Statin Use and the Risk of Cataracts: A Systematic Review and Meta-Analysis

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Background—Cataracts are the main cause of poor vision and blindness worldwide. The effects of statin administration on cataracts remain debated. Therefore, we conducted a systematic review and meta-analysis to determine whether statin use affects the risk of cataracts.

Methods and Results—We performed a systematic search of the electronic databases PubMed, EMBASE, and the Cochrane Library through January 2016. Weighted averages were reported as relative risk values with 95% CIs. Statistical heterogeneity scores were assessed with the standard Cochran's Q test and the I^2 statistic. A total of 6 cohort studies, 6 case–control studies, and 5 randomized controlled trials, together involving more than 313 200 patients, were included in our study. The pooled estimates of cohort studies indicated that the use of statins moderately increases the risk of cataracts (relative risk, 1.13; 95% CI, 1.01–1.25). The pooled estimates of case–control studies (relative risk=1.10, 95% CI, 0.99–1.23) and randomized controlled trials (relative risk, 0.89; 95% CI, 0.72–1.10) indicated that the use of statins does not increase the risk of cataracts. The sensitivity analysis confirmed the stability of the results. Heterogeneity was found among the cohort and case–control studies.

Conclusions—Based on the present meta-analysis of these studies, we could only conclude that there is no clear evidence showing that statin use increases the risk of cataracts. The most likely case is that there is no association between statin use and cataracts. Because of the considerable benefits of statins in cardiovascular patients, this issue should not deter their use. (*J Am Heart Assoc*. 2017;6:e004180. DOI: 10.1161/JAHA.116.004180.)

Key Words: cataract • meta-analysis • observational studies • randomized controlled trial • statin

C ataracts are the main cause of low vision and blindness worldwide.[1] Nearly 13 million people in the United States are reported to suffer from cataracts.[2] Statins are widely prescribed to treat hyperlipidemia, as they reduce the risk of cardiovascular disease by inhibiting 3-hydroxy–3-methyl-glutaryl-CoA reductase.[3,4] Although it has been established that statins can significantly reduce cardiovascular mortality,[5–8] some adverse effects related to statins have been recognized because of their increasing use.[9,10]

Concern about the cataractogenic effect of statins arose from animal studies in which dogs were administered high doses of statins, such as simvastatin, fluvastatin, and lovastatin.[10,11] However, in human studies, investigations into the association between statin use and the incidence of cataracts and cataract surgery have yielded inconsistent and conflicting results.[12–22] Some studies have reported no association between statin use and cataracts,[12–14,23–26] whereas others have found that statin use is protective against the incidence of cataracts,[15,16,27] or that it is associated with an increased risk of cataracts.[17–22] To address this issue, Kostis et al[28] performed a meta-analysis in 2013. However, they combined the unadjusted odds ratio directly without considering potential confounding factors in some studies, which may have led to inaccurate results. In addition, some studies have been published in the 2 years since the study by Kostis et al[28] was published, of which most yielded results that conflicted with those included in Kostis et al.[18,19,21,22] Therefore, we performed a new meta-analysis to investigate the association between statin use and cataracts.

Methods

We conducted this meta-analysis following the guidance provided by the Cochrane Handbook[29] and Kanwal and White.[30] Two authors (Yu and Chu) independently performed

the literature search, article screening, study selection, quality evaluation, and data extraction. Disagreements were resolved by discussion, and a consensus was achieved in the selection of the articles for analysis.

Search Strategy

The Cochrane Library, PubMed, and EMBASE databases were searched from January 1980 to January 2016 for English language publications, including abstracts. The search was performed using the following terms: "statins OR HMG-CoA reductase inhibitors OR Simvastatin OR Lovastatin OR Fluvastatin OR Pravastatin OR Rosuvastatin OR Atorvastatin" AND "cataract." We also manually searched for relevant articles from the reference lists of the retrieved articles. When the available information was incomplete, we attempted to contact the study investigators for additional information.

Study Selection

Studies were included in this meta-analysis if they fulfilled the following criteria: (1) the study was a case–control, cohort study, or randomized controlled trials (RCTs); (2) non–statin users were included in the comparison group; (3) cataracts and/or cataract surgery was an outcome; (4) the association between statin use and the risk of cataracts/cataract surgery was investigated; (5) risk estimates of morbidity and 95% CIs were reported or the information required to calculate them was available. Basic science studies, reviews, editorials/ letters, case reports, and studies without comparison groups were excluded.

Data Extraction and Quality Assessment

Data extraction was performed independently by 2 of the authors (Yu and Chu). The following information was extracted from each study: the last name of the first author, year of publication, study design, country of origin of the population studied, patient characteristics, statin use, information source for exposure ascertainment, risk estimates and corresponding 95% CIs, and covariates adjusted for in the multivariable analysis. For studies that provided more than 1 risk estimate, we extracted the estimate that was adjusted for the greatest number of confounding factors. We assessed the method-ological quality of the included studies based on the Newcastle–Ottawa Scale (NOS) for observational studies,[31] which was developed to assess the quality of nonrandomized studies in meta-analysis. Using this scale, observational studies were scored across 3 categories as follows: selection (4 questions) and comparability (2 questions) of the study group and ascertainment of the outcome of interest (3 questions), with all questions having a score of 1 except for

the comparability of study groups, for which separate points were awarded for controlling for age and/or sex (maximum, 2 points). A score of ≥7 points was suggestive of a high-quality study. The quality of the included RCTs was assessed by Cochrane risk of bias assessment,[29] which allots scores for the following: random sequence generation (1), allocation concealment (1), blinding of participants and personnel (1), blinding of outcome assessment (1), incomplete outcome data (1), selective reporting (1), and other sources of bias (1). Scores of 1 to 4 indicate low quality, and scores of 5 to 7 indicate high quality.

Outcomes Assessed

The primary analysis focused on assessing the risk of cataracts and cataract surgery among users of statins. We also performed subgroup analyses based on study design (case–control, cohort, or RCT), type of statin, the method-ological quality of the study (high or low), study location (Europe, North America, Asia or Australia), age, sex, follow-up duration, outcome and outcome assessment, and whether potential confounders were included in the adjusting model (eg, low-density lipoprotein included/missing, cardiovascular disease [CVD] included/missing, smoking included/missing).

Statistical Analysis

STATA 12.0 software (StataCorp LP, College Station, TX) was used for statistical analysis. Heterogeneity was assessed using the Cochran Q χ^2 test and the I^2 statistic.[32] An I^2 value of >50% or a P value of <0.05 for the Q-statistic indicated significant heterogeneity.[33] Adjusted effect estimates (odds ratios, relative risks [RRs], and hazard risks) between the outcome and use of statins were extracted. In the presence of heterogeneity, we used a random-effects model because its assumptions account for the presence of variability among studies. The association between statin use and cataract or cataract surgery risk was estimated using the RRs and corresponding 95% CIs. Because the outcomes were relatively uncommon and the odds ratios in the case–control studies were close to 1, odds ratios were considered approximations of RR.[34]

Results

Search Results

By searching the 3 databases, 615 potentially eligible articles were identified. In total, 489 articles were excluded after reading the title and abstract, and the full texts of the remaining 120 articles were evaluated in detail. Of these 120 articles, 16 met our inclusion criteria. One of these articles
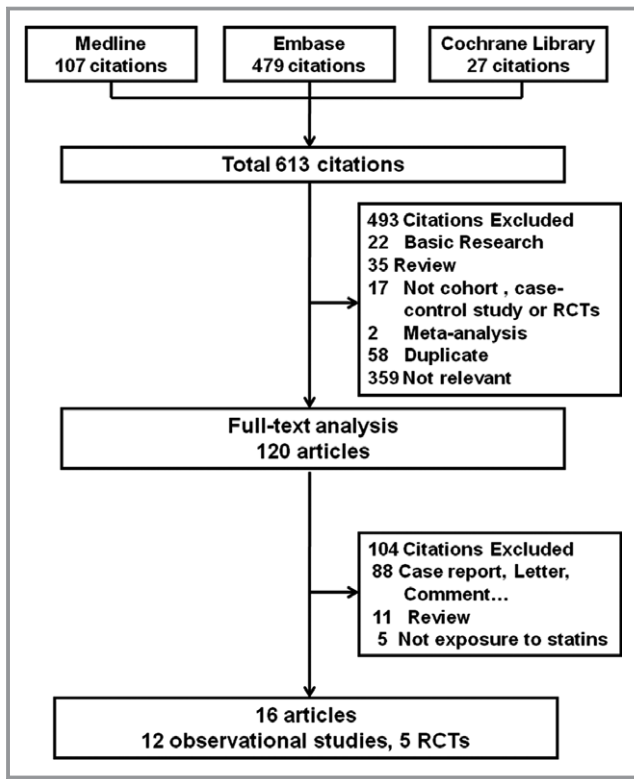
Figure 1. Flow chart of the studies considered and selected for review. RCTs indicates randomized controlled trials.

included 2 studies.[21] In total, 17 studies consisting of 6 cohort studies, 6 case–control studies, and 5 RCTs were included in the meta-analysis and involved more than 313 200 cataract cases. The number of articles according to reason for exclusion at each stage of the eligibility assessment is outlined in Figure 1.

Characteristics of the Included Studies

The main characteristics of the cohort and case–control studies are shown in Tables 1 and 2. Among the cohort studies, 3 studies were performed in North America, and the remaining 3 studies were performed in Europe, Asia, and Australia.[15–20] Among the case–control studies, 4 studies were performed in North America, and 2 were performed in Europe.[12–14,21,22] The extent of adjustment for potential clinical risk factors varied considerably across the cohort and case–control studies (Table S1). Based on the methodological quality assessment scores (Tables S2 and S3), the mean score of the 6 cohort studies included in the analysis was 7. Four studies were of high quality (NOS ≥7), and 3 studies were of low quality (NOS <7). The mean score of the 6 case–control studies was 6.5. Three studies were of high quality (NOS ≥7), and 3 studies were of low quality (NOS <7). The characteristics of the RCTs are shown in Table 3.[23–27] Two

Table 1. Characteristics of the Cohort Studies

Study, Year	Location	Follow-Up Period, y	Age (Mean), y	Outcome	Outcome Assessment	Ascertainment of Statins Exposure	Cases, n	Controls, n	Overall Quality
Klein, 2006[15]	US	5	63.2	Cataract	Wisconsin Cataract Grading System	Private census	185/834	42/214	7
Tan, 2007[16]	AUS	>5	≥50 (>60)	Cataract Cataract surgery	Wisconsin Cataract Grading System	Questionnaires	17/72	365/1152	6
Hippisley-Cox, 2010[17]	UK	<5	30 to 84 (<60)	Cataract	Medical records	Drug prescription Computerized record	36 541	2 004 692	8
Waudby, 2011[20]	US	>5	>60	Cataract Cataract surgery	ICD-9 CPT code	Drug prescription Computerized record	1959/7470	1645/12 579	6
Lai, 2013[19]	Asia	>5	70.4	Cataract surgery	ICD-9	Drug prescription Computerized record	1533/6830	16 137/43 335	8
Leuschen, 2013[18]	US	<5	30 to 85 (<60)	Cataract	ICD-9	Drug prescription Computerized record	2477/6972	2337/6972	7

CPT indicates current procedural terminology; ICD, International Classification of Diseases.

Table 2. Characteristics of the Case–Control Studies

Study, Year	Location	Follow-Up Period, y	Age (Mean), y	Outcome	Outcome Assessment	Ascertainment of Statins Exposure	Cases, n	Controls, n	Overall Quality
Schlienger, 2001[12]	UK	<5	40 to 79 (>60)	Cataract / Cataract surgery	ICD-8, OMXIS procedure code 156	Drug prescription Computerized record	7405	28 327	7
Smeeth, 2003[13]	UK	<5	≥40 (75)	Cataract	ICD-8	Drug prescription Computerized record	15 479	15 479	7
Fong, 2012[14]	US	<5	≥50 (>60)	Cataract surgery	CPT code	Drug prescription Computerized record	13 583	34 049	6
Wise-BC, 2014[21]	Canada	<5	>70	Cataract / Cataract surgery	Computerized record	Drug prescription Computerized record	162 501	650 004	6
Wise-IMS, 2014[21]	Canada	<5	40 to 85 (>70)	Cataract / Cataract surgery	Computerized record	Drug prescription Computerized record	45 065	450 650	7
Erie, 2016[22]	US	<5	≥50 (>60)	Cataract Surgery	ICD-9 CPT code	Drug prescription Computerized record	6024	6024	6

CPT indicates current procedural terminology; ICD, International Classification of Diseases; OMXIS, Oxford Medical Information System.

trials were performed in the United States, and 3 trials were performed in Europe. The mean score of the RCTs included in the analysis was 5.4 (Table S4).

Main Analysis

The pooled RR of the cohort studies was 1.13 (95% CI, 1.01–1.25), which indicated that the use of statins was associated with a 13% increase in cataract incidence or cataract surgery (Figure 2). The I^2 value indicated significant heterogeneity across the studies (I^2=90.5%; P<0.001). However, the pooled RRs of the case–control studies and RCTs were 1.10 (95% CI, 0.99–1.23) (Figure 3) and 0.89 (95% CI, 0.72–1.10) (Figure 4),[23–27] which indicated that the use of statins was not associated with cataract incidence or cataract surgery. The I^2 value of the case–control studies was 95.9%, which indicated significant heterogeneity across the studies. However, the I^2 value of the RCTs was 30.5%, which indicated low heterogeneity across the RCTs. We also performed a sensitivity analysis for the cohort studies (Figure S1), case–control studies (Figure S2), and RCTs (Figure S3), and the results showed that the sequential omission of individual studies did not alter the overall effect. The pooled estimate effect size changed from 1.07 (95% CI, 0.91–1.25) to 1.17 (95% CI, 1.06–1.25) for the cohort studies, from 1.06 (95% CI, 0.96–1.19) to 1.14 (95% CI, 1.03–1.28) for the case–control studies, and from 0.82 (95% CI, 0.58–1.15) to 0.96 (95% CI, 0.85–1.09) for the RCTs.

Subgroup Meta-Analyses

The results of the subgroup analyses of the cohort and case–control studies are presented in Tables S5 and S6. In the subgroup analysis of cohort studies, there were significant associations in the subgroups of high methodological quality, outcome assessment, cataract, no older than 60, less than 5 years follow-up duration, low-density lipoprotein missing model, CVD included model, consultation rate included model, and hypertension included model. No associations were observed in the low methodological quality, studies performed in North America, older than 60 years, more than 5 years follow-up duration, low-density lipoprotein included model, CVD missing model, smoking missing model, consultation rate missing model, and hypertension missing model subgroups (Table S5, Figures S4 through S15). In the subgroup analysis of case–control studies, significant associations were observed in the subgroups of atorvastatin, lovastatin, high methodological quality, cataract surgery, CVD included model, smoking missing model, consultation rate missing model, and hypertension included model. No associations were observed in the fluvastatin, rosuvastatin, pravastatin, simvastatin, low methodological quality, studies

Table 3. Characteristics of RCTs

Study, Year	Location	Study Design	Follow-Up Period	Age (Mean), y	Outcome	Outcome Assessment	Type of Statins	Cases/Statins Group	Cases/Control Group
Laties, 1991[23]	US	RCT	48 weeks	18 to 70 (<60)	Cataract surgery	Slit-lamp examination	Lovastatin	25/6582	7/1663
Harris, 1995[24]	EU	RCT	18 months	40 to 75 (>60)	Cataract and Cataract surgery	OXGRAE	Simvastatin	30/414	10/207
Pederson, 1996[25]	EU	RCT	5.4 years	35 to 70 (>60)	Cataract	Slit-lamp examination	Simvastatin	66/2221	53/2223
Heart protection study, 2002[26]	US	RCT	5 years	40 to 80 (NA)*	Cataract	Medical records	Simvastatin	393/10 232	404/10 237
Bang, 2015[27]	US	RCT	4.3 years	45 to 85 (>60)	Cataract	Medical records	Simvastatin plus Ezetimibe	NA/944†	NA/929†

RCTs indicates randomized controlled trials; NA indicates not available; OXGRADE, Oxford grading system.
*The authors did not show the mean age of subjects.
†The authors showed the relative risk value instead of number of cases.

performed in North America and Europe, outcome assessment, cataract and cataract surgery, CVD missing model, smoking included model, consultation rate included model, and hypertension missing model subgroups (Table S6, Figures S16 through S25).

The results of the subgroup analysis of RCTs are presented in Table S7.

When the studies were grouped according to patient age, no association was observed in the older than 60 years subgroup (RR, 0.82; 95% CI, 0.53–1.26) and the no older than 60 years subgroup (RR, 0.97; 95% CI, 0.84–1.11) (Figure S26). Although the mean age of the Heart Protection Study subjects was not presented, the results did not change regardless of which group we placed this study in (Figure S27).

