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Association between anxiety and mortality in patients with coronary artery disease: a meta-analysis

Christopher M. Celano, M.D.[1,2], **Rachel A. Millstein, Ph.D.**[1,2], **C. Andres Bedoya, Ph.D.**[1,2], **Brian C. Healy, Ph.D.**[2,3], **Annelieke Roest, Ph.D.**[4], and **Jeff C. Huffman, M.D.**[1,3]

[1]Department of Psychiatry, Massachusetts General Hospital, Boston, MA [2]Harvard Medical School, Boston, MA [3]Department of Neurology, Massachusetts General Hospital, Boston, MA [4]Interdisciplinary Center Psychopathology and Emotion Regulation, Department of Psychiatry, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands

Abstract

Background—Depression and anxiety are common in patients with coronary artery disease (CAD). While depression clearly has been associated with mortality in this population, the relationship between anxiety and mortality is less clear. Accordingly, we performed a series of meta-analyses to (1) examine the relationship between anxiety and mortality in patients with established CAD and (2) determine if this relationship differs in patients with stable CAD compared to those who have just suffered an acute coronary syndrome (ACS).

Methods and Results—Systematic literature searches identified 44 articles (total N=30,527) evaluating the prospective relationship between anxiety and mortality in individuals with established CAD. A series of eight adjusted and unadjusted meta-analyses were performed to examine this relationship across all patients, with sensitivity analyses completed in post-ACS and stable CAD cohorts. In unadjusted analyses, anxiety was associated with a moderate increase in mortality risk (odds ratio=1.21 per standard deviation increase in anxiety). However, when adjusting for covariates, nearly all associations became non-significant. In sensitivity analyses, anxiety was associated with an increased risk of poor outcomes in the stable CAD—but not post-ACS—cohort.

Conclusions—These analyses confirm that anxiety is associated with increased risk of mortality in patients with CAD; however, this relationship is not as strong as that of depression and may be explained partly by other clinical factors. If anxiety screening is performed, it should be performed during a period of clinical stability and should target anxiety disorders rather than anxiety symptoms alone.

Address for Correspondence: Christopher M. Celano, MD, Massachusetts General Hospital, 55 Fruit Street/Blake 11, Phone: (617) 726-6485 Fax: (617) 724-9155, ccelano@partners.org.

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None.

Keywords

Anxiety; cardiovascular disease; mortality

Introduction

Among individuals with coronary artery disease (CAD), negative psychological states are common, persistent, and associated with poor medical outcomes, including reduced functioning, recurrent cardiac events, and mortality.[1] Depression, the most commonly studied psychological syndrome in cardiac patients, has been linked to the development and progression of CAD,[2,3] and in patients who suffer from an acute coronary syndrome (ACS) has been associated with a 2–2.7 fold increased risk of mortality.[4–6] These findings led to the American Heart Association's recommendation that depression be considered a risk factor for poor outcomes in patients in the post-ACS period.[7]

The relationship between anxiety and mortality is less well-established. Though anxiety symptoms and anxiety disorders are highly prevalent in patients with CAD,[8] studies evaluating the impact of anxiety on cardiac health have yielded mixed results. Five years ago, Roest and colleagues published two meta-analyses, which aimed to determine the relationship between anxiety and medical outcomes in patients with and without CAD. These analyses found that anxiety was prospectively related to the development of CAD[9] and, in patients who have suffered from an ACS, associated with recurrent cardiac events and mortality.[10] Since those analyses were performed, however, more recent studies have suggested that anxiety may have differential effects in patients with different types of cardiac disease, with some suggesting that anxiety may act as a protective factor in certain instances.[11]

Several questions remain regarding how anxiety is linked to outcomes in cardiac patients. First, what is the relationship between anxiety and mortality in patients with CAD, and does it apply equally across the spectrum of CAD patients (from stable CAD to post-ACS patients)? Second, does the relationship between anxiety and mortality persist when controlling for other important covariates, such as depression or severity of cardiac disease? Finally, how does the relationship between anxiety and mortality change when including other outcomes, such as recurrent cardiac events or rehospitalizations, with mortality (i.e., a composite outcome)? To answer these questions, we performed a series of meta-analyses and sensitivity analyses to determine the prospective relationship between anxiety and mortality in individuals with established CAD.

Methods

The guidelines and criteria outlined in Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) were applied to ensure proper reporting of the data (see eTable 1).[12]

Search strategy

The literature search was conducted by two authors (CC and CAB). A systematic review was completed using keyword-based queries in the PubMed and PsycInfo electronic databases. Keywords related to the population of interest (patients with CAD) were combined with keywords related to anxiety, as outlined in Table 1. An advanced search was performed in each database, with each sub-search consisting of three keywords, such as "anxiety AND unstable angina AND mortality." The search was conducted in March 2014 and included articles from the earliest covered dates of the electronic databases (1945 for PubMed, 1967 for PsycInfo) to March 10, 2014.

Selection procedure

English and Spanish language manuscripts published in peer reviewed journals were eligible for this review. Eligible studies were assessed with criteria in line with the Participants, Interventions, Comparators, Outcomes, and Study Design (PICOS) search strategy.[13] Inclusion criteria were the following: (1) studies were prospective and enrolled at least 75 patients with established CAD (stable CAD, patients awaiting coronary artery bypass graft [CABG] surgery, post-ACS, or post-percutaneous coronary intervention [PCI]) but without any pre-defined psychiatric illness, (2) studies included at least one self-report or interview-based assessment of anxiety symptoms or anxiety disorder at baseline, (3) studies included at least one measure of mortality (cardiac mortality, all-cause mortality, or a composite outcome including mortality and other cardiac events) as an outcome, and (4) studies measured outcomes at least 30 days after the baseline assessment. These inclusion criteria largely mirrored those in the American Heart Association's systematic review of depression as a risk factor for poor prognosis in the post-ACS period.[7]

Data extraction

Article review proceeded in several steps. First, two authors (CC and CAB) removed duplicate articles and screened the titles and abstracts of the remaining articles to rule out excluded studies. Next, full texts were read and screened for eligibility criteria by three authors (CC, CAB, and RM). Once eligible studies were identified, relevant data were extracted independently by the same three authors and entered into a database. All extracted data were reviewed by the first author to ensure that the data were transferred accurately and consistently across studies. If sufficient data were not provided in potentially eligible studies, authors were contacted for additional data.

