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**Meta-analysis: Epidemiology of Non-cardiac Chest Pain in
the Community**

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Ford *et al.*

1 of 33

TITLE PAGE**Title:** Meta-analysis: Epidemiology of **Non-cardiac** Chest Pain in the Community.**Short running head:** Meta-analysis: **Non-cardiac** Chest Pain.**Authors:** Alexander C Ford^{1,2}, Nicole C Soares¹, Nicholas J Talley³.¹Leeds Gastroenterology Institute, Leeds General Infirmary, Leeds, UK.²Leeds Institute of Molecular Medicine, University of Leeds, Leeds, UK.³Faculty of Health, University of Newcastle, New South Wales, Australia.

Abbreviations:	CI	confidence interval
	GERD	gastro-oesophageal reflux disease
	GI	gastrointestinal
	IBS	irritable bowel syndrome
	MeSH	medical subject headings
	OR	odds ratio

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Ford *et al.*

2 of 33

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Ford *et al.*

3 of 33

SUMMARY

Background: Prevalence of, and risk factors for, **non-cardiac** chest pain in the community have not been well studied.

Aims: To conduct a systematic review and meta-analysis to examine these issues.

Methods: MEDLINE, EMBASE, and EMBASE Classic were searched (up to March 2011) to identify population-based studies reporting prevalence of **non-cardiac** chest pain in adults (≥ 15 years) according to self-report, questionnaire, or specific symptom-based criteria. Prevalence of **non-cardiac** chest pain was extracted for all studies, and according to study location and certain other characteristics including presence or absence of gastro-oesophageal reflux disease (GERD) symptoms, where reported. Pooled prevalence overall, as well as odds ratios (OR), with 95% confidence intervals (CIs) were calculated.

Results: Of 18 papers evaluated, 16 reported prevalence of **non-cardiac** chest pain in 14 separate populations, containing 24 849 subjects. Pooled prevalence of **non-cardiac** chest pain in all studies was 13% (95% CI 9%-16%). The prevalence of **non-cardiac** chest pain was higher in Australian studies, and in studies using a questionnaire to define its presence, compared with those using Rome I or II criteria. Prevalence was no different in females versus males (OR 0.99; 95% CI 0.82-1.20). The prevalence was markedly higher in subjects who also reported GERD (OR 4.71; 95% CI 3.32-6.70), and increased according to frequency of GERD symptoms.

Conclusions: Pooled prevalence of **non-cardiac** chest pain in the community was 13%, but there were few studies. Rates did not appear to differ according to gender or age. Presence of GERD was strongly associated with **non-cardiac** chest pain.

INTRODUCTION

Non-cardiac chest pain is a disorder **thought to relate to** the gastrointestinal (GI) tract, characterised by episodes of unexplained chest pain **that are** potentially of oesophageal origin. Patients with **non-cardiac** chest pain report impairments in quality of life and activities of daily living that are of a similar magnitude to those with chest pain caused by structural coronary disease, (1) and rates of healthcare seeking and work absenteeism are also comparable. (2) Severity of symptoms and anxiety about the underlying cause appear to drive consultation behaviour. (2)

The pathophysiological mechanisms behind symptom generation remain poorly understood. Proposed mechanisms include visceral hypersensitivity, (3) abnormal pain processing, (4) altered autonomic activity, (5) and sustained oesophageal contractions, (6) while the role of oesophageal dysmotility remains unclear. (7) Potential risk factors for **non-cardiac** chest pain include obesity, family history of gastro-oesophageal reflux disease (GERD), smoking, analgesic use, and symptoms of GERD, (8-10) although data are sparse.

There have been several cross-sectional surveys that have reported the prevalence of **non-cardiac** chest pain in the community, (8;11-13) but the prevalence of **non-cardiac** chest pain according to geographical location has not been well-studied to date. Nor has any single study synthesised all the available evidence to examine potential risk factors for **non-cardiac** chest pain, the relationship between the disorder and symptoms of GERD, or the degree of overlap between other functional GI disorders and **non-cardiac** chest pain. **Systematic analysis of studies that report these types of data is important to allow physicians consulting with patients complaining of these symptoms to provide more precise estimates of the prevalence**

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and risk factors for the condition, as well as identify areas where further research is needed. We have therefore conducted a systematic review and meta-analysis of the prevalence of non-cardiac chest pain in the community to examine these issues.

For Peer Review

Ford *et al.*

6 of 33

METHODS

Search Strategy and Study Selection

A search of the medical literature was conducted using MEDLINE (1948 to March 2011), EMBASE, and EMBASE Classic (1947 to March 2011) to identify population-based cohort studies, case-control studies, cross sectional surveys, or randomised controlled trials that reported the prevalence of **non-cardiac** chest pain in adults aged 15 years or over. Studies conducted among convenience samples, such as university students or hospital employees, were not eligible for inclusion. The diagnosis of **non-cardiac** chest pain could be on the basis of symptoms self-reported by the individual, defined according to a questionnaire, based on the Rome I, II, or III criteria, (14-16) or according to a physician's diagnosis. Studies were only eligible for inclusion if they contained 50 or more individuals. Detailed eligibility criteria for study inclusion, which were defined prospectively, are provided in Table 1.

