospital ($P < 0.001$), and a positive history of depression ($P = 0.049$). Using the more stringent criterion of a BDI score ≥ 16, the adjusted odds of a high depression score in patients with anaemia were similar (4.08, 95% C.I. 1.08 to 15.41, $P = 0.038$). Additional statistical control for preadmission disease burden (diabetes, hypertension, previous MI) or for medication 3 weeks after admission did not change these results.

The association between anaemia and depression following ACS did not depend on the specific criterion for anaemia utilized. When haemoglobin level was regressed onto BDI score as a continuous variable, the inverse association was significant (B = -0.88, 95% C.I. -1.42 to -0.33, $P = 0.002$), adjusting for the same covariates (see Table 3). We also tested whether the effect was due to a preponderance of somatic symptoms of depression in ACS patients with anaemia, by analysing the somatic/affective and cognitive/affective subscales of the BDI. In both cases, patients with anaemia had elevated scores, although the effect was more robust for somatic/affective (adjusted means 6.79 ± 5.7 and 4.67 ± 4.5 for anaemia and no anaemia groups, $P = 0.026$) than cognitive/affective (adjusted means 4.04 ± 5.7 and 2.48 ± 3.8, $P = 0.051$) symptoms of depression.

Anaemia and major adverse cardiac events

Thirty four (15.2%) patients experienced a major adverse cardiac event in the 12 months following ACS. A higher proportion of adverse events occurred among patients with anaemia than no anaemia on admission (26.7% versus 13.5%). The odds of major adverse cardiac events among patients with anaemia were 3.30 (C.I. 1.21 to 8.99, $P = 0.020$) after controlling for age, gender, marital status, educational attainment, smoking, Grace risk score, history of depression, and creatine kinase levels in hospital. The study was not powered to test the association between depressed mood following ACS and adverse cardiac outcomes.

Discussion

This study involved a relatively small sample of patients, so conclusions must be tentative. Nevertheless, the analyses indicated that mild to moderate anaemia measured on admission to hospital with an ACS predicted depression symptoms 3 weeks later. The mean scores on the BDI were 48% higher in anaemic patients, and the odds of a BDI score above the threshold for moderate/severe depression (≥ 10) were elevated threefold. These associations were independent of sociodemographic factors, clinical cardiological indices, patients' mood in hospital and history of depression. Anaemia in turn predicted major adverse coronary events over the following 12 months, again independently of sociodemographic and other clinical characteristics.

The prevalence of anaemia was 13.5%, which is comparable with that reported in other studies of older adults. A recent systematic review concluded that the prevalence of anaemia was 12% in community-based studies,[21] suggesting that the levels in this sample of cardiac patients was not notably elevated. Other studies of acute cardiac patients have described rates of between 12 and 17%.[8 10 16] For example, around 13% of the 2,082 patients with acute MI in the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial were anaemic.[9] The mean level of haemoglobin (11.67 g/dL) indicates that anaemia was typically mild, and none of the patients had haematocrit levels

<25%, the currently accepted threshold for blood transfusion.[16] Several different criteria for anaemia have been proposed, and slightly higher haemoglobin thresholds were recommended by Beutler and Waalen.[22] Our sensitivity analysis indicated that the relationship with depression following ACS did not depend on the particular threshold selected, since effects were continuous across the haemoglobin distribution.

We tested three sets of factors that could theoretically contribute to the association between anaemia and depression following ACS. First, both anaemia and depression are associated with lower SES and ethnic minority status,[23] so sociodemographic factors could be relevant. We found no differences in the occurrence of anaemia in relation to ethnic minority status, and controlled statistically for educational attainment as a marker of SES. Second, poor clinical cardiological status is associated with anaemia,[10] and might also predict depression following ACS. Grace risk scores were included to take cardiological status into account. Additional analyses (not described here) showed that the relationship between anaemia and depression was also independent of other clinical indicators such as previous MI, type of ACS, presence of heart failure, and number of vessels with significant stenosis, or with pre-admission illness burden. Third, it is possible that anaemia is associated with depressed mood irrespective of the occurrence of ACS,[13 14] and that the relationship with depression following ACS reflects more persistent effects. The impact of pre-existing depressed mood cannot be completely ruled out, since the BDI was not administered on admission and depression before ACS was measured retrospectively. However, we reasoned that if prevailing depression was responsible, differences between patients with and without anaemia would have been apparent in history of depression, or in negative moods assessed in hospital. This was not the case, suggesting that anaemia has a specific impact on depressive symptoms that evolve after an acute cardiac event.