Data abstraction

To assess the quantitative relationships between anxiety and the outcome variables (mortality or a composite outcome), data were abstracted from articles in the following categories: patient/study characteristics, measures of anxiety, outcome measures, adjusted and unadjusted effect estimates with 95% confidence intervals (CIs), and *p*-values. In those studies that examined anxiety as a continuous variable, analyses were standardized to assess the odds ratio (OR) of a 1 standard deviation (SD) change in the anxiety measure. When the SD of an anxiety measure (e.g., Hospital Anxiety and Depression Scale, anxiety subscale [HADS-A]) was not available in the manuscript or through contact with the authors, it was

estimated using the pooled SD of the other included studies that used the same measure.[14–17]

If an OR or hazard ratio was not provided in a manuscript, an OR was calculated using the available information. In three articles,[18–20] we calculated the OR by using the mean anxiety score in survivors vs. non-survivors, and in another four[15,19,21,22] we used the mortality rates in anxious vs. non-anxious individuals.

If a study used anxiety as both a continuous and dichotomized variable, we included them separately in different meta-analyses so that no study's data were counted twice in a single meta-analysis. To obtain a global assessment of effect size, the effect sizes in individual studies were weighted by the magnitude of the standard error, to account for the precision of the effect size estimate in each study.[23]

Meta-analysis

To examine the relationship between anxiety and mortality in CAD, eight meta-analyses were conducted. The eight permutations were combinations of the following factors: (1) anxiety as a continuous or dichotomous (anxious vs. non-anxious) variable, (2) use of mortality or a composite outcome (i.e., mortality and other negative outcomes, such as rehospitalizations or recurrent cardiac events), and (3) unadjusted analyses or adjustment for covariates. In addition, due to significant heterogeneity in the eight main meta-analyses, sensitivity analyses were performed to determine if the relationship between anxiety and mortality was different in patients with stable CAD compared to those in the post-ACS period (with baseline anxiety measured within 2 months of an ACS). If an article reported the results of several adjusted analyses using the same predictor variable, the most fully adjusted models were included in our meta-analyses.

Study heterogeneity was explored using chi-square analysis of heterogeneity (Q), the I^2 statistic derived from Q, and the degrees of freedom. I^2 estimates the degree of variance in a pooled effect size that can be accounted for by heterogeneity. Values of 25%/50%/75% are considered low, moderate, and high, respectively.[24] Publication bias was assessed using the Egger test,[25] followed by visual inspection of funnel plots when bias was suggested. Stata (StataCorp; College Station, TX) was used for quantitative analyses, with $p<.05$ considered significant and all tests two-tailed.

Study quality assessment

Study quality was assessed by three authors (CC, RM, CAB) using a modified version of the Quality Assessment Tool for Quantitative Studies by the Effective Public Health Practice Project.[26,27] The revised quality tool assessed six domains: (1) selection bias, (2) confounders, (3) blinding, (4) data collection methods, (5) withdrawals and drop outs, and (6) statistical analyses, with sections scored using the Effective Public Health Practice Project dictionary. However, we did not assign quantitative quality scores to each study, as doing so may be problematic.[28,29]

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Results

Search

Our literature search of PubMed and PsycInfo resulted in a total of 1,818 articles, with 1,624 articles left once duplicates were removed. Abstracts for all 1,624 articles were reviewed, and 162 received a full-text evaluation. Ultimately, 44 articles—including 30,527 patients—met criteria for inclusion in at least one meta-analysis (see Figure 1 for a flow diagram of study selection, Table 2 for study characteristics, and eTable 2 for more complete description of studies and outcomes). The most common reasons for exclusion during the full text review included lack of mortality as an outcome variable (n=35), lack of anxiety as a predictor variable (n=30), and lack of CAD in all subjects (n=16). Finally, five articles were included based on analyses performed by the authors at our request.[15,30–33]

Meta-analysis results

A summary of all meta-analysis results, including the articles included in each analysis, is available in Table 3.

Unadjusted analyses—The relationship between anxiety and mortality was mixed in unadjusted analyses. When comparing anxious to non-anxious individuals, those with elevated anxiety were not at significantly increased risk of mortality (OR 1.24, 95% CI 0.93 to 1.66, p=0.15, see Figure 2). In contrast, anxiety as a continuous predictor was associated with a significant increase in mortality risk (OR 1.21 per SD increase, 95% CI 1.06 to 1.39, p=0.006, see Figure 3). This increase in risk became more pronounced when examining anxiety's relationship to composite outcomes, with anxious individuals having a 59% increased risk of poor outcomes (OR 1.59, 95% CI 1.29 to 1.97, p<0.001, see Figure 4) and anxiety symptoms as a continuous predictor leading to a 25% increased risk of poor outcomes per SD increase in symptoms (OR 1.25, 95% CI 1.12 to 1.41, p<0.001, see Figure 5).

Adjusted analyses—Controlling for relevant covariates led to less significant relationships between anxiety and mortality (see eFigures 1–4). After covariate adjustment, anxious patients were not significantly more likely to suffer from mortality or poor composite outcomes than their non-anxious counterparts (mortality: OR 1.30, 95% CI 0.98 to 1.73, p=0.07; composite outcomes: OR 1.20, 95% CI 0.91 to 1.58, p=0.20). Likewise, as a continuous measure, anxiety was not associated with mortality in adjusted analyses (OR 1.08, 95% CI 0.90 to 1.30, p=0.41). The only relationship that remained significant after covariate adjustment was the relationship between anxiety as a continuous variable and

composite outcomes, where a one SD increase in anxiety was associated with a 21% increased risk of poor outcomes (OR 1.21, 95% CI 1.05 to 1.39, p=0.009).

