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Prevalence, risk factors and associations of primary Raynaud's phenomenon: systematic review and meta-analysis of observational studies

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ABSTRACT

Objective: To systematically review the literature with regard to the prevalence, incidence, risk factors and associations of primary Raynaud's phenomenon (PRP).

Method: A systematic review of the literature of observational studies for PRP was undertaken using five electronic databases. Any studies reporting prevalence, incidence and risk factors of PRP were collected. Relative risk or OR and 95% CI were extracted or calculated to present the association between risk factors and PRP. Random effects model was used to pool the results.

Results: 33 articles assessing a total of 33 733 participants were included in this analysis (2 cohort, 17 cross-sectional and 14 case–control studies). The pooled prevalence of PRP was 4.85% (95% CI 2.08% to 8.71%) in the general population. The pooled annual incidence of PRP was 0.25% (95% CI 0.19% to 0.32%). Risk factors and associations for PRP included female gender (OR=1.65, 95% CI 1.42 to 1.91), family history (OR=16.6, 95% CI 7.44 to 36.8), smoking (OR=1.27, 95% CI 1.06 to 1.53), manual occupation (OR=2.66 95% CI 1.73 to 4.08), migraine (OR=4.02, 95% CI 2.62 to 6.17), cardiovascular disease (OR=1.69, 95% CI 1.22 to 2.34) and marital status (married, OR=0.60, 95% CI 0.43 to 0.83). The definition of PRP varied considerably between studies.

Conclusions: This is the first systematic review of the prevalence, incidence, risk factors and associations of PRP. Further study using uniform strict criteria for the condition is required to confirm these findings, particularly the possible association with cardiovascular disease.

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Strengths and limitations of this study

- This is the first meta-analysis of the literature for the global epidemiology of primary Raynaud's phenomenon (PRP).
- The prevalence and incidence of PRP in different countries were estimated. Female gender, positive family history, smoking and migraines were found to be the major risk factors for PRP.
- The lack of original data restricted an adequate estimation of the age effect on PRP.
- Different definitions of PRP handicapped a comparison between countries.

INTRODUCTION

In the 19th century, Maurice Raynaud first described Raynaud's phenomenon (RP) as an episodic, symmetrical, vasospastic disorder resulting in classic triphasic colour change, trophic changes limited to the skin and uncomfortable sensory symptoms of the extremities in the absence of arterial occlusion.[1] Further criteria have been suggested to distinguish primary RP (PRP) from secondary RP, which include detail regarding symptom duration, negative autoimmune serology, normal serum inflammatory markers and capillaroscopy and the clinical absence of any underlying disease.[1–4] Use of colour charts to aid diagnosis has also been used.[4 5] Despite this, there is no unifying definition that is used worldwide for PRP.

There have been a number of studies performed in various countries reporting the prevalence of RP. The reported prevalence ranges from less than 1% (in men) and up to 20% (in women) depending on definitions and population selected.[6] In contrast, few studies have examined the incidence of PRP, and the true burden of PRP in the general population remains unclear. PRP is thought to be more common in women, particularly when it develops at a young age.[7] There are also reports of a hereditary component and links with other vasospastic conditions such as migraine.[8–11] It is uncertain whether other comorbidities or risk factors particularly related to vascular diseases such as ischaemic heart disease and/or smoking have an association with PRP.

The primary objective of this study was to perform a systematic review of observational studies to summarise the literature with regard to the prevalence, incidence and risk factors/associations of PRP. The secondary objective was to examine the current definitions used to define PRP worldwide.

METHODS
Literature search—data sources and search strategy
A comprehensive systematic literature search was undertaken in June 2011 and rerun in October 2014 using five databases: MEDLINE, EMBASE, CINAHL, AMED and PubMed. The search terms for "Raynauds" or "Raynauds disease" were combined with the terms "epidemiology", "prevalence", "risk" or "incidence" to generate the citations (see online supplementary appendix 1 for full details of search strategy). "Cross sectional", "case-control" or "cohort" studies and "systematic review" were also applied for types of studies.

Abstracts were reviewed and the full papers were sought where abstracts were felt to be relevant. Any duplicate articles were excluded (figure 1 and appendix 1 and 2). Where there was difficulty in article retrieval, the authors were contacted via email. The literature search and abstract review was completed by RG and validated by WZ. Reference lists of the review articles were also examined for relevant studies.

Inclusion and exclusion criteria
Inclusion criteria: studies reporting the prevalence and/or incidence of PRP; studies reporting potential risk factors associated with PRP; studies reporting human data on PRP in people of any age; studies in any language (4 articles required translation—1 Japanese, 1 Turkish, 1 French, 1 Italian).

Exclusion criteria (figure 1): studies assessing treatment of PRP; studies involving participants with RP secondary to other diseases; studies assessing RP in a specific occupation, for example, people using vibration tools; unpublished material, case reports, editorials, letters or reviews.

Data extraction and quality assessment
Study characteristics including age range, gender ratio and total number of participants in the study were documented. The study design, country, setting (ie, hospital

Figure 1 Flow chart diagram showing results of systematic literature search.
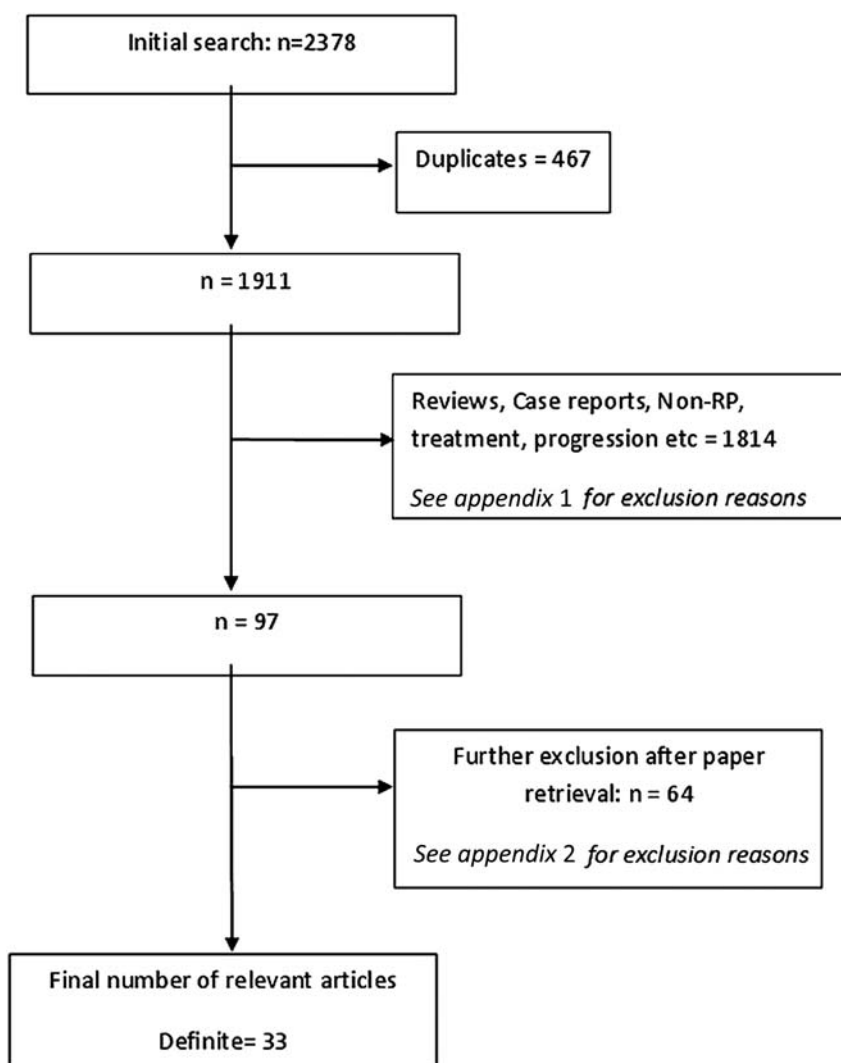
or community based) were also assessed and noted. If more than one article used the same study population, the article where the data were felt to be presented most clearly was used in the study. The definition of PRP and instruments used to confirm the condition were also documented. The number of cases of PRP out of the number of people studied in a certain time in the general population was documented as unadjusted crude prevalence. Incidence figures were documented if the number of new cases of PRP in the population at risk studied over a given period of time was stated.

Individual OR, relative risk (RR) or HR and their 95% CI were extracted or calculated for the following:

▶ Constitutional: age, gender
▶ Environmental: employment, education, marital status and sex hormone medications
▶ Genetic: family history in 1st degree relatives
▶ Associations: smoking, alcohol, cardiovascular disease (CVD) and migraine

All studies were reviewed by RG to assess study quality and for data extraction and were validated by WZ. An independent reviewer (RK) assessed a random selection of articles to ensure quality of data extraction. Study quality was assessed according to study design (cohort, cross-sectional and case–control), setting (community or hospital), sample size, case definition, exposure definition, confounding factors and adjustment. Quality scoring for studies was not performed as it is not possible or fair to assign equal weight to different quality aspects related to the study. However, current consensus standards of reporting meta-analysis of observational studies in epidemiology[12] were followed, and subgroup/sensitivity analysis was undertaken to examine the changes of the estimate according to different quality aspects.

Statistical analysis

Individual data for prevalence and incidence were derived from the original report either directly or indirectly from the information provided in each study. The pooled proportion was calculated as the back transform of the weighted mean of the transformed proportion, using inverse arcsine variance weights for the fixed effects model and DerSimonian and Laird[13] weights for the random effects model.[14] Cumulative incidence and 95% CI were transformed into incidence rate data (ie, incidence per 100 person-years) and pooled incidence rate was estimated. Individual data for OR, RR and HR were pooled to present the overall relative risk of all observational studies, as well as separately for each specific risk measure or study design as appropriate. Random effects mode was used to pool the data.[15] Heterogeneity was examined using Forest plots, Cochran Q tests and I^2 statistic as a measure for inconsistency due to chance.[16 17] Publication bias was assessed using funnel plots and Eggers test or the Harbord test if the number of studies included in the meta-analysis was too small (≤4).[18] All analyses were undertaken using StatsDirect V.2.7.9.

RESULTS

Study characteristics

In total, 2378 citations were found in the initial literature search. All 467 duplicates were removed and 1878 citations were excluded as they did not meet the inclusion criteria (figure 1). The final number of studies available for analysis was 33 (33 733 participants). There were two cohort studies[19 20] (1 632 participants), 17 cross-sectional studies[6 21–36] (25 797 participants) and 14 case–control studies[7–11 37–45] (6 304 participants; table 1). Data for incidence and prevalence were taken from cohort and cross-sectional studies, respectively. Data for risk factors were taken from all studies as long as the results were reported.

Age ranges across different study designs were as follows: case–control (16–79 years), cohort (18–81 years), cross-sectional (12–84 years). Sixty-seven per cent of the studies involved participants recruited in a community-based setting. The majority of studies were conducted in Europe (18)[6 9 19 22 24 26 27 29 30 32 33 35–37 39 41–43] or the USA (10),[7 8 10 11 20 21 23 38 40 44] however, other countries of origin included Japan (2),[25 28] New Zealand (1)[34] and Israel (1).[45] One comparison study included participants from the USA and France.[31]

Participants were surveyed by means of phone, face-to-face interview and/or postal questionnaire. Twenty-six studies included a physical examination that also included blood testing (including serology), nailfold capillaroscopy and use of colour chart/photographs (table 1).

Ten studies used specific criteria to define PRP (3 studies[8 21 32] Allen and Brown;[1] 3[9 36 37] LeRoy and Medsger[2]; 4[6 22 33 34] UK Scleroderma Study Group[4]). The remaining studies used a combination of cold sensitivity, varying degrees of colour change and sensory symptoms via questionnaire or interview to define PRP. Colour charts or photographs to indicate colour change were used in 12 studies[6 7 9 10 19 20 25 28 29 31 33 35] and nailfold capillaroscopy was performed as part of the examination in 10 studies.[8 9 19 31 36 37 39 41–43] In 15 studies, blood testing including serology and/or inflammatory markers was performed.[6 8 9 11 24 30 33 36 37 39–44]

Studies with clear definition of PRP or clear exclusion criteria for secondary RP were categorised as 'definite PRP' in this study. Studies with less clear definition of PRP were categorised as 'possible PRP'. Studies with clear definition of secondary RP were excluded.