Anaemia has previously been related to fatigue in various illnesses including cancer, heart failure and chronic lung disease.[11 12 24] We therefore conjectured that anaemia might be associated more strongly with somatic symptoms of depression such as fatigue, loss of appetite and insomnia than with cognitive/affective symptoms such as guilt and sense of

failure. However, both components of the BDI identified by de Jonge et al [19] were elevated in the patients with anaemia. Inspection of individual items from the BDI indicated that anaemic and non-anaemic patients showed differential responses on non-somatic symptoms such as sense of failure, loss of interest, crying and negative body image as well as more somatic items such as tiredness and sleep problems.

Anaemia on hospitalization was a predictor of major adverse cardiac events over the subsequent 12 month period, replicating findings from larger studies.[8-10] The study was not powered to test the impact of depression following ACS on cardiac mortality and morbidity. Previous reviews of this topic have criticized the publication of equivocal findings from underpowered studies.[25] We were not therefore able to investigate the extent to which the presence of anaemia in some patients with depression following ACS contributes to the association between depression and future cardiac morbidity.

It has been estimated that around one third of anaemia in older people is due to blood loss or nutritional deficiencies, one third to chronic diseases involving inflammation, while the remaining third is unexplained.[26] The contribution of nutritional deficiencies in this sample is unknown, and measures of iron-restricted haematopoiesis were not carried out. Inflammatory processes may be relevant, since acute inflammation during ACS has been postulated to be a cause of subsequent depressed mood.[7] Possible causes of unexplained anaemia that are potentially relevant to these findings include sarcopenia, more subtle dysregulation of the immune system, and the impact of some medications.[27]

A number of processes may be involved in mediating the effects of anaemia on cardiovascular risk. The reduction in haemoglobin concentration can adversely affect oxygen supply to the myocardium, promoting arrhythmia and increasing infarct size.[26] At the same time, anaemia leads to increased myocardial oxygen demand though stimulating raised cardiac output,[28] and may have an effect on nitric oxide bioavailability.[29] The impact of anaemia on future depressed mood may be due in part to reduced physical performance and strength which will impair physical activity during recovery from ACS.[30] Decreased physical

activity may in turn enhance depressed mood. Dyspnoea is also characteristic of anaemia, and could reduce physical and social activity, promoting depressed mood following ACS.

Studies relating depression following ACS with subsequent cardiac morbidity and mortality have assessed a number of indices of cardiac status and other physical health issues using the Grace index, Killip class, and measures of comorbidity such as the Charleson index.[6 19] But to our knowledge, the relationship between anaemia and depression following ACS has not been investigated in previous research. The present findings indicate that attention needs to be paid in larger studies in the future to anaemia as a possible contributor to depression following acute cardiac events, and as a determinant of future cardiac morbidity. Studies evaluating the effects of anaemia management on depression following ACS will help delineate the role of this pathway more precisely.

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Competing interests: None.

Contributors: AS and J-C K conceived the research, AS, AW, and GCM carried out research, data analysis and drafted the paper. All authors approved the final manuscript.

Data sharing statement: There are no additional data available.

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Table 1 **Details of the study participants**
Mean ± standard deviation and N (%)

	Anaemia (n = 30)	**No Anaemia (n = 193)**	***P* difference**
Men Women	22 (73.3%) 8 (26.7%)	166 (86.0%) 27 (14.0%)	0.10
Age (yrs)	61.70 ± 11.4	59.28 ± 11.7	0.29
Ethnicity (White)	27 (90.0%)	159 (82.4%)	0.43
Married	21 (70.0%)	139 (72.0)	0.83
Education (secondary and above)	15 (50.0%)	85 (44.3%)	0.45
Smoking	10 (33.3%)	75 (38.9%)	0.69
History of depression	11 (36.7%)	56 (29.0%)	0.40
Negative mood in hospital	3.18 ± 2.6	3.76 ± 2.8	0.69
Grace score	97.67 ± 28.5	90.54 ± 26.0	0.17
Vessels with significant stenosis	1.97 ± 0.55	1.83 ± 0.56	0.43
ACS type (STEMI)	25 (83.3%)	171 (88.6%)	0.88
Previous MI	6 (20.0%)	21 (10.9%)	0.22
CK level IU/L[1]	1209.9 ± 960	1806.4 ± 1639	0.028
Haemoglobin g/dL	11.67 ± 1.15	14.88 ± 1.22	0.001
Haematocrit %	35.64 ± 3.9	42.61 ± 3.8	0.001