Sensitivity analyses

Given significant heterogeneity in the main analyses, sensitivity analyses were performed to examine the association between anxiety and medical outcomes in patients with stable CAD and in those who were post-ACS at the time of the anxiety evaluation. These analyses were performed only when three or more studies were eligible for analysis.

Post-ACS Patients—Six sensitivity analyses were performed in the post-ACS population. However, none of these analyses found a significant relationship (harmful or protective) between anxiety and mortality or composite outcomes (unadjusted: all p≥0.08; adjusted: all p≥0.15).

Stable CAD—Four sensitivity analyses were performed in the stable CAD cohort. In unadjusted analyses, anxiety was associated with an elevated risk of poor medical outcomes (anxious vs. non-anxious individuals: OR 1.47, 95% CI 1.12 to 1.92, p=0.005; continuous anxiety: OR 1.37, 95% CI 1.22 to 1.55, p<0.001). Adjusting for covariates attenuated these associations. After adjusting for covariates, the association between dichotomous anxiety and medical outcomes remained significant (OR 1.43, 95% CI 1.12 to 1.82, p=0.004), while the link between continuous anxiety and outcomes became marginally significant (OR 1.21, 95% CI 0.99 to 1.47, p=0.06).

Heterogeneity, publication bias

Tests of heterogeneity revealed a wide range of heterogeneity among the meta-analyses. In eleven of eighteen analyses, study heterogeneity accounted for a low amount of the variance (mean I^2=29.7% in this group) in the analyses. In another four, I^2 was in the moderate range (mean I^2=64.8%), while I^2 was high in the final three (mean I^2=79.3%).

To evaluate publication bias, the Egger test was performed. Funnel plots were visually inspected for those analyses where the Egger test suggested the presence of publication bias. The Egger test revealed evidence of publication bias in three analyses: the unadjusted analysis of dichotomous anxiety and composite outcomes (coefficient=1.66, p=0.02), the unadjusted sensitivity analysis of anxiety as a dichotomous predictor and mortality as an outcome in post-ACS patients (coefficient=2.54, p=0.04), and the unadjusted sensitivity analysis of anxiety as a continuous predictor and a composite outcome (coefficient=1.83, p=0.03). Inspection of the funnel plots (eFigures 5–7) confirmed the likelihood of publication bias in these analyses. The Egger test suggested no evidence of publication bias in any other analysis (all ps>0.05).

Discussion

Overall, these meta-analysis results reinforce the findings of prior studies that anxiety can be detrimental to cardiac health in patients with CAD. Specifically, our primary results confirm that when not controlling for other factors, elevated anxiety is associated with a mild to moderate increase in risk for poor cardiac outcomes in patients with CAD. In three of four

unadjusted analyses, anxiety was associated with a significantly increased risk of mortality or recurrent cardiac events, with a 1.21–1.25 fold increased risk of poor outcomes per standard deviation increase in anxiety score. This is consistent with the literature, including Roest and colleagues' 2010 meta-analysis of anxiety in post-MI patients (unadjusted OR 1.36).[10] While these findings are significant, it should be noted that the risk associated with anxiety in this population is not as great as that associated with depression, which has been linked to a 2–2.7 fold increased mortality risk in unadjusted meta-analyses.[4–6]

Though anxiety was associated with poor outcomes in unadjusted analyses, controlling for covariates rendered three of four meta-analyses non-significant, suggesting that other factors may be driving the relationships seen in our unadjusted analyses. One notable potential factor is depression, which is highly correlated with anxiety[34] and has been linked to increased mortality in patients with established CAD.[4–6] In our adjusted meta-analyses, 13 of the 32 studies included depression as a covariate. In sensitivity analyses including only these 13 studies, no sensitivity analysis found anxiety to be associated with a significantly increased risk of mortality. Given their high correlation rates and the consistently demonstrated risk that depression poses for CAD patients, it is likely that the inclusion of depression attenuated the relationship between anxiety and outcomes. Another possibility is that controlling for depression may have obscured the true extent of the relationship between anxiety and cardiac outcomes. Given the high correlation between these two psychological states, controlling for depression in multivariate analyses could cause a disproportionate weakening of the association between anxiety and outcomes.

Our sensitivity analyses provided additional information about how the relationship between anxiety and mortality changes in the setting of acute vs. chronic CAD. Specifically, these analyses suggest that this relationship is more pronounced when anxiety is evaluated in patients with stable CAD, as compared to patients in the immediate post-ACS period. We hypothesize that anxiety in the immediate post-ACS period may be more likely to be transient and related to the cardiac event itself; this is supported by the findings that in most patients, anxiety in the year following an ACS improves over time.[8,35] If this is the case, elevated anxiety may be insufficient as a prognostic indicator when measured in the immediate post-ACS period.

These findings have implications regarding the identification and treatment of anxiety in patients with CAD. First, while our findings confirm the link between anxiety and mortality, this association is more modest than that between depression and mortality. Therefore, screening for depression—when appropriate follow-up and depression treatment is available—should be the first major concern for clinicians. Second, if anxiety screening is performed, we recommend examining anxiety during a period of relative clinical stability, such as in patients with stable, chronic CAD. The relationship between anxiety and mortality is stronger when measured in this setting, and screening stable ACS patients would allow clinicians to avoid false-positive anxiety screens related to the (often transient) anxiety experienced in response to an acute cardiac event.

Finally, given that a certain degree of anxiety may be normal in many situations (e.g. following cardiac catheterization), screening for anxiety using a cut-off score on an anxiety

scale may be suboptimal in patients with CAD. In place of measuring anxiety as a single symptom, it may be more appropriate to evaluate patients for anxiety disorders, such as generalized anxiety disorder (GAD), which is highly prevalent in patients with CAD.[1] By definition, anxiety in the setting of GAD is persistent,[36] suggesting that it may have long-lasting and continued effects on cardiac health. Furthermore, there are several easy-to-use tools available for the identification of GAD,[37,38] making screening more feasible. Finally, several evidence-based treatments are available for GAD,[39] raising the possibility of risk reduction if GAD is identified as a risk factor for poor cardiac outcomes.