When we grouped the studies by follow-up duration, no significant association was observed in the no more than 5 years group (RR, 0.86; 95% CI, 0.48–1.51) and in the more than 5 years group (RR, 0.95; 95% CI, 0.83–1.08) (Figure S28).

Discussion

In this comprehensive meta-analysis of 6 cohort, 6 case–control studies, and 5 RCTs, we analyzed the effect of statin use on the risk of cataracts in more than 313 200 patients. Analysis of the cohort studies showed that statin use was associated with a 13% increased risk of cataracts. However, analysis of the case–control studies and RCTs revealed no association between statin use and the risk of cataract. The effect size of the case–control studies was marginal, namely, RR=1.10 (95% CI, 0.99–1.23). Based on the differing characteristics of observational (case–control and cohort) studies and RCTs, such discordant results are not unexpected. Because of the rigorous criteria of RCTs, individuals at greatest risk for adverse events may be excluded. Furthermore, the subjects of RCTs may be healthier than the subjects of observational studies.[35] The RCTs in this analysis had good internal validity, but the external validity was limited. The conclusion could not be extended to the whole population. In a population similar to the study population, the conclusion was reliable. Moreover, there may be a large portion of patients similar to the patients enrolled in these RCTs. However, there are also many patients who are not similar to the patients enrolled in these RCTs. The observational studies involve more cases with different health conditions. However, in observational studies, baseline confounders can be present, which may affect the results. In such studies, relative to non–statin users, statin users may be expected to be of poorer health or to have higher risk factors that necessitate statin therapy. As a result, adverse event rates may be higher among statin users. Although most observational studies (including the present meta-analysis) have attempted to characterize

their patients and identify validated markers of morbidity and mortality, potential unidentified confounders may exist.[35,36] This may lead to a calculated effect size that is slightly higher than the real one. Therefore, the real effect may be no significant association.

The analyses of cohort and case–control studies were limited by the considerable heterogeneity across studies. In the subgroup analysis of cohort studies, the I^2 values decreased significantly when subgrouped by sex, outcome assessment, age, follow-up duration, or consultation rate included/missing model (Table S5, Figures S6, S7, S9, S10, and S14). In the female (Figure S6B), no older than 60 years (Figure S9B), and less than 5 years follow-up subgroups (Figure S10B), the I^2 values decreased because the weight of Cox's study was much higher (more than 70%). In the consultation rate included model subgroup (Figure S14A), the I^2 value decreased because the weight of Lai's study was much higher (more than 80%). Consequently, the heterogeneity may be partly attributed to the outcome assessment. The evaluation criterion of various assessment methods may have varied among the studies, and patients diagnosed with cataracts by 1 method may not be so diagnosed when another method is used. Furthermore, even when the same

method for diagnosis is used, different physicians may make different decisions, especially regarding cataract surgery. In the subgroup analysis of case–control studies, the I^2 values were significantly decreased when subgrouped by quality assessment, study location, type of statin, CVD included/missing model, smoking included/missing model, consultation rate included/missing model, or hypertension included/missing model (Table S6, Figures S16, S17, S19, S21, S22, S23, and S25). In the quality assessment and hypertension included/missing model subgroups, the I^2 values of the high quality group (Figure S16A) and the hypertension missing model (Figure S25B) decreased because the weights of the Wise-IMS study (more than 95%) and the Fong study (more than 70%) were much higher than those of the other studies. In the subgroup analyses of the study performed in Europe (Figure S17B), the CVD missing model (Figure S21B), and the consultation rate included model (Figure S23A), the I^2 values decreased because the included studies were derived from the same database. Therefore, the heterogeneity may be partly attributed to the types of statins. Statins have extensive pleotropic effects that extend beyond their cholesterol-lowering properties.[35,37] Different types of statins may affect cataract development by different mechanisms. Therefore,

Study ID		ES (95% CI)	% Weight
Klein 2006 [15]		0.60 (0.39, 0.93)	4.87
Tan 2007 [16]		0.52 (0.29, 0.93)	2.96
Cox 2010 [17]		1.31 (1.28, 1.34)	25.17
Waudby 2011 [20]		1.18 (1.06, 1.32)	20.06
Lai 2013 [19]		1.20 (1.14, 1.27)	23.90
Leuschen 2013 [18]		1.09 (1.02, 1.17)	23.04
Overall (I-squared = 90.5%, p = 0.000)		1.13 (1.01, 1.25)	100.00

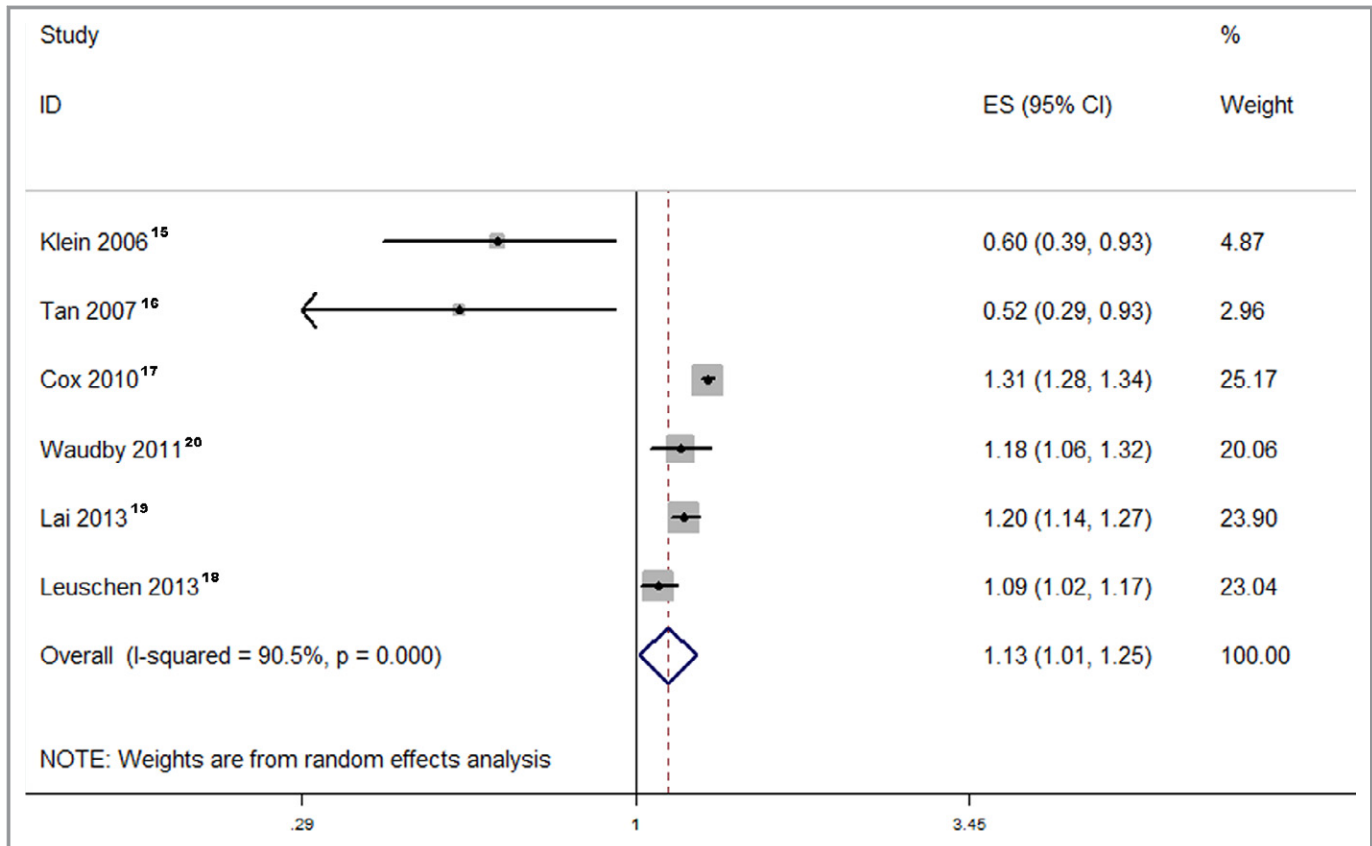NOTE: Weights are from random effects analysis

Figure 2. Forest plot of the cohort studies. The pooled RR of the cohort studies was 1.13 (95% CI, 1.01–1.25). The I^2 value indicated considerable heterogeneity across these cohort studies (I^2=90.5%; *P*<0.001). ES indicates effect size; RR, relative risk.
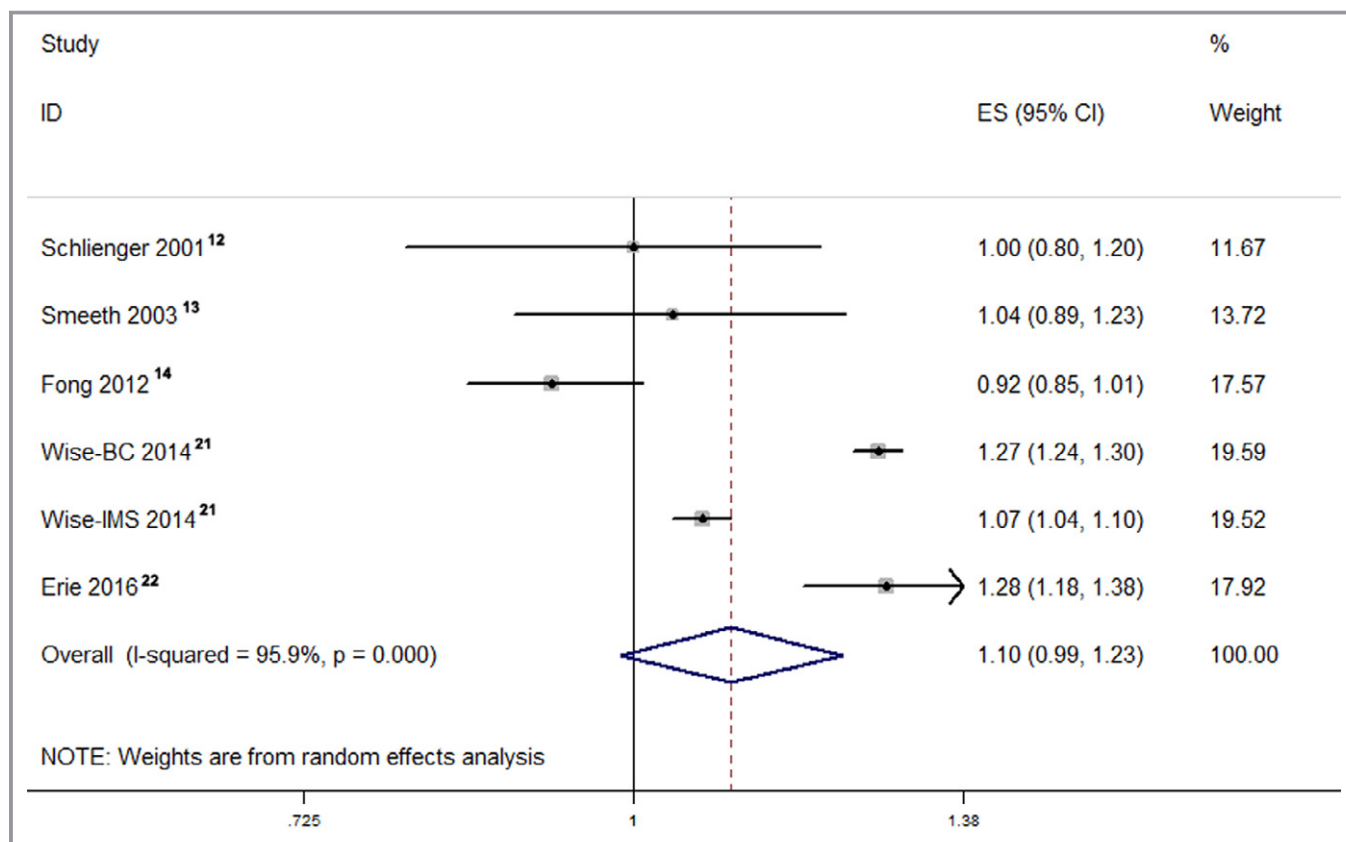
Figure 3. Forest plot of the case–control studies. The pooled RR of the case–control studies was 1.10 (95% CI, 0.99–1.23). The I^2 value revealed considerable heterogeneity across these case–control studies (I^2=95.9%; P<0.001). ES indicates effect size; RR, relative risk.

patients taking different statins may have different risks for developing cataracts. In our subgroup analysis based on statin type, the I^2 values of fluvastatin and pravastatin were significantly decreased compared with that of the overall result (Figure S19). Furthermore, the dose of statins also differed among studies. In addition to the fact that these factors may contribute to the heterogeneity, some other factors, such as ethnicity,[14] ultraviolet exposure, and education level, may also lead to heterogeneity.[38–40] The difference in the ascertainment method of statin use was also a source of heterogeneity. Klein et al[15] and Tan et al[16] determined statin use according to patient interviews, whereas in other studies, statin use was ascertained according to computerized prescription records.[12–14,17–22] However, even if prescription records or interviews showed that a patient was prescribed statins, differences in patient compliance may have resulted in different degrees of exposure, which may have led to heterogeneity. Some previous studies have found that statin use has different effects on different types of cataract;[35,37] therefore, heterogeneity may result from study variations in the types of cataract and the proportions of statin types used.

Two of the included studies reported that statin use was protective against cataracts.[15,16] These 2 studies are long-term prospective cohort studies that followed patients using periodical lens photographs. Such a design tends to achieve reliable results. However, these studies had limitations. The rate of loss to follow-up was relatively high in these 2 studies (more than 20% at the 5th year).[15,16] Moreover, the sample sizes of these 2 studies were relatively small.

The analysis of the RCTs indicated that statin use does not increase the risk of cataract. Most of the individual results of included studies are consistent with this overall result. In the subgroup analyses by age and follow-up duration, no association was observed between statin use and cataract risk (Table S7). The SEAS study reported that patients with aortic stenosis that were treated with simvastatin and ezetimibe had a lower risk of cataract than did patients treated with placebo.[27] Because the treatment group received ezetimibe, which is a cholesterol-lowering agent, this result may be overlooked in this study.[41] Heterogeneity may have also arisen from this study.

The strengths of our meta-analysis include the analysis of both observational studies and RCTs and the large sample size. Despite its strengths, there are several limitations of our analysis. First, evidence of among-study heterogeneity of the observational studies was apparent. Although we performed
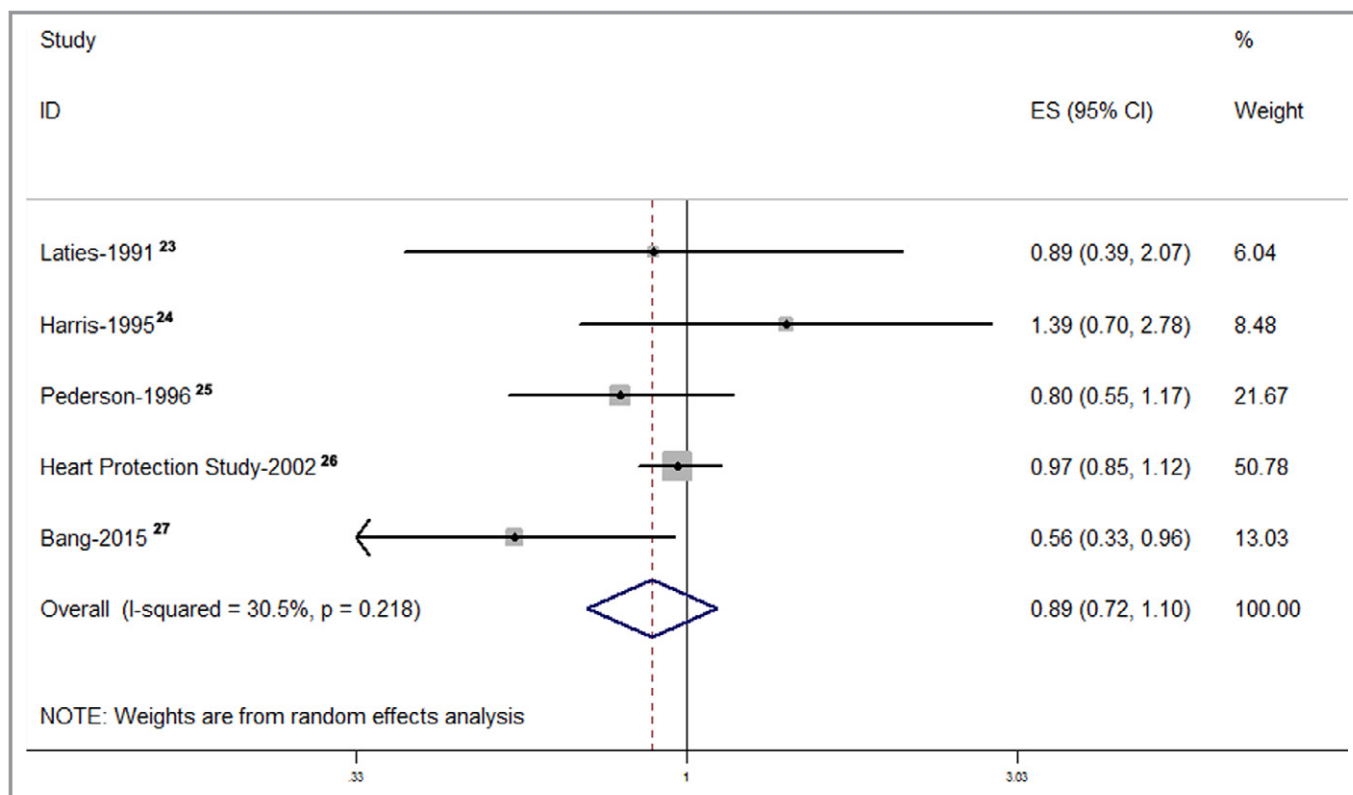
Figure 4. Forest plot of the RCTs. The pooled RR of the RCTs was 0.89 (95% CI, 0.72–1.10). The I^2 value indicated slight heterogeneity across these RCTs (I^2=30.5%; *P*=0.218). ES indicates effect size; RCT, randomized controlled trial; RR, relative risk.

subgroup analyses in an attempt to identify the sources of heterogeneity, these variables could not fully explain the observed heterogeneity, suggesting that other unknown, confounding variables might be responsible. Second, the confounding factors varied among the included studies.