[1] n = 210. Analysed following log transformation

Table 2 Predictors of raised depressive symptom levels three weeks after ACS

Predictor	Adjusted odds ratio	95% C.I.	*P*
Gender (male)[1]	0.65	0.21 – 1.97	0.44
Age	0.94	0.88 – 1.01	0.055
Education (lowest)[1]	0.79	0.53 – 1.18	0.25
Marital status (married)[1]	1.31	0.56 – 3.04	0.53
Smoking status (non-smoker)[1]	1.09	0.48 – 2.49	0.84
Grace score	1.01	0.99 – 1.04	0.39
Negative mood in hospital	1.33	1.17 – 1.52	0.001
History of depression (negative)[1]	2.23	1.01 – 4.97	0.049
Anaemia (no anaemia)[1]	4.03	1.48 – 11.00	0.006

[1] Reference category

Table 3 Regression on depression symptoms three weeks after ACS

Predictor	Regression coefficient B	95% C.I.	*P*
Gender (male)[1]	-0.44	-2.98 – 2.11	0.74
Age	-0.13	-0.26 – 0.00	0.05
Education (lowest)[1]	-0.42	01.22 – 0.39	0.31
Marital status (married)[1]	1.31	-0.53 – 3.15	0.16
Smoking status (non-smoker)[1]	-0.41	-1.78 – 1.70	0.96
Grace score	0.02	-0.04 – 0.08	0.68
Negative mood in hospital	0.99	0.70 – 1.30	0.001
History of depression (negative)[1]	1.94	0.15 – 3.74	0.034
Anaemia (no anaemia)[1]	-0.88	-1.42 – -0.33	0.002

[1] Reference category

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Title page
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	2
Objectives	3	State specific objectives, including any prespecified hypotheses	2
Methods			
Study design	4	Present key elements of study design early in the paper	3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	3
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4,5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4,5
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	3
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4,5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	4,5
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	5,6
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	3,
		(b) Give reasons for non-participation at each stage	3,5
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	5
		(b) Indicate number of participants with missing data for each variable of interest	5
		(c) Summarise follow-up time (eg, average and total amount)	3
Outcome data	15*	Report numbers of outcome events or summary measures over time	5-7
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	6,7
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	6
Discussion			
Key results	18	Summarise key results with reference to study objectives	7
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8-10
Generalisability	21	Discuss the generalisability (external validity) of the study results	8,10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	10

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Anaemia and the development of depressive symtpoms following acute coronary syndrome: Longitudinal clinical observational study

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Anaemia and the development of depressive symptoms following acute coronary syndrome

Longitudinal clinical observational study

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Brief title: Anaemia and depression following ACS

Keywords: Myocardial infarction; Depression; Anaemia

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Article summary

Article focus

- Depressive symptoms are common among survivors of acute myocardial infarction and other acute coronary syndromes, and predict a poor long-term outcome.
- Depressive symptoms appear to be independent of clinical disease severity.
- However, anaemia is common in acute coronary syndrome patients, and has not previously been examined as a predictor of depressive symptoms.

Key messages

- Anaemia on admission with acute coronary syndrome predicted depressive symptoms three weeks later, independently of covariates.
- Anaemia also predicted major adverse cardiac events over the next 12 months.
- Anaemia and haemoglobin levels should be considered as biological determinants of depressive symptoms following myocardial infarction and other acute coronary syndromes.

Strengths and limitations

- This is the first study to investigate anaemia and subsequent depression in acute coronary syndrome patients using a prospective design.
- The study was small scale, and was not powered to investigate the impact of depression on long-term cardiac outcomes.

Abstract

Objective: Depressive symptoms are common following acute coronary syndrome and predict subsequent cardiovascular morbidity. Depression in acute cardiac patients appears to be independent of clinical disease severity and other cardiovascular measures. One factor that has not been considered previously is anaemia, which is associated with fatigue and adverse cardiac outcomes. This study assessed the relationship between anaemia on admission and depressive symptoms following acute coronary syndrome.

Design: Longitudinal clinical observational study

Setting: Coronary care unit

Patients: 223 patients with documented acute coronary syndrome

Main outcome measures: Depressive symptoms measured with the Beck Depression Inventory (BDI) 3 weeks after admission

Results: Anaemia was defined with World Health Organization criteria, and was present in 30 (13.5%) of patients. Anaemia predicted raised depression scores 3 weeks later independently of age, gender, marital status, educational attainment, smoking, Global Registry of Acute Cardiac Events (Grace) risk scores, negative mood in hospital and history of depression (P = 0.003). The odds of a BDI score ≥10 among anaemic patients were 4.03 (95% confidence intervals 1.48 – 11.00), adjusted for covariates. Sensitivity analyses indicated that effects were also present when haemoglobin was analysed as a continuous measure. Anaemia also predicted major adverse cardiac events over the subsequent 12 months.