As in any meta-analysis, this synthesis has several limitations related to the included studies. First and foremost is the inclusion of multiple studies of patients with different clinical characteristics and medical diagnoses. While we aimed to include a wide range of range of patients with CAD (e.g., post-percutaneous coronary intervention, post-ACS, post-coronary artery bypass graft surgery, stable CAD) to get a broader sense of the impact of anxiety on cardiac health in CAD, this likely added heterogeneity into our analyses. Furthermore, different studies had varying methodologies, used different measures of anxiety, and controlled for different covariates in their adjusted analyses, adding heterogeneity to those analyses. It is possible that different types of anxiety (e.g., phobic vs. non-phobic anxiety) in particular have differential associations with cardiac outcomes. Another potential limitation is the possibility of publication bias. However, in our evaluation only three of eighteen analyses (one primary meta-analysis and two sensitivity analyses) had evidence of publication bias. Also, our meta-analyses assumed a linear relationship between anxiety and cardiac outcomes; however, this assumption may not be entirely true for anxiety. For example, a small to moderate amount of anxiety may actually enable patients to engage in care more fully, while severe anxiety may hinder engagement in care. Our analyses were unable to examine these types of relationships fully. Finally, our sensitivity analyses were limited by the number of available studies, with several analyses including only three studies. The results from these analyses in particular should be interpreted with caution and suggest a need for replication in future studies.

Despite these limitations, the results from these meta-analyses suggest that anxiety is significantly associated with a mildly increased risk of mortality and poor cardiac outcomes in individuals with CAD, though this risk is attenuated when controlling for relevant covariates. This risk appears to be greatest when anxiety is measured in a period of clinical stability (≥ 2 months after a cardiac event) and is less established in the immediate post-ACS period. These results illustrate the need for further research to identify those cardiac populations for whom anxiety is associated with the highest risk for mortality or poor medical outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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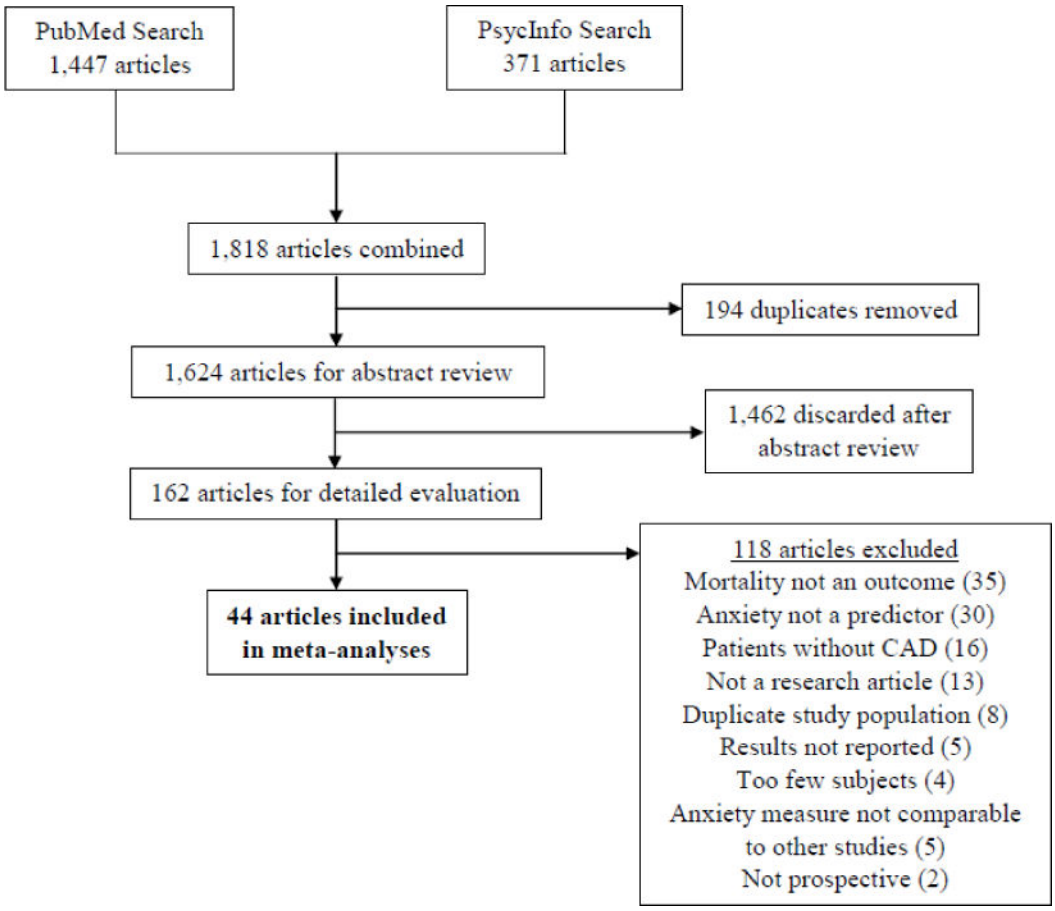

