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Van Beek, Maria H. C. T.; Zuidersma, Marij; Lappenschaar, Martijn; Pop, Gheorghe; Roest, A. M.; Van Balkom, Anton J. L. M.; Speckens, Anne E. M.; Oude Voshaar, Richard C.

Published in:
The British Journal of Psychiatry

DOI:
[10.1192/bjp.bp.115.174870](https://doi.org/10.1192/bjp.bp.115.174870)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Final author's version (accepted by publisher, after peer review)

Publication date:
2016

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Van Beek, M. H. C. T., Zuidersma, M., Lappenschaar, M., Pop, G., Roest, A. M., Van Balkom, A. J. L. M., ... Oude Voshaar, R. C. (2016). Prognostic association of cardiac anxiety with new cardiac events and mortality following myocardial infarction. *The British Journal of Psychiatry*, 209(5), 402-408. DOI: 10.1192/bjp.bp.115.174870

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Prognostic association of anxiety following myocardial infarction with mortality and new cardiac events: a meta-analysis.

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Abbreviated running title: Anxiety and cardiac prognosis.

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Number of words: 5157

Number of tables and figures: 5

Funding/Support

Dr. de Jonge is supported by a VIDI grant from the Dutch Medical Research Council (grant 016.086.397).

Dr. Denollet is supported by a VICI grant from the Dutch Organization for Scientific Research (grant 453.04.004).

There are no conflicts of interest.

**Prognostic association of anxiety following myocardial infarction with mortality
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Abstract

Objective: To assess the association of anxiety following myocardial infarction (MI) with cardiac prognosis. **Methods:** A meta-analysis of references derived from MEDLINE, EMBASE and PSYCINFO (1975- March 2009) was performed without language restrictions. Endpoint was cardiac outcome defined as all-cause mortality, cardiac mortality and cardiac events. The authors selected prospective studies with at least 6 months follow-up and anxiety had to be assessed within 3 months after MI with reliable and valid instruments. **Results:** Twelve papers met selection criteria. These studies described follow-up (on average 2.6 years) of 5750 MI patients. Anxious patients were at risk of adverse events (odds ratio (OR) fixed: 1.36; 95% confidence interval (CI): 1.18-1.56; $p<.001$). Anxiety was also specifically associated with all-cause mortality (OR fixed: 1.47; 95% CI: 1.02-2.13; $p=.04$), cardiac mortality (OR fixed: 1.23; 95% CI: 1.03-1.47; $p=.02$) and new cardiac events (OR fixed: 1.71; 95% CI: 1.31-2.23; $p<.001$).

Conclusions: Post-MI anxiety is associated with a 36% increased risk of adverse cardiac outcomes in bivariate analyses. Since the existing literature is quite small and contains several limitations, more research is needed to the association of anxiety and prognosis in MI patients and to assess the extent to which this association is independent of clinical variables, such as disease severity, and other psychological variables, especially depression.

Key words: Anxiety, myocardial infarction, meta-analysis, prognosis, mortality.

BMI=body mass index; CABG=coronary artery bypass graft; CHD=coronary heart disease; CI=confidence interval; CBAHF=Cognitive Behavioral Assessment Hospital

Form; ENRICHD=Enhancing Recovery in Coronary Heart Disease Patients;
FEM=fixed effects model; GAD=generalized anxiety disorder; HADS=Hospital
Anxiety and Depression Scale; HR=Hazard ratio; LVEF=left ventricular ejection
fraction; MI=myocardial infarction; MIND-IT=Myocardial Infarction and Depression
Intervention Trial; NA=not available; OR=odds ratio; REM=random effects model;
STAI=State Trait Anxiety Inventory; STPI=State Trait Personality Inventory;
UA=unstable angina.