Conclusions: Anaemia appears to contribute to depression following ACS, and is associated with future cardiac morbidity. Studies evaluating the effects of anaemia management will help delineate the role of this pathway more precisely.

Keywords: Myocardial infarction; Depression; Anaemia

Introduction

Depression is common in the weeks following an ACS, with around 20% of patients fulfilling the criteria for major depressive disorder, while a substantial number report symptoms of subclinical dysphoria.[1] Clinical depression and depressed mood are predictors of future cardiac mortality and morbidity,[2] and this has led to intensive efforts to understand the biology linking depression with CHD, and to manage depression effectively.

One possibility is that depression following ACS is related to the extent of underlying coronary artery disease or to the severity of the cardiac event. Although the evidence is inconsistent [3], a number of studies have demonstrated that depression among cardiac patients is not related to left ejection fraction, Killip class, previous myocardial infarction (MI) and other indices of disease severity.[4 5] The association between depression future morbidity and mortality has also been shown to be independent of cardiovascular risk factors and aggregate measures of post-MI risk such as the Global Registry of Acute Cardiac Events (Grace) risk score.[2 6] Nevertheless, other biological factors present during ACS that are only weakly associated with the extent of underlying coronary disease or severity of the cardiac event may be relevant. Acute inflammation is one such mechanism,[7] but a factor that has received less attention is anaemia.

Anaemia is relatively common in acute cardiac patients, with rates ranging from 12 – 16%.[8 9] An association between anaemia on admission for ACS and adverse cardiac outcomes is now well documented, with significant effects on 30 day and longer-term mortality.[8-10] Anaemia is also associated with fatigue and impaired quality of life in various patient groups,[11 12] and two population studies of men and women aged 50 and over have documented positive relationships between anaemia and depressive symptoms.[13 14] We therefore tested the hypothesis that mild anaemia on admission with an ACS would be associated with greater symptoms of depression three weeks after the ACS, and with the occurrence of major adverse cardiac events over the following 12 months. In these analyses we also examined previous history of depression and negative moods during hospitalization in order to examine the possibility that anaemia is related to longer standing depressed mood.

Methods

Patients

Participants were 223 ACS patients admitted to St. George's Hospital in South London between June 2007 and October 2008 as part of a larger study of psychobiological aspects of ACS.[15] Inclusion criteria were a diagnosis of ACS based on the presence of chest pain plus verification by diagnostic ECG changes, troponin T or troponin I ≥ 99th percentile of the upper reference limit. Patients were required to be aged 18 or over, not to have comorbid conditions that might influence either symptom presentation or mood, and ability to complete interviews and questionnaires in English. Patients with severe anaemia (haematocrit <25%) were eligible for blood transfusion and were excluded from the study.[16] 666 potentially eligible patients were admitted on the days of recruitment. Of these, 125 patients (19%) had been discharged or transferred to a different hospital before they could be recruited into the study, 90 (14%) were too clinically fragile (e.g. critical ischemia, ventricular tachyarrhythmia) to take part, 58 patients (9%) declined to participate, 75 (11%) did not complete measures of depression 3 weeks after hospitalization, 27 (4%) could not speak English, 23 (3%) were in confusional states, 7 (1%) patients died in hospital, and a further 38 (6%) were excluded for other reasons. The study was approved by the Wandsworth Research Ethics Committee, and written consent was obtained.

Clinical measures

Admission ECGs were reviewed for presentation as STEMI or non-STEMI / unstable angina (NSTEMI/UA). Cardiovascular history, clinical factors during admission and management were obtained from clinical notes, and the extent of significant stenosis of coronary arteries from angiography records. Clinical risk was assessed using the Grace risk score.[17] This uses nine indicators (age, history of congestive heart failure, history of MI, systolic blood pressure and heart rate on admission, ST segment depression, initial serum creatinine, elevated cardiac enzymes and in-hospital percutaneous coronary intervention) to define risk of 6-month

post-discharge death applicable to all types of ACS. Creatine kinase was measured in 210 patients. Anaemia on admission was defined according to WHO criteria as <13 g/dL for men and <12 g/dL for women. Major adverse cardiac events over the 12 months following ACS were defined as cardiovascular death, readmission with reinfarction or UA, coronary artery bypass surgery, or angioplasty.