Prevalence of PRP

The overall prevalence for *definite* PRP varied from 1.6% to 7.2% in six cross-sectional studies in the general population (women: 2.1–15.8% and men: 0.8–6.5%).[21 23 25 27 29 33] The pooled prevalence was 4.85% (95% CI 2.08% to 8.71%; figure 2), with 5.74% (95% CI 2.74% to 9.75%) in women and 4.12% (95% CI 1.60% to 7.74%) in men. We used the Harbord test to detect publication bias (1.59, 92.5% CI −21.6 to 24.8; p=0.87). The overall prevalence for *possible* PRP ranges from 3.98% to 12.7% (women: 4.5–17.9% and men: 3.4–7.2%) in three cross-sectional

Table 1 Characteristics of studies

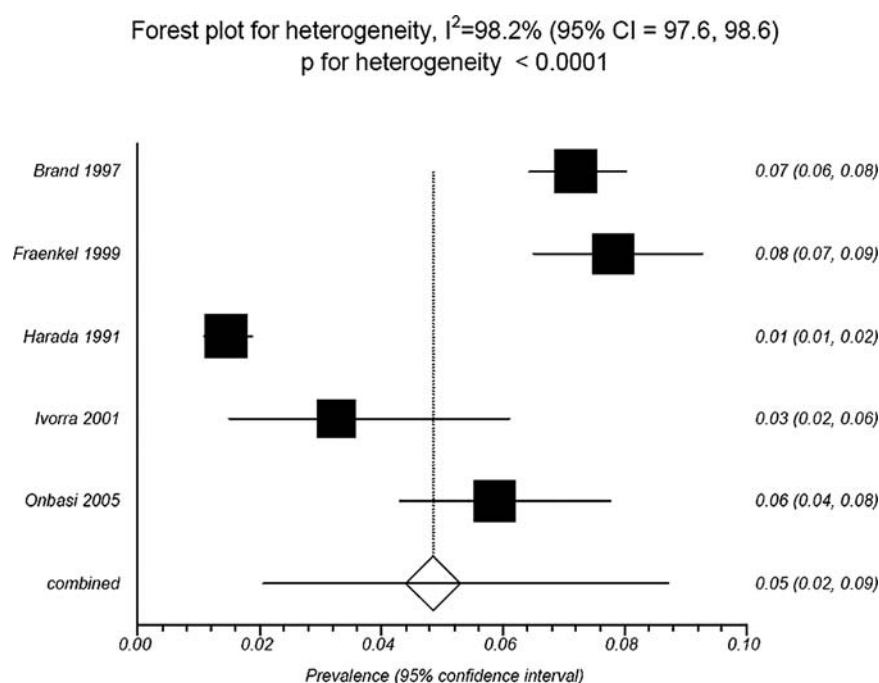|	Cohort	Cross-sectional	Case–control	All studies
Number of studies	2	17	14	33
Number of participants	1632	25 797	6304	33 733
Age	18–81	12–84	16–79	12–84
Setting				
Community based	2	14	5	21
Hospital based	0	2	9	11
Community and hospital	0	1	0	1
Region of study				
USA	1	2	7	10
Europe	1	11	6	18
France and USA	0	1	0	1
Japan	0	2	0	2
New Zealand	0	1	0	1
Israel	0	0	1	1
Diagnosis*				
Questionnaire	0	5	2	7
Questionnaire+examination	2	9	12	23

*Diagnosis was classified as questionnaire based or questionnaire and examination based. The former includes phone survey, postal questionnaire and face-to-face interview whereas the latter includes clinical examination, blood testing including serology, use of colour chart/photographs and capillaroscopy in addition to the questionnaire. Colour chart/photographs were used in 12 studies (cohort 2, cross-sectional 7, case–control 3) and capillaroscopy was used in 10 studies (cohort 1, cross-sectional 2, case–control 7).

studies.[26 34 35] The prevalence in specific populations varies depending on the studies (table 2).

In six studies assessing the general population we found the lowest prevalence of PRP in Japan, with an overall prevalence of 1.6 (2.1% in women, 1.1% in men).[25] Highest overall prevalence figures were found in the USA with a median prevalence of 7.5% (7.8% in women, 5.8% in men).[21 23] A study from France also showed high prevalence figures of 11.75% in women and 6.3% in men (median values;[31] table 3).

Five studies reported prevalence of PRP by age.[6 28–30 34] Three did not find any age-related prevalence.[6 28 30] Purdie et al[34] reported a higher prevalence of PRP in younger compared to older age groups, whereas Fraenkel et al[38] reported higher prevalence in older age groups in men (adjusted OR=2.3, 95% CI 1.0 to 5.2 highest vs lowest tertile) but not in women (adjusted OR=0.9, 95% CI 0.4 to 1.6). Jones et al[29] also showed a slight increase in prevalence by age in yearly increments between ages 12 and 15 years.

Figure 2 Forest plot showing the pooled prevalence of definite primary Raynaud's phenomenon for five general population studies.

Forest plot for heterogeneity, I^2=98.2% (95% CI = 97.6, 98.6)
p for heterogeneity < 0.0001

Study	Prevalence (95% CI)
Brand 1997	0.07 (0.06, 0.08)
Fraenkel 1999	0.08 (0.07, 0.09)
Harada 1991	0.01 (0.01, 0.02)
Ivorra 2001	0.03 (0.02, 0.06)
Onbasi 2005	0.06 (0.04, 0.08)
combined	0.05 (0.02, 0.09)

Prevalence (95% confidence interval)

Table 2 Prevalence of primary Raynaud's phenomenon in 17 studies

First author	Country	Setting	Sample size	Age mean (SD)/range	Female (%)	Prevalence Overall (%)	Prevalence Female (%)	Prevalence Male (%)
Prevalence of definite primary Raynaud's phenomenon in general population studies								
Brand (1997)	Boston, USA	Com	4182	51.8	52.2	7.2	7.8	6.5
Fraenkel (1999)	Boston, USA	Com	1525	53.9	52.5	7.8	9.6	5.8
Harada (1991)	Ehime, Japan	Hosp	3873	20–70	51.6	1.6	2.1	1.1
Ivorra (2001)	Valencia, Spain	Com	276	54.4	74.3	3.3	3.4	2.8
Maricq (1997)*	South Carolina, USA	Com	2086/432	18+	NS	NS	3.4	0.8
	Toulon, France	Com	1998/189	18+	NS	NS	11.4	2.8
	Nyons, France	Com	1996/345	18+	NS	NS	5.8	6.2
	Grenoble, France	Com	2069/272	18+	NS	NS	12.1	6.4
	Tarentaise, France	Com	2000/296	18+	NS	NS	15.8	6.3
Onbasi (2005)	Van, Turkey	Com	768	29.2 (10.4)	46.6	5.9	7.0	4.9
Prevalence of possible primary Raynaud's phenomenon in general population studies								
Heslop (1983)	Southampton, UK	Com	450	20–59	50.9	12.7	17.9	7.2
Purdie (2009)	New Zealand	Com	234	18+	56.8	11.5	17.3	4.0
Sahin (2003)	Van, Turkey	Hosp	251	28.9	53.4	3.98	4.5	3.4
Prevalence of primary Raynaud's phenomenon in single gender only population studies								
Leppert (1987)	Vasteras, Sweden	Com	2705	18–59	100	–	15.6	–
Olsen (1978)	Copenhagen, Denmark	Com	67	21–50	100	–	22.4	–
Tzilalis (2011)	Athens, Greece	Com	3912	18–28	0	–	–	0.18
Prevalence of primary Raynaud's phenomenon in studies using hospital personnel								
Cakir (2008)	Edirne, Turkey	Com	1414	27.2	59.3	3.6	4.8	1.9
Gallo (1994)	Milan, Italy	Com	1920	15–84	68	4.2	4.5	3.9
Iwata (1987)	Japan	C&H	1470	18–59	56.8	4.8	6.5	2.5
Voulgari (2000)	Ioannina, Greece	Com	500	33.7 (6.2)	77.8	5.2	6.4	0.9
Prevalence of primary Raynaud's phenomenon in studies assessing children								
Jones (2003)	Manchester, UK	Com	716	12–15	50.8	14.9	17.6	12.2

*This study involved two stage sampling.
C&H, Community and Hospital; Com, Community; Hosp, Hospital; NS, not significant.

Incidence of primary Raynauds phenomenon

Only two studies reported incidence rates.[19] [20] Carpentier *et al* reported an annual incidence rate of 0.25% (95% CI 0.17% to 0.33%), with 0.24% in women and 0.26% in men and Suter *et al* reported a 7-year incidence of 1.87% (2.2% in women and 1.5% in men), which was converted to an annual incidence rate of 0.26% (95% CI 0.17% to 0.39%). The pooled annual incidence rate of these two studies was therefore 0.25% (95% CI 0.19% to 0.32%).

Risk factors and associations

In 18 studies (23 197 participants), there was a positive association between female gender and PRP (OR=1.65, 95% CI 1.42 to 1.91).[6] [7] [9] [20–29] [33–35] [37] [44] Family history, assessed in two studies looking at first-degree relatives, also had a positive significant association with PRP (OR=16.6, 95% CI 7.44 to 36.8).[8] [9] No significant association was found with education beyond primary school age[6] [37] (table 4). Manual occupation (not including vibration

Table 3 Regional variation of prevalence of primary Raynaud's phenomenon for general population studies including prevalence rates for males and females

Country	Number of studies	Number of participants	Prevalence (%) Male	Prevalence (%) Female	Prevalence (%) Total
USA*	3	6 139	5.8	7.8	7.5
France*	1	1 102	6.3	11.75	–
Spain	1	276	2.8	3.4	3.3
Turkey	1	768	4.9	7.0	5.9
Japan	1	3 873	1.1	2.1	1.6
Total	6	12 158			

*Median values calculated for prevalence. The US gender figures include data from Maricq *et al*[31] (France and the USA). Total US prevalence figure includes data from two US-only studies.

Table 4 Risk factors of Raynaud's phenomenon

Risk factor	Number of studies (Number of participants)	Pooled OR	95% CI	I²% (95% CI)*	p (heterogeneity)
Female	18 (23 197)	**1.65**	**1.42 to 1.91**	17.2 (0 to 53)	0.25
Family history of RP	2 (421)	**16.6**	**7.44 to 36.8**	–	0.34
Marital status†	4 (2 650)	**0.60**	**0.43 to 0.83**	16.9 (0 to 73)	0.31
Education‡	2 (891)	1.52	0.89 to 2.59	–	0.24
Manual occupation	1 (3 873)	**2.66**	**1.73 to 4.08**	–	–
Smoking	9 (8 501)	**1.27**	**1.06 to 1.53**	6.2 (0.8 to 57.1)	0.38
Alcohol	2 (4 967)	0.33	0.02 to 5.37	–	<0.0001
Migraine§	6 (2 595)	**4.02**	**2.62 to 6.17**	35.9 (0 to 73.6)	0.17
Diabetes	1 (1 525)	0.51	0.2 to 1.27	–	–
Hypertension	2 (1 711)	1.00	0.67 to 1.48	–	0.46
Hypercholesterolaemia	1 (1 525)	0.86	0.53 to 1.40	–	–
Coronary heart disease	1 (81)	0.58	0.1 to 3.31	–	–
Cardiovascular disease¶	1 (3 442)	**1.69**	**1.22 to 2.34**	–	–
*Helicobacter pylori***	2 (265)	0.91	0.51 to 1.63	–	0.07
CP	2 (268)	0.69	0.34 to 1.38	–	0.88
Oestrogen replacement therapy††	2 (1 242)	**2.34**	**1.42 to 3.84**	–	0.81

Bold typeface indicates statistically significant results.
*The I² values are stated where more than three studies were assessed.
†Marital status references used are single/separated/widowed/divorced apart from Fraenkel et al[38] and Keil et al,[7] where references used are widowed/separated/divorced.
‡References for education used are primary school[37] and <12 years education.[6]
§O'Keeffe[11] did not report whether their calculation for OR was adjusted/unadjusted. All other reported calculations for OR are unadjusted.
¶Cardiovascular disease includes history of angina, myocardial infarction, coronary insufficiency, intermittent claudication, congestive cardiac failure, stroke and transient ischaemic attack.
**Positive investigation for *H. pylori* uses urea breath test[41] and serology.[39]
††Adjusted for age, BMI, alcohol, cigarettes and B adrenoreceptor antagonists in the study by Fraenkel et al.[38]
BMI, body mass index; CP, contraceptive pill; RP, Raynaud's phenomenon.

tool use) had an OR of 2.66 (95% CI 1.73 to 4.08) in one study of 3873 participants.[25] In four studies, being married was associated with a lower risk of PRP with OR of 0.60 (95% CI 0.43 to 0.83) compared with being single/divorced/widowed.[6–7 23 37] Smoking was found to have an association in nine studies giving a pooled OR of 1.27 (95% CI 1.06 to 1.53).[7 9–11 20 22 23 32 44] Alcohol use,[23 44] participants with positive *Helicobacter pylori* investigations[39 41] and those with conditions such as diabetes,[23] hypertension[11 23] and hypercholesterolaemia[23] did not have a significant association with PRP.