Introduction

Cardiovascular disease, and in particular acute myocardial infarction (MI), is one of the leading causes of morbidity and mortality in industrialized countries [1,2]. Several meta-analyses indicate depression as a risk factor for the development of coronary heart disease (CHD) in the general population [3,4] and as a prognostic risk factor in post-MI patients [5]. In contrast, anxiety is a negative emotion on which much less research has focused. Although anxiety is often comorbid with depression, it is a distinct emotion [6]. Studies in healthy populations have demonstrated that anxiety is significantly related to the development of CHD [7,8]. In addition, anxiety is very common in MI patients, with an in-hospital incidence of 30-40% [9-11]. Anxiety has been found to be predictive of disability, increased physical symptoms, worse functional status and worse quality of life in CHD patients [12-14].

The role of anxiety regarding cardiac prognosis is unclear. Several studies in CHD patients have shown that anxiety is related to adverse cardiac outcomes, defined as fatal and nonfatal cardiac events and in-hospital ischemic and arrhythmic complications [15-19]. However, others did not find a relationship between anxiety and cardiac and all-cause mortality [20-23], or even found a protective impact of anxiety on all-cause death, recurrent MI and revascularization [24,25]. Moreover, one study showed that when entering both anxiety and depression in a single prediction model, the effects of depression were explained away by those of anxiety [26], but this finding was not confirmed by other studies [27].

Therefore, the present paper focuses on anxiety as a predictor of medical prognosis after MI. To our knowledge, this is the first meta-analysis on the prognostic association of anxiety in heart disease patients with medical outcome. Objective of

this study was to investigate the association of anxiety after MI with all-cause death, cardiac death and cardiac events and to assess this association in the light of available covariates.

Methods

Aim

To identify all studies that were available by March 2009, comparing cardiac prognosis of anxious and non-anxious MI patients. Systematic identification, appraisal, synthesis, statistical aggregation and reporting of results resembled known guidelines [28,29].

Literature search

Regarding literature search, the electronic databases MEDLINE, EMBASE and PSYCINFO (1975- March 2009) were searched using the following terms: “myocardial infarction” and “anxiety”, without language restrictions. We included both published and unpublished data (e.g. doctoral dissertations). In addition, reference lists of included studies and review articles were hand searched to identify additional studies meeting selection criteria.

Selection

In the resulting pool of studies, two independent raters (A.R. and E.M.) identified studies that met the following inclusion criteria:

1. Studies should contain patients who were hospitalized for acute MI.

2. Anxiety (non-phobic) had to be measured within 3 months of hospitalization for acute MI using reliable and validated instruments to assess anxiety (either self-report or interview-based).

3. Studies had to be prospective in nature with at least 6 months follow-up and endpoints had to contain: all cause mortality, cardiac mortality, and/or cardiac events (e.g. hospitalization for unstable angina pectoris (UA), revascularization) in combination with mortality and/or recurrent MI, using a reliable and valid assessment strategy.

4. Studies had to present original data (e.g. reviews and editorials were excluded).

During the selection procedure, in case of disagreement between the two independent raters, the four investigators discussed the difference of opinion until consensus was reached. Regarding multiple reports on the same dataset, only one paper was included based on endpoint and follow-up period, preferring hard medical endpoints (e.g. mortality) and longer follow-up periods. Two studies presented an analysis on a combined sample of MI and UA patients and we also included these studies [18,30]. Data derived from patients randomized to placebo from a blind placebo-controlled medication trial in which anxiety was measured as part of an ancillary study, was included [31]. If necessary, the coordinators of the eligible studies were asked for details.

The following aspects of methodological quality were evaluated: sample size, study population (e.g. did the researchers include specific in-/exclusion criteria such as gender or disease severity), percentage lost to follow-up, follow-up duration and multivariable adjustment. We did not weigh the contribution of each study to the meta-analysis on the basis of quality scoring for there are no validated measures of quality and the use of subjective rating scales may lead to bias [32].

Endpoint

The endpoint was all-cause mortality, cardiac mortality and/or cardiac events.