Studies on **non-cardiac** chest pain were identified using the search terms: *chest pain* (both as a medical subject heading (MeSH) and free text term), as well as *noncardiac*, *non cardiac*, *non-cardiac*, or *functional* as free text terms. These were combined with the set operator AND with studies identified with the search term *prevalence* as both a MeSH and free text term. There were no language restrictions. All abstracts identified by the search were evaluated for appropriateness to the study question, and all potentially relevant papers were obtained and assessed in detail. A recursive search of the literature was conducted using the bibliographies of all eligible studies. Foreign language papers were translated where required. Studies were assessed independently by two investigators, using pre-designed eligibility forms, according to the eligibility criteria. All disagreements were resolved by consensus.

Data Extraction

Data were extracted independently by two investigators on to a Microsoft Excel spreadsheet (XP professional edition; Microsoft, Redmond, WA, USA), with discrepancies resolved by consensus. The following data were collected for each study: type of study, year(s) conducted, country and geographical region, method of data collection (postal questionnaire, interview-administered questionnaire, face-to-face interview, telephone interview), criteria used to define non-cardiac chest pain, total number of subjects recruited, and number of subjects with non-cardiac chest pain. We also extracted number of subjects with non-cardiac chest pain according to gender, age group, socioeconomic status, presence or absence of other functional GI disorders, and presence or absence of typical symptoms of GERD, as well as frequency of GERD symptoms, in order to examine any effect of these factors on prevalence of non-cardiac chest pain, where individual studies reported these data.

Data Synthesis and Statistical Analysis

The proportion of individuals with non-cardiac chest pain in each study was combined to give a pooled prevalence of non-cardiac chest pain for all studies. Heterogeneity between studies was assessed using the I^2 statistic with a cut off of 50%, (17) and the χ^2 test with a P value < 0.10, used to define a statistically significant degree of heterogeneity. We planned to conduct sensitivity analyses according to geographical region, criteria used to define presence of non-cardiac chest pain, study publication year, validation status of the questionnaire (where used), gender, age, presence or absence of other functional GI disorders, and GERD symptom status to examine whether this had any effect on the pooled prevalence of non-cardiac chest pain. The prevalence of non-cardiac chest pain was also compared

Ford *et al.*

8 of 33

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3 according to age group, gender, socioeconomic status, presence or absence of other
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5 functional GI disorders, and GERD symptom status using an odds ratio (OR), with a
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7 95% confidence interval (CI).
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10 Data were pooled using a random effects model, (18) to give a more
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12 conservative estimate of the prevalence of **non-cardiac** chest pain and the odds of **non-**
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14 **cardiac** chest pain in these various groups. StatsDirect version 2.7.2 (StatsDirect Ltd,
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16 Sale, Cheshire, England) was used to generate Forest plots of pooled prevalences and
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18 pooled ORs with 95% CIs. We planned to assess for evidence of publication bias by
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20 applying Egger's test to funnel plots of odds ratios. (19)
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RESULTS

The search strategy identified 2076 citations (Figure 1). From these we identified 18 papers that appeared to be relevant to the study question. Of these, 16 studies, reporting prevalence of **non-cardiac** chest pain in 14 separate adult study populations, were eligible for inclusion. (8;11-13;20-31) Agreement between investigators for assessment of study eligibility was good (kappa statistic = 0.64). Detailed characteristics of all included studies are provided in Table 2. Most studies were cross-sectional surveys, but one was a case-control study conducted among diabetic patients and non-diabetic controls from the general population. (30) For the purposes of the present analysis only data for the non-diabetic controls were extracted from this study. None of the identified studies reported the prevalence of **non-cardiac** chest pain according to the presence or absence of other functional GI disorders.

Prevalence of **Non-cardiac** Chest Pain in All Studies

The pooled prevalence of **non-cardiac** chest pain in all 14 studies containing 24 849 participants using the primary definition for **non-cardiac** chest pain in each study, was 13.0% (95% CI 9.0% to 16.0%), with statistically significant heterogeneity between studies ($I^2 = 98.6\%$, $P < 0.001$). Nine studies excluded cardiac causes of chest pain from their definition of **non-cardiac** chest pain. (8;11-13;20;23-25;29) Seven of these used self-report of a cardiac cause by the participant in the symptom questionnaire, (11;13;20;23-25;29) and the remaining two studies used both a physician's diagnosis of ischaemic heart disease and the Rose angina questionnaire. (8;12) The pooled prevalence in studies that excluded cardiac causes of chest pain

Ford *et al.*

10 of 33

was 17.0% (95% CI 13.0% to 21.0%), compared with 6.0% (95% CI 3.0% to 11.0%) in those that did not exclude cardiac causes.

Global Prevalence of **Non-cardiac** Chest Pain

Seven of the studies were conducted in North America or Europe. (11;13;25;26;29-31) There were no identified studies conducted in South Asia, Africa, or Central America, and only a few studies from other regions. The pooled prevalence of **non-cardiac** chest pain according to geographical location of the study is provided in Table 3. This was similar for the four geographical regions where more than one study had been conducted, with the exception of Australian studies, where the prevalence was 16.0%. The prevalence in the study from Turkey was 19.5%, (20) whilst that in the Argentinean survey was 24.1%. (23)

Prevalence of **Non-cardiac** Chest Pain According to Criteria Used to Define its Presence

Eleven studies used a questionnaire to define the presence of **non-cardiac** chest pain. (8;11-13;20;22-24;26;29;30) Three studies used the Rome II criteria, (21;27;31) two used the Rome I criteria, (25;28) and no identified studies used the Rome III criteria. The pooled prevalence of **non-cardiac** chest pain according to the various criteria used to define its presence is provided in Table 4. Pooled prevalence was lower when either the Rome I or II criteria were used to define its presence, with a prevalence of 9.0% and 2.7% respectively.