Migraine had a positive significant association with a pooled OR of 4.02 (95% CI 2.62 to 6.17) in six studies.[6 9–11 22 45] One study of 3442 participants reported a positive association of CVD with PRP with an OR of 1.69 (95% CI 1.22 to 2.34).[44] CVD in this study included a history of ischaemic heart disease, intermittent claudication, congestive cardiac failure and cerebrovascular disease. A single study using 81 participants did not show a positive significant association of coronary heart disease with PRP.[40]

A positive association was found in participants taking oestrogen replacement therapy alone in two studies with an OR of 2.34 (95% CI 1.42 to 3.84).[23 38] However, no significant association was found in combined oestrogen and progesterone replacement therapy[38] in postmenopausal women or in contraceptive pill (CP)[10 11] use in two other studies. A study by Smyth *et al*[9] looking at allele

frequencies of known polymorphisms of candidate vasoactive mediator genes (eNOS, BKRG, ET01 and ETA receptor genes) did not show any association. Shemirani *et al*[42] looked at clotting factors in participants with PRP and found a significant association with methyltetrahydrofolate reductase C677T mutations (OR=0.4, 95% CI 0.2 to 0.9) but no difference in other thrombosis-associated alleles (FVLeiden, prothrombin G20210 A).

DISCUSSION

This is the first meta-analysis of the literature for the prevalence, incidence, risk factors and associations of PRP. Overall, the pooled mean prevalence of PRP in the general population was 4.85% (95% CI 2.08% to 8.71%; figure 2) and the mean incidence was 0.25% (95% CI 0.17% to 0.33%) per annum.[19] Major risk factors/associations of PRP include female gender, family history of PRP, migraine, smoking, CVD, manual occupation, oestrogren replacement therapy and possibly, marital status (table 4).

Variations in prevalence were observed between countries (table 3), though this could reflect use of different diagnostic criteria rather than real differences in prevalence. The heterogeneity of prevalence figures may also reflect the differences in the way the studies were conducted, the selection of participants (eg, age and gender) and the disease definition. All studies (except for Maricq *et al*[31]) demonstrate a higher prevalence of

PRP in women. This may be due to a relationship with female hormones as two studies found an association between PRP and use of oestrogen replacement therapy alone,[23][38] although no association was found between combined oestrogen and progesterone replacement or the CP.[10–11][38] In contrast, prevalence of PRP does not increase with age in five published studies with a wide age range of participants from 12 up to 84 years.[6][28–30][34] This accords with the clinical observation that PRP usually starts in teenage years and that later development, which is far less common, is characteristic of secondary RP. While the former may be driven predominantly by genetic risk factors, later onset 'primary' Raynaud's may be predominantly influenced by environmental exposures such as vascular microtrauma from manual usage and vibrating tools. In terms of other environmental factors we did find a weak negative association between marital status and PRP with an OR of 0.60 (95% CI 0.43 to 0.83) in those that are married versus single/separated/widowed/divorced.[6–7][23][37] However, there is no plausible biological explanation for this and the reported data may not be free from confounding bias.

The association of CVD and autoimmune disease is well documented and thought to be due to accelerated atherosclerosis as a result of chronic inflammation, treatment such as glucocorticoids as well as the traditional risk factors for CVD.[46–52] A link between CVD and PRP has been shown in only one study[44] and the reason for this association is not known. It is unlikely to be due to an inflammatory process or related to medication, and with PRP having predominance for the female population and onset at a young age, it is not clear if traditional cardiovascular risk factors play a part. However, smoking was found to have a positive association with PRP in our study (OR=1.27, 95% CI 1.06 to 1.53). It is well known that smoking is one of the three (smoking, hypertension and hyperlipidaemia) main risk factors for cardiovascular and cerebrovascular disease.[53–59] Smoking may have the same risk factor for PRP and CVD. Whether smoking causes PRP first and then CVD is an interesting question that deserves further research. More interestingly, we found a very strong association between migraine and PRP (OR=4.02, 95% CI 2.62 to 6.17). It has been previously shown that migraine is due to a cascade of vascular and neural events.[46][47] However, a review by Rosamund suggested that migraine was not shown to be linked with coronary heart disease but possibly shares a common underlying pathophysiology with RA and other vasospastic disorders such as variant angina.[60][61] It is thought there may be other factors that could affect the underlying mecanism for these vasospastic conditions as episodes occur at different times with differing precipitants.[62][63] Further study may help clarify whether PRP is a benign vasospastic disorder or whether there is underlying pathology affecting the vascular wall associated with traditional risk factors seen in CVD.

There are a number of caveats to this study. Firstly, it was striking that there was no uniform definition for diagnosis of PRP. Only 39% of studies looking at prevalence had a precise definition for PRP, thereby reducing the number of studies we used to assess pooled prevalence. It is possible that the variation in definition of PRP together with the way participants were recruited and assessed may have led to underestimation or overestimation of the true prevalence of PRP in the general population. We feel that an amalgamation of the generally more commonly used definitions would ensure that the diagnosis is clear by assessing symptoms, using a colour chart or photographs for confirmation of colour change and carefully exclude underlying conditions including checking for digital infarcts/ulceration, nailfold capillaroscopy, and assessing autoimmune screen and inflammatory markers. Secondly, as our objective was to specifically examine the epidemiology of PRP, a large proportion of studies were excluded because they focused on secondary Raynaud's phenomenon, especially related to connective tissue diseases and vibration white finger. In addition, we also excluded studies that looked at investigation or treatment of PRP. This left only a small number of studies to assess. From the studies included, there was a great deal of variation in the population of participants used. Nine of the 17 studies used investigated participants in the general population, whereas the remainder examined specific populations such as single gender, children or hospital/medical personnel. Furthermore, there was considerable variation in the risk factors addressed in each study and this may have affected the significance and association, or lack of association between the risk factors and PRP. We tried to extract as many risk factors from each study as possible to use in our analysis. In the future, a larger multinational population study may help us to get a better understanding of the disease. This would be particularly useful if standardised criteria were used to include participants in the studies, using strict definition for PRP (as mentioned previously), and data were collected in a similar fashion assessing a wide variety of possible risk factors (particularly related to CVD and vasospastic disorders) for more accurate data analysis.

CONCLUSION
This first systematic review summarises the burden of PRP in the general population using published literature. It is not a rare condition (prevalence 4.85% and annual incidence 0.25%). It starts at a young age, is more common in women, and associates with a family history and with smoking. In addition, people with PRP are four times more likely to have migraine than those without this condition.

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Appendix 1 Exclusion reasons for 1814 papers

Review (219), Case report (34), Letter (14), Webpage (5), Animal studies unrelated to Raynaud's phenomenon (RP) (4), Connective tissue disease (602), Vibration induced disease (169), Diagnosis/investigation of RP (11), Secondary progression from primary RP (4), Drugs related to RP (53), RA/inflammatory arthritis (21), Other musculoskeletal (37), Fibromyalgia (9), Genetics not related to RP (11), Autoantibodies (13), Treatment involving sympathectomy (45), Ophthalmology studies (14), Psychiatric conditions (11), Haematological disease (14), Infectious disease (24), cardiovascular disease (64), Respiratory disease (17), Gastrointestinal disease (27), Renal disease (27), Dermatological (30), Endocrine disease (31), Neurological disease (43), Cancer (106), Drugs not related to RP (63), Vascular intervention (64), Laser Doppler flowmetry (8), Breast implant rupture (4), Others: including motor vehicles, dentists, seafarers, fishermen, aircrafts, breast feeding (17)

Appendix 2 Exclusion reasons for 64 papers

Letter to editor (1)
Review (5)
Diagnosis/Investigation of RP (14)
Secondary RP (39)
Treatment RP (1)
Same patient sample as is already included in another study used (3)
Case only study (1)

Supplementary file

Appendix 1: Medline/Embase/Cinahl/AMED search strategy

Any field
No limitations
1: Randomised control trial (exploded)
2: Double blind (exploded)
3: Single blind (exploded)
4: Placebo (exp)
5: Comparative study (exp)
6: 1 OR 2 OR 3 OR 4 OR 5
7: meta-analysis or systematic review
8: metanalysis exp
9: quantitative review
10: quantitative overview
11: statistical pool
12: 7 or 8 or 9 or 10 or 11
13: Cohort studies exp
14: cohort stud
15: exp prospective studies
16: prospective stud
17: relative risk
18: incidence exp
19: 13 or 14 or 15 or 16 or 17 or 18
20: exp case- control studies
21: case control stud
22: exp retrospective studies
23: retrospective stud
24: exp odds ratio
25: odds ratio
26: 20 or 21 or 22 or 23 or 24 or 25
27: exp cross sectional
28: cross sectional
29: exp risk
30: prevalence exp
31: 27 or 28 or 29 or 30
32: Raynaud Disease
33: Raynaud
34: 32 or 33
35: Epidemiology
36: 19 or 26 or 31 or 35
37: 34 and 36 (incidence or risk or prevalence or epidemiology) and raynauds
38: 32 and 35 (raynauds and epidemiology)
39: 30 and 32 (prevalence and raynaud disease)
40: 18 and 32 (incidence and raynaud disease)
41: 12 and 33 (systematic review and raynauds disease)
42: 6 and 32 (RCT and Raynauds disease)

PubMed search strategy

#1 Search **randomised control trials**
#2 Search **double blind**
#3 Search **single blind**
#4 Search **placebo**
#5 Search **comparative study**
#6 Search **(((((#1) OR #2) OR #3) OR #4) OR #5**
#7 Search **meta-analysis**
#8 Search **systematic review**
#9 Search **quantitative review**
#10 Search **quantitative overview**
#11 Search **statistical pool**
#12 Search **((((#7) OR #8) OR #9) OR #10) OR #11**
#13 Search **cohort studies**
#14 Search **"cohort studies"[All Fields]**
#15 Search **prospective studies**
#16 Search **"prospective studies"[All Fields]**
#17 Search **relative risk**
#18 Search **incidence**
#19 Search **(((((#13) OR #14) OR #15) OR #16) OR #17) OR #18**
#20 Search **case control**
#21 Search **"case control"[All Fields]**
#22 Search **retrospective studies**
#23 Search **"retrospective studies"[All Fields]**
#24 Search **odds ratio**
#25 Search **"odds ratio"[All Fields]**
#26 Search **(((((#20) OR #21) OR #22) OR #23) OR #24) OR #25**
#27 Search **cross sectional**
#28 Search **"cross sectional"[All Fields]**
#29 Search **risk**
#30 Search **prevalence**
#31 Search **(((#27) OR #28) OR #29) OR #30**
#33 Search **Raynauds Disease**
#34 Search **Raynaud**
#35 Search **(#33) OR #34**
#36 Search **Epidemiology**
#37 Search **(((#19) OR #26) OR #31) OR #36**
#38 Search **(#35) AND #37** (incidence or risk or prevalence or epidemiology) and raynauds

#39 Search **(#33) AND #36** raynauds and epidemiology

#40 Search **(#30) AND #33** prevalence and raynaud disease

#41 Search **(#18) AND #33** incidence and raynaud disease

#42 Search **(#12) AND #33** systematic review and raynauds disease

#43 Search **(#6) AND #33** RCT and Raynauds disease

Summary meta-analysis for risk factors/associations (Female)