Quantitative data synthesis

Data from all studies were pooled using the program Comprehensive Meta-Analysis version 2. To pool data across studies, we converted the time-related data into simple 2 x 2 tables. Thus, for all studies, irrespective of the presented effect measure (i.e. odds ratio (OR) or hazard ratio (HR)), data were converted into (unadjusted) dichotomous outcomes. Subsequently, ORs and 95% confidence intervals (CI) were calculated. The fixed and the random effect method (REM) were used to generate summary estimates of ORs. The appropriateness to combine results was tested with the I^2 test, which shows the proportion of total variance explained by heterogeneity. If I^2 was found to be less than 25% it was considered as low [33] and variation in the results of different studies thought to be due to chance alone [29]. In that case we based our main conclusions on the OR reported by the fixed effect method (FEM). We provided both estimates in the results section for the purpose of completeness.

In two studies [11,27], more than one measure of anxiety was included. In these cases the most representative measure of anxiety (i.e. State Trait Anxiety Inventory (STAI)), as compared to the anxiety measures in other included studies, was chosen.

In three studies [11,31,34], anxiety symptoms were presented as a continuous variable. In these cases, the number of patients above and below the established cut-off point of the anxiety scale was estimated using the reported mean anxiety score and standard deviation based on the assumption of normal distribution. For studies using the STAI [11,31] a cut-off score ≥ 44 was chosen. For the study of Mayou et al. [23],

the OR was calculated based on earlier information given by the author to one of the authors of the current study (P.d.J.). In two studies [9,27], the number of anxious and non-anxious patients in the event versus non-event group was calculated from the given OR or HR.

The study of Pedersen et al. [35] was excluded based on the questionnaire used, namely the Trauma Symptom Checklist, which intends to measure traumas. Moreover, one study that measured anxiety before the MI was excluded [36].

If study outcomes were heterogeneous based on the I^2 test, the possible effects of follow-up duration, year of data collection, study population (MI versus MI and UA patients) and trait versus state anxiety would be studied. Differences in ORs between specified subgroups were assessed by comparing the pooled ORs using chi-squared analysis, comparing logarithms of the ORs. In order to evaluate the presence of publication bias, a funnel plot was constructed by plotting the effect measure against the inverse of its standard error.

Additional information by personal communication

Authors of four included studies were contacted for further information on study characteristics. Michael et al. confirmed that the reported endpoint consisted of ischemic cardiac events as verified by a cardiologist [30]. The study of Pfiffner and Hoffmann [37] was excluded because reported survival data was imprecise and we were not able to reproduce the reported OR. The article of Legault et al. [38] was excluded because reported data was limited and we could not compute an OR. We used the age- and gender-adjusted HR given in the paper of Frasure-Smith and Lespérance [27] to estimate the numbers of anxious and non-anxious patients in the event and non-event group.

Results

A flow diagram of the literature search is shown in Figure 1. The agreement rates (Cohen's kappa) for the 2 steps in the selection procedure were 0.72 and 0.93 respectively, indicating good to very good consistency of judgment by raters [39]. Twelve studies met selection criteria and study characteristics are shown in table 1. Fifteen analyses reported on the pre-specified endpoint (4 on all-cause mortality, 4 on cardiac mortality and 7 on cardiac events). These studies described follow-up (on average 2.6 years) of 5750 MI patients. The mean age at time of the index MI ranged from 54 to 63 years and 82.5% of patients was male. The proportion of MI patients with anxiety symptoms at baseline ranged from 13.4% to 59.5%. Five analyses (2 on cardiac mortality and 3 on cardiac events) reported a significant association between anxiety and prognosis in bivariate analysis. In 2 studies the association was no longer significant when controlling for demographic (e.g. age, gender) and clinical (e.g. disease severity) variables. Three analyses, 2 reporting on the association between anxiety and cardiac mortality or recurrent MI and one reporting on cardiac mortality, remained significant in multivariable analysis (Table 2).