Figure 1.
CONSORT diagram revealing search results and reasons for exclusion

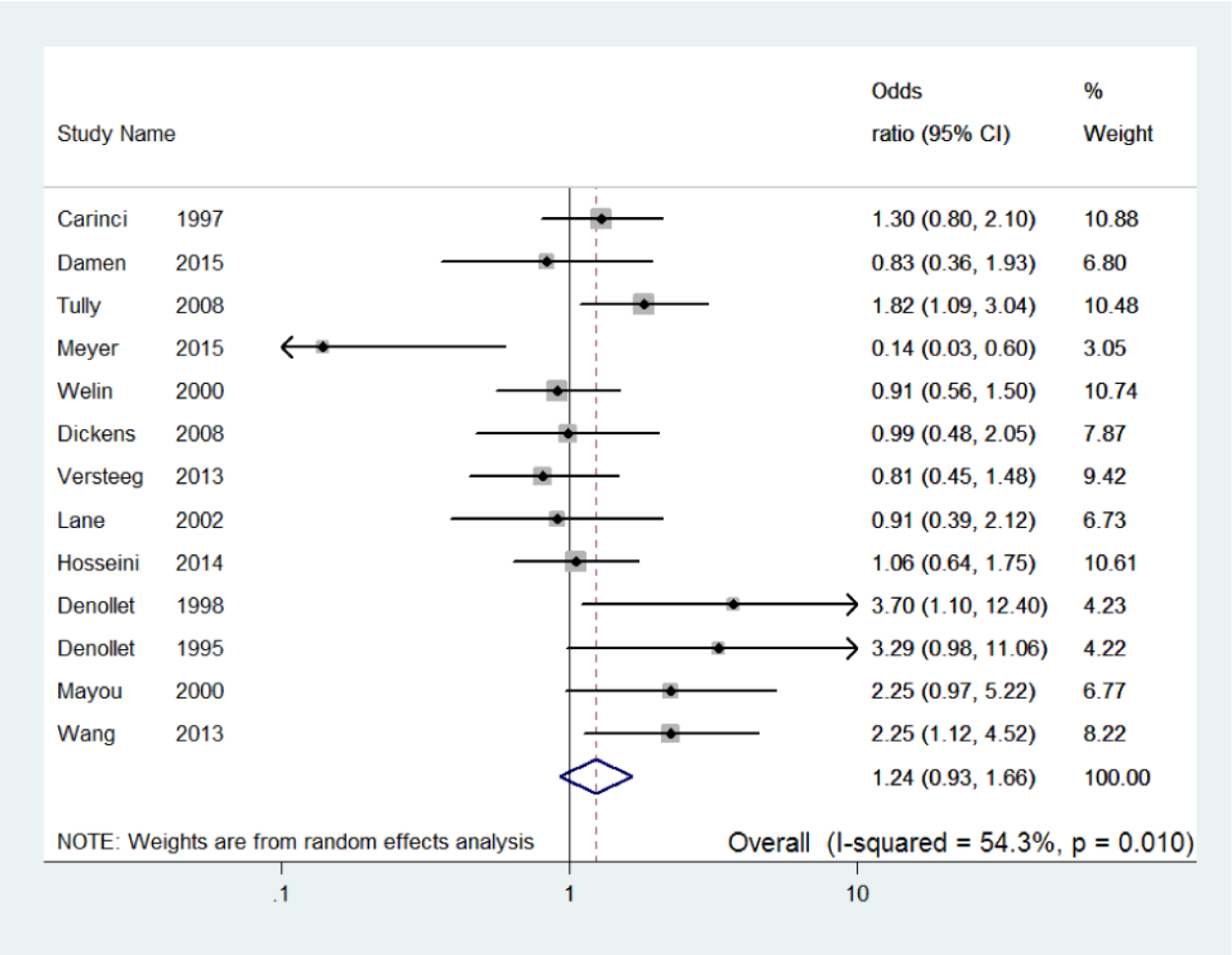

Figure 2.

Meta-analysis of studies with anxiety as a dichotomous predictor and all-cause or cardiac mortality as an outcome (unadjusted)

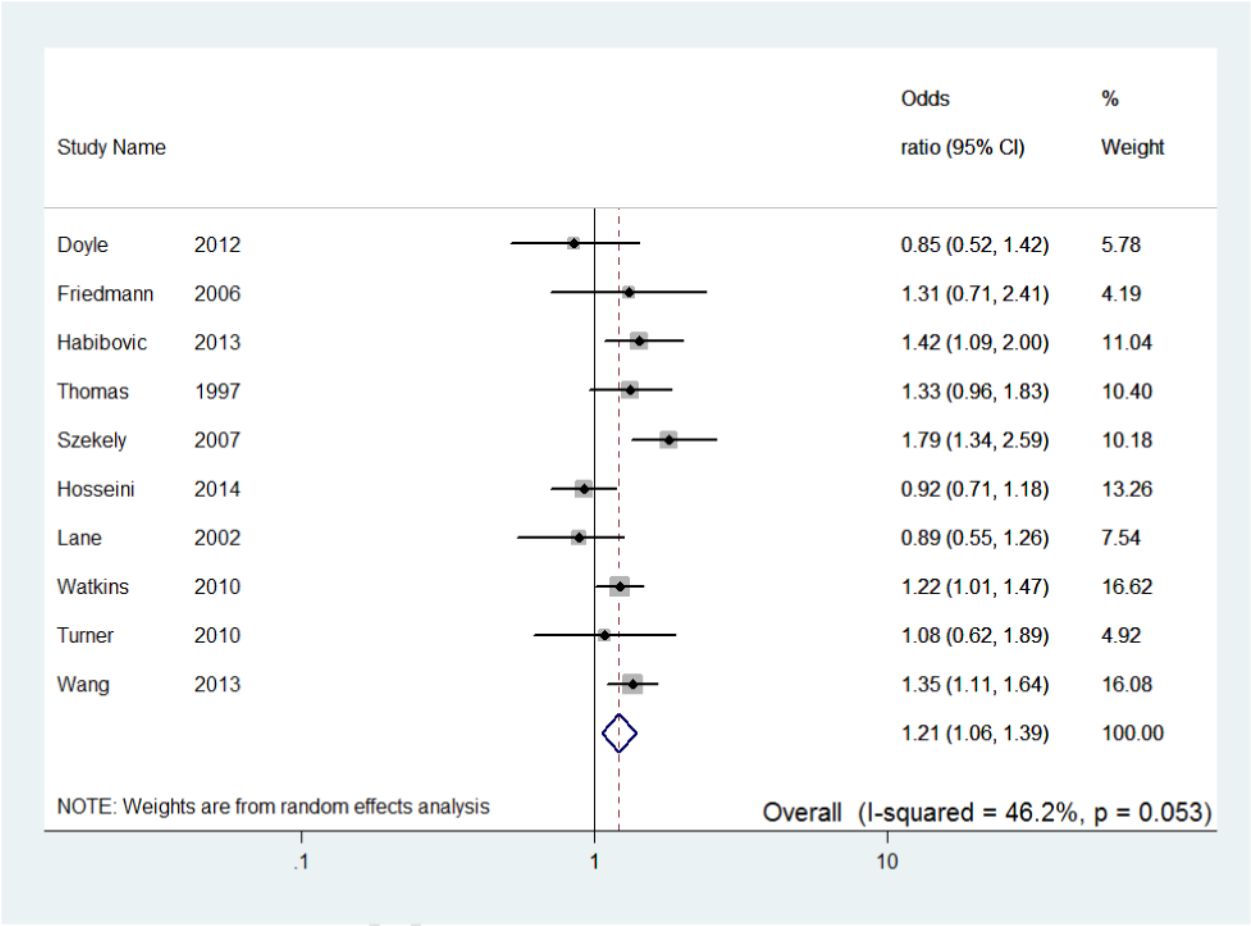

Figure 3.