Stratum	Odds Ratio	SE	Approximate 95% CI		% Weight (fixed, random)		
1	2.57	0.344736	1.31	5.06	3.508497	4.076417	Cakir 2008
2	1.1	0.327019	0.58	2.09	3.898949	4.47044	De Angelis 2008
3	1.57	0.248413	0.71	1.88	6.756849	7.066386	Gallo 1994
4	1.73	0.199749	1.17	2.56	10.45015	9.81425	Fraenkel 1999
5	1.54	0.213248	1.01	2.33	9.169014	8.92689	Jones 2003
6	2.17	0.385362	1.02	4.62	2.807731	3.342234	Keil 1991
7	2.18	0.291754	1.23	3.86	4.89848	5.433383	Harada 1991
8	2.67	0.289061	1.52	4.72	4.990162	5.518575	Iwata 1991
9	5.07	0.560023	1.69	15.18	1.32948	1.668923	Purdie 2009
10	1.22	0.811168	0.25	6.01	0.633684	0.816444	Ivorra 2001
11	2.14	0.286461	1.22	3.75	5.081172	5.602642	Heslop 1983
12	1.46	0.308414	0.8	2.68	4.383549	4.945275	Onbasi 2005
13	0.91	0.380383	0.43	1.91	2.881721	3.421448	Smyth 1999
14	1.48	0.158466	1.08	2.01	16.604425	13.328821	Suter 2007
15	7.55	1.026172	1.01	56.4	0.395962	0.514798	Voulgari 2000
16	1.22	0.206463	0.69	1.55	9.781622	9.359185	Brand 1997
17	1.44	0.190619	0.99	2.09	11.475179	10.480253	Suter 2005
18	1.32	0.661326	0.36	4.81	0.953374	1.213637	Sahin 2003

Fixed effects (inverse variance)
Pooled odds ratio = 1.625034 (95% CI = 1.431853 to 1.844279)
Z (test test odds ratio differs from 1) = 7.519142 P < 0.0001

Non-combinability of studies
Cochran Q = 20.538923 (df = 17) P = 0.2476
Moment-based estimate of between studies variance = 0.016185
I² (inconsistency) = 17.2% (95% CI = 0% to 53%)

Random effects (DerSimonian-Laird)
Pooled odds ratio = 1.647191 (95% CI = 1.424271 to 1.905002)
Z (test test odds ratio differs from 1) = 6.726861 P < 0.0001

Bias indicators
Begg-Mazumdar: Kendall's tau = 0.215686 P = 0.2291
Egger: bias = 1.035266 (95% CI = -0.298385 to 2.368917) P = 0.1193

Summary meta-analysis for risk factors/associations (Female)

Bias assessment plot

Summary meta-analysis plot [fixed effects]

Study		Odds ratio (95% CI)
Cakir 2008		2.57 (1.31, 5.06)
De Angelis 2008		1.10 (0.58, 2.09)
Gallo 1994		1.57 (0.71, 1.88)
Fraenkel 1999		1.73 (1.17, 2.56)
Jones 2003		1.54 (1.01, 2.33)
Keil 1991		2.17 (1.02, 4.62)
Harada 1991		2.18 (1.23, 3.86)
Iwata 1991		2.67 (1.52, 4.72)
Purdie 2009		5.07 (1.69, 15.18)
Ivorra 2001		1.22 (0.25, 6.01)
Heslop 1983		2.14 (1.22, 3.75)
Onbasi 2005		1.46 (0.80, 2.68)
Smyth 1999		0.91 (0.43, 1.91)
Suter 2007		1.48 (1.08, 2.01)
Voulgari 2000		7.55 (1.01, 56.40)
Brand 1997		1.22 (0.69, 1.55)
Suter 2005		1.44 (0.99, 2.09)
Sahin 2003		1.32 (0.36, 4.81)
combined		1.63 (1.43, 1.84)

odds ratio (95% confidence interval)

Summary meta-analysis for risk factors/associations (Female)

Summary meta-analysis plot [random effects]

Cakir 2008	2.57 (1.31, 5.06)
De Angelis 2008	1.10 (0.58, 2.09)
Gallo 1994	1.57 (0.71, 1.88)
Fraenkel 1999	1.73 (1.17, 2.56)
Jones 2003	1.54 (1.01, 2.33)
Keil 1991	2.17 (1.02, 4.62)
Harada 1991	2.18 (1.23, 3.86)
Iwata 1991	2.67 (1.52, 4.72)
Purdie 2009	5.07 (1.69, 15.18)
Ivorra 2001	1.22 (0.25, 6.01)
Heslop 1983	2.14 (1.22, 3.75)
Onbasi 2005	1.46 (0.80, 2.68)
Smyth 1999	0.91 (0.43, 1.91)
Suter 2007	1.48 (1.08, 2.01)
Voulgari 2000	7.55 (1.01, 56.40)
Brand 1997	1.22 (0.69, 1.55)
Suter 2005	1.44 (0.99, 2.09)
Sahin 2003	1.32 (0.36, 4.81)
combined	1.65 (1.42, 1.91)

0.2   0.5   1   2   5   10   100

odds ratio (95% confidence interval)

Summary meta-analysis for risk factors/associations (Family history)

Stratum	Odds Ratio	SE	Approximate 95% CI		% Weight (fixed, random)		
1	11.8	0.540395	4.1	34.1	56.95728	56.95728	Freedman 1996
2	25.9	0.621636	7.66	87.6	43.04272	43.04272	Smyth 1999

Fixed effects (inverse variance)
Pooled odds ratio = 16.551505 (95% CI = 7.441944 to 36.81193)
Z (test test odds ratio differs from 1) = 6.881377 P < 0.0001

Non-combinability of studies
Cochran Q = 0.91092 (df = 1) P = 0.3399
Moment-based estimate of between studies variance = 0
I² (inconsistency) = *% (95% CI = *% to *%)

Random effects (DerSimonian-Laird)
Pooled odds ratio = 16.551505 (95% CI = 7.441944 to 36.81193)
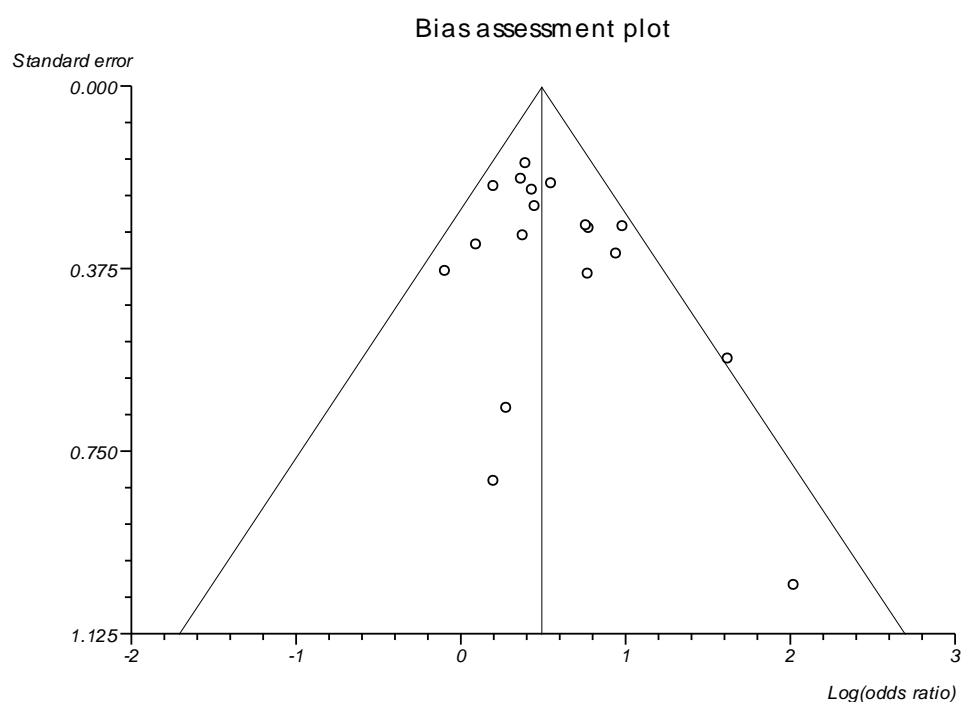Z (test test odds ratio differs from 1) = 6.881377 P < 0.0001

Bias indicators
Begg-Mazumdar: Kendall's <too few strata> *
Egger: bias = <too few strata> (95% CI = * to *) P = *

Summary meta-analysis plot [fixed effects]

Freedman 1996	11.80 (4.10, 34.10)
Smyth 1999	25.90 (7.66, 87.60)
combined	16.55 (7.44, 36.81)

odds ratio (95% confidence interval)
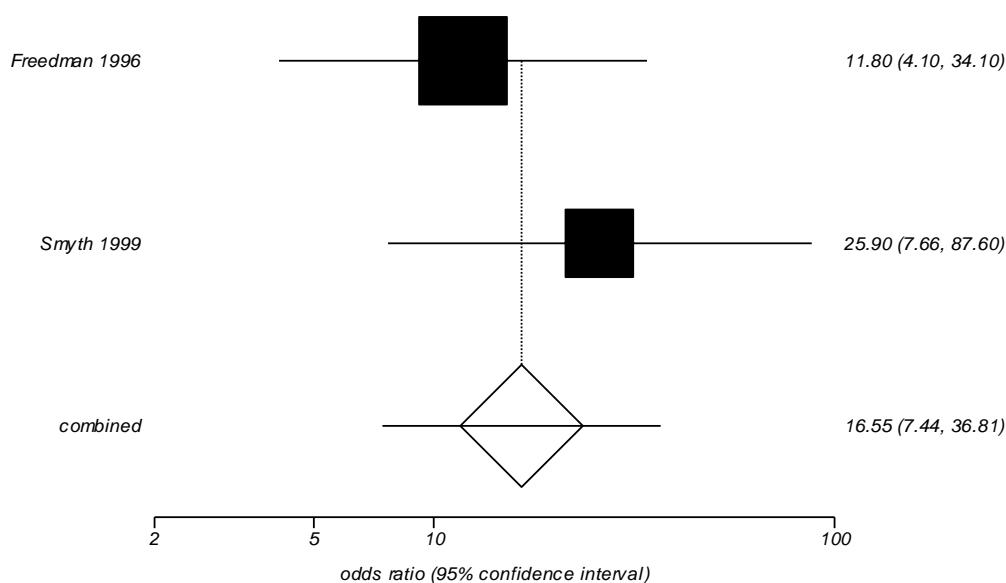
Summary meta-analysis for risk factors/associations (Family history)

Summary meta-analysis plot [random effects]

Study		Odds ratio (95% CI)
Freedman 1996		11.80 (4.10, 34.10)
Smyth 1999		25.90 (7.66, 87.60)
combined		16.55 (7.44, 36.81)

2   5   10   100

odds ratio (95% confidence interval)
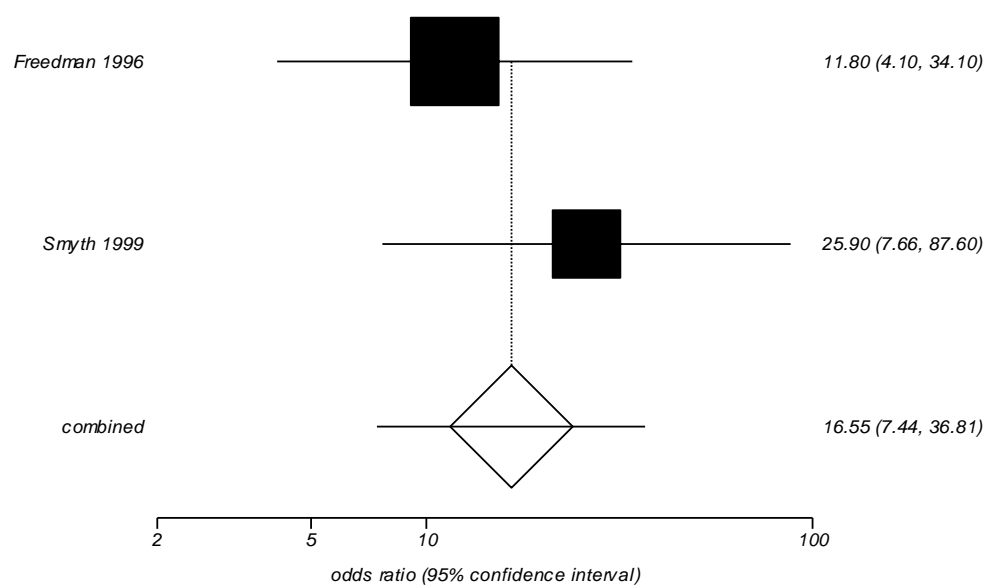
Summary meta-analysis for risk factors/associations (marital status)