Mortality and cardiac events

Twelve studies reported on the combined endpoint. Cardiac mortality was chosen as endpoint in case the study reported on more than one endpoint. The pooled OR for all-cause and cardiac mortality and cardiac events in 1649 anxious compared with 4101 non-anxious MI patients was 1.36 (95% CI: 1.18-1.56; $p < .001$) in the FEM (Figure 2). No heterogeneity was observed in the model ($I^2 = 0.00\%$) and therefore no difference in the OR given by the FEM and REM.

The pooled OR for all-cause mortality in 925 anxious compared with 2241 non-anxious MI patients was 1.47 (95% CI: 1.02-2.13; $p=.04$) in the FEM and 1.53 (95% CI: 0.95-2.46; $p=.08$) in the REM. For cardiac mortality, the pooled OR comparing 265 anxious with 1072 non-anxious MI patients was 1.23 (95% CI: 1.03-1.47; $p=.02$) in the FEM and 1.33 (95% CI: 0.89-1.98; $p=.16$) in the REM.

Although the included events varied across studies, all studies reporting on cardiac events included cardiac death and recurrent MI as endpoint. The pooled OR for cardiac events in 579 anxious compared with 1075 non-anxious MI patients was 1.71 (95% CI: 1.31-2.23; $p<.001$) in the FEM and REM.

The influence of anxiety on prognosis varied between endpoints. The impact of anxiety was significantly larger for cardiac events than for cardiac mortality ($p=.04$). The impact of anxiety on cardiac events was not significantly different from the impact on all-cause mortality ($p=.52$).

Because the 12 studies reporting on the combined endpoint did not show significant heterogeneity, no further secondary analyses were conducted.

A funnel plot of selected studies on the combined outcome suggests the presence of publication bias (Figure 4). Further inspection of the studies divided by endpoint revealed a possible bias for all-cause and cardiac mortality, but not for cardiac events (not shown).

Discussion

This is the first meta-analysis focusing on the association of anxiety with prognosis in heart disease patients. The results show a consistent association between anxiety and impaired prognosis after MI, with a 36% increased risk. This increased risk applies to both mortality (cardiac and all-cause) and cardiac events. Although the association between anxiety and cardiac events was significantly larger compared with that of cardiac death, these results should be interpreted with caution because the pooled OR for cardiac death was based on only 4 studies. Overall, these findings support the conclusion that anxiety is associated with adverse medical outcomes after MI.

In this meta-analysis, only one study reported on anxiety disorder, namely generalized anxiety disorder (GAD) [20]. In bivariate analysis, both self-reported symptoms and GAD were predictors of cardiac events. In multivariable analysis, only the association between GAD and prognosis remained significant. To date there is little information about the association between different anxiety disorders and cardiac outcome. Clearly, further research on the relationship between anxiety disorders and prognosis is warranted.

There are several potential mechanisms that may help to explain the adverse association between anxiety and cardiac prognosis. Anxiety is potentially related to several pathophysiological processes in MI patients, including arrhythmic mechanisms [42] and dysfunction of the autonomic nervous system, such as reduced baroreflex cardiac control [43] and reduced heart rate variability [44]. Theoretically, it

may be that anxiety has a more influential role in electrical instability rather than in atherosclerotic or vascular disease conditions. In two studies cardiac arrest was included as endpoint [18,31]. One study found a significant association between anxiety and cardiac events (including survived cardiac arrest) [18] and the other found no association between anxiety and all-cause mortality or cardiac arrest in patients at risk of sudden death [31]. However, both studies did not assess the association between anxiety and cardiac arrest specifically. More research is needed to the association of anxiety with arrhythmic mechanisms.