Because of the limitations of observational studies and RCTs, large, multicenter, pragmatic, prospective observational studies or registries should be performed in the future to assess the risk of cataracts. The primary end points should include not only cardiovascular diseases but also total comorbidity. Moreover, patients should be stratified according to baseline confounders. Cataracts should be confirmed by objective serial testing using validated tools, and per-protocol analysis should be used to determine the protocol effects on results. Finally, investigators should attempt to characterize and follow the outcomes of those patients who drop out of the trials.[35]

Conclusion

Based on the present meta-analysis of these studies, we could only conclude that there is no clear evidence showing that statin use increases the risk of cataract. The most likely case is that there is no association. Because of the considerable

benefits of statins in cardiovascular patients, this issue should not deter the use of statins.

Disclosures

None.

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Table S1. Detailed Definition of cataract and Adjustment Factors for cataract of observational studies

Study,year	Cataract definition	Adjustment
Schlienger, 2001[1]	Patients who had a first-time diagnosis of cataract(ICD-8)followed by a referral to a specialist or by a hospitalization because of cataract diagnosis, cataract surgery was identified by Oxford Medical Information System procedure code 156	age, sex, practice attended, calender time(by matching), BMI, smoking, number of general practitioner visit, corticosteroid use
Smeeth, 2003[2]	Patients who had a first-time diagnosis of cataract(ICD-8).	age, sex, observational period(by matching), smoking habit; body mass index; diabetes mellitus; glaucoma; hypertension; and exposure to aspirin, oestrogen (as hormone replacement therapy) and systemic corticosteroids, annual consultation rate
Fong, 2012[3]	Patient who had cataract extraction, identified with the CPT (current procedural terminology) code 66982, 66983,or 66984.	age, sex, ethnicity, coronary heart disease, diabetes, smoking
Wise-BC, 2014[4]	A cataract was defined as the first date of an ophthalmologist visit for cataract, and having a cataract surgical code within a year of the date of this visit	age, index date , follow-up years(by matching), sex (for the BC cohort), diabetes, hypertension, glaucoma, chronic obstructive pulmonary disease, uveitis, history of cardiovascular or cerebrovascular disease (previous history of stroke or myocardial infarction), and the following prescription drugs: antipsychotics, oral steroids, inhaled corticosteroids, and selective serotonin reuptake inhibitors
Wise-IMS, 2014[4]	A cataract was defined as the first date of an ophthalmologist visit for cataract, and having a cataract surgical code within a year of the date of this visit	age, index date , follow-up years(by matching), diabetes, hypertension, glaucoma, chronic obstructive pulmonary disease, uveitis, history of cardiovascular or cerebrovascular disease (previous history of stroke or

		myocardial infarction), and the following prescription drugs: antipsychotics, oral steroids, inhaled corticosteroids, and selective serotonin reuptake inhibitors
Erie, 2016[5]	Cataract and cataract surgery were retrospectively identified using the ICD-9 codes and CPT codes.	age, sex, diabetes, cardiovascular disease, cerebrovascular disease, peripheral vascular disease, renal disease, oral and inhaled steroid use, and selective serotonin reuptake inhibitor use.
Klein, 2006[6]	Cataract was diagnosed by Wisconsin Cataract Grading System	age, sex, total cholesterol, high-density lipoprotein cholesterol, smoking, and diabetes
Tan, 2007[7]	Cataract was diagnosed by Wisconsin Cataract Grading System	sex, total cholesterol, high-density lipoprotein cholesterol, smoking, obesity, and diabetes
Cox, 2010[8]	Cataract was confirmed by patients' electronic records	age^3, $age^3 \ln(age)$, $\ln(bmi)$, $bmi^{0.5}$, ethnicity, smoking, cardiovascular disease, type 1 diabetes, type 2 diabetes, rheumatoid arthritis, atrial fibrillation, corticosteroids; Cataract men: age^3, $age^3 \ln(age)$, bmi^{-2}, bmi^{-1}, Townsend score, ethnicity, smoking, cardiovascular disease, type 1 diabetes, type 2 diabetes, atrial fibrillation, corticosteroids
Waudby, 2011[9]	Cataract and cataract surgery were identified using the ICD-9 codes and CPT codes.	sex, diabetes, smoking, steroid use, BMI, HDL, antioxidant
Lai, 2013[10]	Cataract surgery was identified by ICD-9 codes	age, sex, diabetes mellitus under treatment, hypertension undertreatment, Charlson Index such as

myocardial infarction, cerebrovascular disease, chronic pulmonary disease, renal disease, liver disease and malignancy, oral estrogen replacement therapy, corticosteroids, non-steroidal anti-inflammatory drugs, aspirin, proton pump inhibitors, H2 receptor antagonists, number of distinct prescription drugs dispensed, number of hospitalizations and number of physician visits were also included in the list of potential confounders.

Leuschen, 2014[11]	Cataracts were difined using ICD-9 codes	age, sex, obesity, smoking, alcohol use, illicit drug use, glaucoma at baseline, vision defects/blindness, number of all admissions during baseline, number of all outpatient visits during baseline, and use of different classes of medications as listed in Table 1. mean low-density lipoprotein cholesterol.

Table S2. NOS for Assessment of Quality of Included Studies: Case-Control Studies

Quality Assessment criteria	Acceptable	Schlienger 2001[1]	Smeeth 2003[2]	Fong 2012[3]	Wise-BC 2014[4]	Wise-IMS 2014[4]	Erie 2016[5]
Selection							
Is the case definition adequate?	Yes, with independent validation	−	−	−	−	−	−
Repsentiveness of cases?	Consecutive or obviously representative series of cases	+	+	−	−	+	−
Selection of controls?	Community controls	+	+	+	+	+	+
Definition of controls?	No history of cataracts	+	+	+	+	+	+
Comparability Study controls for age/sex	Yes	+	+	+	+	+	+
Study controls for any other confounding factors?	Yes	-	−	−	−	−	−
Exposure Ascertain of exposure?	Secure record, Structured interview where blind to case-control status	+	+	+	+	+	+
Same method of ascertainment of cases/controls?	Yes	+	+	+	+	+	+
Nonresponse rate	Same for both the groups	+	+	+	+	+	+
Overall quality score (maximum=10)		7	7	6	6	7	6

Table S3. NOS for Assessment of Quality of Included Studies: Cohort Studies

Quality assessment criteria	Acceptable	Klein 2006[6]	Tan 2007[7]	Cox 2010[8]	Waudby 2011[9]	Lai 2013[10]	Leuschen 2014[11]
Selection Representativeness of exposed cohort?	Representative of average adult in community (age/sex/being at risk of disease)	+	–	+	+	+	-
Selection of the nonexposed cohort?	Drawn from same community as exposed cohort	+	+	+	+	+	+
Ascertainment of exposure?	Secured records, structured interview	+	+	+	+	+	+
Demonstration that outcome of interest was not present at the start of the study?	Only incident cases of cataracts	+	+	+	+	+	+
Comparability Study controls for age/sex	Yes	+	+	+	+	+	+
Study controls for any other confounding factors?	Yes	–	–	–	–	–	–
Exposure Assessment of outcomes?	Independent blind assessment record linkage	+	+	+	+	+	+
Was follow-up evaluation long enough for outcome to occur?	Yes	+	+	+	+	+	+
Adequacy of follow-up evaluation of cohorts	Complete follow-up evaluation, or subjects lost to follow-up evaluation unlikely to introduce bias	–	–	+	–	+	+
Overall quality score(maximum=10)		7	6	8	6	8	7

Table S4. Quality of the included RCTs assessed by Cochrane risk of bias assessment

Quality assessment criteria	Laties 1991[12]	Harris 1995[13]	Pederson 1996[14]	Bang 2015[15]	Heart Protection Study 2015[16]
Random sequence generation	-	+	+	-	+
Allocation concealment	+	+	+	-	+
Blinding participants and personnel	+	-	+	+	+
Blinding of outcome assessment	+	-	-	-	-
Incomplete outcome data	-	+	+	+	+
Selective reporting	+	+	+	+	+
Other bias	+	+	+	+	+
Overall quality score (maximum=7)	5	5	6	5	6

Table S5. Subgroup analysis of cohort studies

Factor	Studies n	RR (95% CI)	I^2
Quality assessment			
High (≥7)	4	1.15(1.02-1.30)	92.8%
Low (<7)	2	0.83 (0.37-1.83)	56.4%
Study location			
North America	3	1.05 (0.89-1.24)	78.0%
Europe	1		
Asia	1		
Australia	1		
Sex			
Male	3	1.24 (1.12-1.37)	64.0%
Female	2	1.30 (1.25-1.34)	0%
Outcome assessment			
ICD codes	3	1.20 (1.14-1.25)	0%
Wisconsin Cataract Grading System	2	0.57 (0.40-0.81)	0%
Outcome			
Cataract	4	1.17 (1.03-1.34)	82.6%
Cataract surgery	1		
Cataract and surgery	1		
Age			
Older than 60 years	4	1.00 (0.82-1.22)	82.6%
No older than 60 years	2	1.28 (1.19-1.38)	48.7%
Follow-up duration			
Less than 5 years	2	1.28(1.19-1.38)	48.7%
5 or more than 5 years	4	1.00(0.82-1.22)	82.6%

Factor	Studies n	RR (95% CI)	I^2
Whether LDL included			
LDL included model	3	0.75 (0.41-1.37)	87.3%
LDL missing model	3	1.24 (1.15-1.34)	82.1%
Whether CVD included			
CVD included model	2	1.26(1.15-1.37)	88.4%
CVD missing model	4	0.96(0.75-1.22)	81.7%
Whether smoking included			
Smoking included model	5	1.13 (0.98-1.30)	82.1%
Smoking missing model	1		
Whether consultation rate included			
consultation rate included model	2	1.20(1.14-1.26)	0%
consultation rate missing model	4	1.01(0.81-1.27)	88.0%
Whether hypertension included			
Hypertension included model	2	1.26 (1.15-1.37)	88.4%
Hypertension missing model	4	1.01(0.82-1.25)	76.2%

Table S6. Subgroup analysis of case-control studies

Factor	Studies n	RR (95% CI)	I^2
Quality assessment			
High (≥7)	3	1.07(1.04-1.10)	0%
Low (<7)	3	1.15 (0.96-1.37)	95.9%
Study location			
North America	4	1.13 (0.99-1.28)	97.5%
Europe	2	1.02 (0.90-1.16)	0%
Outcome assessment			
ICD codes	3	1.12 (0.94-1.33)	77.1%
Medical records	2	1.17 (0.99-1.38)	98.8%
Type of statins			
Artovastatin	4	1.17 (1.04-1.31)	90.0%
Fluvastatin	3	1.23 (0.96-1.56)	53.1%
Lorvastatin	3	1.22 (1.07-1.39)	74.1%
Pravastatin	3	1.23 (0.96-1.56)	53.1%
Simvastain	4	1.13 (0.99-1.30)	92.9%
Rosuvastatin	2	1.21 (0.89-1.65)	94.2%
Outcome			
Cataract surgery	3	1.16 (0.95-1.42)	86.8%
Cataract and surgery	2	1.13(0.97-1.31)	97.7%
Cataract	1	1.04(0.89-1.23)	
Whether CVD included			
CVD included model	4	1.17(1.04-1.31)	96.7%
CVD missing model	2	1.02(0.92-1.18)	0%

Factor	Studies n	RR (95% CI)	I^2
Whether smoking included			
Smoking included model	3	1.03 (0.96-1.13)	0%
Smoking missing model	3	1.12 (1.05-1.37)	97.7%
Whether consultation rate included			
consultation rate included model	2	1.02(0.90-1.16)	0%
consultation rate missing model	4	1.17(1.04-1.31)	96.7%
Whether diabetes included			
Diabetes included model	5	1.15 (1.03-1.27)	95.8%
Diabetes missing model	1	1.00(0.80-1.20)	
Whether hypertension included			
Hypertension included model	4	1.17 (1.04-1.32)	96.7%
Hypertension missing model	2	1.03 (0.93-1.15)	0%

Table S7. Subgroup analysis of RCTs

Factor	Studies n	RR	I^2
Age			
Older than 60 years	3	0.82 (0.53-1.26)	52.2%
Young than 60 years	1	0.89 (0.39-2.07)	
Follow-up duration			
More than 5 years	2	0.95 (0.83-1.08)	0%
Less than 5 years	3	0.86 (0.48-1.51)	53%

Figure S1. Sensitivity analysis of cohort studies

Meta-analysis random-effects estimates (exponential form)
Study ommited
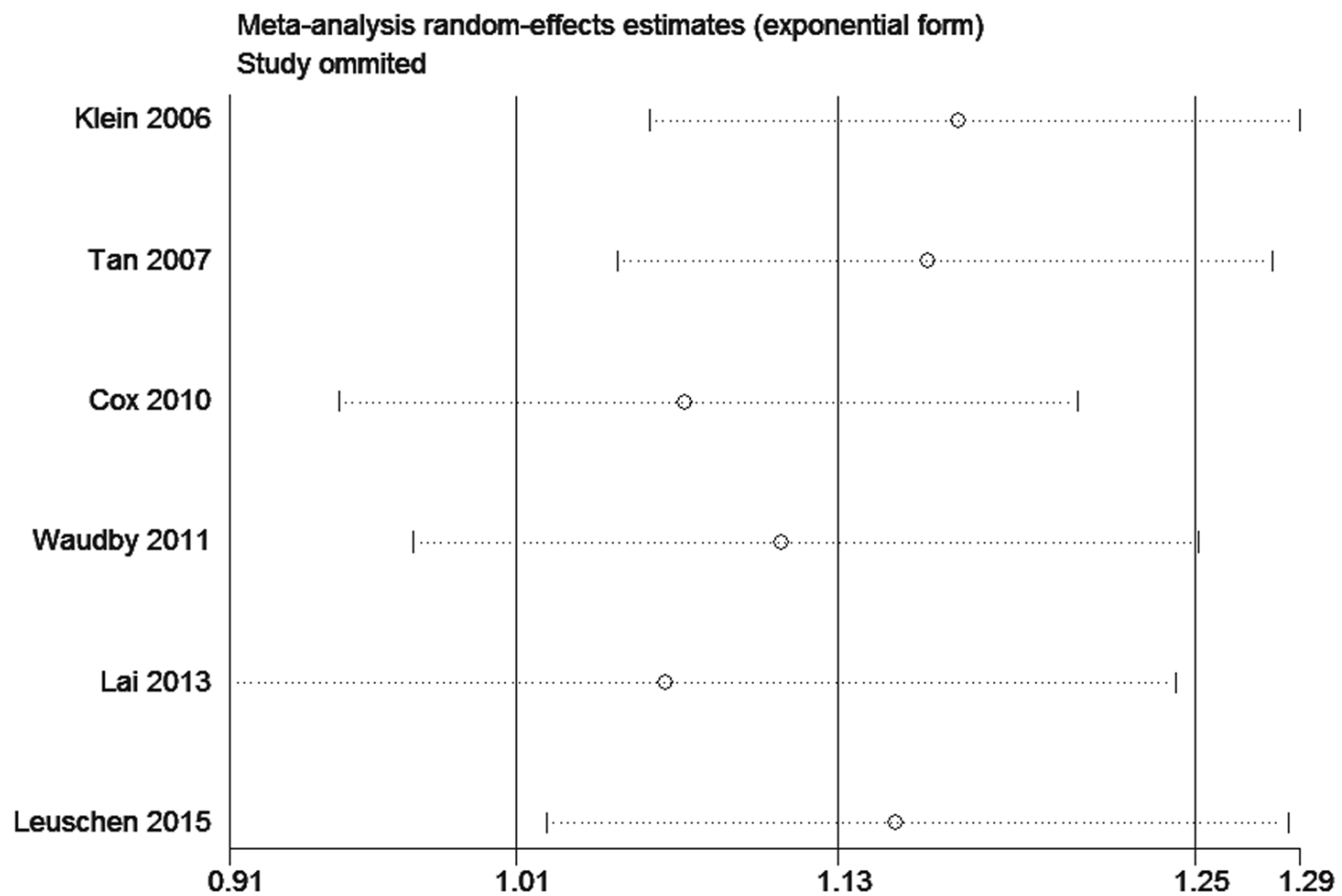
Figure S2. Sensitivity analysis of case-control studies