Assessment of depressive symptoms

Patients were interviewed in their own homes an average 21.6 days following admission to hospital, and the BDI was administered.[18] This consists of 21 items rated on a scale of 0-3, so maximum scores can range from 0 - 63. In addition to the standard scoring of the BDI, we also computed the somatic/affective and cognitive/affective subscales identified by De Jonge et al [19]. The somatic/affective subscale comprised 13 items (e.g. crying, irritability, fatigue, pessimism), while the cognitive/affective subscale included 12 items (e.g. sense of failure, guilt, indecisiveness). The Cronbach α was 0.86 for the complete scale, and 0.80 and 0.83 for the somatic/affective and cognitive/affective components respectively. History of depression was ascertained by interview.

Other measures

Patients' emotional state in hospital was assessed with a shortened version of the Profile of Mood States (POMS), as used previously.[20] Six high-loading items were taken from each of the original POMS scales (vigour, tension–anxiety, depression–dejection, confusion, anger-hostility, and fatigue). Current feelings on each item were rated on a 5-point scale ranging from 0 = *not at all* to 4 = *extremely*. Negative mood was indicated by summarizing the five negative scales. SES was measured in terms of educational attainment, and participants were classified on whether they had secondary (high school) and college qualifications or less than this (primary education only). Marital and smoking status were assessed by self-report.

Statistical analysis

Comparisons between patients with and without anaemia were made using t-tests for continuous variables and X^2 tests for categorical variables. The relationship between anaemia on hospital admission and depression 3 weeks later was assessed using analysis of covariance on BDI scores, with age, gender, marital status, smoking, educational attainment, Grace risk score, negative mood in hospital and history of depression as covariates. These factors were included as covariates since they could potentially be related both to anaemia and elevated depressive symptoms, so confound any association between the two. Similar methods were used to analyse the association between anaemia and somatic and cognitive symptoms of depression. Additionally, we computed the proportion of patients with BDI scores ≥ 10, the recognized threshold for possible depression. Logistic regression computed the odds of elevated depression in patients with anaemia compared with no anaemia, and odds ratios with 95% confidence intervals adjusted for the same covariates were calculated. In order to test whether associations depended on the diagnosis of anaemia or persisted across the entire spectrum of haemoglobin concentrations, linear regression of haemoglobin on depression scores was also carried out. The association of anaemia and future cardiac morbidity was investigated by regressing anaemia onto major adverse cardiac events recorded over the 12 months following ACS, controlling for age, gender, marital status, smoking, educational attainment, Grace risk score, maximum creatine kinase and history of depression.

Results

Haemoglobin levels ranged from 8.3 to 19.0 g/dL, and 30 patients (13.5%) were defined as anaemic according to WHO criteria. There were no differences between the anaemia and no anaemia groups in gender distribution, age, ethnicity, educational attainment or marital status (Table 1). There were also no differences in history of depression or in negative mood assessed during hospitalization, though 30% of patients had a history of depression. There was a tendency for Grace risk scores to be higher in patients with anaemia, but the differences was not significant. However, creatine kinase levels were lower among patients

with anaemia ($P = 0.028$). The groups did not differ in extent of coronary disease, history of MI, or in presentation with STEMI or NSTEMI/UA. There were also no differences in preadmission rates of diabetes (15.2%), hypertension (44%) or raised cholesterol (74%). Percutaneous coronary intervention (PCI) was performed on 164 patients, 48 were managed medically, and 11 were referred for coronary artery bypass surgery. Treatment plans did not differ in patients with and without anaemia.

Anaemia and depression following ACS

The mean score on the BDI measured 3 weeks following admission for ACS was 6.70 ± 6.7, and 43 patients (19.3%) had BDI scores ≥ 10. A small proportion (3.3%) of patients were taking antidepressant medication. BDI scores were significantly higher in patients with anaemia (mean 9.35 ± 8.7) than no anaemia (mean 6.28 ± 6.3) after controlling for age, gender ($P = 0.017$), and the difference was maintained after additional adjustment for marital status, educational attainment, smoking, Grace risk score, negative mood in hospital, and history of depression (means 9.73 ± 8.7 and 6.23 ± 6.3 respectively, $P = 0.003$). A higher proportion of patients with anaemia had BDI scores ≥ 10 compared with the no anaemia groups (33.3% and 17.1% respectively), and prescription of antidepressants tended to be higher in patients with anaemia (10.7% versus 2.2%). The odds of a high depression score in patients with anaemia were 4.03 (95% C.I. 1.48 to 11.00, $P = 0.006$) after adjustment for age, gender, marital status, educational attainment, smoking, Grace risk score, negative mood and history of depression (Table 2). Other independent predictors in the model were negative mood in hospital ($P < 0.001$), and a positive history of depression ($P = 0.049$). Using the more stringent criterion of a BDI score ≥ 16, the adjusted odds of a high depression score in patients with anaemia were similar (4.08, 95% C.I. 1.08 to 15.41, $P = 0.038$). Additional statistical control for preadmission disease burden (diabetes, hypertension), type of ACS, or for medication 3 weeks after admission did not change these results.