In addition, a behavioral pathway of depression influencing prognosis is unhealthy behavior, like less compliance, smoking, unhealthy diet and inactivity [5]. This may also hold for anxious patients. Reversely, it is possible that anxious patients seek more help from their doctors and try to improve their medical status [11]. However, Benninghoven et al. found that patients with higher anxiety levels showed neither better medication compliance nor had more contact with their cardiologists [11]. Given that some studies have found a protective effect of anxiety on outcome [25] it might be that it is anxiety in combination with nonprotective patient behavior that leads to worse prognosis, possibly due to an avoidant coping strategy [11] or social inhibition [45]. Further research regarding the behavioral and pathophysiological mechanisms responsible for the relationship between anxiety and prognosis is warranted.

The prognostic association between anxiety and prognosis after MI seems smaller than that of depression [5], but larger as compared to the effects of anger and hostility.

A recent meta-analysis showed that anger and hostility were associated with a 24% increased risk of poor prognosis in CHD patients [46]. Overall, these results show that various psychological factors, of which depression is probably the most important one, are consistently associated with adverse outcome in heart disease patients.

It is important to assess the extent to which the association between anxiety and prognosis is independent of other clinical and psychological variables, such as depression. Studies have found rather mixed results, with some studies retaining depression [27] and others anxiety [15,26]. In addition, anxiety and depression have a moderate to strong correlation [47], yet anxiety and depression also have distinctive features [47]. It is possible that anxiety and depression are both part of a larger and more stable factor influencing prognosis in heart disease patients, like negative affectivity [47] or Type D personality (a combination of negative affectivity and social inhibition) [45].

Somatic symptoms of depression such as fatigue are known to be related to disease severity [48]. In a meta-analysis on the association between depression and CHD prognosis, adjustment for left ventricular function reduced the relative risk with almost 50% [49]. On the contrary, disease severity adjusted ORs of the association between anxiety and medical prognosis after MI are only slightly or not attenuated [18,26,27]. This could indicate that the association between anxiety and medical outcome is less confounded by disease severity as compared to depression.

Results of this meta-analysis indicate that treatment of distressed MI patients should not focus on depression exclusively. Large intervention trials have failed to improve medical prognosis in depressed MI patients [50-51], perhaps because related anxiety

was not treated [47]. There is a need for more behavioral medicine programs performing clinical outcomes research [52], in which various risk factors (e.g. depression, anxiety and hostility/anger) should be targeted.

The results need to be considered in light of the study limitations. One of the most important limitations in conducting a meta-analysis is the inevitability of combining data from studies that are not equally designed. Patient samples were heterogeneous regarding gender and disease severity, and follow-up duration differed substantially across studies. However, the results of the included studies were quite homogeneous and it therefore seems that the finding of a significant prospective association between anxiety and CHD prognosis is robust.

Anxiety is a very heterogeneous emotion and individuals may experience different kinds of anxiety symptoms. In order to limit heterogeneity we excluded studies on phobia and post traumatic stress disorder. Still, it remains unclear which aspects of anxiety contribute to cardiac outcomes. Further, 6 studies measured anxiety using the STAI. Research has shown that the STAI does not clearly differentiate anxiety from depression [53]. There is a need for more research to the construct of anxiety, its core features and development of new instruments. An additional limitation is the lack of temporal information about onset of anxiety. We do not know if included patients became anxious as a result of their MI or were already anxious prior to developing CHD. Although studies suggest an association between anxiety and heart disease in initially healthy persons as well [8], more research should focus on this topic and the possible differences between these groups. Another limitation is that two studies had to be excluded because of insufficient data. Of these studies, one reported a significant [37] and one reported a non-significant [38] effect of anxiety on outcome.

Another limitation concerns the proneness of meta-analyses to publication bias. We tried to minimize important sources of publication bias by including both non-English and nonpublished work in our literature search. We found a possible publication bias for mortality suggesting that the association between anxiety and mortality might be smaller than reported here. However, for the largest association found in this meta-analysis, namely between anxiety and cardiac events, we did not find indications of publication bias.