Meta-analysis random-effects estimates (exponential form)
Study ommited
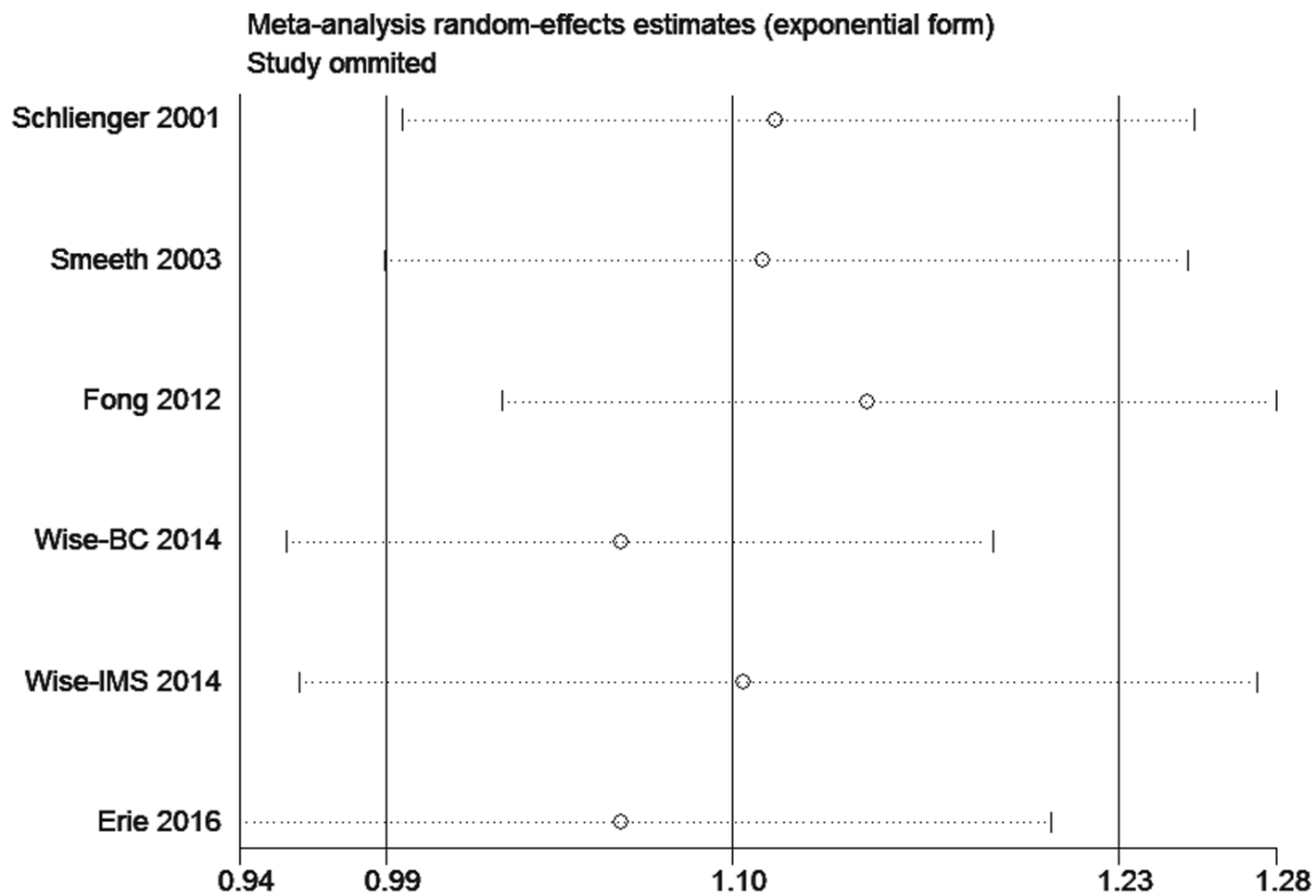
Figure S3. Sensitivity analysis of RCTs

Meta-analysis random-effects estimates (exponential form)
Study ommited
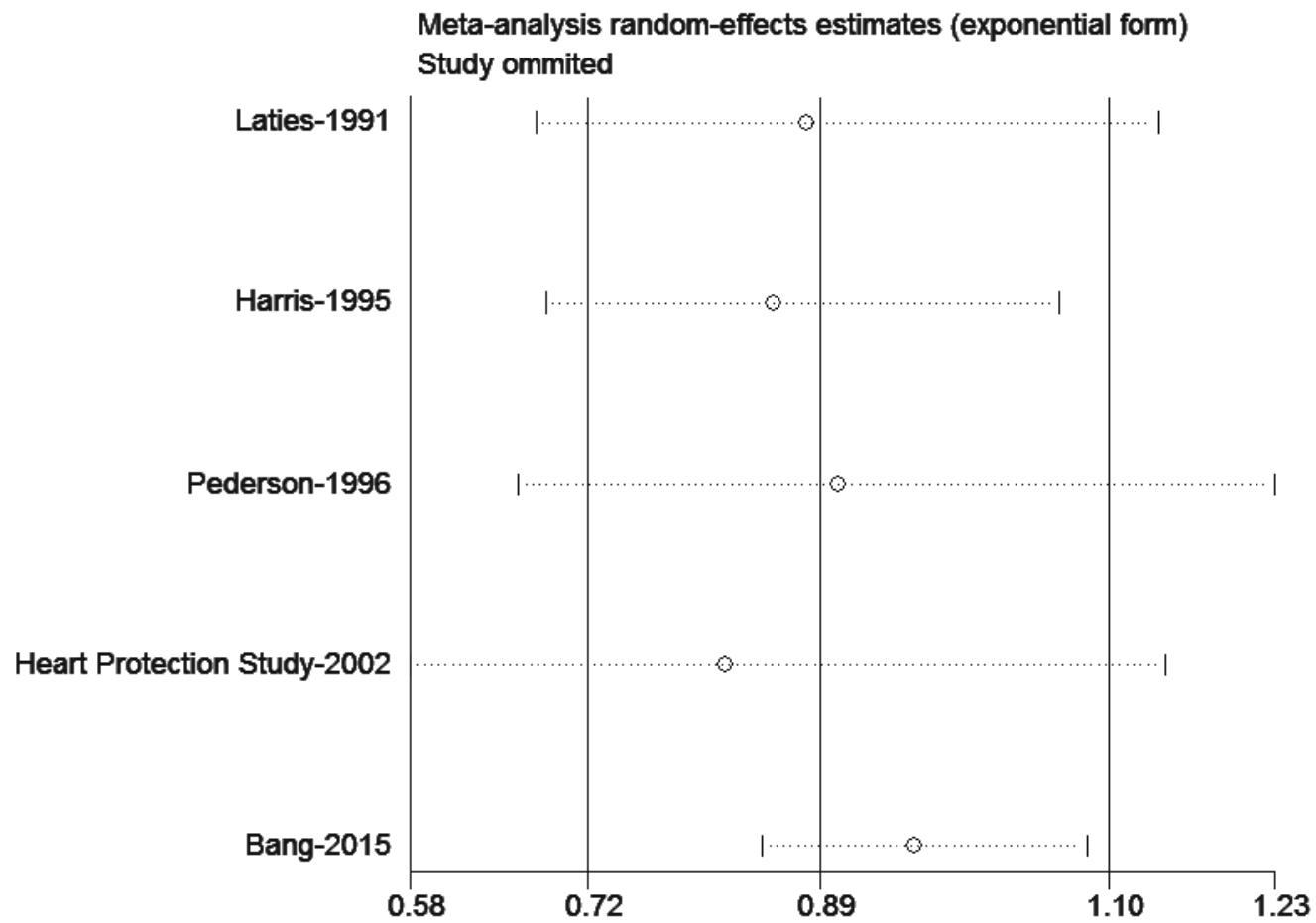
Figure S4. Subgroup analysis of cohort by quality assessment

A. High quality

Study ID	ES (95% CI)	% Weight
Klein	0.60 (0.39, 0.93)	6.03
Lai	1.20 (1.14, 1.27)	31.14
Leuschen	1.09 (1.02, 1.17)	29.94
Cox	1.31 (1.28, 1.34)	32.90
Overall (I-squared = 92.8%, p = 0.000)	1.15 (1.02, 1.30)	100.00

NOTE: Weights are from random effects analysis

.39   1   2.56

B. Low quality

Study ID	ES (95% CI)	% Weight
Tan	0.52 (0.29, 0.93)	43.65
Waudby	1.18 (1.06, 1.32)	56.35
Overall (I-squared = 86.4%, p = 0.007)	0.83 (0.37, 1.83)	100.00

NOTE: Weights are from random effects analysis
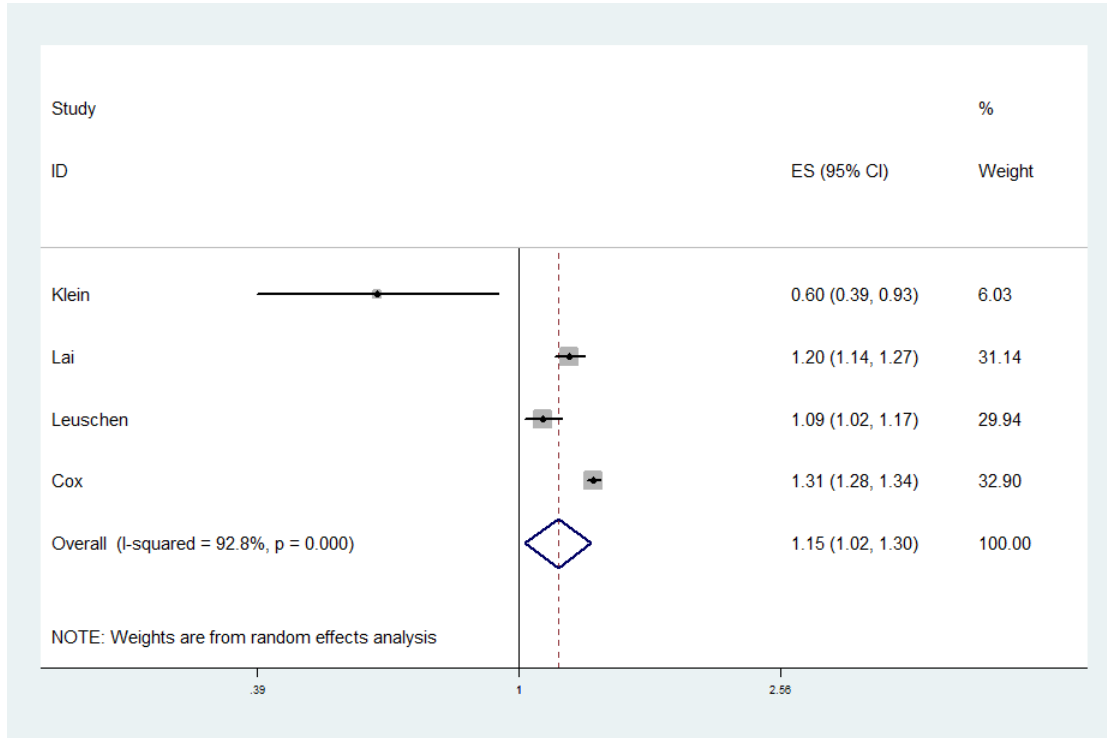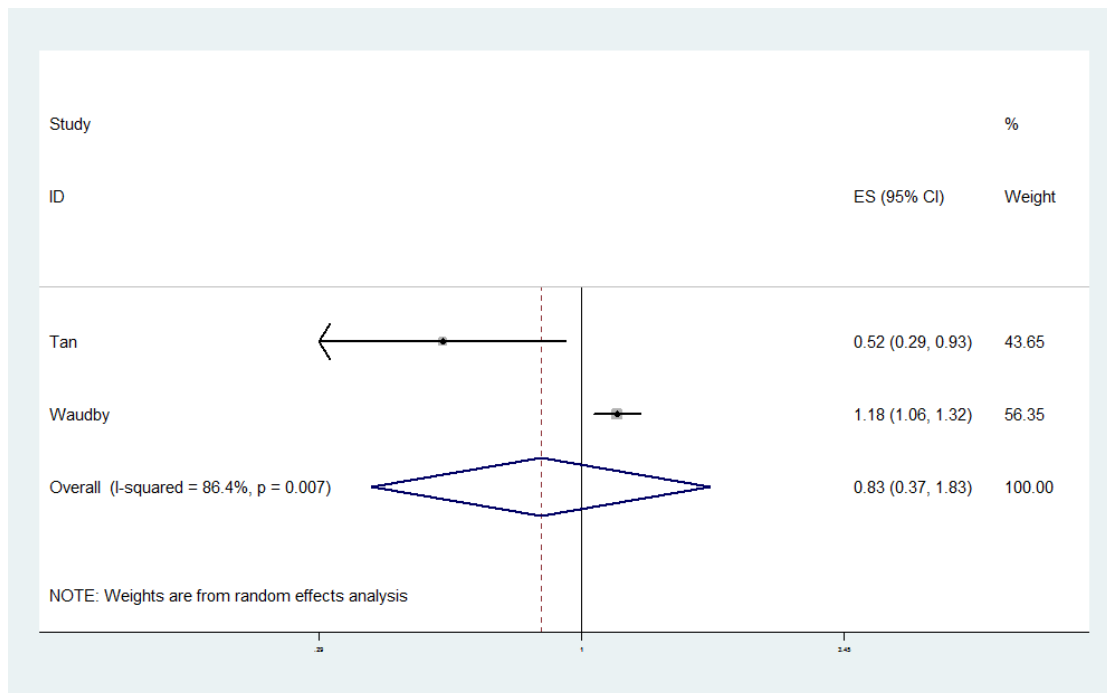
Figure S5. Subgroup analysis of cohort by location (North America)

Study		
ID	ES (95% CI)	Weight
Klein	0.60 (0.39, 0.93)	11.54
Leuschen	1.09 (1.02, 1.17)	46.76
Waudby	1.18 (1.06, 1.32)	41.70
Overall (I-squared = 78.0%, p = 0.011)	1.05 (0.89, 1.24)	100.00