Meta-analysis of studies with anxiety as a continuous predictor and all-cause or cardiac mortality as an outcome (unadjusted)

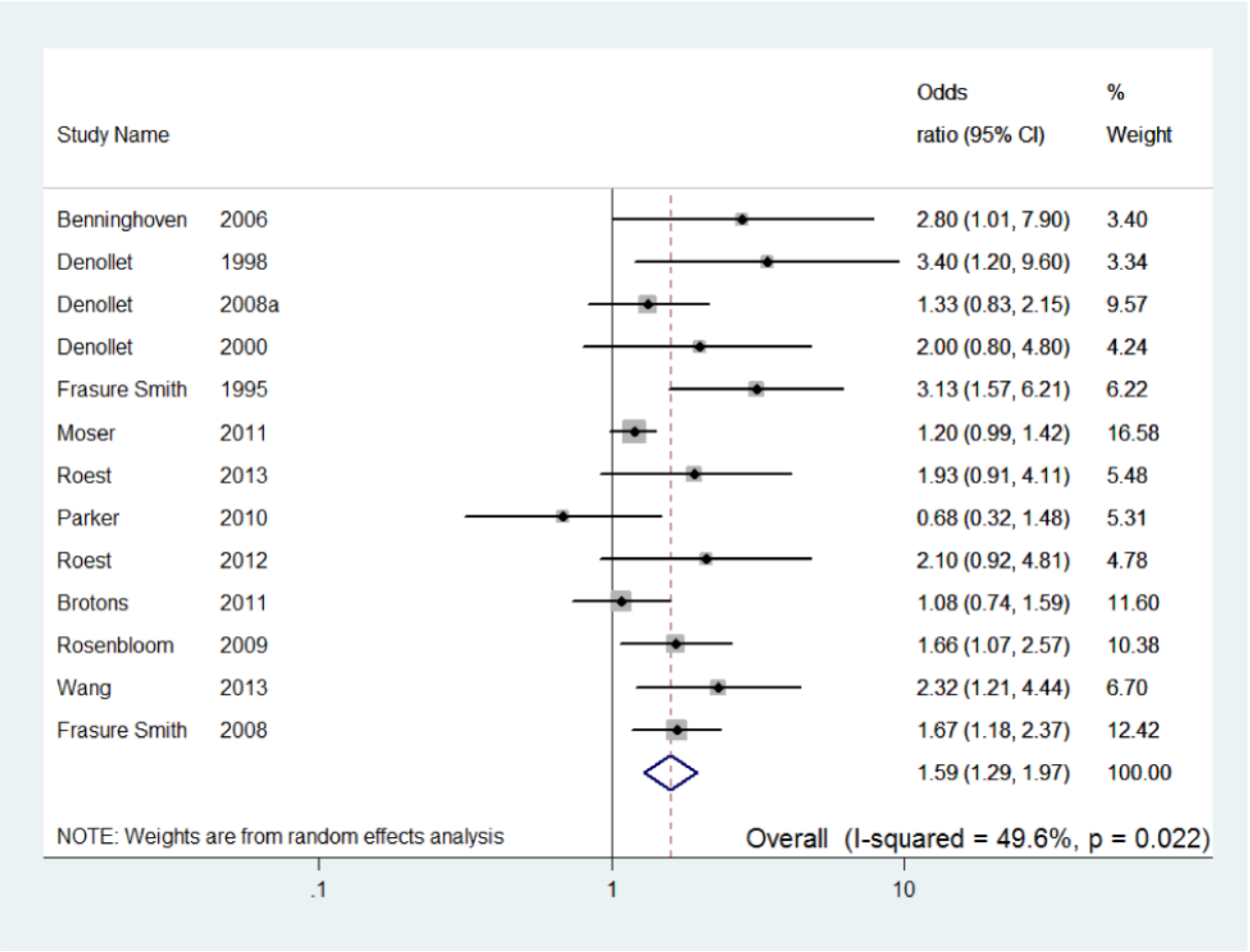

Figure 4.
Meta-analysis of studies with anxiety as a dichotomous predictor and a composite outcome (unadjusted)