The association between anaemia and depression following ACS did not depend on the specific criterion for anaemia utilized. When haemoglobin level was regressed onto BDI

score as a continuous variable, the inverse association was significant (B = -0.88, 95% C.I. -1.42 to -0.33, *P* = 0.002), adjusting for the same covariates (see Table 3). We also tested whether the effect was due to a preponderance of somatic symptoms of depression in ACS patients with anaemia, by analysing the somatic/affective and cognitive/affective subscales of the BDI. In both cases, patients with anaemia had elevated scores, although the effect was more robust for somatic/affective (adjusted means 6.79 ± 5.7 and 4.67 ± 4.5 for anaemia and no anaemia groups, *P* = 0.026) than cognitive/affective (adjusted means 4.04 ± 5.7 and 2.48 ± 3.8, *P* = 0.051) symptoms of depression. In case the difference between patients with and without anaemia was due to high scores on the two items on the BDI that relate to sleep disturbance and fatigue (symptoms of anaemia), we repeated the analyses with a reduced BDI that omitted these items. The difference between patients with and without anaemia remained significant (*P* = 0.010) after adjusting for age, gender, marital status, educational attainment, smoking, Grace risk score, negative mood in hospital and history of depression. Similarly, the regression of haemoglobin concentration on the reduced BDI was replicated (B = -0.71, 95% C.I. -1.15 to -0.26, *P* = 0.002).

In a further assessment of whether the elevated BDI ratings of patients with anaemia were due to symptom overlap, patients with and without anaemia were compared on individual BDI items. In the fully adjusted models, ratings on all items except for loss of appetite were higher in patients with anaemia, with differences significant at P = 0.075 or less for 8 items: sense of failure, suicidal thoughts, crying, irritability, social withdrawal, body image change, sleep problems, and fatigue.

Anaemia and major adverse cardiac events

Thirty four (15.2%) patients experienced a major adverse cardiac event in the 12 months following ACS. A higher proportion of adverse events occurred among patients with anaemia than no anaemia on admission (26.7% versus 13.5%). The odds of major adverse cardiac events among patients with anaemia were 3.26 (C.I. 1.19 to 8.91, *P* = 0.021) after controlling for age, gender, marital status, educational attainment, smoking, Grace risk score, negative

mood in hospital, history of depression, and creatine kinase levels in hospital. The study was not powered to test the association between depressed mood following ACS and adverse cardiac outcomes.

Discussion

This study involved a relatively small sample of patients, so conclusions must be tentative. Nevertheless, the analyses indicated that mild to moderate anaemia measured on admission to hospital with an ACS predicted depression symptoms 3 weeks later. The mean scores on the BDI were 48% higher in anaemic patients, and the odds of a BDI score above the threshold for moderate/severe depression (≥ 10) were elevated threefold. These associations were independent of sociodemographic factors, clinical cardiological indices, patients' mood in hospital and history of depression. Anaemia in turn predicted major adverse coronary events over the following 12 months, again independently of sociodemographic and other clinical characteristics.

The prevalence of anaemia was 13.5%, which is comparable with that reported in other studies of older adults. A recent systematic review concluded that the prevalence of anaemia was 12% in community-based studies,[21] suggesting that the levels in this sample of cardiac patients was not notably elevated. Other studies of acute cardiac patients have described rates of between 12 and 17%.[8 10 16] For example, around 13% of the 2,082 patients with acute MI in the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial were anaemic.[9] The mean level of haemoglobin (11.67 g/dL) indicates that anaemia was typically mild, and none of the patients had haematocrit levels <25%, the currently accepted threshold for blood transfusion.[16] Several different criteria for anaemia have been proposed, and slightly higher haemoglobin thresholds were recommended by Beutler and Waalen.[22] Our sensitivity analysis indicated that the relationship with depression following ACS did not depend on the particular threshold selected, since effects were continuous across the haemoglobin distribution.