NOTE: Weights are from random effects analysis

.39   1   2.56
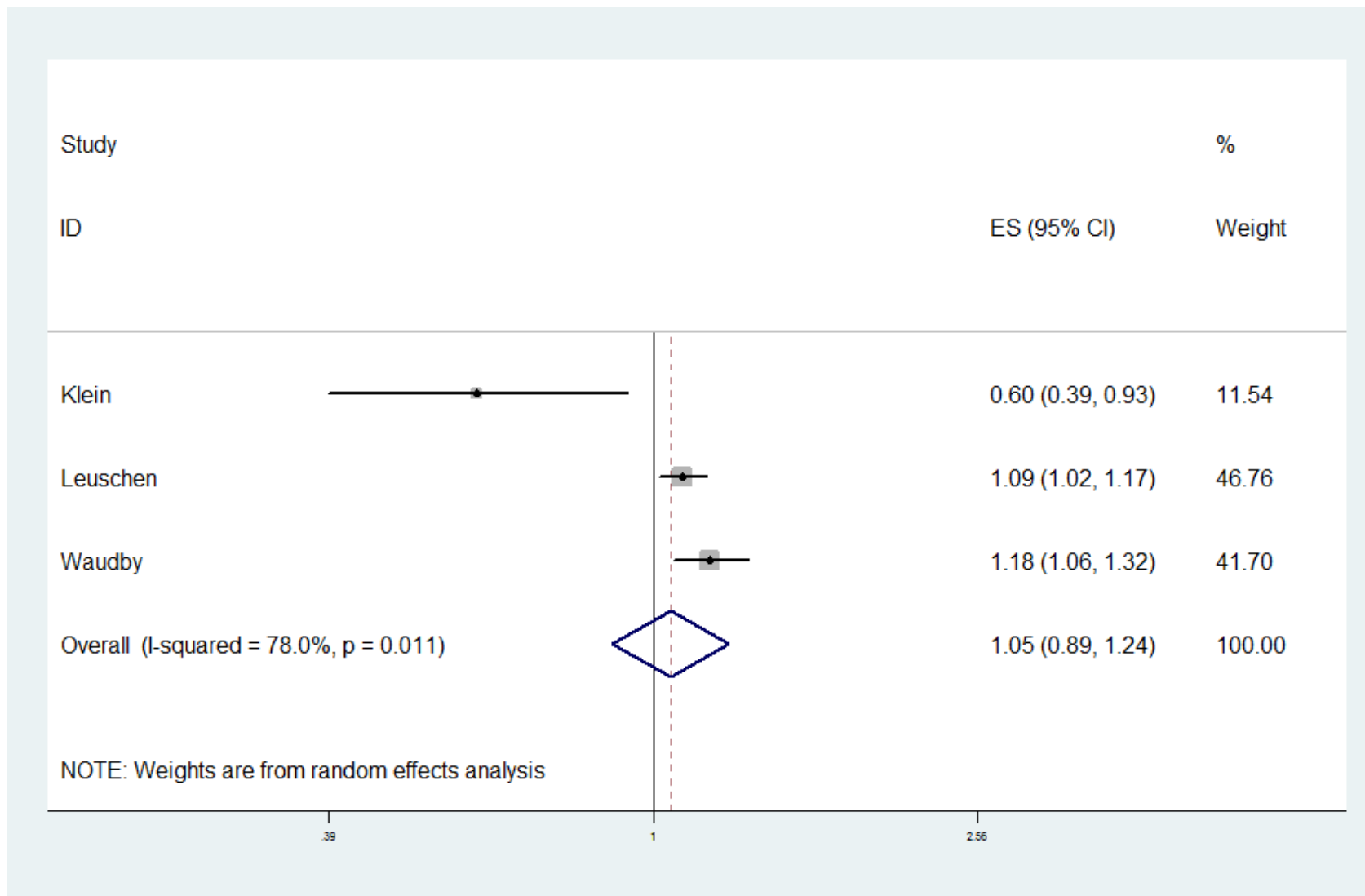
Figure S6. Subgroup analysis of cohort by sex

A. Male
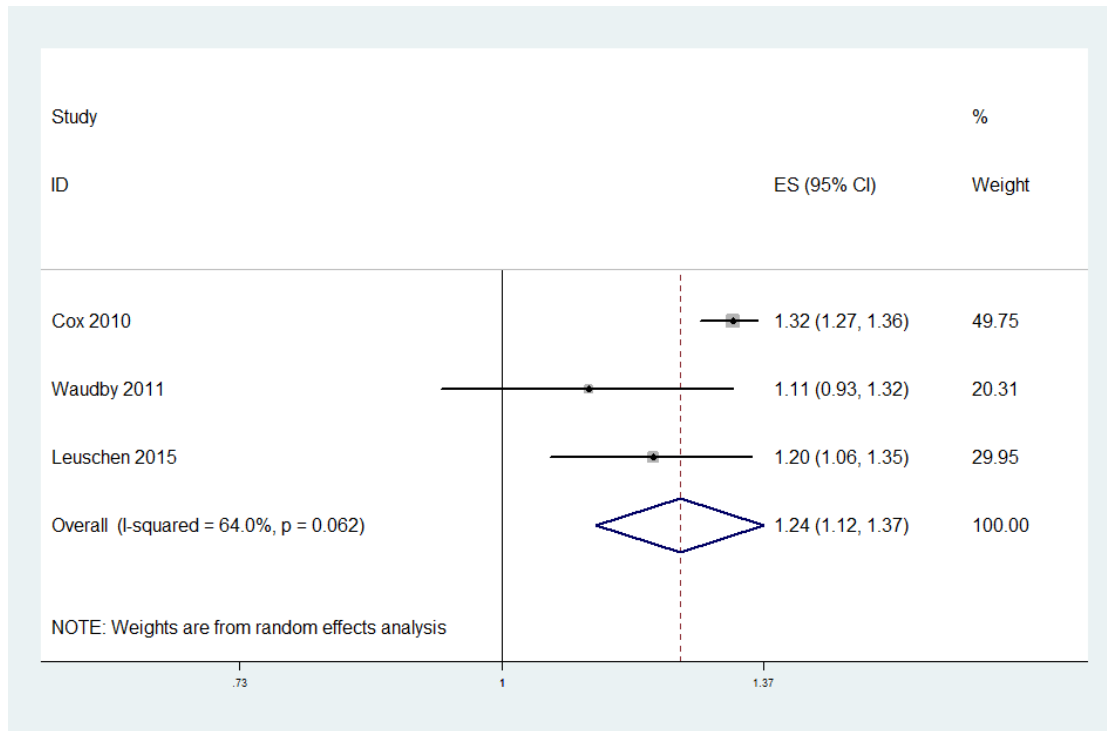
B. Female
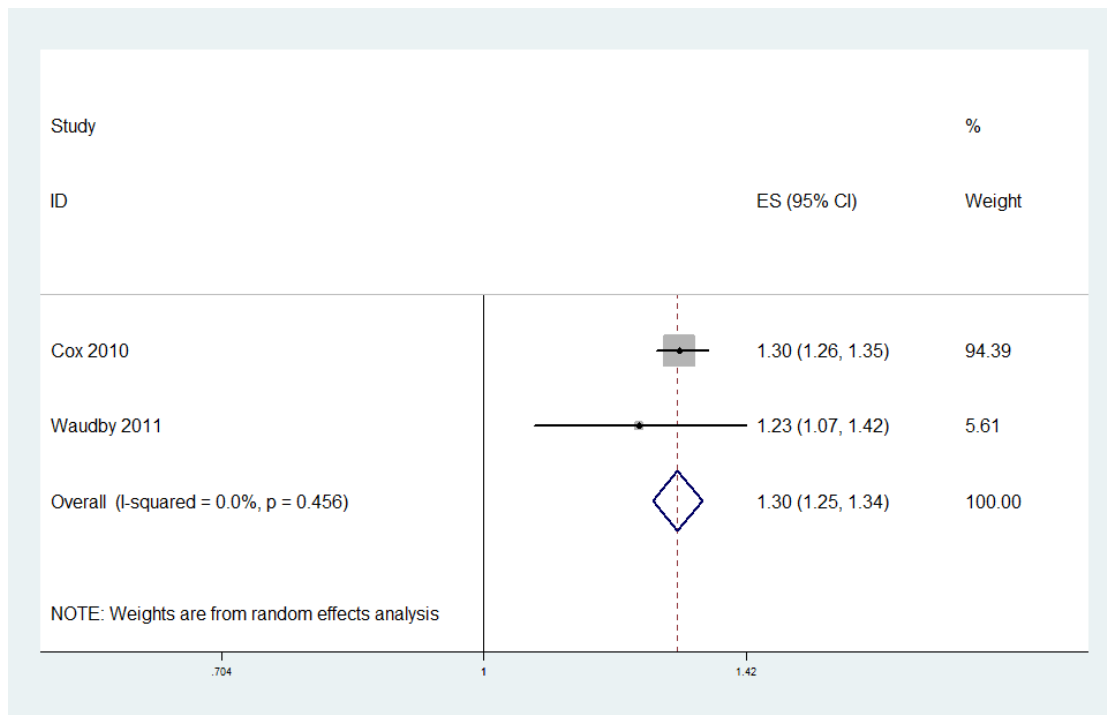
Figure S7. Subgroup analysis of cohort by outcome assessment

A. ICD codes

Study		
ID	ES (95% CI)	% Weight
Waudby 2011	1.18 (1.06, 1.32)	16.81
Lai 2013	1.20 (1.14, 1.27)	69.36
Leuschen 2015	1.20 (1.06, 1.35)	13.83
Overall (I-squared = 0.0%, p = 0.963)	1.20 (1.14, 1.25)	100.00

NOTE: Weights are from random effects analysis

.741   1   1.35

B. Grading system

Study		
ID	ES (95% CI)	% Weight
Klein 2006	0.60 (0.39, 0.93)	64.26
Tan 2007	0.52 (0.29, 0.93)	35.74
Overall (I-squared = 0.0%, p = 0.700)	0.57 (0.40, 0.81)	100.00

NOTE: Weights are from random effects analysis

.29   1   3.45
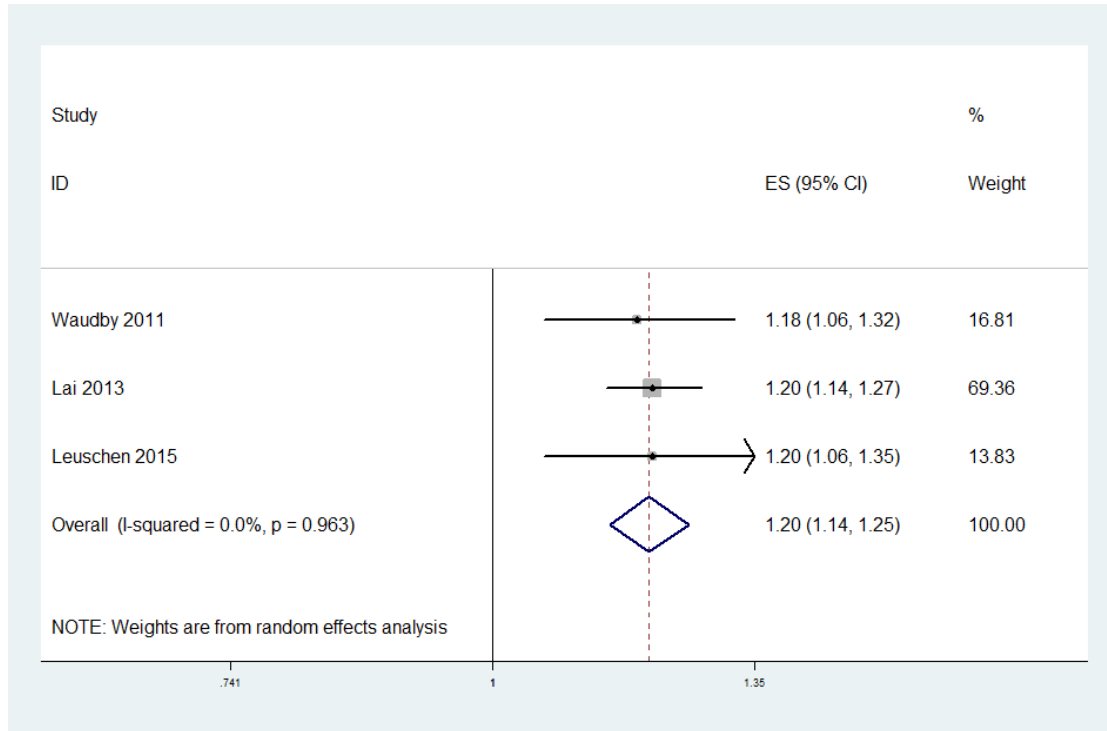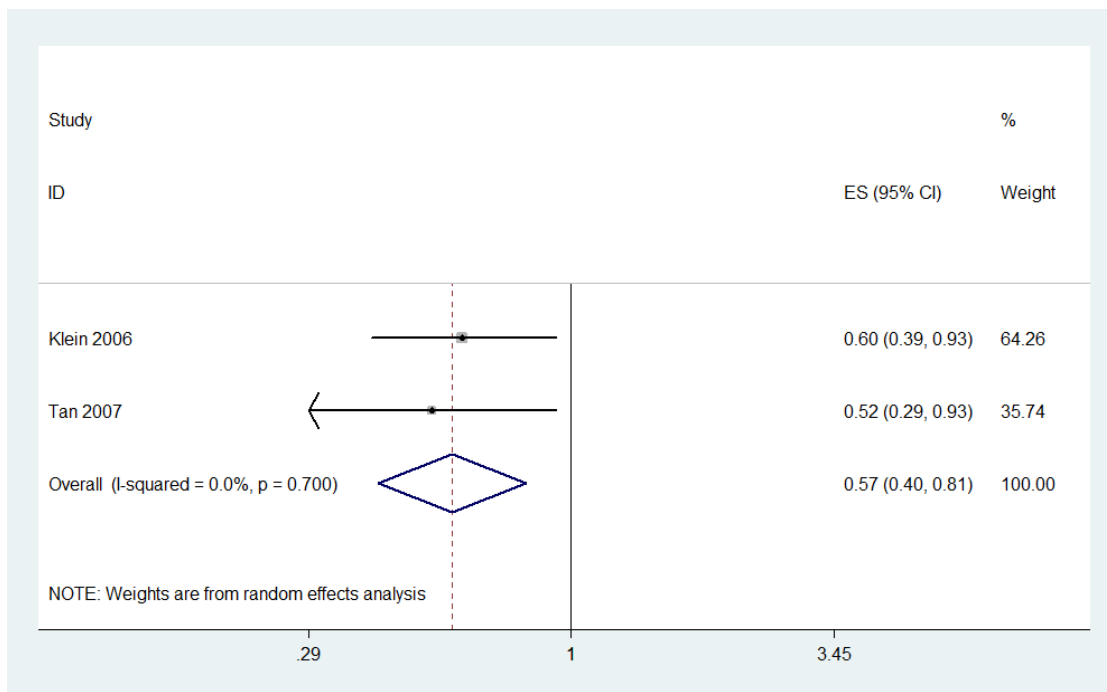
Figure S8. Subgroup analysis of cohort by outcome (Cataract)

Study ID		ES (95% CI)	% Weight
Klein		0.60 (0.39, 0.93)	7.36
Leuschen		1.20 (1.06, 1.35)	27.80
Waudby		1.18 (1.06, 1.32)	28.99
Cox		1.31 (1.28, 1.34)	35.85
Overall (I-squared = 82.6%, p = 0.001)		1.17 (1.03, 1.34)	100.00

NOTE: Weights are from random effects analysis

.39   1   2.56
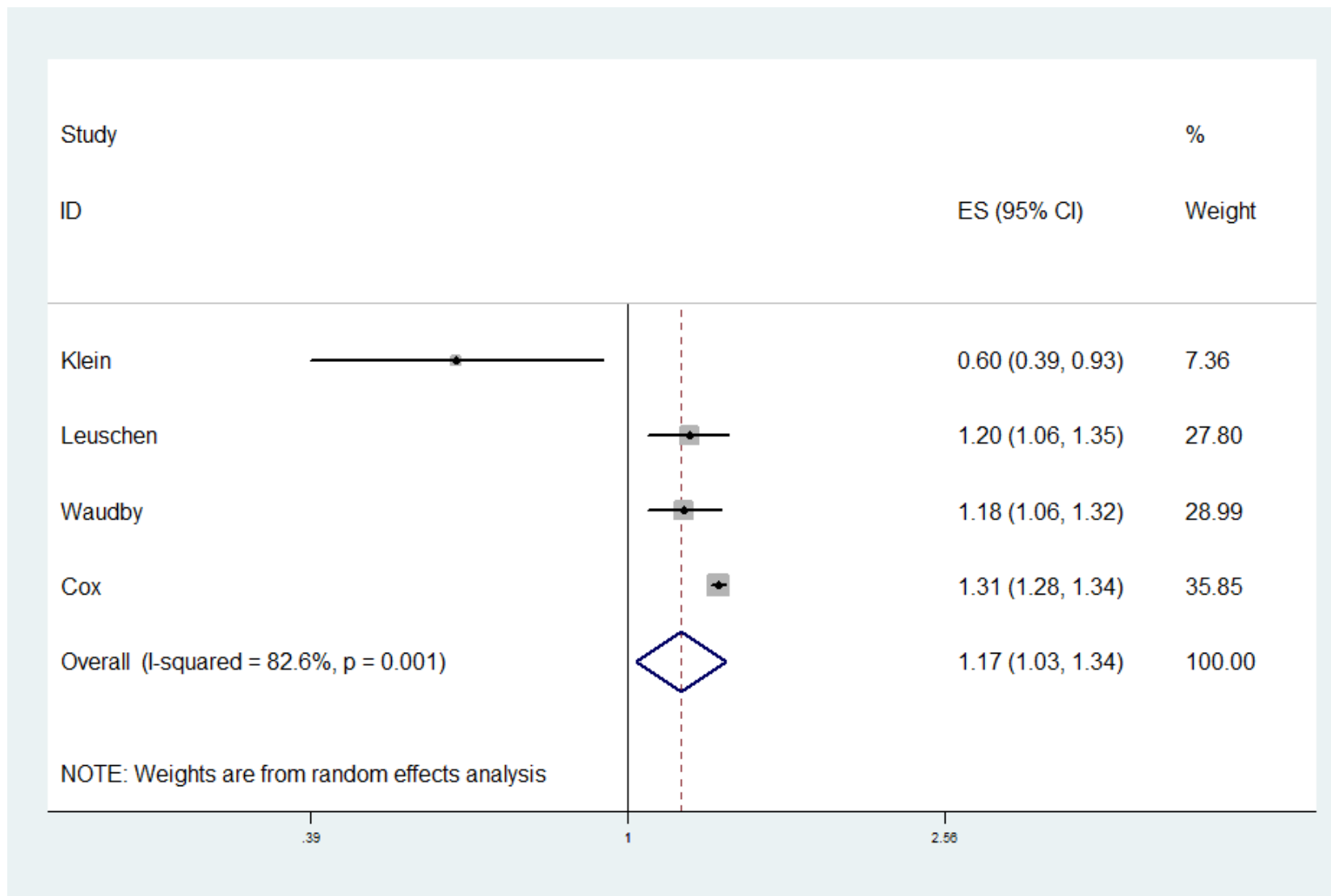
Figure S9. Subgroup analysis of cohort by age