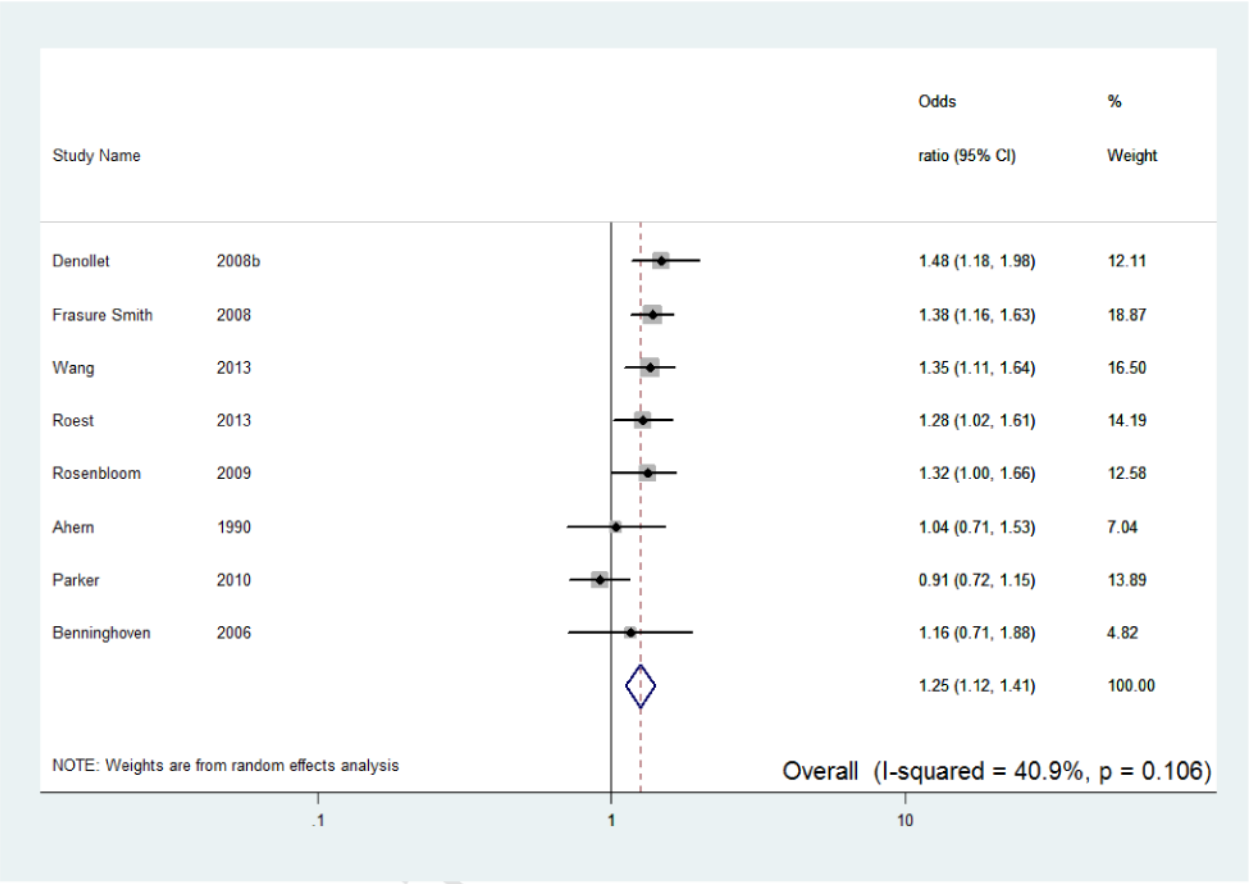

Figure 5.
Meta-analysis of studies with anxiety as a continuous predictor and a composite outcome (unadjusted)

Table 1

Search terms utilized in search strategy.[†]

Any of the following:	AND any of the following:	AND any of the following:
Anxiety	Mortality	Coronary heart disease
Tension	Survival	Coronary artery disease
Post-traumatic stress disorder	Prognosis	Ischemic heart disease
Panic	Adverse	Myocardial infarction
Phobic anxiety	Event*	Unstable angina
Phobia		Acute coronary syndrome
Worry		Coronary artery bypass graft
		Atherosclerosis
		Sudden death
		Ventricular fibrillation
		Ventricular tachycardia

[†]**Note:** This was entered into PubMed as a single search, as follows: (((((((((anxiety) OR tension) OR “post-traumatic stress disorder”) OR panic) OR “phobic anxiety”) OR phobia) OR worry)) AND (((((mortality) OR survival) OR prognosis) OR event*) OR adverse)) AND ((((((((((“coronary heart disease”) OR “coronary artery disease”) OR “ischemic heart disease”) OR “coronary artery bypass graft”) OR atherosclerosis) OR “sudden death”) OR “ventricular fibrillation”) OR “ventricular tachycardia”) OR “acute coronary syndrome”) OR “myocardial infarction”) OR “unstable angina”).

Table 2

Characteristics of studies included in meta-analyses.

Study	CAD Type	N	Anxiety Measure	Outcome Measure
Ahern 1990[18]	Post-MI patients with arrhythmias on Holter monitoring	351	STAI-S	Composite
Benninghoven 2006[40]	Post-MI patients (acute or subacute MI)	76	LIPS (anxiety subscale), STAI-S	Composite
Brotons 2011[21]	Patients with ischemic heart disease	559–567	GADS (anxiety subscale)	Composite
Carinci 1997[41]	Post-MI patients (acute MI)	2449	CBAHF (anxiety subscale)	All-cause mortality
Damen 2013[42]	CAD patients treated with PCI	1234	HADS-A	All-cause mortality
Damen 2015[30]	CAD patients treated with PCI	1094–1166	HADS-A	All-cause mortality
Denollet 1995[43]	Post-MI patients	105	STAI-T	All-cause mortality
Denollet 1998[44]	MI patients with LVEF ≤50%	87	State Anxiety Scale	Cardiac mortality, Composite
Denollet 2008a[45]	CAD patients	731	STAI-T	Composite
Denollet 2008b[14]	CAD patients treated with PCI with stent implantation	874	HADS-A	Composite
Denollet 2000[46]	CAD patients (with MI or CABG/PCI within 2 months) attending cardiac rehab	319	State Anxiety Scale	Composite
Dickens 2008[15]	Post-MI patients (acute MI)	440	HADS-A	Cardiac mortality
Doyle 2012[47]	Patients with ACS	316	HADS-A	All-cause mortality
Frasure-Smith 2003[48]	Post-MI patients	893	STAI-S	Cardiac mortality
Frasure-Smith 2008[49]	Patients with stable CAD	804	HADS-A	Composite
Frasure-Smith 1995[50]	Patients with acute MI	222	STAI-S	Composite
Friedmann 2006[31]	CAD patients with heart failure	83	STAI	All-cause mortality
Grace 2004[8]	Patients hospitalized for UA or MI	913	PRIME-MD (anxiety subscale); MHQ (phobic anxiety subscale)	Composite
Habibovic 2013[32]	CAD patients with their first ICD placed	672	STAI-S	All-cause mortality
Hendrickson 2013[51]	Outpatients with documented CAD	1021	CDIS subscale for GAD	Composite
Hermann 2000[52]	Patients with CAD undergoing stress test	2432	HADS-A	All-cause mortality
Hosseini 2014[53]	Patients with acute MI	274	STAI-S	Cardiac mortality
Jolly 2009[33]	Heart failure patients with established CAD	97	HADS-A	All-cause mortality
Lane 2002[54]	Patients with acute MI	288	STAI-S	Cardiac mortality
Martens 2010[55]	Patients with stable CAD	1015	CDIS, subscale for GAD	All-cause mortality
Mayou 2000[56]	Patients with likely history of MI	344	HADS-A	All-cause mortality