Prevalence of **Non-cardiac** Chest Pain According to Gender, Age, and Socioeconomic Status

There were seven studies that reported the prevalence of **non-cardiac** chest pain according to the gender of participants. (8;12;13;21;25;27;31) Overall, the pooled prevalence in 7340 women was 9.7% (95% CI 5.0% to 15.7%), compared with 9.7% (95% CI 4.7% to 16.1%) in 6773 men. The OR for **non-cardiac** chest pain in women, compared with men, was 0.99 (95% CI 0.82 to 1.20) (Figure 2), with borderline heterogeneity between studies ($I^2 = 54.7%$, $P = 0.04$), but no evidence of funnel plot asymmetry (Egger test, $P = 0.99$).

Data concerning prevalence of **non-cardiac** chest pain according to age and socioeconomic status were scarce. Only four studies reporting prevalence according to age. (8;13;22;25) However, due to different age bands used to report prevalence of **non-cardiac** chest pain, data available for pooling were limited. Two studies provided data according to age less than 45 years, or 45 years or more. (22;25) The prevalence of **non-cardiac** chest pain in those aged 45 years or more was not significantly different to those aged less than 45 years (OR 0.85; 95% CI 0.39 to 1.86). There was only one study that reported the prevalence of **non-cardiac** chest pain according to socioeconomic status. (12) This demonstrated a declining prevalence with increasing monthly income, from 33% in those with no income to only 9% in those individuals with a monthly salary of more than US\$3200.

Prevalence of **Non-cardiac** Chest Pain According to Presence of GERD

There were six studies, containing 9104 subjects, which collected data on both typical GERD symptoms and presence of **non-cardiac** chest pain. (12;13;20;23;24;29) The pooled prevalence of **non-cardiac** chest pain in 3276 individuals with typical

Ford *et al.*

12 of 33

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3 symptoms of GERD was 31.0% (95% CI 27.0% to 36.0%), compared with 9.0%
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5 (95% CI 6.0% to 12.0%) in 5828 subjects without. The OR for **non-cardiac** chest pain
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7 in those with typical symptoms of GERD was 4.71 (95% CI 3.32 to 6.70) (Figure 3),
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9 with significant heterogeneity between studies ($I^2 = 86.6\%$, $P < 0.001$), but no
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11 evidence of funnel plot asymmetry (Egger test, $P = 0.28$).
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16 Five studies reported the prevalence of **non-cardiac** chest pain according to
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18 frequency of typical GERD symptoms. (13;20;23;24;29) The pooled prevalence of
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20 **non-cardiac** chest pain in 4278 subjects with no GERD symptoms was 8.0% (95% CI
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22 5.0% to 12.0%), compared with 27.0% (95% CI 22.0% to 32.0%) in 1699 individuals
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24 with occasional GERD symptoms, and 36.0% (95% CI 31.0% to 41.0%) in 918 with
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26 frequent GERD symptoms. The ORs for **non-cardiac** chest pain in those with
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28 occasional or frequent GERD symptoms compared with those without were 4.20
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30 (95% CI 2.59 to 6.82) (Figure 4) and 6.37 (95% CI 4.08 to 9.96) (Figure 5)
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32 respectively, with statistically significant heterogeneity between studies in both
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34 analyses, but no evidence of funnel plot asymmetry.
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DISCUSSION

This systematic review and meta-analysis has demonstrated a pooled prevalence for **non-cardiac** chest pain in the community of 13%, with a similar prevalence across the geographical regions studied, although slightly higher in Australian studies. Prevalence appeared lower when the Rome I or II criteria were used to define **non-cardiac** chest pain, compared with a questionnaire-based diagnosis. There were no studies examining prevalence according to the most recent Rome III criteria. Perhaps unexpectedly, prevalence was also lower in studies that did not exclude possible cardiac causes of chest pain from their definition using self-report, a physician opinion, or validated questionnaire. The presence of **non-cardiac** chest pain did not appear to be affected by gender or age, although studies reporting prevalence according to the latter were sparse, whilst prevalence declined with increasing income in one study. (12) Finally, there was a significant association between GERD and **non-cardiac** chest pain, with an almost five-fold increase in the odds of **non-cardiac** chest pain in those reporting symptoms compatible with GERD. The magnitude of this association increased with the frequency of GERD symptoms, with a greater than six-fold increase in odds of **non-cardiac** chest pain in those with frequent GERD symptoms, suggesting a gradient of effect.

Strengths of this study include our exhaustive literature search, which included a recursive search of the literature, as well as electronic databases. In addition, eligibility assessment and data extraction were performed independently by two investigators, with all discrepancies resolved by consensus. We only considered population-based studies, and excluded convenience samples and studies conducted in primary care or GI clinics, in order not to overestimate the prevalence of **non-cardiac**

Ford *et al.*

14 of 33

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3 chest pain in the community, and ensure our results were applicable to the general
4 population. We performed subgroup analyses according to study location, criteria
5 used to define **non-cardiac** chest pain, and other study characteristics in order to assess
6 the impact of these on pooled prevalence. Finally, we were able to extract data in
7 order to study the relationship between GERD and **non-cardiac** chest pain.