A. Older than 60

Study ID	ES (95% CI)	% Weight
Klein 2006	0.60 (0.39, 0.93)	14.00
Tan 2007	0.52 (0.29, 0.93)	9.16
Lai 2013	1.20 (1.14, 1.27)	40.10
Waudby 2011	1.18 (1.06, 1.32)	36.74
Overall (I-squared = 82.6%, p = 0.001)	1.00 (0.82, 1.22)	100.00

NOTE: Weights are from random effects analysis

.29   1   3.45

B. Younger than 60

Study ID	ES (95% CI)	% Weight
Cox 2010	1.31 (1.28, 1.34)	73.85
Leuschen 2015	1.20 (1.06, 1.35)	26.15
Overall (I-squared = 48.7%, p = 0.162)	1.28 (1.19, 1.38)	100.00

NOTE: Weights are from random effects analysis

.724   1   1.38

Figure S10. Subgroup analysis of cohort by follow-up duration

A. More than 5 years

Study		
ID	ES (95% CI)	% Weight
Klein 2006	0.60 (0.39, 0.93)	14.00
Tan 2007	0.52 (0.29, 0.93)	9.16
Waudby 2011	1.18 (1.06, 1.32)	36.74
Lai 2013	1.20 (1.14, 1.27)	40.10
Overall (I-squared = 82.6%, p = 0.001)	1.00 (0.82, 1.22)	100.00

NOTE: Weights are from random effects analysis

.29   1   3.45

B. Less than 5 years

Study		
ID	ES (95% CI)	% Weight
Cox 2010	1.31 (1.28, 1.34)	73.85
Leuschen 2015	1.20 (1.06, 1.35)	26.15
Overall (I-squared = 48.7%, p = 0.162)	1.28 (1.19, 1.38)	100.00

NOTE: Weights are from random effects analysis

.724   1   1.38
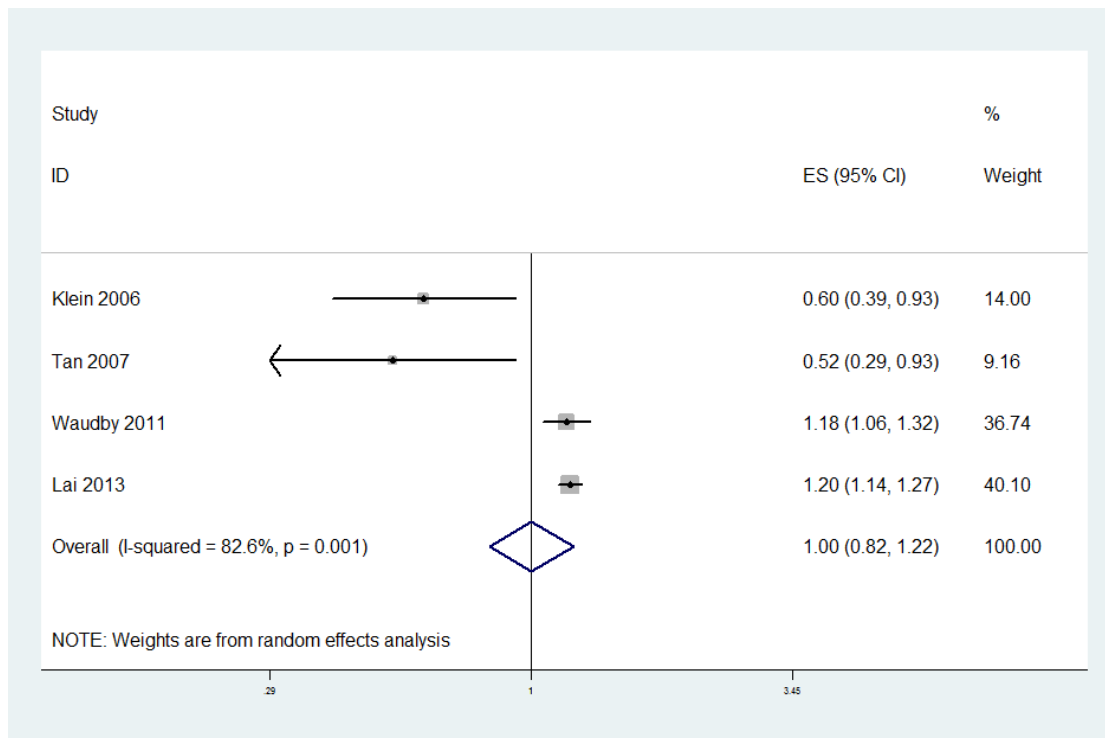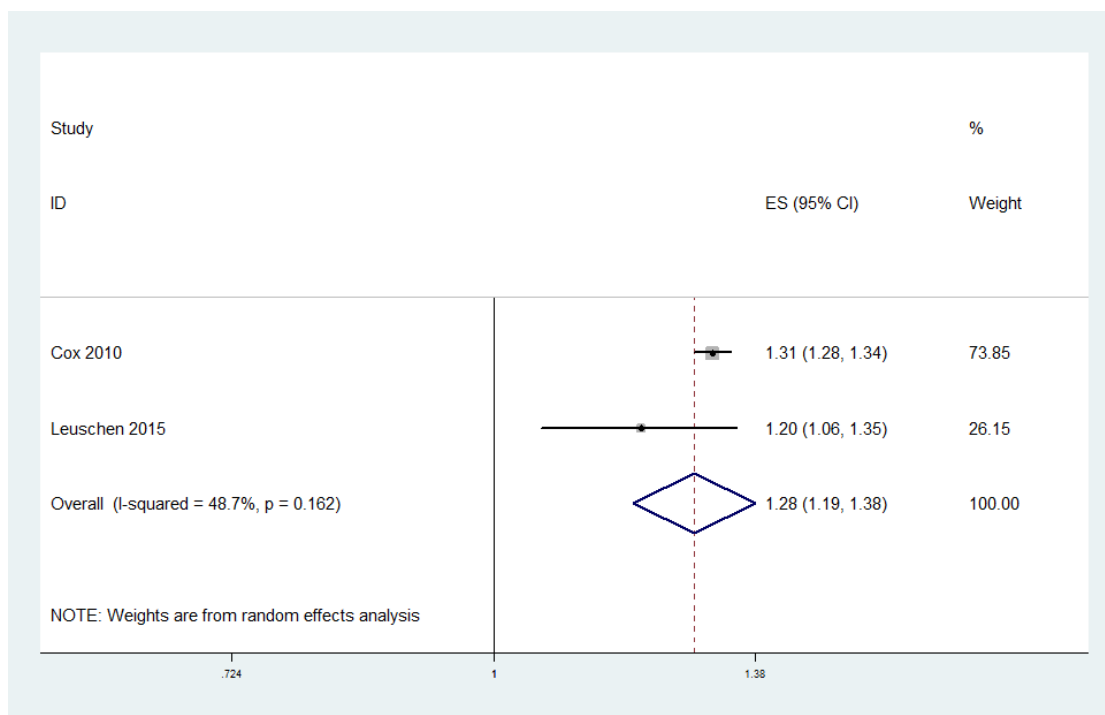
Figure S11. Subgroup analysis of cohort by whether LDL included

A. LDL included

Study		
ID	ES (95% CI)	Weight
Klein 2006	0.60 (0.39, 0.93)	32.60
Tan 2007	0.52 (0.29, 0.93)	28.68
Leuschen 2015	1.20 (1.06, 1.35)	38.72
Overall (I-squared = 87.3%, p = 0.000)	0.75 (0.41, 1.37)	100.00

NOTE: Weights are from random effects analysis

B. LDL missing

Study		
ID	ES (95% CI)	Weight
Cox 2010	1.31 (1.28, 1.34)	41.99
Waudby 2011	1.18 (1.06, 1.32)	22.45
Lai 2013	1.20 (1.14, 1.27)	35.56
Overall (I-squared = 82.1%, p = 0.004)	1.24 (1.15, 1.34)	100.00

NOTE: Weights are from random effects analysis

Figure S12. Subgroup analysis of cohort by CVD

A. CVD included

Study ID	ES (95% CI)	% Weight
Cox 2010	1.31 (1.28, 1.34)	54.05
Lai 2013	1.20 (1.14, 1.27)	45.95
Overall (I-squared = 88.4%, p = 0.003)	1.26 (1.15, 1.37)	100.00

NOTE: Weights are from random effects analysis

B. CVD missing

Study ID	ES (95% CI)	% Weight
Klein 2006	0.60 (0.39, 0.93)	17.27
Tan 2007	0.52 (0.29, 0.93)	12.00
Waudby 2011	1.18 (1.06, 1.32)	35.64
Leuschen 2015	1.20 (1.06, 1.35)	35.09
Overall (I-squared = 81.7%, p = 0.001)	0.96 (0.75, 1.22)	100.00

NOTE: Weights are from random effects analysis

Figure S13. Subgroup analysis of cohort by smoking (Smoking included)

Study ID	ES (95% CI)	% Weight
Klein 2006	0.74 (0.50, 1.10)	9.16
Tan 2007	0.52 (0.29, 0.93)	4.95
Cox 2010	1.31 (1.28, 1.34)	32.36
Waudby 2011	1.18 (1.06, 1.32)	27.24
Leuschen 2015	1.20 (1.06, 1.35)	26.30
Overall (I-squared = 82.1%, p = 0.000)	1.13 (0.98, 1.30)	100.00

NOTE: Weights are from random effects analysis

.29   1   3.45

Figure S14. Subgroup analysis of cohort by consultation rate

A. Consultation rate included

Study		
ID	ES (95% CI)	Weight
Lai 2013	1.20 (1.14, 1.27)	83.38
Leuschen 2015	1.20 (1.06, 1.35)	16.62
Overall (I-squared = 0.0%, p = 1.000)	1.20 (1.14, 1.26)	100.00

NOTE: Weights are from random effects analysis

.741   1   1.35

B. Consultation rate missing

Study		
ID	ES (95% CI)	Weight
Klein	0.60 (0.39, 0.93)	15.52
Tan	0.52 (0.29, 0.93)	10.50
Cox	1.31 (1.28, 1.34)	38.59
Waudby	1.18 (1.06, 1.32)	35.38
Overall (I-squared = 88.0%, p = 0.000)	1.01 (0.81, 1.27)	100.00

NOTE: Weights are from random effects analysis

.29   1   3.45
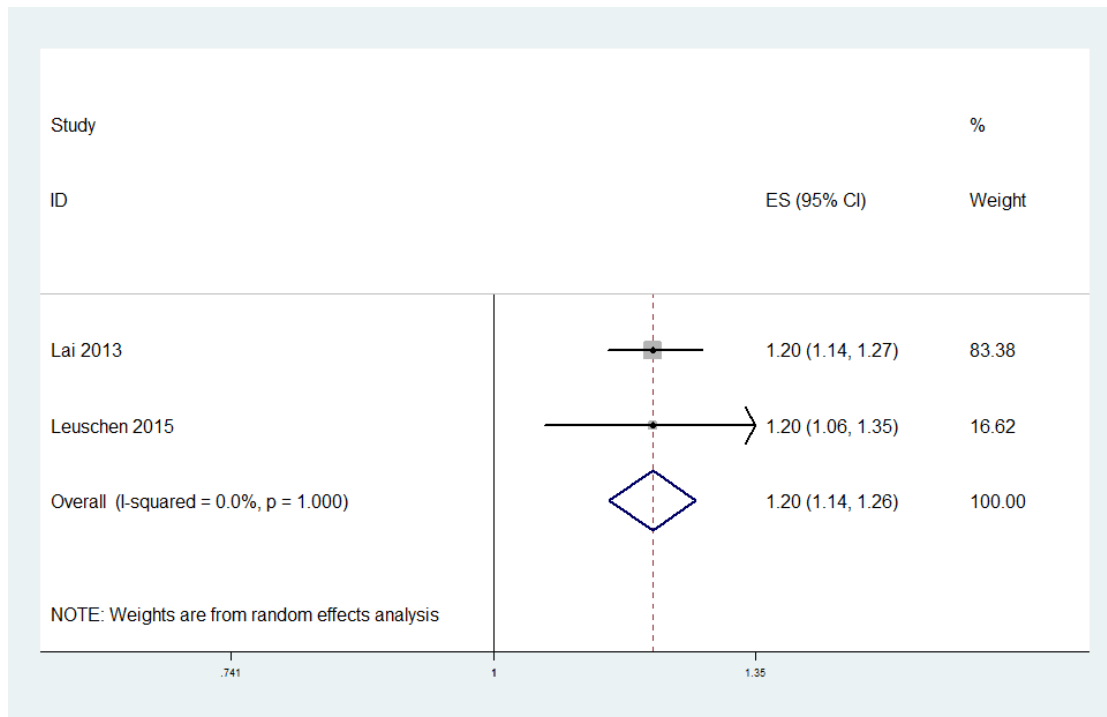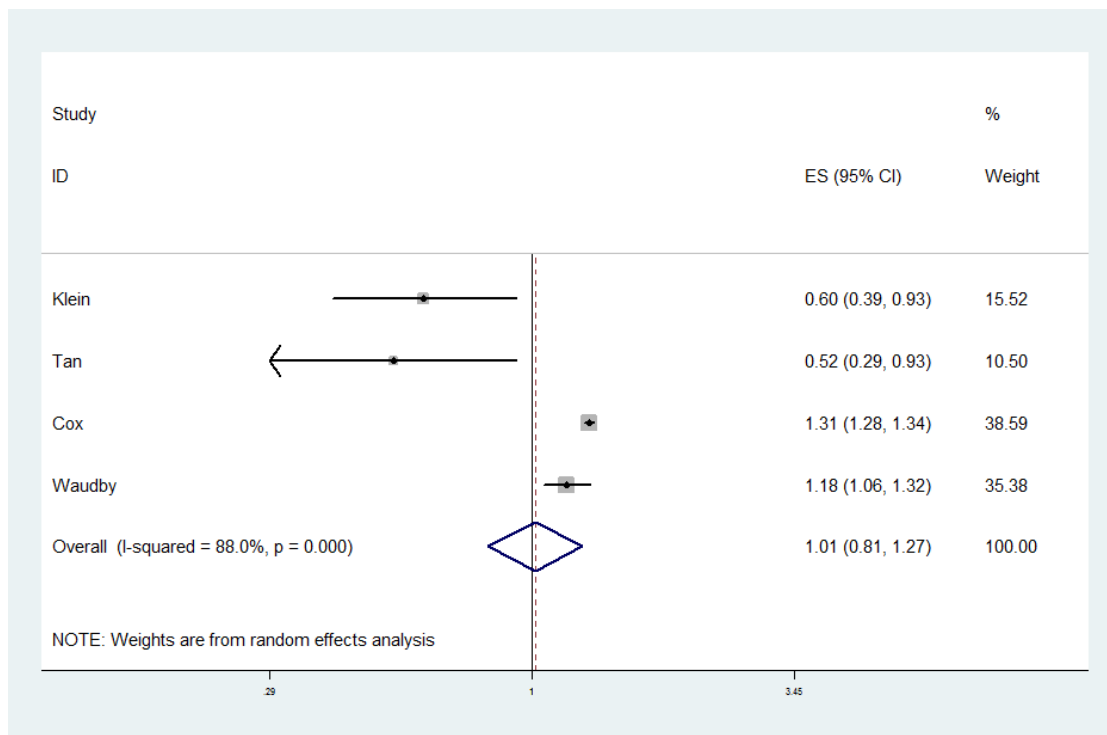
Figure S15. Subgroup analysis of cohort by hypertension