Stratum	Odds Ratio	SE	Approximate 95% CI		% Weight (fixed, random)		
1	0.79	0.256126	0.48	1.31	32.962102	32.903595	De Angelis 2008
2	0.49	0.217288	0.32	0.75	45.798641	41.901554	Fraenkel 1999
3	0.39	0.448991	0.16	0.93	10.726264	12.712597	Keil 1991
4	0.87	0.453522	0.36	2.13	10.512994	12.482255	Voulgari 2000

Fixed effects (inverse variance)
Pooled odds ratio = 0.594495 (95% CI = 0.445635 to 0.793078)
Z (test test odds ratio differs from 1) = -3.536538 P = 0.0004

Non-combinability of studies
Cochran Q = 3.61024 (df = 3) P = 0.3067
Moment-based estimate of between studies variance = 0.020022
I² (inconsistency) = 16.9% (95% CI = 0% to 73%)

Random effects (DerSimonian-Laird)
Pooled odds ratio = 0.598367 (95% CI = 0.430621 to 0.831457)
Z (test test odds ratio differs from 1) = -3.059622 P = 0.0022

Bias indicators
Begg-Mazumdar: Kendall's tau = 0.333333 P = 0.75 (low power)
Egger: bias = 0.318768 (95% CI = -9.008236 to 9.645771) P = 0.8966

Bias assessment plot
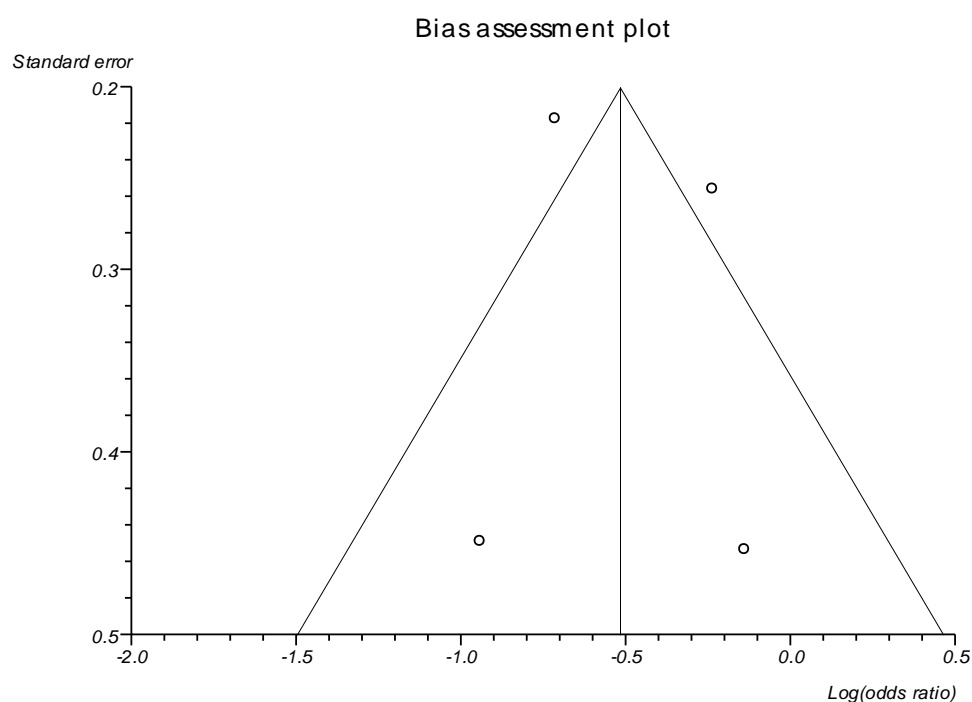
Summary meta-analysis for risk factors/associations (marital status)

Summary meta-analysis plot [fixed effects]
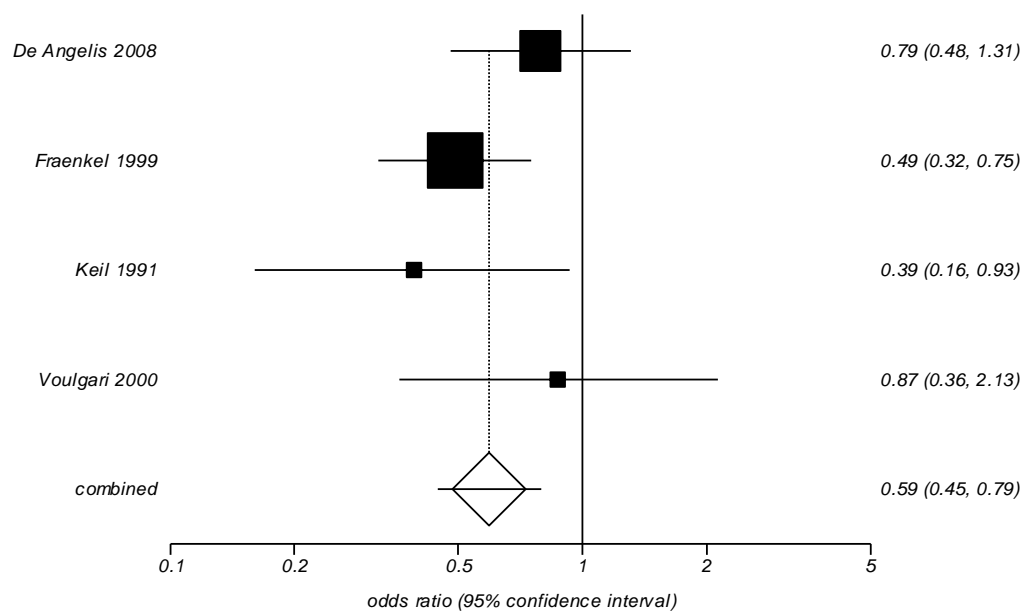
De Angelis 2008		0.79 (0.48, 1.31)
Fraenkel 1999		0.49 (0.32, 0.75)
Keil 1991		0.39 (0.16, 0.93)
Voulgari 2000		0.87 (0.36, 2.13)
combined		0.59 (0.45, 0.79)

0.1   0.2   0.5   1   2   5

odds ratio (95% confidence interval)

Summary meta-analysis plot [random effects]

De Angelis 2008		0.79 (0.48, 1.31)
Fraenkel 1999		0.49 (0.32, 0.75)
Keil 1991		0.39 (0.16, 0.93)
Voulgari 2000		0.87 (0.36, 2.13)
combined		0.60 (0.43, 0.83)

0.1   0.2   0.5   1   2   5

odds ratio (95% confidence interval)
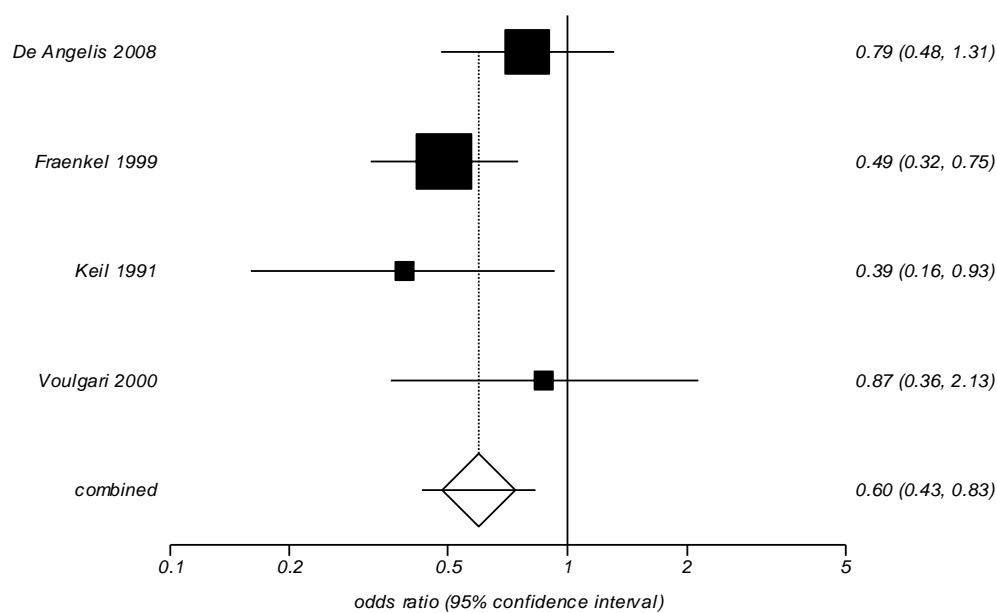
Summary meta-analysis for risk factors/associations (smoking)

Stratum	Odds Ratio	SE	Approximate 95% CI		% Weight (fixed, random)		
1	2.03	0.28827	1.15	3.56	9.637121	10.150947	Cakir 2008
2	1.01	0.198398	0.68	1.48	20.345756	20.110221	Fraenkel 1999
3	1.86	0.375611	0.89	3.88	5.676358	6.12781	Keil 1991
4	2.21	0.596484	0.69	7.15	2.250861	2.483328	Olsen 1978
5	1.31	0.196141	0.89	1.92	20.816596	20.520026	Suter 2005
6	0.81	0.311168	0.44	1.49	8.270975	8.785547	Smyth 1999
7	1.3	0.167147	0.94	1.81	28.665028	27.039027	Suter 2007
8	1.28	0.709785	0.32	5.17	1.589619	1.761272	O Keefe 1993
9	0.86	0.539871	0.3	2.49	2.747685	3.021822	O Keefe 1992

Fixed effects (inverse variance)
Pooled odds ratio = 1.267571 (95% CI = 1.063649 to 1.510589)
Z (test test odds ratio differs from 1) = 2.649493 P = 0.0081

Non-combinability of studies
Cochran Q = 8.529249 (df = 8) P = 0.3835
Moment-based estimate of between studies variance = 0.005218
I² (inconsistency) = 6.2% (95% CI = 0% to 57.1%)

Random effects (DerSimonian-Laird)
Pooled odds ratio = 1.27026 (95% CI = 1.055109 to 1.529283)
Z (test test odds ratio differs from 1) = 2.526517 P = 0.0115

Bias indicators
Begg-Mazumdar: Kendall's tau = 0 P = 0.9195 (low power)
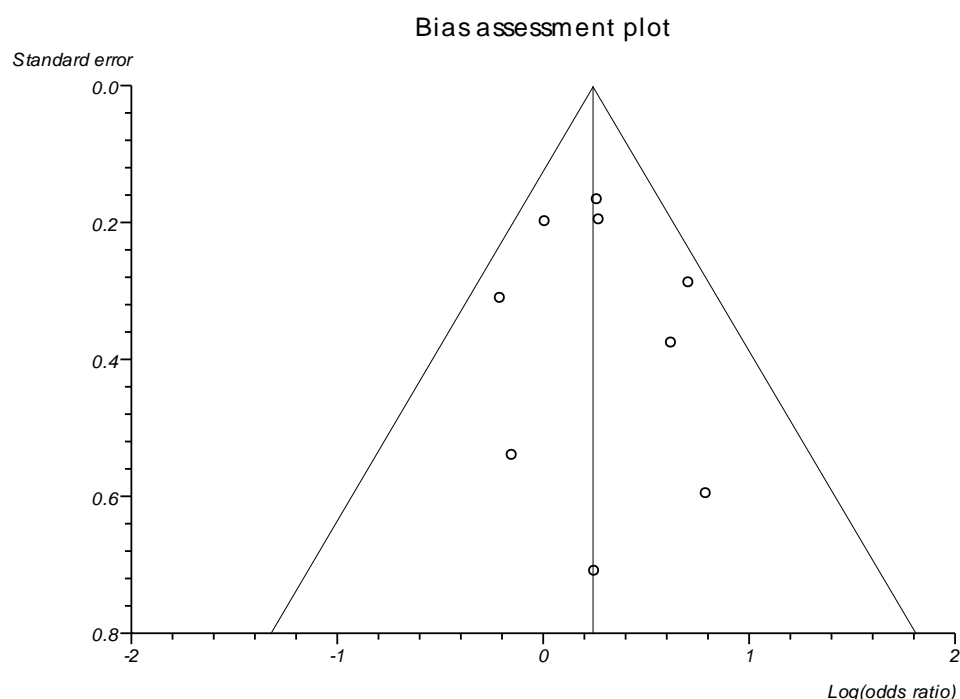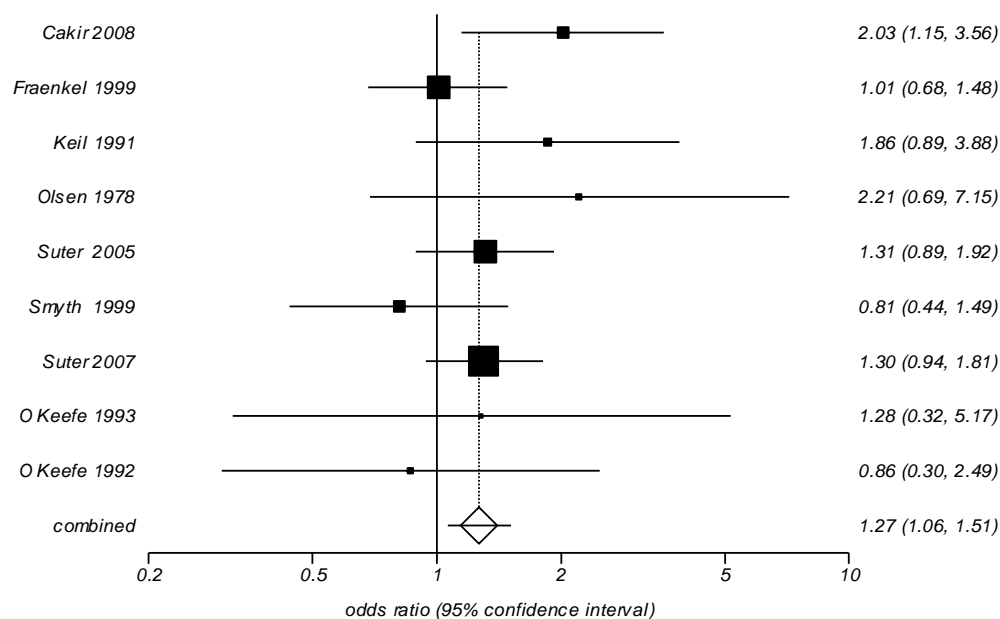Egger: bias = 0.386133 (95% CI = -1.650354 to 2.422619) P = 0.6674