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15 Limitations of the study, as with any systematic review and meta-analysis,
16 arise from the studies that were eligible and available for inclusion. Our search
17 identified only 16 studies, conducted in 14 separate adult populations, emphasizing
18 the relative paucity of population-based data concerning the prevalence of **non-cardiac**
19 chest pain, when compared to other functional GI disorders such as dyspepsia,
20 irritable bowel syndrome (IBS), and chronic idiopathic constipation. When
21 calculating pooled prevalence, there was a notable absence of studies conducted in
22 certain geographical regions, making an accurate assessment of true global prevalence
23 difficult. There were few studies reporting the effect of age or socioeconomic status
24 on prevalence of **non-cardiac** chest pain, and no studies reported the degree of overlap
25 with the other functional GI disorders, such as IBS. In addition, there was
26 heterogeneity between study results, which was not explained by any of the subgroup
27 analyses we conducted. **Finally, the differences in definitions of non-cardiac chest**
28 **pain used in the identified studies may limit the usefulness of the pooled estimate of**
29 **prevalence.**

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51 There have been no previous systematic reviews published that have examined
52 the epidemiology of **non-cardiac** chest pain in the community. This emphasises the
53 need for a definitive study to identify and summarise all available evidence in this
54 field. One previous systematic review reported that evidence from three population-
55 based studies supported a link between **non-cardiac** chest pain and GERD. (32)
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Ford *et al.*

15 of 33

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3 However, there has not been any formal meta-analysis conducted, to our knowledge,
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5 which has synthesised all available evidence to quantify this relationship. Our
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7 observation that **non-cardiac** chest pain was reported almost five times more
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9 frequently by those who met symptom criteria for GERD, and that the magnitude of
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11 this association increased with a higher frequency of symptoms, suggest that there is
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13 considerable overlap between the two conditions and possibly a causal connection.
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17 Physiological reflux of acid may therefore play a role in the generation of
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19 symptoms in individuals with **non-cardiac** chest pain. This theory is supported by a
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21 study that used wireless pH monitoring in patients with **non-cardiac** chest pain, and
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23 demonstrated that extended monitoring time led to higher rates of detection of GERD.
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25 (33) A meta-analysis of randomised controlled trials of proton pump inhibitors (PPIs)
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27 in **non-cardiac** chest pain suggested that acid suppression is superior to placebo in
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29 terms of improvement in symptoms, with a number needed to treat of only three. (34)
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31 Furthermore, in a recent study using ambulatory pH monitoring indicators of GERD,
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33 including acid exposure time, evidence of relevant acid reflux was present in almost
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35 two-thirds of **non-cardiac** chest pain patients, and these predicted a response to
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37 medical therapy. (35) **Some investigators have demonstrated that acid exposure**
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39 **reduces pain thresholds in the oesophagus in healthy volunteers, (36) and that this**
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41 **effect is exaggerated in patients with non-cardiac chest pain, (37) and may be**
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43 **attenuated by PPIs. (38)**
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51 Recent research has demonstrated considerable overlap between some of the
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53 functional GI disorders, (39;40) but unfortunately none of the studies identified in this
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55 systematic review examined this issue. An Australian case-control study, which
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57 recruited patients with **non-cardiac** chest pain and age-matched individuals randomly
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59 selected from the general population, reported that the prevalence of both functional
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Ford *et al.*

16 of 33

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3 dyspepsia and IBS in those with non-cardiac chest pain were at least two-fold those of
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5 controls without. (41) However, more studies replicating these data are required in
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7 order to confirm this association. This systematic review and meta-analysis has also
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9 identified other areas of need for future research. Only a minority of the studies we
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11 identified were designed with prevalence of non-cardiac chest pain as the primary
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13 outcome of interest, and hence risk factors for the condition have been poorly
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15 assessed. In addition, as yet, no single study has reported the prevalence of chest pain
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17 using the Rome III criteria, and this needs to be addressed.
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22 In conclusion, this systematic review and meta-analysis has demonstrated a
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24 global prevalence of non-cardiac chest pain of 13%. Rates were higher according to a
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26 questionnaire-based diagnosis compared with the Rome I or II criteria. Unlike most of
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28 the other functional GI disorders, there was no significant difference in prevalence
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30 according to gender. Finally, the presence of non-cardiac chest pain seemed to be
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32 strongly associated with GERD symptoms, suggesting common pathophysiological
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34 mechanisms.
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41 **STATEMENTS OF INTEREST**

42 **Authors' Declaration of Personal Interests:**

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47 Alexander C Ford: none. Nicole C Soares: none. Nicholas J Talley: none.
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52 **Declaration of Funding Interests:**

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60 None.