Study	CAD Type	N	Anxiety Measure	Outcome Measure
Meyer 2015[11]	CHD patients treated with PCI	462	HADS-A	All-cause mortality, MACE
Moser 2011[57]	Patients with CHD	3048	BSI (anxiety subscale)	Acute cardiac events
Parker 2010[19]	Patients hospitalized with ACS	461	CIDI (GAD subscale)	Composite
Roest 2013[58]	Patients with acute MI	418	HARS	Composite
Roest 2012[22]	Patients with MI (acute)	438	CIDI	Composite
Rosenbloom 2009[17]	Patients with CAD with a history of CABG	1317	STAI-S	Composite
Shibeshi 2007[59]	Outpatients with CAD	516	Kellner's Symptom Questionnaire	Composite
Simsek 2009[60]	Post-PCI patients	658	HADS-A	All-cause mortality
Strik 2003[61]	Men after first MI	318	Symptom Check List-90, Anxiety subscale	Composite
Szekely 2007[62]	CAD patients post-CABG	180	STAI-T	All-cause mortality
Thomas 1997[20]	Patients post-MI (with asymptomatic PVCs, on non-active medication)	424	STAI-S	Mortality
Tully 2008[63]	Patients undergoing first-time CABG	440	DASS (anxiety subscale)	All-cause mortality
Turner 2010[64]	CAD patients in cardiac rehabilitation	301	HADS-A	All-cause mortality
Versteeg 2013[16]	Patients treated for MI, angina or ischemic heart failure	610	HADS-A	All-cause mortality
Wang 2013[65]	Patients with CAD	1007	Zung Self-Rating Anxiety Scale	All-cause mortality; Composite
Watkins 2010[66]	CAD patients hospitalized for coronary angiography	947	MHQ (phobic anxiety subscale)	Cardiac mortality
Watkins 2013[67]	CAD patients hospitalized for coronary angiography	934	HADS-A	All-cause mortality
Welin 2000[68]	Patients post-first MI	275	STAI-T	All-cause mortality

BSI=Brief Symptom Inventory; CABG=coronary artery bypass grafting; CAD=coronary artery disease; CBAHF=Cognitive Behavioral Assessment Hospital Form; CDIS=Computerized Diagnostic Interview Schedule; CIDI=Composite International Diagnostic Interview; DASS=Depression Anxiety and Stress Scale; GAD=generalized anxiety disorder; GADS=Goldberg Anxiety-Depression Scale; HADS-A=Hospital Anxiety and Depression Scale, Anxiety subscale; HARS=Hamilton Anxiety Rating Scale; ICD=implantable cardioverter defibrillator; LIPS=Luebeck Interview for Psychosocial Screening; LVEF=left ventricular ejection fraction; MHQ=Middlesex Hospital Questionnaire; MI=myocardial infarction; PCI=percutaneous coronary intervention; PRIME-MD=Primary Care Evaluation of Mental Disorders; PVC=premature ventricular contraction; STAI-S=State-Trait Anxiety Inventory, State subscale; STAI-T=State-Trait Anxiety Inventory, Trait subscale

Table 3

Summary of Meta-analysis Findings.

		Articles	Predictor Type	Outcome Type	N	Odds Ratio	95% Confidence Interval	z-score	p-value
Main Analyses	**Unadjusted**	11,15,16,30,41,43,44,53,54,56,63,65,68	Dichotomous	Mortality	7,947	1.24	0.93 to 1.66	1.44	0.15
		20,31,32,47,53,54,62,64–66	Continuous	Mortality	4,492	1.21	1.06 to 1.39	2.75	**0.006**
		17,19,21,22,40,44–46,49,50,57,58,65	Dichotomous	Composite	9,499	1.59	1.29 to 1.97	4.37	**<0.001**
		14,17–19,40,49,58,65	Continuous	Composite	5,308	1.25	1.12 to 1.41	3.83	**<0.001**
	Adjusted	11,15,30,42,47,55,63,65,67	Dichotomous	Mortality	6,942	1.30	0.98 to 1.73	1.82	0.07
		15,16,20,32,33,47,48,52,60,62,65,66	Continuous	Mortality	8,676	1.08	0.90 to 1.30	0.82	0.41
		11,17,19,21,22,45,49–51,58,59,61,65	Dichotomous	Composite	8,274	1.20	0.91 to 1.58	1.29	0.20
		8,40,49,57–59,65	Continuous	Composite	6,782	1.21	1.05 to 1.39	2.62	**0.009**
Post-ACS	**Unadjusted**	15,41,43,44,53,54,56,68	Dichotomous	Mortality	4,262	1.28	0.95 to 1.72	1.60	0.11
		20,47,53,54	Continuous	Mortality	1,302	1.00	0.81 to 1.23	0.01	0.99
		19,40,44,50	Dichotomous	Composite	846	2.07	0.92 to 4.64	1.76	0.08
		18,19,40	Continuous	Composite	888	0.97	0.81 to 1.17	0.31	0.76
	Adjusted	15,20,47,48	Continuous	Mortality	2,073	1.18	0.94 to 1.49	1.46	0.15
		19,50,61	Dichotomous	Composite	1,001	1.51	0.49 to 4.64	0.72	0.47
Stable CAD	**Unadjusted**	22,49,57,58	Dichotomous	Composite	4,708	1.47	1.12 to 1.92	2.82	**0.005**
		14,49,58	Continuous	Composite	2,096	1.37	1.22 to 1.55	5.13	**<0.001**
	Adjusted	22,51,58,59	Dichotomous	Composite	2,393	1.43	1.12 to 1.82	2.90	**0.004**
		49,57–59	Continuous	Composite	4,786	1.21	0.99 to 1.47	1.88	0.06