Bias assessment plot

Summary meta-analysis for risk factors/associations (smoking)

Summary meta-analysis plot [fixed effects]

Study		Odds ratio (95% CI)
Cakir 2008		2.03 (1.15, 3.56)
Fraenkel 1999		1.01 (0.68, 1.48)
Keil 1991		1.86 (0.89, 3.88)
Olsen 1978		2.21 (0.69, 7.15)
Suter 2005		1.31 (0.89, 1.92)
Smyth 1999		0.81 (0.44, 1.49)
Suter 2007		1.30 (0.94, 1.81)
O Keefe 1993		1.28 (0.32, 5.17)
O Keefe 1992		0.86 (0.30, 2.49)
combined		1.27 (1.06, 1.51)

odds ratio (95% confidence interval)

Summary meta-analysis plot [random effects]

Study		Odds ratio (95% CI)
Cakir 2008		2.03 (1.15, 3.56)
Fraenkel 1999		1.01 (0.68, 1.48)
Keil 1991		1.86 (0.89, 3.88)
Olsen 1978		2.21 (0.69, 7.15)
Suter 2005		1.31 (0.89, 1.92)
Smyth 1999		0.81 (0.44, 1.49)
Suter 2007		1.30 (0.94, 1.81)
O Keefe 1993		1.28 (0.32, 5.17)
O Keefe 1992		0.86 (0.30, 2.49)
combined		1.27 (1.06, 1.53)

odds ratio (95% confidence interval)

Summary meta-analysis for risk factors/associations (alcohol)

Stratum	Odds Ratio	SE	Approximate 95% CI		% Weight (fixed, random)		
1	0.08	0.154629	0.06	0.11	75.389314	50.30415	Suter 2007
2	1.38	0.270636	0.81	2.34	24.610686	49.69585	Fraenkel 1999

Fixed effects (inverse variance)
Pooled odds ratio = 0.16124 (95% CI = 0.123934 to 0.209775)
Z (test test odds ratio differs from 1) = -13.592001 P < 0.0001

Non-combinability of studies
Cochran Q = 83.476205 (df = 1) P < 0.0001
Moment-based estimate of between studies variance = 4.00644
I² (inconsistency) = *% (95% CI = *% to *%)

Random effects (DerSimonian-Laird)
Pooled odds ratio = 0.329399 (95% CI = 0.020217 to 5.366998)
Z (test test odds ratio differs from 1) = -0.7799 P = 0.4354

Bias indicators
Begg-Mazumdar: Kendall's <too few strata> *
Egger: bias = <too few strata> (95% CI = * to *) P = *

Summary meta-analysis plot [fixed effects]

odds ratio (95% confidence interval)

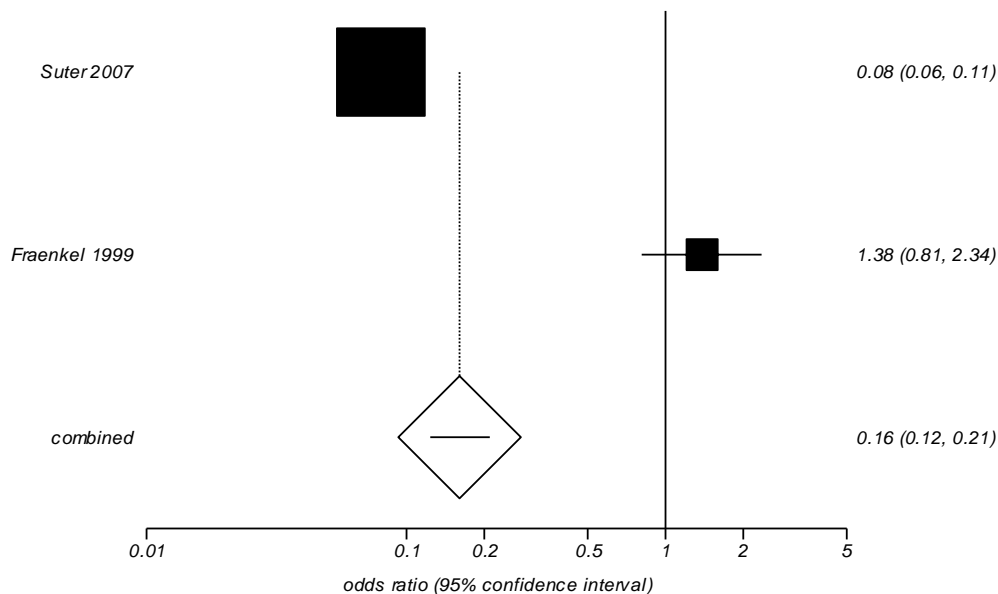**Summary meta-analysis for risk factors/associations (alcohol)**

Summary meta-analysis plot [random effects]

Suter 2007   0.08 (0.06, 0.11)

Fraenkel 1999   1.38 (0.81, 2.34)

combined   0.33 (0.02, 5.37)

0.01   0.1   0.2   0.5   1   2   5   10

odds ratio (95% confidence interval)
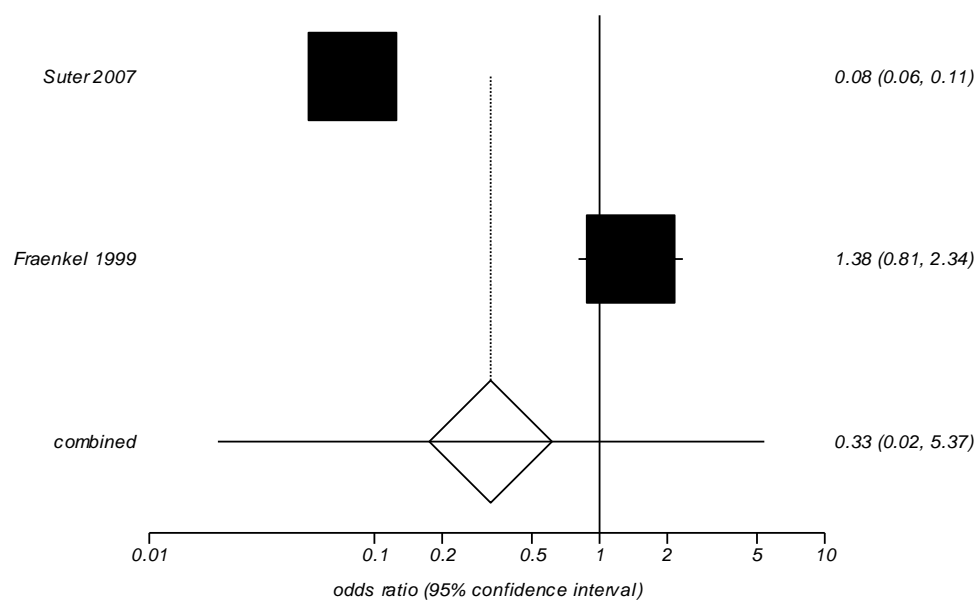
Summary meta-analysis for risk factors/associations (migraine)

Stratum	Odds Ratio	SE	Approximate 95% CI		% Weight (fixed, random)		
1	1.29	0.482176	0.5	3.31	12.803631	14.232237	Cakir 2008
2	5.25	0.446385	2.19	12.6	14.939157	15.80307	Zahavi 1984
3	5.4	0.332283	2.8	10.3	26.960553	22.417622	O Keefe 1992
4	4.38	0.482538	1.7	11.27	12.784405	14.21737	O Keefe 1993
5	3.46	0.409258	1.55	7.71	17.772532	17.666869	Voulgari 2000
6	6.23	0.449394	2.58	15.02	14.739722	15.662831	Smyth 1999

Fixed effects (inverse variance)
Pooled odds ratio = 4.112672 (95% CI = 2.932674 to 5.767458)
Z (test test odds ratio differs from 1) = 8.195956 P < 0.0001

Non-combinability of studies
Cochran Q = 7.802203 (df = 5) P = 0.1675
Moment-based estimate of between studies variance = 0.101857
I² (inconsistency) = 35.9% (95% CI = 0% to 73.6%)

Random effects (DerSimonian-Laird)
Pooled odds ratio = 4.023554 (95% CI = 2.623783 to 6.170096)
Z (test test odds ratio differs from 1) = 6.381951 P < 0.0001

Bias indicators
Begg-Mazumdar: Kendall's tau = -0.2 P = 0.4694 (low power)
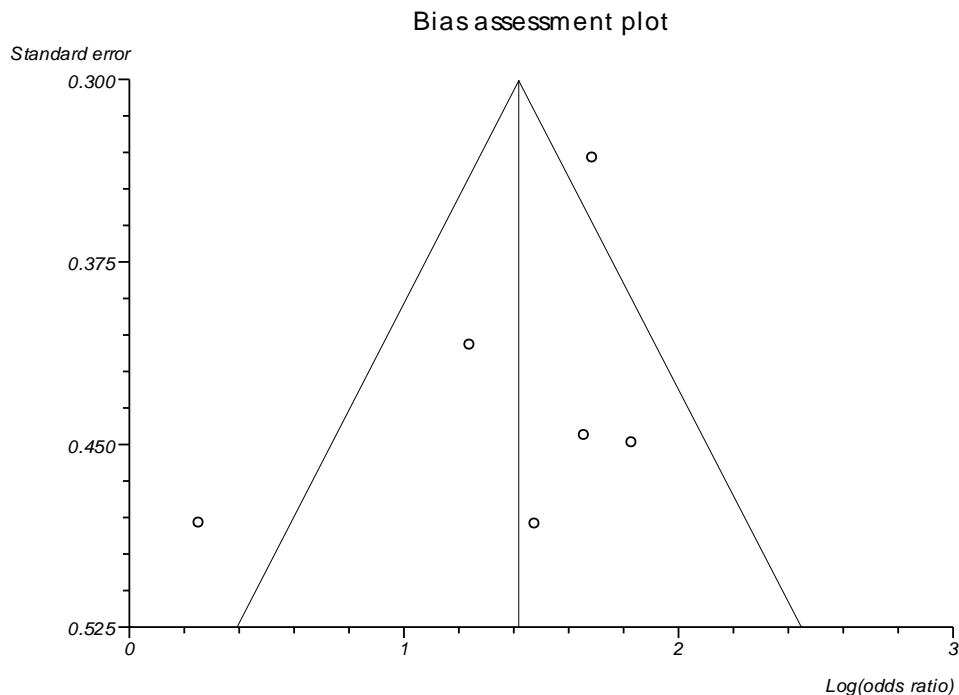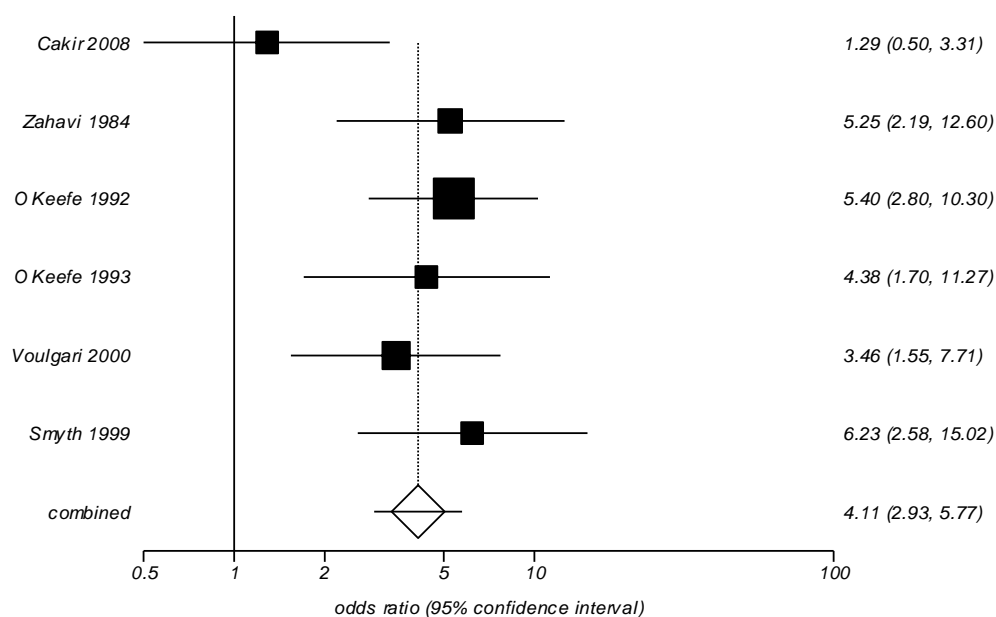Egger: bias = -3.637628 (95% CI = -14.093988 to 6.818732) P = 0.3888