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Ford *et al.*

18 of 33

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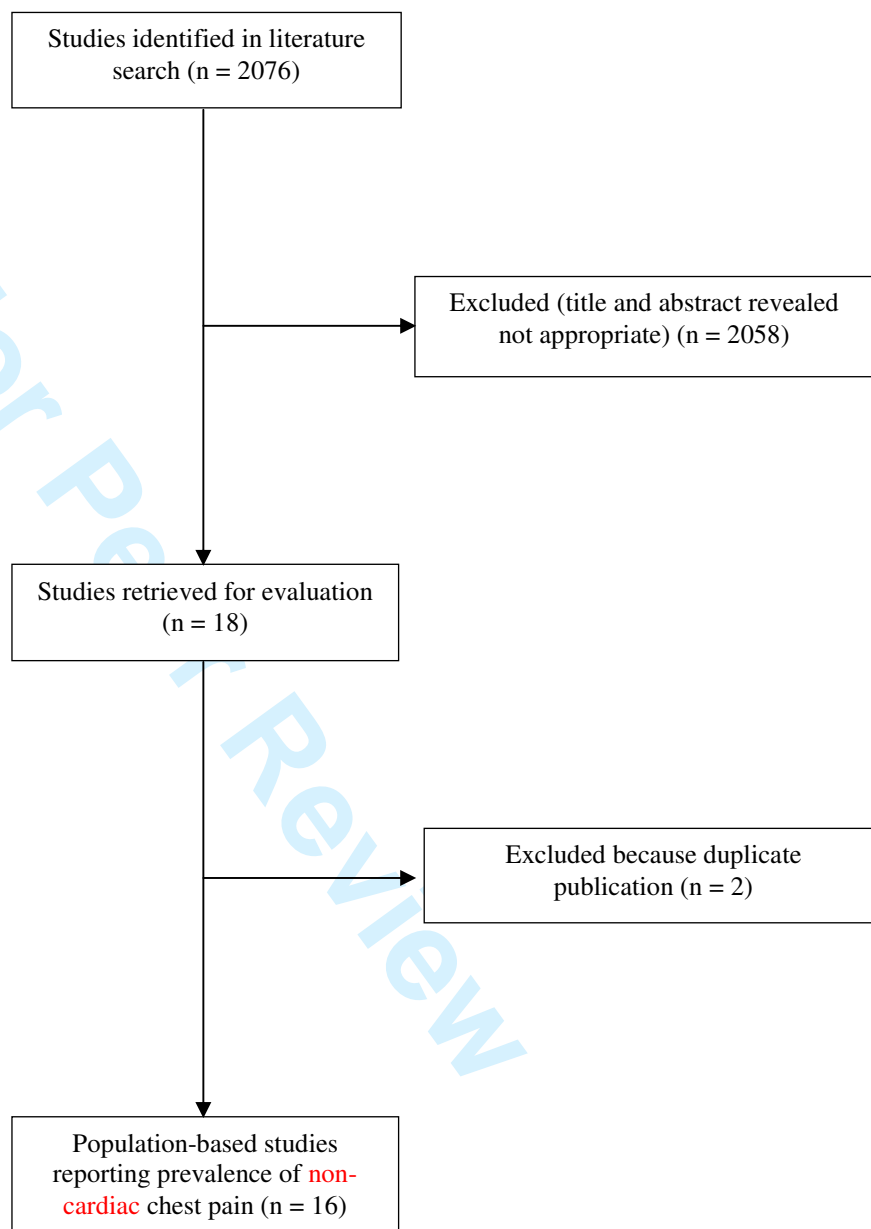
Ford *et al.*

22 of 33

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FIGURES

Figure 1. Flow Diagram of Assessment of Studies Identified in the Systematic Review and Meta-analysis.



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Figure 2. Pooled Odds Ratio for Non-cardiac Chest Pain in Women Compared with Men.

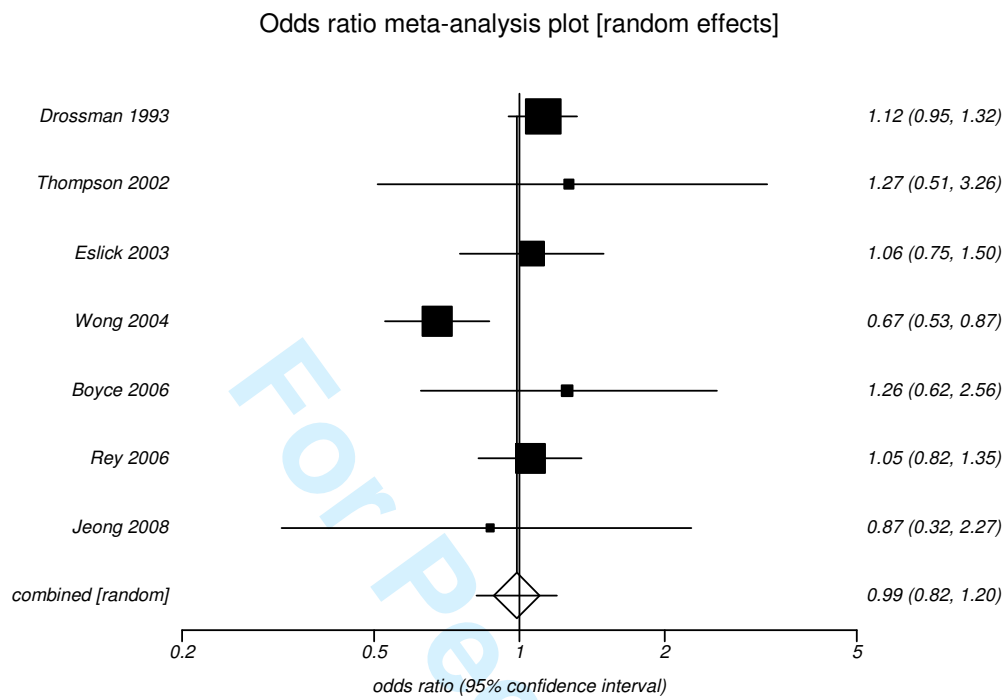


Figure 3. Pooled Odds Ratio for **Non-cardiac** Chest Pain in Individuals with Typical Symptoms of GERD Compared with Those Without.