Since the existing literature is quite small and contains several limitations, there is a need for further research to the association of anxiety and cardiac prognosis in MI patients. In the future, when more studies are published on this subject, this meta-analysis should be brought up to date.

In summary, post-MI anxiety is consistently related to adverse cardiac events in bivariate analyses. Findings are homogeneous and reliable, although more research is needed to assess the extent to which this association is independent of other psychological and clinical variables. The association between anxiety and outcome seems less strong than it is for depression, however, it might be less confounded by disease severity. The results from this study indicate the need for future research directed to the association between anxiety and prognosis after MI, to the identification of the underlying processes by which anxiety contributes to cardiac prognosis and to the testing of interventions to alleviate the associated risk.

Acknowledgments

The authors thank Drs. Moser, Michael, Frasure-Smith and Legault for supplying additional information on their study characteristics, and Pamela Schendelaar, Nick Nieborg and Madelein van der Stouwe for their assistance in the literature search.

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Table 1. Overview of selected studies investigating the association of anxiety with prognosis in post-MI patients

Study	Patients	n	Mean age (yr)	Male (%)	Instrument	Anxiety assessment (days post MI)	Anxiety (%)	Lost to FU (%)	Endpoint(s)	FU (yr)	State v. trait	Start data collection	Statistically significant association
Mayou (23)	MI	347	63	73	HADS-A	≤3	18.5	0	All-cause mortality	1.5	State	1994	No
Carinci (9)	MI	2449	NA	88	CBAHF Anxiety subscale	≤3	30.1	0	All-cause mortality	0.5	State	1989	No
Denollet (40)	MI	105	54	100	STAI	21-42	49.5	0	Cardiac + all-cause mortality	3.8	Trait	1986	No
Lane (22)	MI	288	63	75	STAI	2-15	26.1	0	Cardiac + all-cause mortality	3.0	State	1997	No
Frasure-Smith (27)	MI	896	59	74	STAI	During hospital admission	13.4	2.9	Cardiac mortality	5.0	State	1991	Yes
Denollet (41)	MI ¹	87	55	93	STAI	≤60	31.0	0	Cardiac mortality + cardiac events*	7.9	State	1985	Yes
Ahern (31)	MI ²	353	59	83	STAI	6 to 60	22.1	0	All-cause mortality/cardiac arrest	1.0	State	1983	No
Strik (26)	First MI	169	58	100	SCL-90 Anxiety subscale	30	59.5	0	Cardiac events*	3.4	State	1994	Yes

Benninghoven (11)	MI	76	NA	80	STAI	<7	30.3	0	Cardiac events**	2.6	State	1999	No
Michael (30)	First MI/UA	65	60	46	HADS-A	During hospital admission	26.2	0	Cardiac ischemic events	0.5	State	NA	No
Frasure-Smith (18)	MI/UA	804	60	81	HADS-A	2 months after discharge	41.4	<1.0	Cardiac events***	2.0	State	1999	Yes
Sydeman (34)	MI	111	62	60	STPI Anxiety subscale	During hospital admission	19.8	9.0	Cardiac events****	0.5	State	1996	No

MI=myocardial infarction; HADS-A=Hospital Anxiety and Depression Scale –Anxiety subscale; NA=not available; UA=unstable angina; CBAHF=Cognitive Behavioral Assessment Hospital Form; STAI=State Trait Anxiety Inventory; SCL=Symptom Check List; STPI=State Trait Personality Inventory.