Bias assessment plot
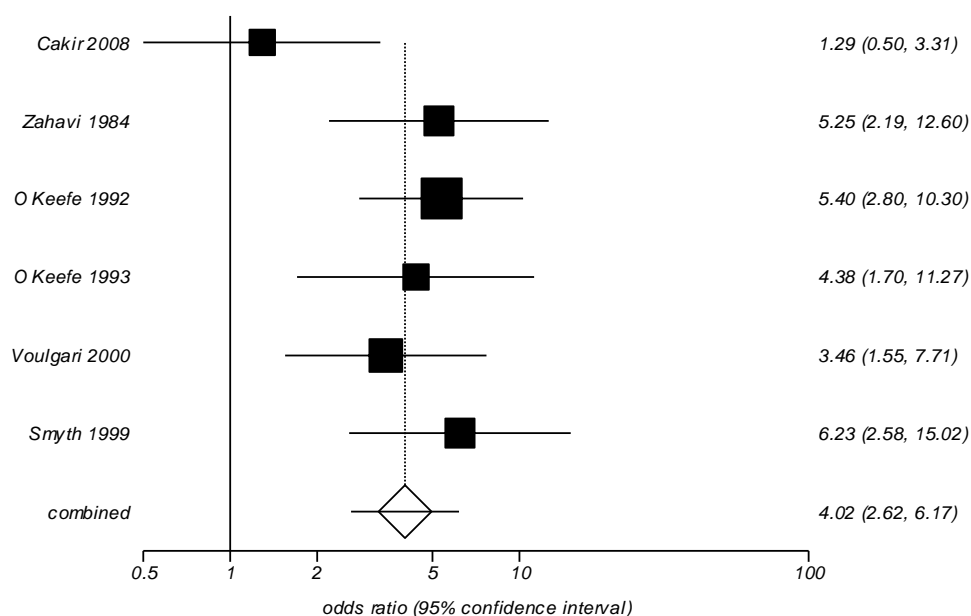
Summary meta-analysis for risk factors/associations (migraine)

Summary meta-analysis plot [fixed effects]

Cakir 2008	1.29 (0.50, 3.31)
Zahavi 1984	5.25 (2.19, 12.60)
O Keefe 1992	5.40 (2.80, 10.30)
O Keefe 1993	4.38 (1.70, 11.27)
Voulgari 2000	3.46 (1.55, 7.71)
Smyth 1999	6.23 (2.58, 15.02)
combined	4.11 (2.93, 5.77)

odds ratio (95% confidence interval)

Summary meta-analysis plot [random effects]

Cakir 2008	1.29 (0.50, 3.31)
Zahavi 1984	5.25 (2.19, 12.60)
O Keefe 1992	5.40 (2.80, 10.30)
O Keefe 1993	4.38 (1.70, 11.27)
Voulgari 2000	3.46 (1.55, 7.71)
Smyth 1999	6.23 (2.58, 15.02)
combined	4.02 (2.62, 6.17)

odds ratio (95% confidence interval)

Summary meta-analysis for risk factors/associations (hypertension)

Stratum	Odds Ratio	SE	Approximate 95% CI		% Weight (fixed, random)		
1	0.96	0.208639	0.64	1.45	92.742301	92.742301	Fraenkel 1999
2	1.7	0.745822	0.395	7.35	7.257699	7.257699	O Keefe 1992

Fixed effects (inverse variance)
Pooled odds ratio = 1.000652 (95% CI = 0.674925 to 1.483581)
Z (test test odds ratio differs from 1) = 0.003246 P = 0.9974

Non-combinability of studies
Cochran Q = 0.544457 (df = 1) P = 0.4606
Moment-based estimate of between studies variance = 0
I² (inconsistency) = *% (95% CI = *% to *%)

Random effects (DerSimonian-Laird)
Pooled odds ratio = 1.000652 (95% CI = 0.674925 to 1.483581)
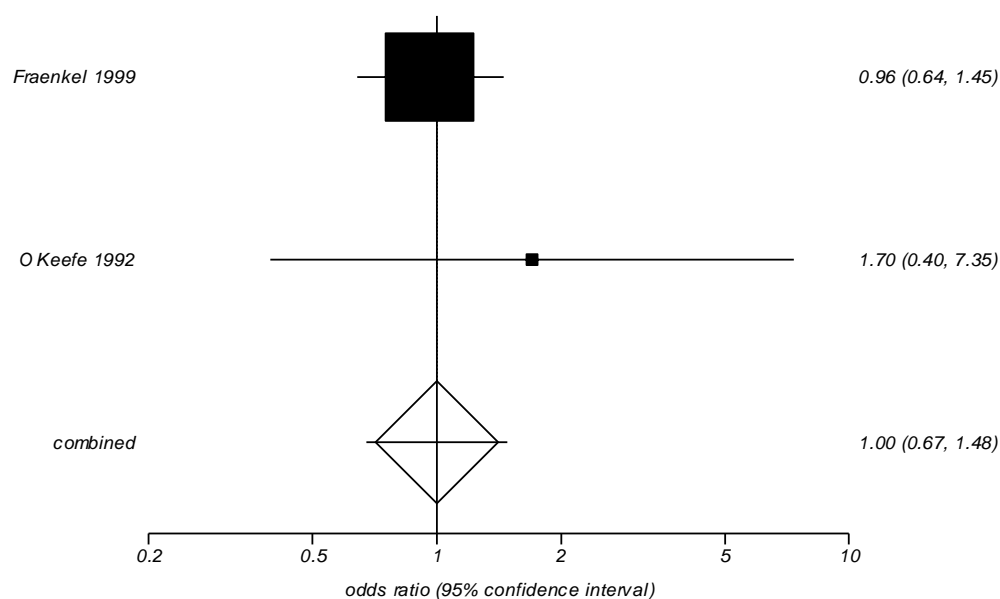Z (test test odds ratio differs from 1) = 0.003246 P = 0.9974

Bias indicators
Begg-Mazumdar: Kendall's <too few strata> *
Egger: bias = <too few strata> (95% CI = * to *) P = *

Summary meta-analysis plot [fixed effects]

Fraenkel 1999		0.96 (0.64, 1.45)
O Keefe 1992		1.70 (0.40, 7.35)
combined		1.00 (0.67, 1.48)

odds ratio (95% confidence interval)

Summary meta-analysis for risk factors/associations (hypertension)

Summary meta-analysis plot [random effects]

Fraenkel 1999	0.96 (0.64, 1.45)
O Keefe 1992	1.70 (0.40, 7.35)
combined	1.00 (0.67, 1.48)

0.2 0.5 1 2 5 10

odds ratio (95% confidence interval)
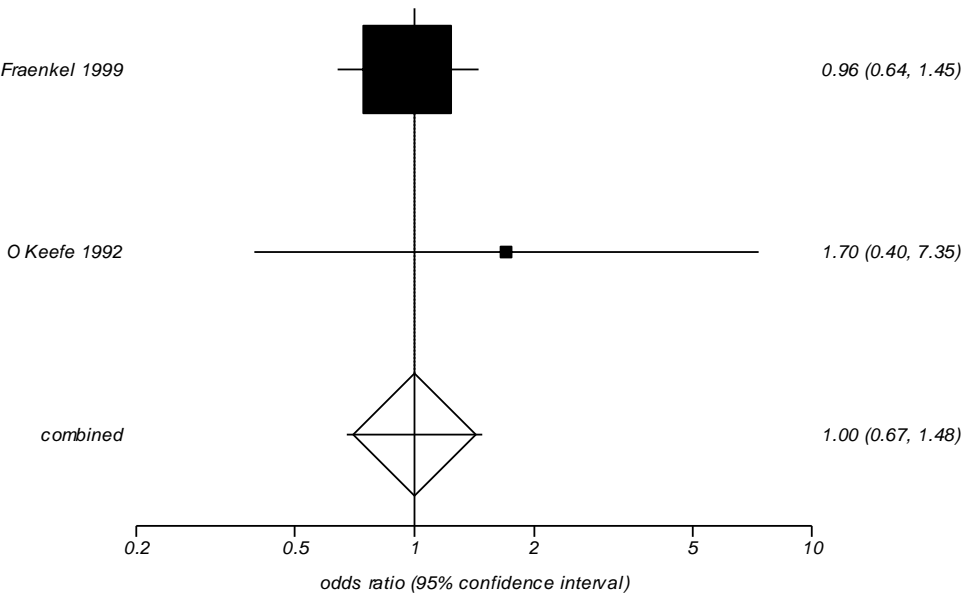
Summary meta-analysis for risk factors/associations (Helicobacter Pylori)

Stratum	Odds Ratio	SE	Approximate 95% CI		% Weight (fixed, random)		
1	0.13	0.764231	0.03	0.6	35.074014	45.3416	Savarino 2000
2	0.71	0.561705	0.24	2.17	64.925986	54.6584	Herve 2006

Fixed effects (inverse variance)
Pooled odds ratio = 0.391428 (95% CI = 0.161211 to 0.950406)
Z (test test odds ratio differs from 1) = -2.072351 P = 0.0382

Non-combinability of studies
Cochran Q = 3.204101 (df = 1) P = 0.0735
Moment-based estimate of between studies variance = 0.991363
I² (inconsistency) = *% (95% CI = *% to *%)

Random effects (DerSimonian-Laird)
Pooled odds ratio = 0.328812 (95% CI = 0.062739 to 1.723299)
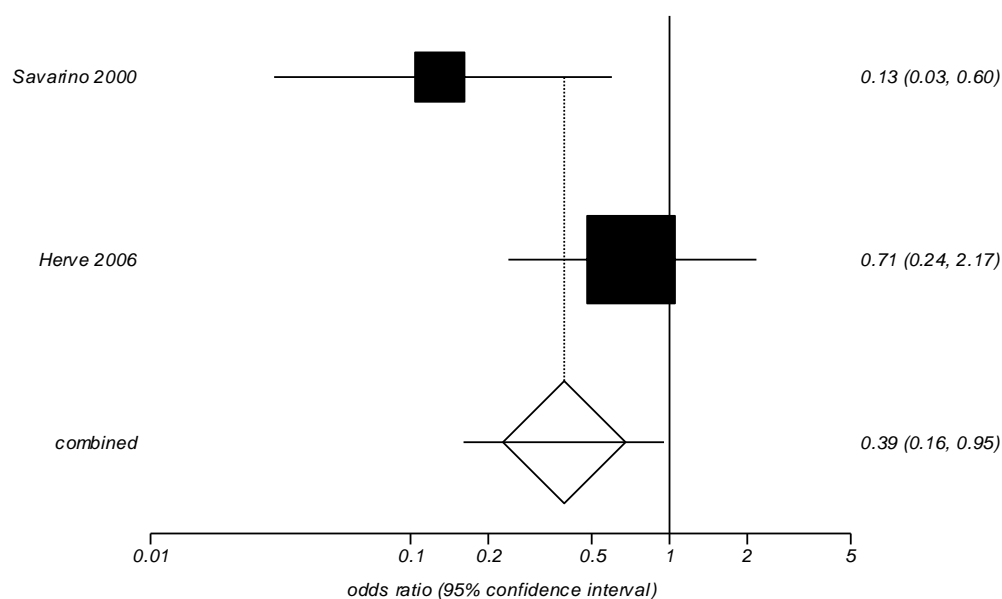Z (test test odds ratio differs from 1) = -1.316025 P = 0.1882