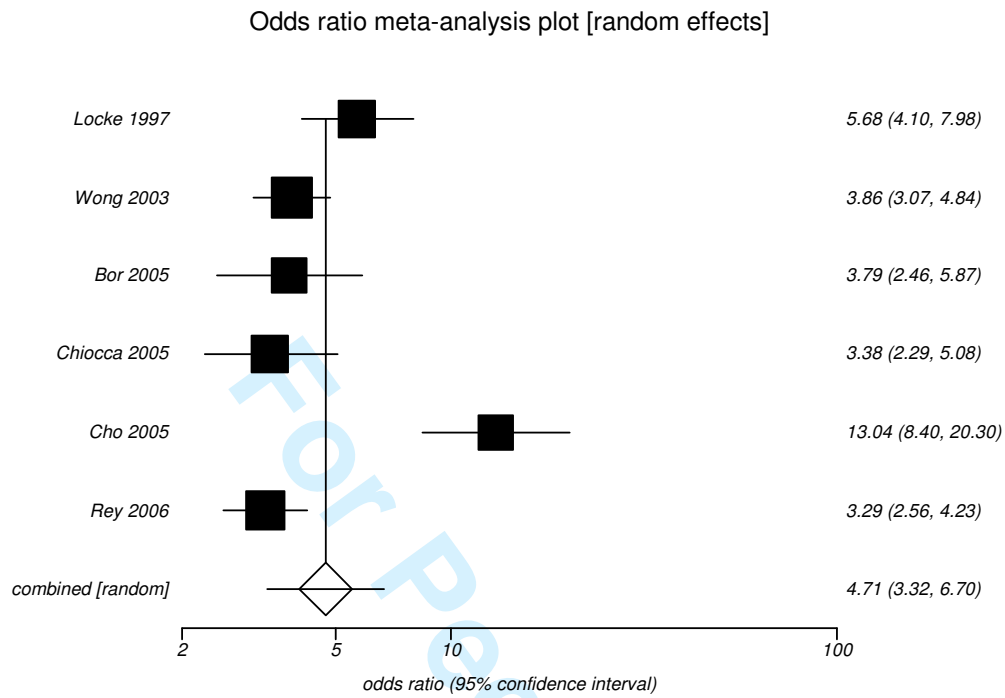


Figure 4. Pooled Odds Ratio for **Non-cardiac** Chest Pain in Individuals with Occasional Symptoms of GERD Compared with Those Without.

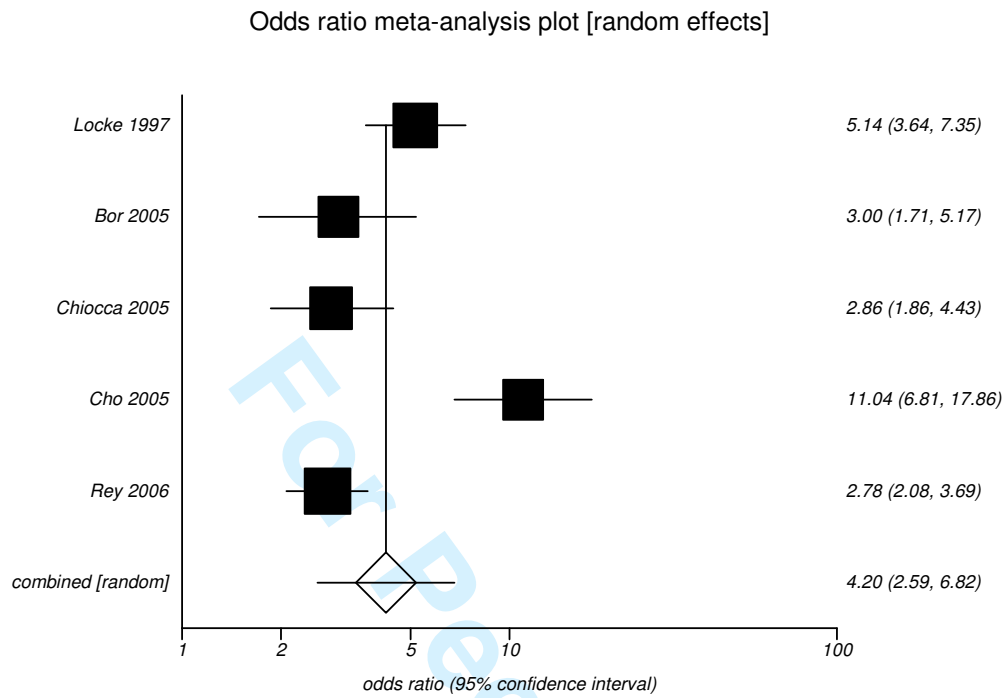
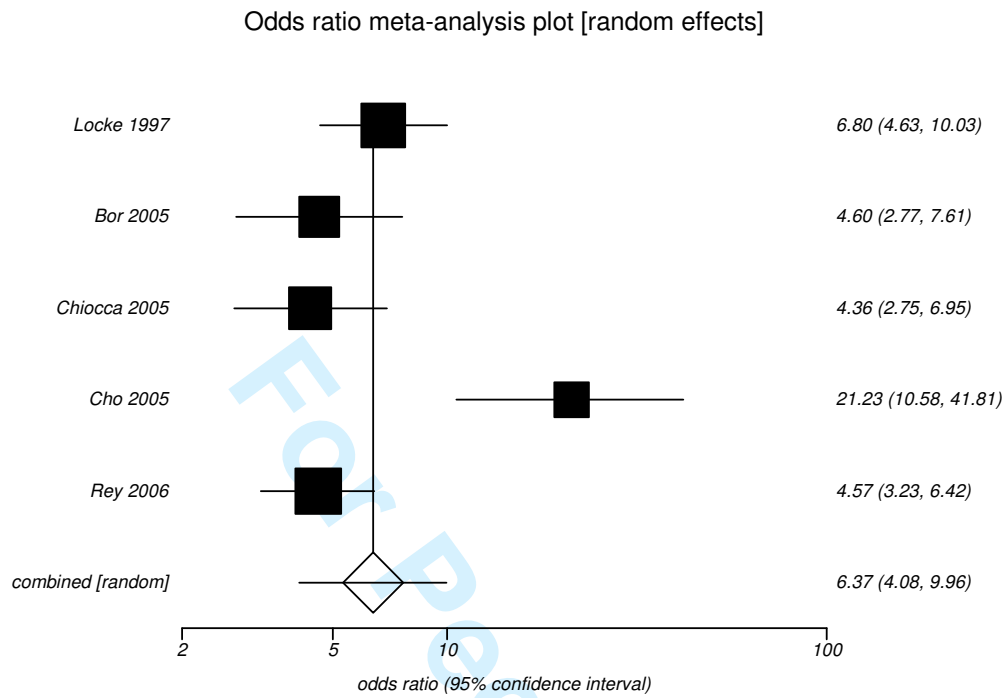