A. Hypertension included

Study		
ID	ES (95% CI)	% Weight
Cox 2010	1.31 (1.28, 1.34)	54.05
Lai 2013	1.20 (1.14, 1.27)	45.95
Overall (I-squared = 88.4%, p = 0.003)	1.26 (1.15, 1.37)	100.00

NOTE: Weights are from random effects analysis

.73   1   1.37

B. Hypertension missing

Study		
ID	ES (95% CI)	% Weight
Klein 2006	0.74 (0.50, 1.10)	16.89
Tan 2007	0.52 (0.29, 0.93)	9.95
Waudby 2011	1.18 (1.06, 1.32)	36.97
Leuschen 2015	1.20 (1.06, 1.35)	36.19
Overall (I-squared = 76.2%, p = 0.006)	1.01 (0.82, 1.25)	100.00

NOTE: Weights are from random effects analysis

.29   1   3.45
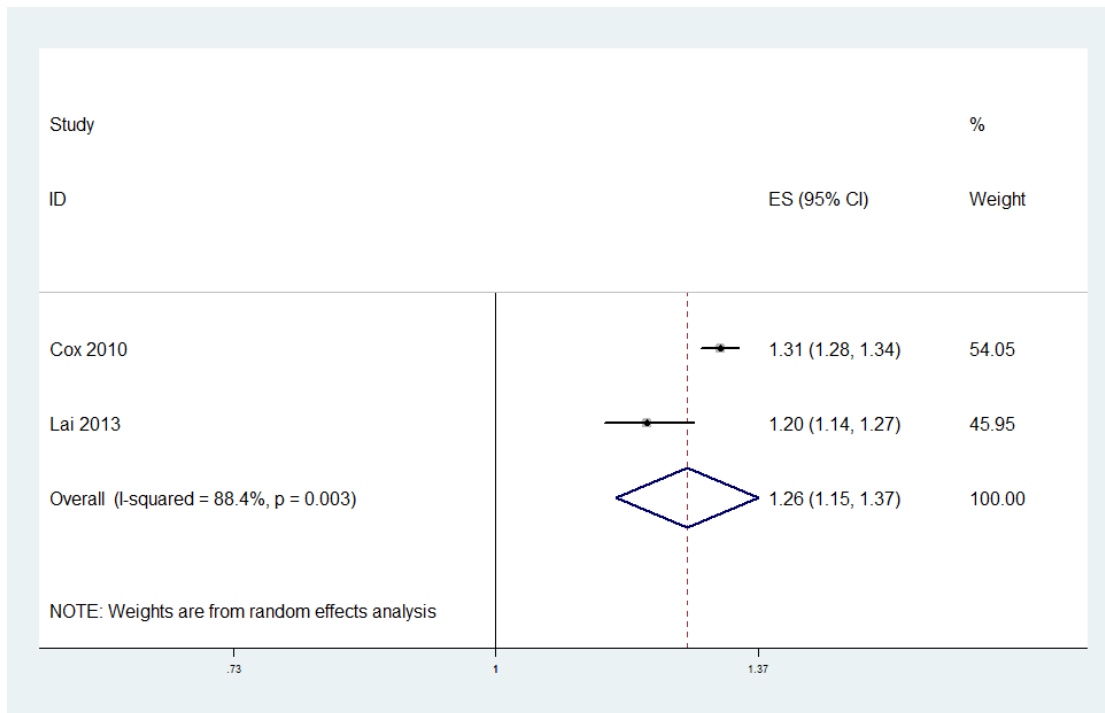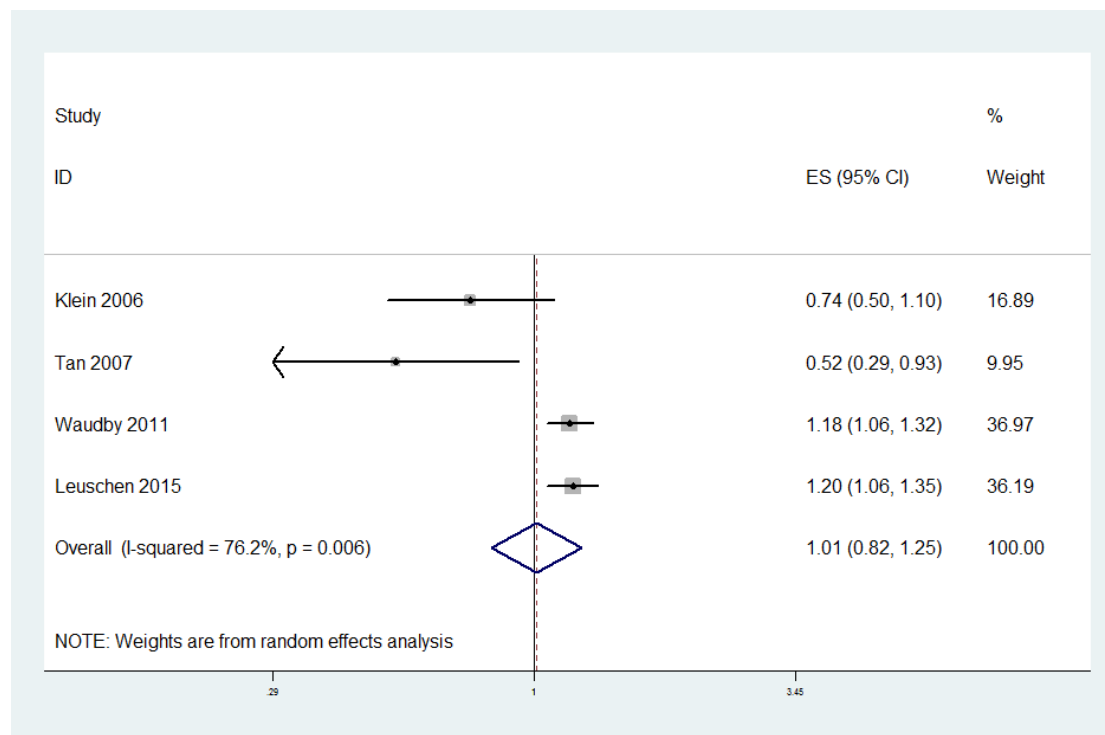
Figure S16. Subgroup analysis of case-control by quality assessment

A. High quality

Study ID — ES (95% CI) — % Weight

Study ID	ES (95% CI)	% Weight
Schlienger	1.00 (0.80, 1.20)	1.82
Smeeth	1.04 (0.89, 1.23)	2.86
Wise-IMS	1.07 (1.04, 1.10)	95.31
Overall (I-squared = 0.0%, p = 0.769)	1.07 (1.04, 1.10)	100.00

NOTE: Weights are from random effects analysis

.8   1   1.25

B. Low quality

Study ID	ES (95% CI)	% Weight
Fong	0.92 (0.85, 1.01)	32.35
Wise-BC	1.27 (1.24, 1.30)	34.85
Erie	1.28 (1.18, 1.38)	32.80
Overall (I-squared = 95.9%, p = 0.000)	1.15 (0.96, 1.37)	100.00

NOTE: Weights are from random effects analysis

.725   1   1.38

Figure S17. Subgroup analysis of case-control by location

A. North America

Study %

ID ES (95% CI) Weight

Study ID	ES (95% CI)	Weight
Fong	0.92 (0.85, 1.01)	23.58
Wise-BC	1.27 (1.24, 1.30)	26.23
Erie	1.28 (1.18, 1.38)	24.04
Wise-IMS	1.07 (1.04, 1.10)	26.14
Overall (I-squared = 97.5%, p = 0.000)	1.13 (0.99, 1.28)	100.00

NOTE: Weights are from random effects analysis

.725   1   1.38

B. Europe

Study %

ID ES (95% CI) Weight

Study ID	ES (95% CI)	Weight
Schlienger	1.00 (0.80, 1.20)	38.90
Smeeth	1.04 (0.89, 1.23)	61.10
Overall (I-squared = 0.0%, p = 0.767)	1.02 (0.90, 1.16)	100.00

NOTE: Weights are from random effects analysis

.8   1   1.25

Figure S18. Subgroup analysis of case-control by outcome assessment

A. ICD codes

Study ID		ES (95% CI)	% Weight
Schlienger		1.00 (0.80, 1.20)	27.55
Smeeth		1.04 (0.89, 1.23)	31.91
Erie		1.28 (1.18, 1.38)	40.53
Overall (I-squared = 77.1%, p = 0.013)		1.12 (0.94, 1.33)	100.00

NOTE: Weights are from random effects analysis

.725   1   1.38

B. Medical records

Study ID		ES (95% CI)	% Weight
Wise-BC		1.27 (1.24, 1.30)	50.10
Wise-IMS		1.07 (1.04, 1.10)	49.90
Overall (I-squared = 98.8%, p = 0.000)		1.17 (0.99, 1.38)	100.00

NOTE: Weights are from random effects analysis

.725   1   1.38

Figure S19. Subgroup analysis of case-control by type of statins

A. Artovastatin

Study ID	ES (95% CI)	% Weight
Smeeth-2003	1.29 (0.79, 2.11)	4.61
Wise-BC-2014	1.26 (1.22, 1.31)	33.98
Wise-IMS-2014	1.07 (1.02, 1.12)	33.17
Erie-2016	1.16 (1.06, 1.28)	28.25
Overall (I-squared = 90.0%, p = 0.000)	1.17 (1.04, 1.31)	100.00

NOTE: Weights are from random effects analysis

.474   1   2.11

B. Fluvastatin

Study ID	ES (95% CI)	% Weight
Smeeth-2003	1.45 (0.62, 3.40)	7.32
Wise-BC-2014	1.39 (1.16, 1.66)	49.80
Wise-IMS-2014	1.03 (0.82, 1.29)	42.88
Overall (I-squared = 53.1%, p = 0.119)	1.23 (0.96, 1.56)	100.00

NOTE: Weights are from random effects analysis

.294   1   3.4

C. Lovastatin

Study ID	ES (95% CI)	% Weight
Wise-BC-2014	1.14 (1.04, 1.26)	37.05
Wise-IMS-2014	1.14 (1.04, 1.26)	37.05
Erie	1.48 (1.25, 1.76)	25.91
Overall (I-squared = 74.1%, p = 0.021)	1.22 (1.07, 1.39)	100.00

NOTE: Weights are from random effects analysis

.568   1   1.76

D. Pravastatin

Study ID	ES (95% CI)	% Weight
Smeeth-2003	1.45 (0.62, 3.40)	7.32
Wise-BC-2014	1.39 (1.16, 1.66)	49.80
Wise-IMS-2014	1.03 (0.82, 1.29)	42.88
Overall (I-squared = 53.1%, p = 0.119)	1.23 (0.96, 1.56)	100.00

NOTE: Weights are from random effects analysis

.294   1   3.4

E. Rosuvastatin

Study ID	ES (95% CI)	% Weight
Wise-BC-2014	1.42 (1.27, 1.59)	49.53
Wise-IMS-2014	1.04 (0.95, 1.15)	50.47
Overall (I-squared = 94.2%, p = 0.000)	1.21 (0.89, 1.65)	100.00

NOTE: Weights are from random effects analysis

.607   1   1.65

F. Simvastatin

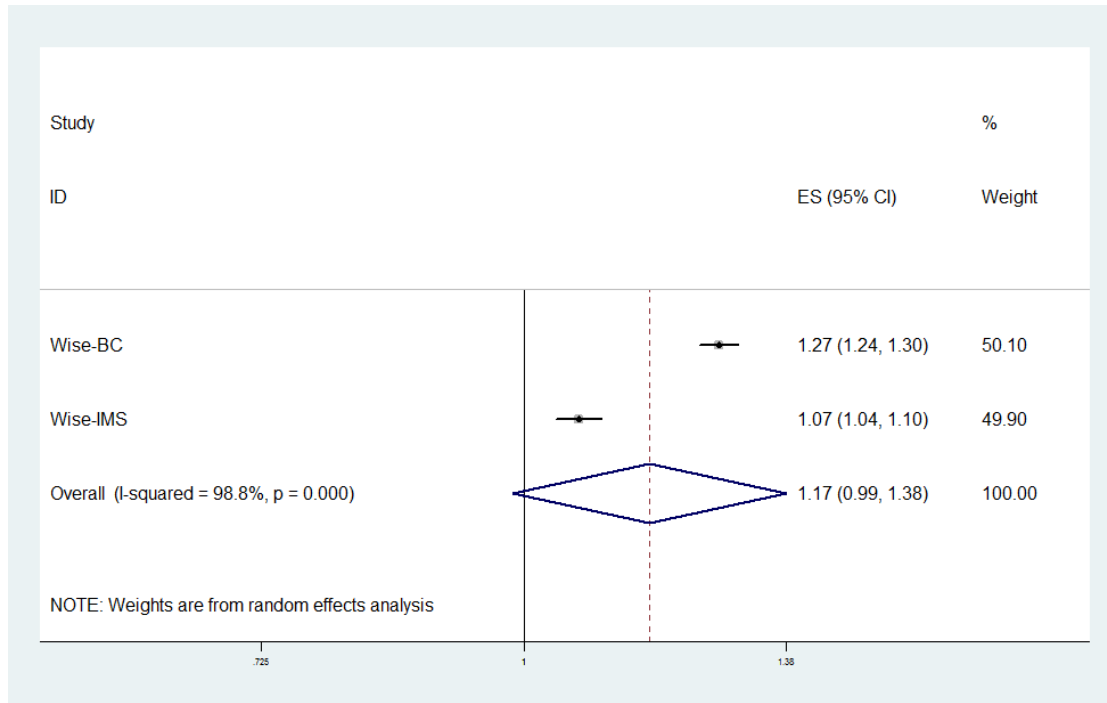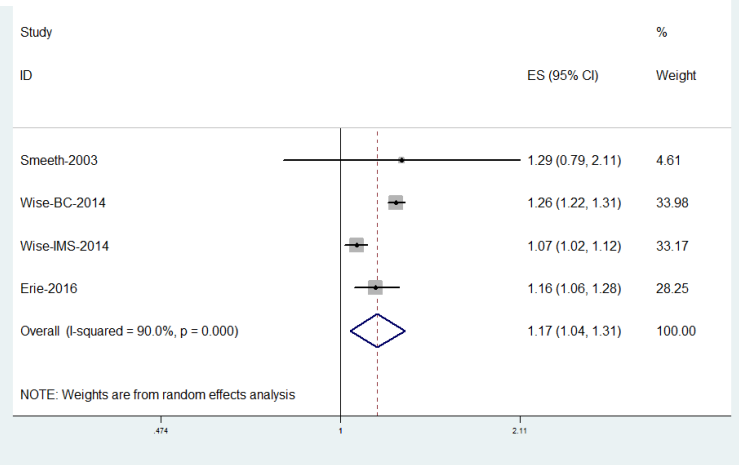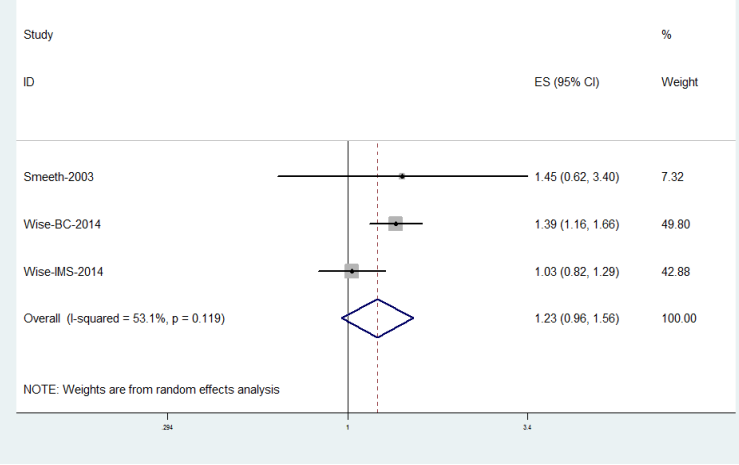| Study ID	ES (95% CI)	% Weight
Smeeth-2003	0.98 (0.80, 1.21)	17.62
Wise-BC-2014	1.31 (1.25, 1.37)	28.33
Wise-IMS-2014	1.05 (1.00, 1.11)	28.07
Erie	1.16 (1.06, 1.27)	25.98
Overall (I-squared = 92.9%, p = 0.000)	1.13 (0.99, 1.30)	100.00

NOTE: Weights are from random effects analysis

.73   1   1.37

Figure S20. Subgroup analysis of case-control by outcome

A. Cataract surgery

Study		
ID	ES (95% CI)	% Weight
Schlienger	1.00 (0.80, 1.20)	22.52
Wise-BC	1.27 (1.24, 1.30)	38.82
Wise-IMS	1.07 (1.04, 1.10)	38.66
Overall (I-squared = 97.7%, p = 0.000)	1.13 (0.97, 1.31)	100.00