¹ Global left ventricular ejection fraction (LVEF) ≤50%

² Patients at risk for sudden death (≥10 ventricular premature complexes/hour or ≥5 episodes of nonsustained ventricular tachycardia)

* Cardiac death or recurrent MI

** Cardiac death, MI or revascularization

*** Cardiac death, MI, survived cardiac arrest, nonelective revascularization

**** Cardiac mortality, MI or unstable angina

Table 2. Overview of positive studies in which the influence of anxiety on endpoints was adjusted for other variables

Study	Endpoint(s)	Bivariate OR (95% CI)	Multivariable OR (95% CI)	Adjustment
Frasure-Smith (27)	Cardiac mortality	1.21 (1.01-1.46)	1.14 (0.93-1.38)	Age, gender, educational level, daily smoking, previous MI, thrombolytic treatment at index admission, Q-wave MI, Killip class >1, revascularization at index admission, LVEF, antidiabetic medication and β -blockers.
Denollet (41)	Cardiac mortality	3.70 (1.10-12.40)	4.66 (1.20-18.17)*#	LVEF \leq 30%
Denollet (41)	Cardiac events	3.40 (1.20-9.60)	3.69 (1.27-10.70)*#	LVEF \leq 30%
Strik (26)	Cardiac events	2.76 (1.09-7.01)**	2.79 (1.11-7.03)#	Age, LVEF \leq 50%, depression, hostility, use of antidepressants.
Frasure-Smith (18)	Cardiac events	1.67 (1.18-2.37)	1.45 (0.95-2.22)	Age, gender, education, current daily smoker, previous MI, CABG or angioplasty, LVEF <45%, CABG during index hospitalization, \geq 1 coronary vessel with \geq 50% blockage after index revascularization, BMI, fasting triglyceride level, diastolic blood pressure, calcium channel blockers, angiotensin-converting enzyme inhibitors, and statins.

LVEF=left ventricular ejection fraction; MI=myocardial infarction; CABG=coronary artery bypass graft; BMI=body mass index,