Figure 5. Pooled Odds Ratio for **Non-cardiac** Chest Pain in Individuals with Frequent Symptoms of GERD Compared with Those Without.



Ford *et al.*

28 of 33

Table 1: Eligibility Criteria

Cohort studies, case-control studies, cross-sectional surveys, or randomised controlled trials

Recruited adults (>90% of participants aged ≥ 15 years)

Participants recruited from the general population / community*

Reported prevalence of **non-cardiac** chest pain (according to self-report, questionnaire data, specific diagnostic criteria[†], or a physician's opinion)

Sample size of ≥ 50 participants

*Convenience samples excluded

[†]Rome I, II, or III criteria

For Peer Review

Ford *et al.*

29 of 33

Table 2. Characteristics of Included Studies.

Study	Country	Method of data collection	Criteria used to define non-cardiac chest pain	Method used to exclude cardiac causes of chest pain	Sample size	Number with non-cardiac chest pain (%)
Ruth 1991 (11)	Sweden	Postal questionnaire	Questionnaire-defined	Self-report on questionnaire	328	40 (12.2)
Drossman 1993 (25)	USA	Postal questionnaire*	Rome I	Self-report on questionnaire	5430	693 (12.8)
Isolauri 1995 (26)	Finland	Postal questionnaire	Questionnaire-defined	Not excluded	1700	244 (14.4)
Locke 1997 (29)	USA	Postal questionnaire*	Questionnaire-defined	Self-report on questionnaire	1511	337 (22.3)

Ford *et al.*

30 of 33

Koloski 2000, (28)	Australia	Postal questionnaire	Rome I	Not excluded	2910	146 (5.0)
Boyce 2006 (21)			Rome II		762	39 (5.1)
Thompson 2002 (31)	Canada	Postal questionnaire*	Rome II	Not excluded	1149	23 (2.0)
Eslick 2003 (8)	Australia	Postal questionnaire*	Questionnaire-defined	According to either a physician's diagnosis of ischemic heart disease or the Rose angina questionnaire	646	210 (32.5)
Mjornheim 2003 (30)	Sweden	Postal questionnaire	Questionnaire-defined	Not excluded	242	13 (5.4)
Wong 2004 (12)	Hong Kong	Telephone interview*	Questionnaire-defined	According to either a physician's diagnosis of ischemic heart disease or the Rose angina questionnaire	2209	307 (13.9)

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Ford *et al.*

31 of 33

Bor 2005 (20)	Turkey	Interview-administered questionnaire*	Questionnaire-defined	Self-report on questionnaire	630	123 (19.5)
Chen 2005 (22)	China	Interview-administered questionnaire*	Questionnaire-defined	Not excluded	3338	257 (7.7)
Cho 2005, (24)	South Korea	Interview-administered questionnaire*	Questionnaire-defined	Self-report on questionnaire	1417	112 (7.9)
Jeong 2008 (27)			Rome II		1417	21 (1.5)
Chiocca 2005 (23)	Argentina	Postal questionnaire*	Questionnaire-defined	Self-report on questionnaire	839	202 (24.1)
Rey 2006 (13)	Spain	Telephone interview*	Questionnaire-defined	Self-report on questionnaire	2500	309 (12.4)

* Validated questionnaire

Ford *et al.*

32 of 33

Table 3. Pooled Prevalence of *Non-cardiac* Chest Pain According to Geographical Location.

	Number of studies	Number of subjects	Pooled prevalence	95% confidence interval	I ²	P value for I ²
All studies	14	24 849	13.0	9.0 – 16.0	98.6%	< 0.001
European studies	4	4770	11.0	9.0 – 14.0	84.9%	< 0.001
North American studies	3	8090	11.0	3.0 – 23.0	99.4%	< 0.001
South East Asian studies	3	6964	10.0	6.0 – 14.0	96.7%	< 0.001
Australasian studies	2	3556	16.0	0.2 – 50.0	N/A	N/A

* N/A; not applicable, too few studies to assess heterogeneity

Table 4. Pooled Prevalence of **Non-cardiac Chest Pain According to Criteria Used to Define its Presence.**

	Number of studies	Number of subjects	Pooled prevalence	95% confidence interval	I ²	P value for I ²
All studies	14	24 849	13.0	9.0 – 16.0	98.6%	< 0.001
Criteria used to define non-cardiac chest pain						
Questionnaire-defined	11	15 360	15.0	11.0 – 19.0	98.0%	< 0.001
Rome II	3	3328	2.7	1.1 – 4.9	91.4%	< 0.001
Rome I	2	8340	9.0	3.0 – 18.0	N/A*	N/A*

* N/A; not applicable, too few studies to assess heterogeneity

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REVIEWERS' COMMENTS TO AUTHOR:**Reviewer: 1****Comments for Transmission to the Authors****Overall, this meta-analysis by Ford et al is a good study.**

We thank the reviewer for their kind comments. No response required.