We tested four sets of factors that could theoretically contribute to the association between anaemia and depression following ACS. First, both anaemia and depression are associated with lower SES and ethnic minority status,[23] so sociodemographic factors could be relevant. We found no differences in the occurrence of anaemia in relation to ethnic minority status, and controlled statistically for educational attainment as a marker of SES. Second, poor clinical cardiological status is associated with anaemia,[10] and might also predict depression following ACS. Grace risk scores were included to take cardiological status into account, since this risk index includes potentially relevant factors such as presence of heart failure and previous MI. Additional analyses showed that the relationship between anaemia and depression was also independent of other clinical indicators such as type of ACS and pre-admission illness burden. Third, it is possible that anaemia is associated with depressed mood irrespective of the occurrence of ACS,[13 14] and that the relationship with depression following ACS reflects more persistent effects. The impact of pre-existing depressed mood cannot be completely ruled out, since the BDI was not administered on admission and depression before ACS was measured retrospectively. We did not ask patients to complete the BDI when they were in hospital, since we thought that patients might find it difficult to recollect their symptoms before hospitalisation and rate them accurately. However, we reasoned that if prevailing depression was responsible for the association between anaemia and later depressive symptoms, differences between patients with and without anaemia would have been apparent in history of depression, or in negative moods assessed in hospital. This was not the case, suggesting that anaemia has a specific impact on depressive symptoms that evolve after an acute cardiac event.

A fourth possibility is that the association was due to symptom overlap, since the BDI includes nonspecific symptoms that may be indications of anaemia. For example, anaemia has previously been related to fatigue in various illnesses including cancer, heart failure and chronic lung disease.[11 12 24] We tested this notion in a several ways. When we constructed a reduced version of the BDI that excluded items related to fatigue and sleep disturbance, differences between patients with and without anaemia persisted. We also conjectured that

anaemia might be associated more strongly with somatic symptoms of depression such as fatigue, loss of appetite and insomnia than with cognitive/affective symptoms such as guilt and sense of failure. However, both components of the BDI identified by de Jonge et al [19] were elevated in the patients with anaemia. Finally, inspection of individual items from the BDI indicated that anaemic and non-anaemic patients showed differential responses on a number of cognitive symptoms such as sense of failure, social withdrawal and irritability as well as more somatic items such as tiredness and sleep problems. In combination, these tests suggest that symptom overlap is unlikely to be the explanation of the findings.

Anaemia on hospitalization was a predictor of major adverse cardiac events over the subsequent 12 month period, replicating findings from larger studies.[8-10] The study was not powered to test the impact of depression following ACS on cardiac mortality and morbidity. Previous reviews of this topic have criticized the publication of equivocal findings from underpowered studies.[25] We were not therefore able to investigate the extent to which the presence of anaemia in some patients with depression following ACS contributes to the association between depression and future cardiac morbidity.

It has been estimated that around one third of anaemia in older people is due to blood loss or nutritional deficiencies, one third to chronic diseases involving inflammation, while the remaining third is unexplained.[26] The contribution of nutritional deficiencies in this sample is unknown, and measures of iron-restricted haematopoiesis were not carried out. Inflammatory processes may be relevant, since acute inflammation during ACS has been postulated to be a cause of subsequent depressed mood.[7] Possible causes of unexplained anaemia that are potentially relevant to these findings include sarcopenia, more subtle dysregulation of the immune system, and the impact of some medications.[27]

A number of processes may be involved in mediating the effects of anaemia on cardiovascular risk. The reduction in haemoglobin concentration can adversely affect oxygen supply to the myocardium, promoting arrhythmia and increasing infarct size.[26] At the same time, anaemia leads to increased myocardial oxygen demand though stimulating raised cardiac output,[28] and may have an effect on nitric oxide bioavailability.[29] The impact of

anaemia on future depressed mood may be due in part to reduced physical performance and strength which will impair physical activity during recovery from ACS.[30] Decreased physical activity may in turn enhance depressed mood. Dyspnoea is also characteristic of anaemia, and could reduce physical and social activity, promoting depressed mood following ACS.

This study has a number of limitations. As noted earlier, the sample size was insufficient to investigate the impact of depressive symptoms following ACS on subsequent adverse cardiac outcomes, so the importance of anaemia in mediating such links was not tested. We had no measure of depressive symptoms in the days preceding the index cardiac event, so cannot definitively rule out an association between anaemia and pre-existing depression. The somatic/affective and cognitive/affective subscales of the BDI used in this study were based on previous work,[19] but were empirically derived and do not precisely separate somatic from affective components. Additionally, although our conclusion is that anaemia may have a specific effect on depressive symptoms that evolve after an acute cardiac event, we cannot rule out the possibility that its impact generalises to the aftermath of other stressors.