Bias indicators
Begg-Mazumdar: Kendall's <too few strata> *
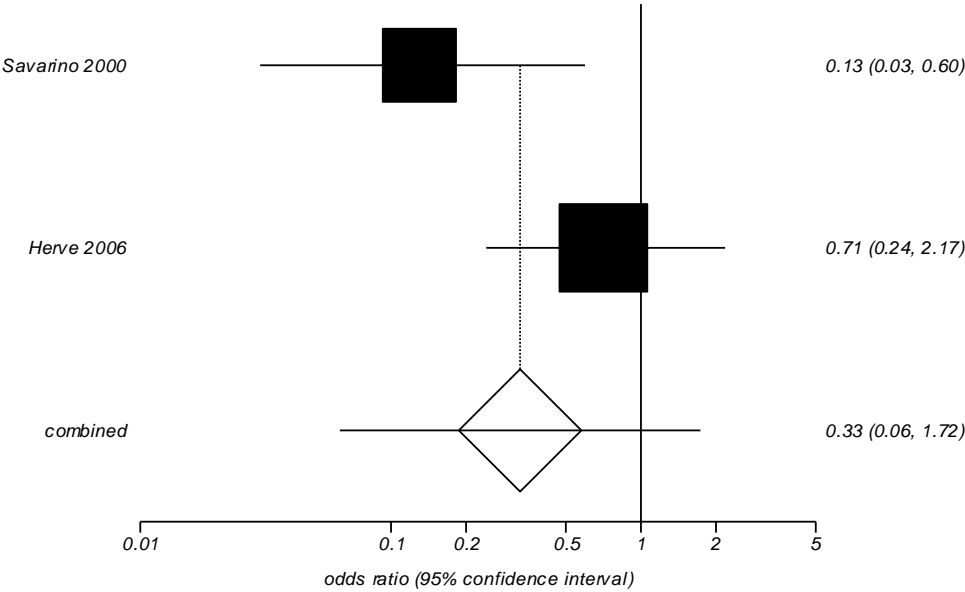Egger: bias = <too few strata> (95% CI = * to *) P = *

Summary meta-analysis plot [fixed effects]

Savarino 2000	0.13 (0.03, 0.60)
Herve 2006	0.71 (0.24, 2.17)
combined	0.39 (0.16, 0.95)

odds ratio (95% confidence interval)

Summary meta-analysis for risk factors/associations (Helicobacter Pylori)

Summary meta-analysis plot [random effects]

Savarino 2000	0.13 (0.03, 0.60)
Herve 2006	0.71 (0.24, 2.17)
combined	0.33 (0.06, 1.72)

odds ratio (95% confidence interval)

Summary meta-analysis for risk factors/associations (oral contraceptive pill)

Stratum	Odds Ratio	SE	Approximate 95% CI		% Weight (fixed, random)		
1	0.63	0.694011	0.16	2.43	25.925557	25.925557	O Keefe 1993
2	0.71	0.410578	0.32	1.6	74.074443	74.074443	O Keefe 1992

Fixed effects (inverse variance)
Pooled odds ratio = 0.688333 (95% CI = 0.344357 to 1.375903)
Z (test test odds ratio differs from 1) = -1.056916 P = 0.2905

Non-combinability of studies
Cochran Q = 0.021979 (df = 1) P = 0.8821
Moment-based estimate of between studies variance = 0
I² (inconsistency) = *% (95% CI = *% to *%)

Random effects (DerSimonian-Laird)
Pooled odds ratio = 0.688333 (95% CI = 0.344357 to 1.375903)
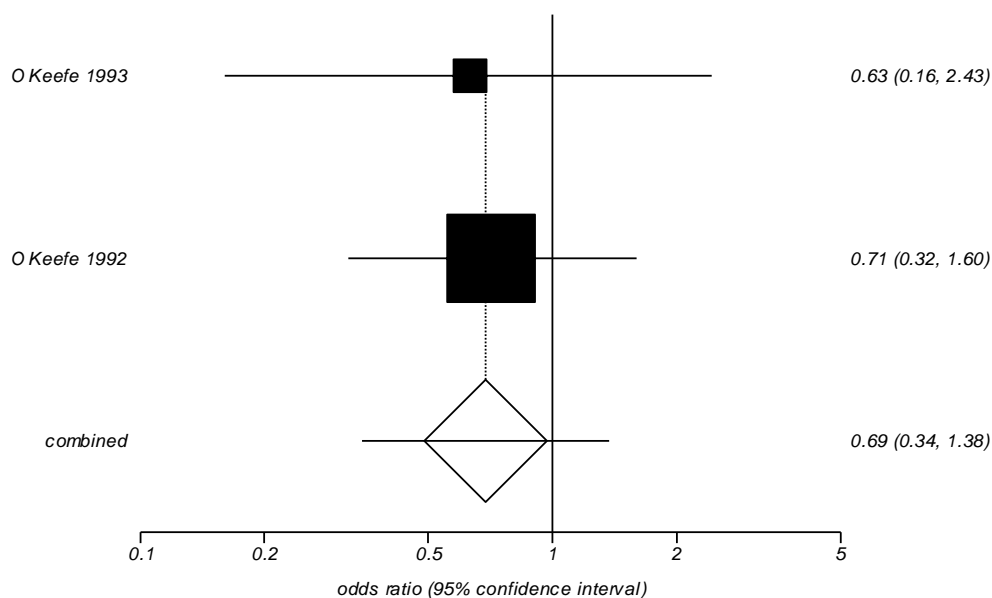Z (test test odds ratio differs from 1) = -1.056916 P = 0.2905

Bias indicators
Begg-Mazumdar: Kendall's <too few strata> *
Egger: bias = <too few strata> (95% CI = * to *) P = *

Summary meta-analysis plot [fixed effects]

O Keefe 1993	0.63 (0.16, 2.43)
O Keefe 1992	0.71 (0.32, 1.60)
combined	0.69 (0.34, 1.38)

0.1   0.2   0.5   1   2   5

odds ratio (95% confidence interval)

Summary meta-analysis for risk factors/associations (oral contraceptive pill)

Summary meta-analysis plot [random effects]

O Keefe 1993	0.63 (0.16, 2.43)
O Keefe 1992	0.71 (0.32, 1.60)
combined	0.69 (0.34, 1.38)

odds ratio (95% confidence interval)
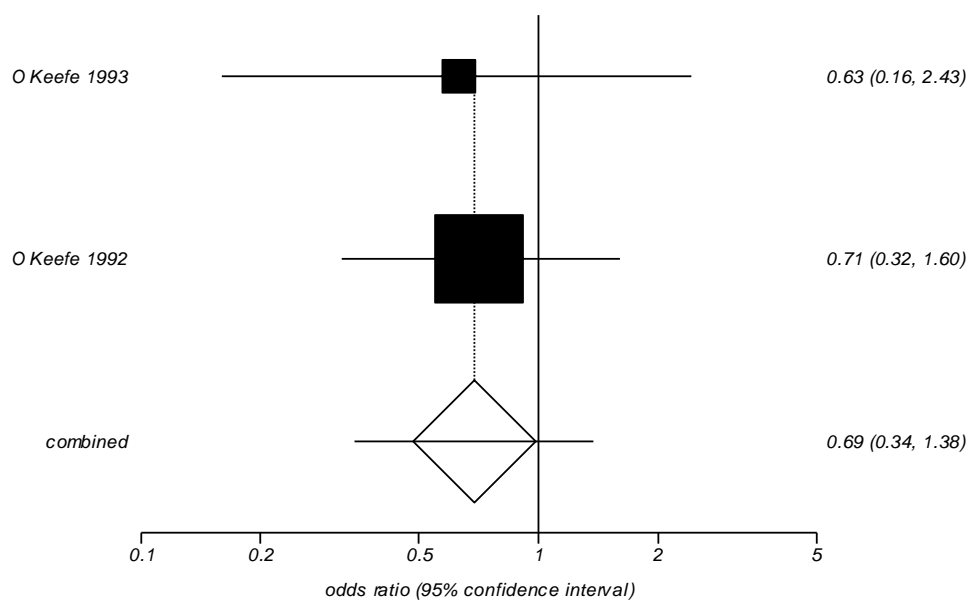
Summary meta-analysis for risk factors/associations (Oestrogren replacement therapy)

Stratum	Odds Ratio	SE	Approximate 95% CI		% Weight (fixed, random)		
1	2.21	0.342108	1.13	4.32	55.093788	55.093788	800
2	2.5	0.378932	1.2	5.3	44.906212	44.906212	442

Fixed effects (inverse variance)
Pooled odds ratio = 2.335815 (95% CI = 1.420015 to 3.842238)
Z (test test odds ratio differs from 1) = 3.340923 P = 0.0008

Non-combinability of studies
Cochran Q = 0.05833 (df = 1) P = 0.8092
Moment-based estimate of between studies variance = 0
I² (inconsistency) = *% (95% CI = *% to *%)

Random effects (DerSimonian-Laird)
Pooled odds ratio = 2.335815 (95% CI = 1.420015 to 3.842238)
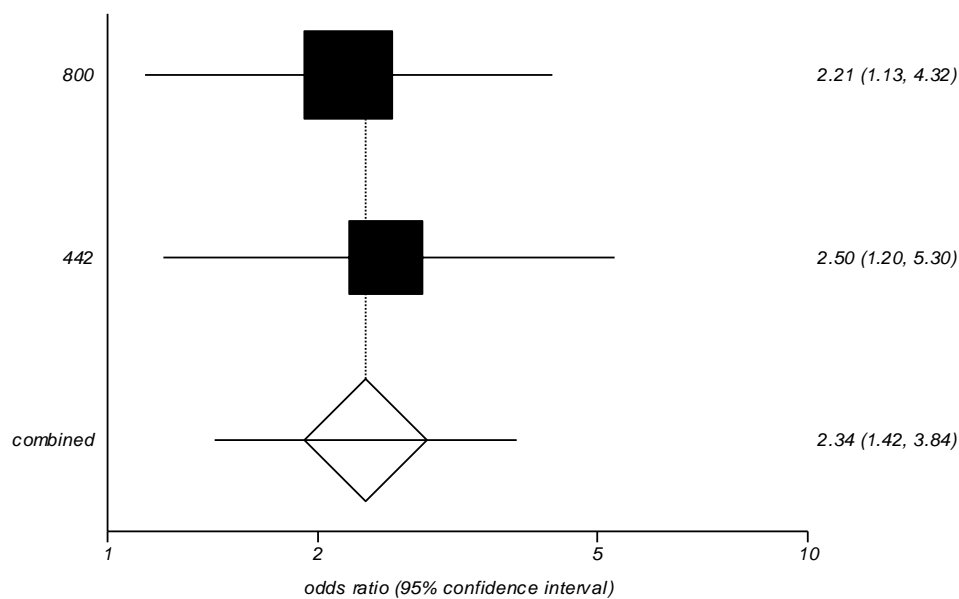Z (test test odds ratio differs from 1) = 3.340923 P = 0.0008

Bias indicators
Begg-Mazumdar: Kendall's <too few strata> *
Egger: bias = <too few strata> (95% CI = * to *) P = *

Summary meta-analysis plot [fixed effects]

800 2.21 (1.13, 4.32)

442 2.50 (1.20, 5.30)

combined 2.34 (1.42, 3.84)

odds ratio (95% confidence interval)

Summary meta-analysis for risk factors/associations (Oestrogren replacement therapy)

Summary meta-analysis plot [random effects]

800	2.21 (1.13, 4.32)
442	2.50 (1.20, 5.30)
combined	2.34 (1.42, 3.84)

odds ratio (95% confidence interval)