Most of the limitations, such as the inclusion of only 16 studies, have been correctly addressed by the authors in the discussion

We thank the reviewer for their kind comments. No response required.

However, I have an important concern about the use of the term functional chest pain as synonymous of non-cardiac chest pain. The definition of functional chest pain requires the exclusion of esophageal and non esophageal disorders. While the term non cardiac chest pain denotes exclusively that the heart is not the origin of the pain and can include patients with a variety of conditions such as GERD. Indeed, most of the studies included in this meta-analysis, with some exceptions, were designed to assess the prevalence of non cardiac chest pain not the prevalence of functional chest pain. The increased association found between GERD and functional chest pain can therefore be explained by the fact that the authors are including patients with GERD related NCCP in the analysis.

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3 We agreed with the reviewer that these two conditions are not synonymous, and
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5 therefore we amended the term “functional chest pain” to “non-cardiac chest pain”
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7 throughout the paper. This modification necessitated some further minor changes to
8
9 the Introduction and Discussion sections of the paper.
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15 **On the other hand, the studies chosen in the discussion to explain the role of**
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17 **GERD in the generation of symptoms in patients with functional chest pain were**
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19 **probably not the best for this purpose. It would be better to include some other**
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21 **references showing that acid exposure can sensitize the esophagus contributing**
22
23 **to the development of visceral hypersensitivity. The authors may probably find**
24
25 **useful to include some of the following references:**
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29 **1. Hu WH, Martin CJ, Talley NJ. Intraesophageal acid perfusion sensitizes the**
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31 **esophagus to mechanical distension: a Barostat study. Am J Gastroenterol.**
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33 **2000;95(9):2189-94.**
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36 **2. Sarkar S, Aziz Q, Woolf CJ et al. Contribution of central sensitisation to the**
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38 **development of non-cardiac chest pain. Lancet 2000;356:1154-9.**
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41 **3. Sarkar S, Thompson DG, Woolf CJ et al. Patients with chest pain and occult**
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43 **gastroesophageal reflux demonstrate visceral pain hypersensitivity which may be**
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45 **partially responsive to acid suppression. Am J Gastroenterol. 2004;99(10):1998-**
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47 **2006.**
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53 We are very grateful to the reviewer for this suggestion to improve our paper. We
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55 added a sentence to the Discussion section of the paper reporting data from these
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57 references on page 15, lines 17 to 20: “Some investigators have demonstrated that
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59 acid exposure reduces pain thresholds in the oesophagus in healthy volunteers, (37)
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3 and that this effect is exaggerated in patients with non-cardiac chest pain, (38) and
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6 may be attenuated by PPIs. (39)”
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For Peer Review

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3 **Reviewer: 2**
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5 **Comments for Transmission to the Authors**
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8 **I have reviewed the data and references for this manuscript.**
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10 **I have not identified any previous meta-analyses addressing the epidemiology of**
11 **functional chest pain. I have not identified any further studies that may be**
12 **eligible for inclusion.**
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17 **I have checked the extracted data and references which are all correct.**
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22 We thank the reviewer for performing this check. No response required.
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3 **Reviewer: 3**
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5 **Comments for Transmission to the Authors**
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8 **This well-written systematic review has been well executed and is the first**
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10 **summation of data related to the prevalence of functional chest pain. I have a**
11
12 **few minor concerns, more based on principle than on the author's analyses:**
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16
17 **1. It is not clear to this reviewer that there is a pressing need to estimate the**
18 **prevalence of functional chest pain. Perhaps the background could make a**
19 **stronger argument as to why such an estimate is needed.**
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27 We agreed with the reviewer that a rationale for the conduct of the meta-analysis was
28 required and added a sentence to the Introduction section on page 4, lines 23 to 25,
29 and page 5, lines 1 to 2: "Systematic analysis of studies that report these types of data
30 is important to allow physicians consulting with patients complaining of these
31 symptoms to provide more precise estimates of the prevalence and risk factors for the
32 condition, as well as identify areas where further research is needed."
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43 **2. The strong association between GERD and functional chest pain challenges**
44 **the definition of such discomfort as "functional". At the end of the day, I'm not**
45 **sure what the phenomenon being captured in this study represents, as most of**
46 **the prevalent cases are reflux-associated and hence part of a GERD presentation.**
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55 Please see our response to reviewer one's first comment above.
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4 **3. There is significant heterogeneity among studies in relation to the**
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6 **inclusion/exclusion of cardiac and reflux-related symptoms. The lack of a**
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8 **standard definition of functional chest pain makes the pooled estimate less**
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10 **meaningful.**
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15 We agreed with the reviewer. We added this point as a further limitation of our study
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17 in the Discussion section on page 14, lines 18 to 20: “Finally, the differences in
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19 definitions of functional chest pain used in the identified studies may limit the
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21 usefulness of the pooled estimate of prevalence.”
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Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4 and 5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6 and 29
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6

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5	Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.
6			
7	Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.
8			
9			
10	Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.
11			
12			
13	Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).
14	Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.
15			
16	Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).
17			
18	Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.
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22	RESULTS		
23	Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.
24			
25	Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.
26			
27	Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).
28			
29	Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.
30			
31	Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.
32			
33	Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).
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35	Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).
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38	DISCUSSION		
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Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13-16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13-16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	16

Peer Review

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