Studies relating depression following ACS with subsequent cardiac morbidity and mortality have assessed a number of indices of cardiac status and other physical health issues using the Grace index, Killip class, and measures of comorbidity such as the Charlson index.[6 19] But to our knowledge, the relationship between anaemia and depression following ACS has not been investigated in previous research. The present findings indicate that attention needs to be paid in larger studies in the future to anaemia as a possible contributor to depression following acute cardiac events, and as a determinant of future cardiac morbidity. Studies evaluating the effects of anaemia management on depression following ACS will help delineate the role of this pathway more precisely.

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Competing interests: None.

Contributors: AS and J-C K conceived the research, AS, AW, GCM and J-C K carried out research, data analysis and drafted the paper. All authors approved the final manuscript.

Data sharing statement: There are no additional data available.

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Table 1 Details of the study participants
Mean ± standard deviation and N (%)

	Anaemia (n = 30)	No Anaemia (n = 193)	*P* difference
Men Women	22 (73.3%) 8 (26.7%)	166 (86.0%) 27 (14.0%)	0.10
Age (yrs)	61.70 ± 11.4	59.28 ± 11.7	0.29
Ethnicity (White)	27 (90.0%)	159 (82.4%)	0.43
Married	21 (70.0%)	139 (72.0)	0.83
Education (secondary and above)	15 (50.0%)	85 (44.3%)	0.45
Smoking	10 (33.3%)	75 (38.9%)	0.69
History of depression	11 (36.7%)	56 (29.0%)	0.40
Negative mood in hospital	3.18 ± 2.6	3.76 ± 2.8	0.69
Grace score	97.67 ± 28.5	90.54 ± 26.0	0.17
Vessels with significant stenosis	1.97 ± 0.55	1.83 ± 0.56	0.43
ACS type (STEMI)	25 (83.3%)	171 (88.6%)	0.88
Previous MI	6 (20.0%)	21 (10.9%)	0.22
CK level IU/L[1]	1209.9 ± 960	1806.4 ± 1639	0.028
Haemoglobin g/dL	11.67 ± 1.15	14.88 ± 1.22	0.001
Haematocrit %	35.64 ± 3.9	42.61 ± 3.8	0.001

[1] n = 210. Analysed following log transformation

Table 2 Predictors of raised depressive symptom levels three weeks after ACS

Predictor	Adjusted odds ratio	95% C.I.	*P*
Gender (male)[1]	0.65	0.21 – 1.97	0.44
Age	0.94	0.88 – 1.01	0.055
Education (lowest)[1]	0.79	0.53 – 1.18	0.25
Marital status (married)[1]	1.31	0.56 – 3.04	0.53
Smoking status (non-smoker)[1]	1.09	0.48 – 2.49	0.84
Grace score	1.01	0.99 – 1.04	0.39
Negative mood in hospital	1.33	1.17 – 1.52	0.001
History of depression (negative)[1]	2.23	1.01 – 4.97	0.049
Anaemia (no anaemia)[1]	4.03	1.48 – 11.00	0.006

[1] Reference category

Table 3 Regression on depression symptoms three weeks after ACS

Predictor	Regression coefficient B	95% C.I.	*P*
Gender (male)[1]	-0.44	-2.98 – 2.11	0.74
Age	-0.13	-0.26 – 0.00	0.05
Education (lowest)[1]	-0.42	01.22 – 0.39	0.31
Marital status (married)[1]	1.31	-0.53 – 3.15	0.16
Smoking status (non-smoker)[1]	-0.41	-1.78 – 1.70	0.96
Grace score	0.02	-0.04 – 0.08	0.68
Negative mood in hospital	0.99	0.70 – 1.30	0.001
History of depression (negative)[1]	1.94	0.15 – 3.74	0.034
Haemoglobin	-0.88	-1.42 – -0.33	0.002

[1] Reference category

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Title page
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	2
Objectives	3	State specific objectives, including any prespecified hypotheses	2
Methods			
Study design	4	Present key elements of study design early in the paper	3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	3
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4,5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4,5
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	3
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4,5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	4,5
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	5,6
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	3,
		(b) Give reasons for non-participation at each stage	3,5
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	5
		(b) Indicate number of participants with missing data for each variable of interest	5
		(c) Summarise follow-up time (eg, average and total amount)	3
Outcome data	15*	Report numbers of outcome events or summary measures over time	5-7
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	6,7
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	6
Discussion			
Key results	18	Summarise key results with reference to study objectives	7
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8-10
Generalisability	21	Discuss the generalisability (external validity) of the study results	8,10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	10

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.