* OR provided by Denollet

** Based on own calculations

OR remained significant in multivariable analysis

Figure 1. Flow-chart of literature search

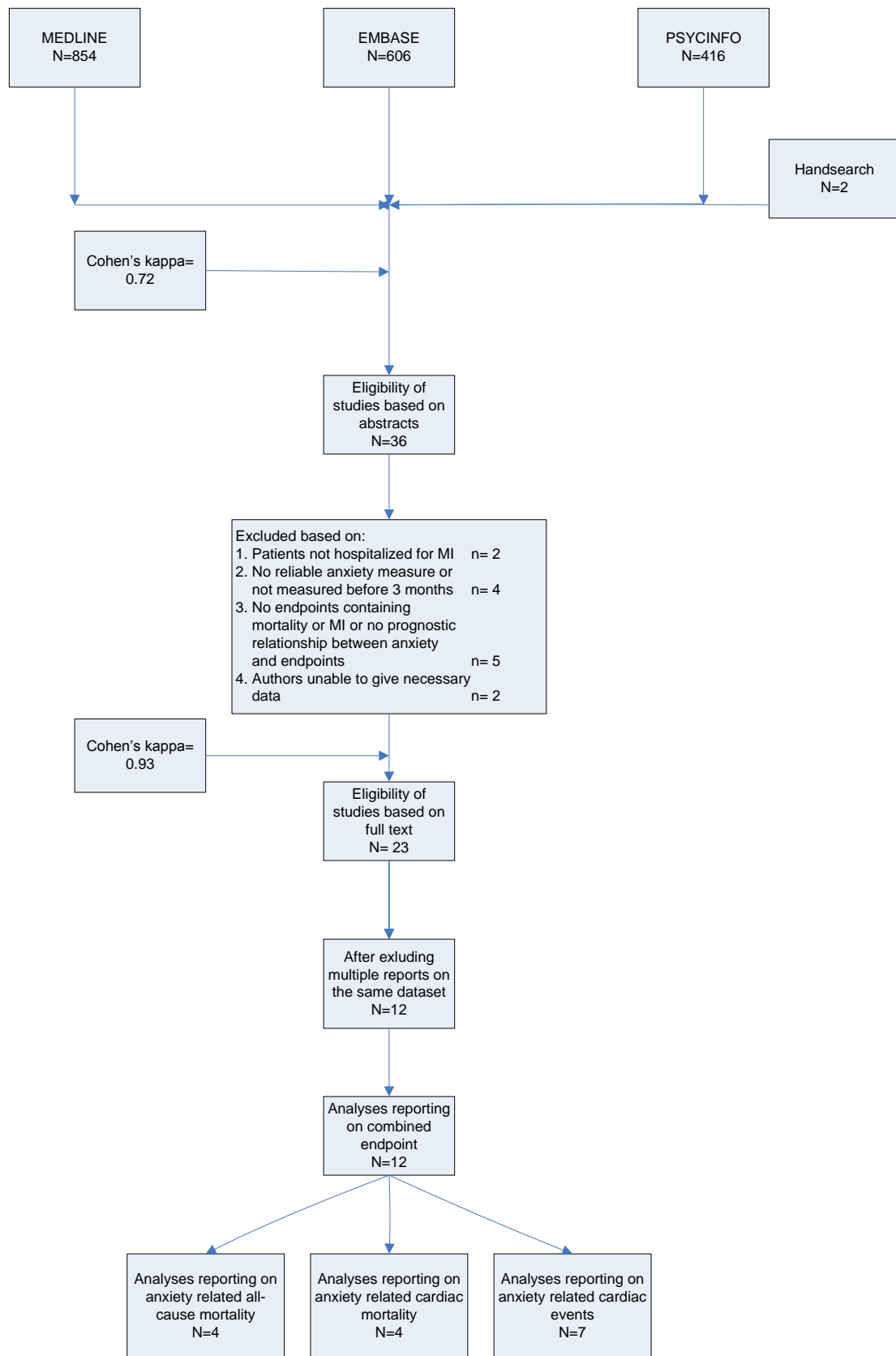


Figure 2. Association between anxiety and adverse outcomes

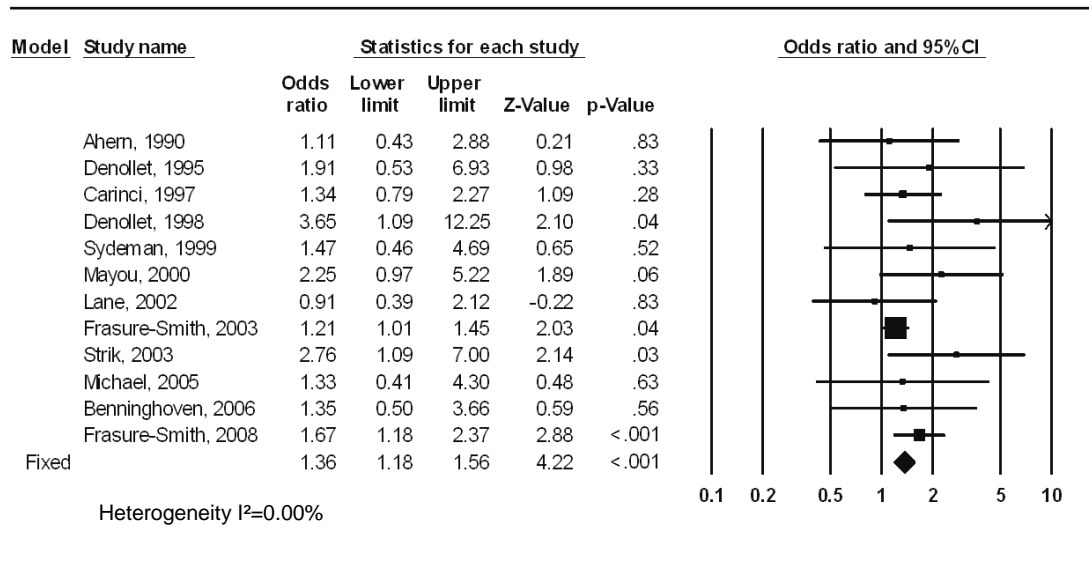


Figure 3. Funnel plot of selected studies