NOTE: Weights are from random effects analysis

B. Cataract and Surgery

Study		
ID	ES (95% CI)	% Weight
Fong	1.04 (0.92, 1.18)	47.23
Erie	1.28 (1.18, 1.38)	52.77
Overall (I-squared = 86.8%, p = 0.006)	1.16 (0.95, 1.42)	100.00

NOTE: Weights are from random effects analysis
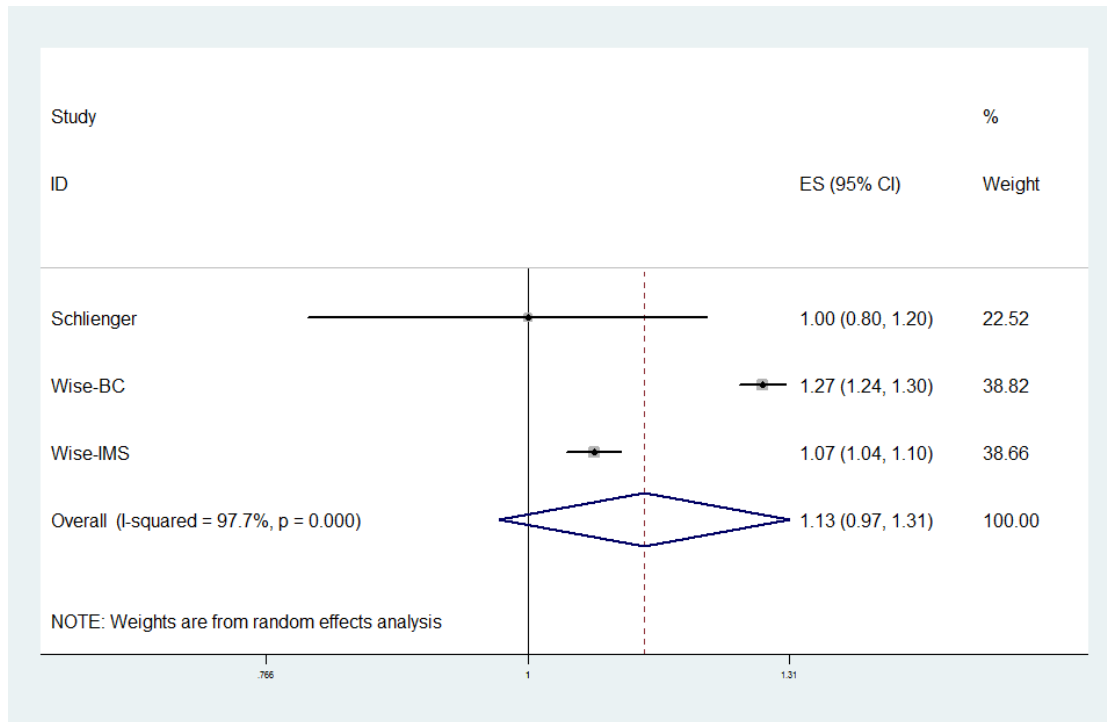
Figure S21. Subgroup analysis of case-control by CVD

A. CVD included

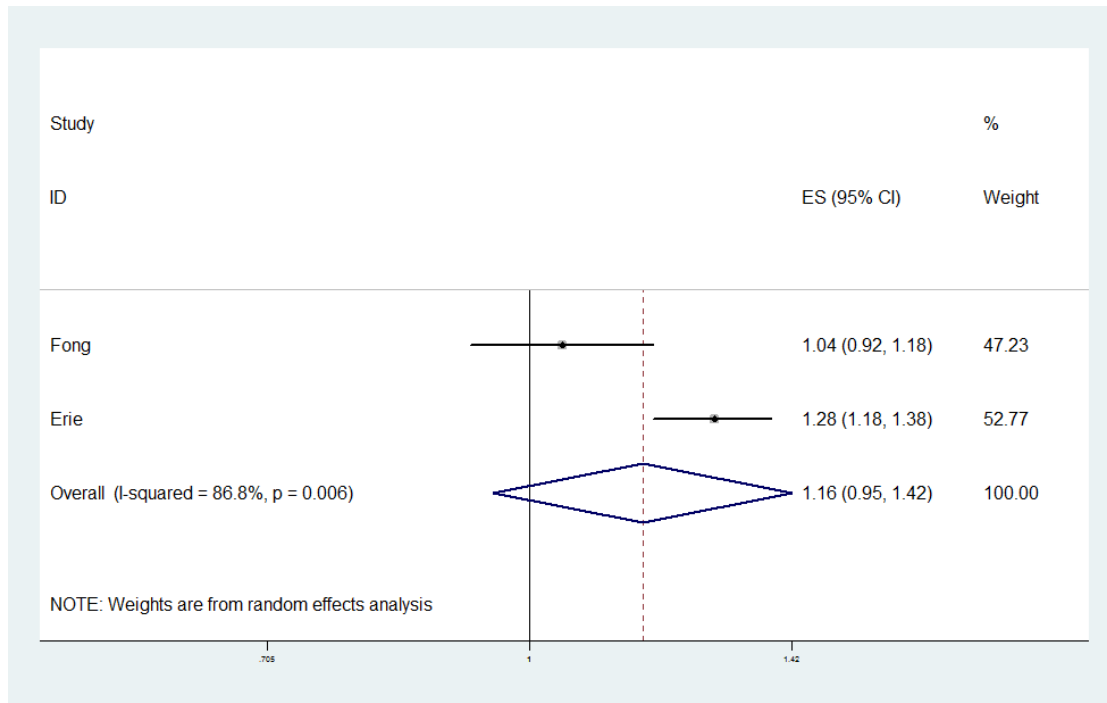| Study ID	ES (95% CI)	% Weight
Wise-BC 2014	1.27 (1.24, 1.30)	27.26
Wise-IMS 2014	1.07 (1.04, 1.10)	27.13
Erie 2016	1.28 (1.18, 1.38)	24.50
Fong 2012	1.04 (0.92, 1.18)	21.11
Overall (I-squared = 96.7%, p = 0.000)	1.17 (1.04, 1.31)	100.00

from random effects analysis

.725   1   1.38

B. CVD missing

Study ID	ES (95% CI)	% Weight
Schlienger 2001	1.00 (0.80, 1.20)	38.90
Smeeth 2003	1.04 (0.89, 1.23)	61.10
Overall (I-squared = 0.0%, p = 0.767)	1.02 (0.90, 1.16)	100.00

NOTE: Weights are from random effects analysis

.8   1   1.25

Figure S22. Subgroup analysis of case-control by smoking

A. Smoking included

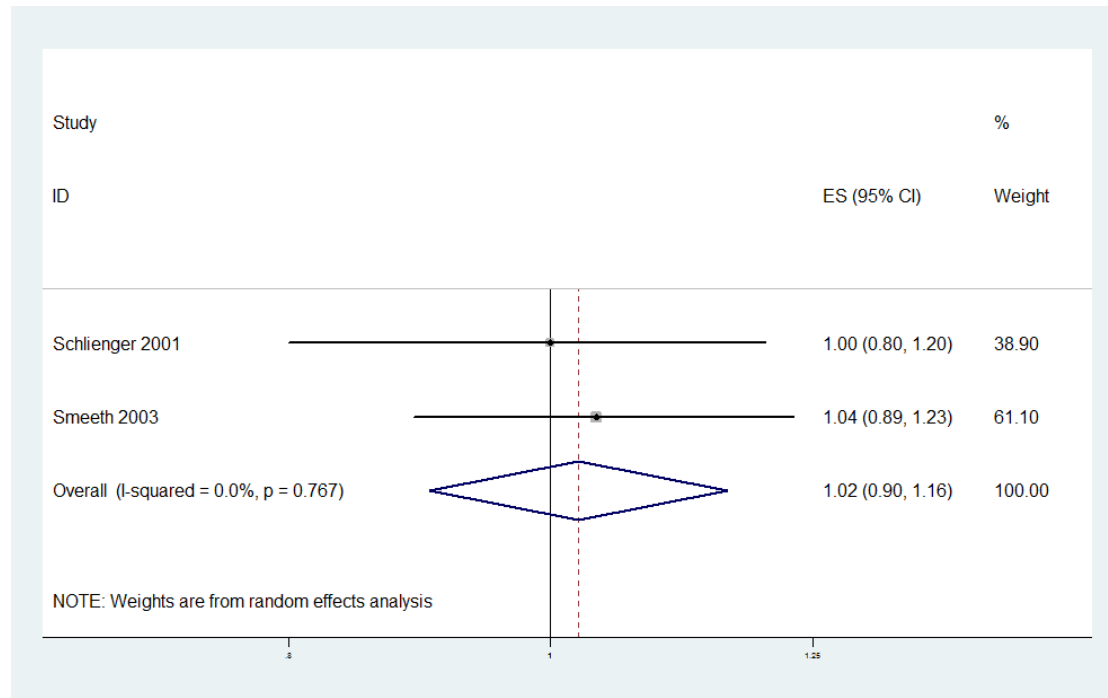| Study ID	ES (95% CI)	% Weight
Schlienger 2001	1.00 (0.80, 1.20)	18.80
Fong 2012	1.04 (0.92, 1.18)	51.68
Smeeth 2003	1.04 (0.89, 1.23)	29.52
Overall (I-squared = 0.0%, p = 0.936)	1.03 (0.95, 1.13)	100.00

NOTE: Weights are from random effects analysis

B. Smoking missing

Study ID	ES (95% CI)	% Weight
Wise-BC 2014	1.27 (1.24, 1.30)	34.53
Wise-IMS 2014	1.07 (1.04, 1.10)	34.38
Erie 2016	1.28 (1.18, 1.38)	31.09
Overall (I-squared = 97.7%, p = 0.000)	1.20 (1.05, 1.37)	100.00

NOTE: Weights are from random effects analysis

Figure S23.   Subgroup analysis by of case-control consultation rate

A. Consultation rate included

Study			
ID		ES (95% CI)	% Weight
Schlienger 2001		1.00 (0.80, 1.20)	38.90
Smeeth 2003		1.04 (0.89, 1.23)	61.10
Overall (I-squared = 0.0%, p = 0.767)		1.02 (0.90, 1.16)	100.00
NOTE: Weights are from random effects analysis			

.8   1   1.25

B. Consultation rate missing

Study			
ID		ES (95% CI)	% Weight
Wise-BC 2014		1.27 (1.24, 1.30)	27.26
Wise-IMS 2014		1.07 (1.04, 1.10)	27.13
Erie 2016		1.28 (1.18, 1.38)	24.50
Fong 2012		1.04 (0.92, 1.18)	21.11
Overall (I-squared = 96.7%, p = 0.000)		1.17 (1.04, 1.31)	100.00
NOTE: Weights are from random effects analysis			

.725   1   1.38
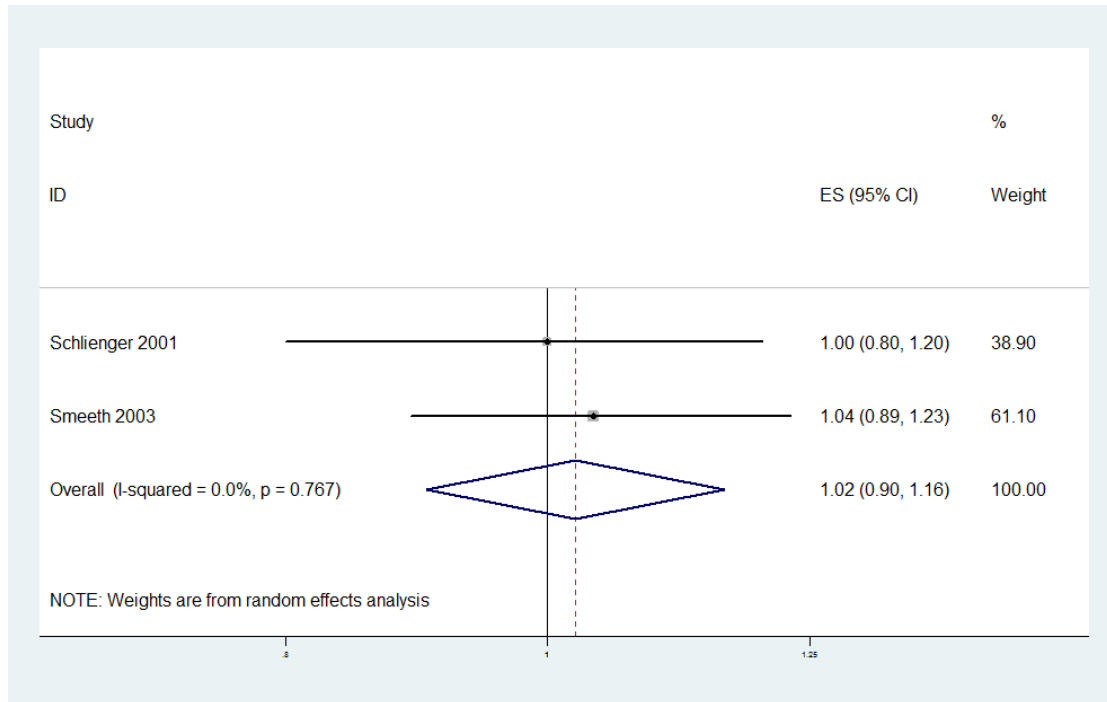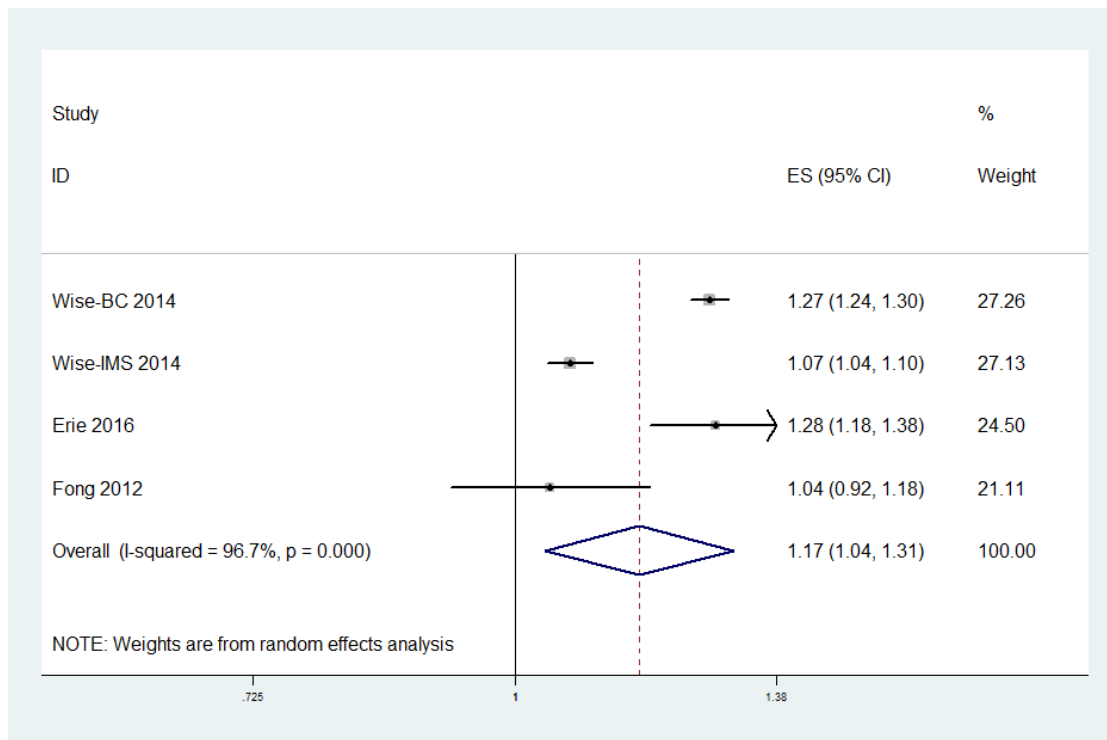
Figure S24.   Subgroup analysis of case-control by diabetes (Diabetes included)

Study ID		ES (95% CI)	% Weight
Smeeth 2003		1.04 (0.89, 1.23)	15.17
Wise-BC 2014		1.27 (1.24, 1.30)	23.15
Wise-IMS 2014		1.07 (1.04, 1.10)	23.04
Erie 2016		1.28 (1.18, 1.38)	20.77
Fong 2012		1.04 (0.92, 1.18)	17.87
Overall (I-squared = 95.8%, p = 0.000)		1.15 (1.03, 1.27)	100.00

NOTE: Weights are from random effects analysis

.725   1   1.38
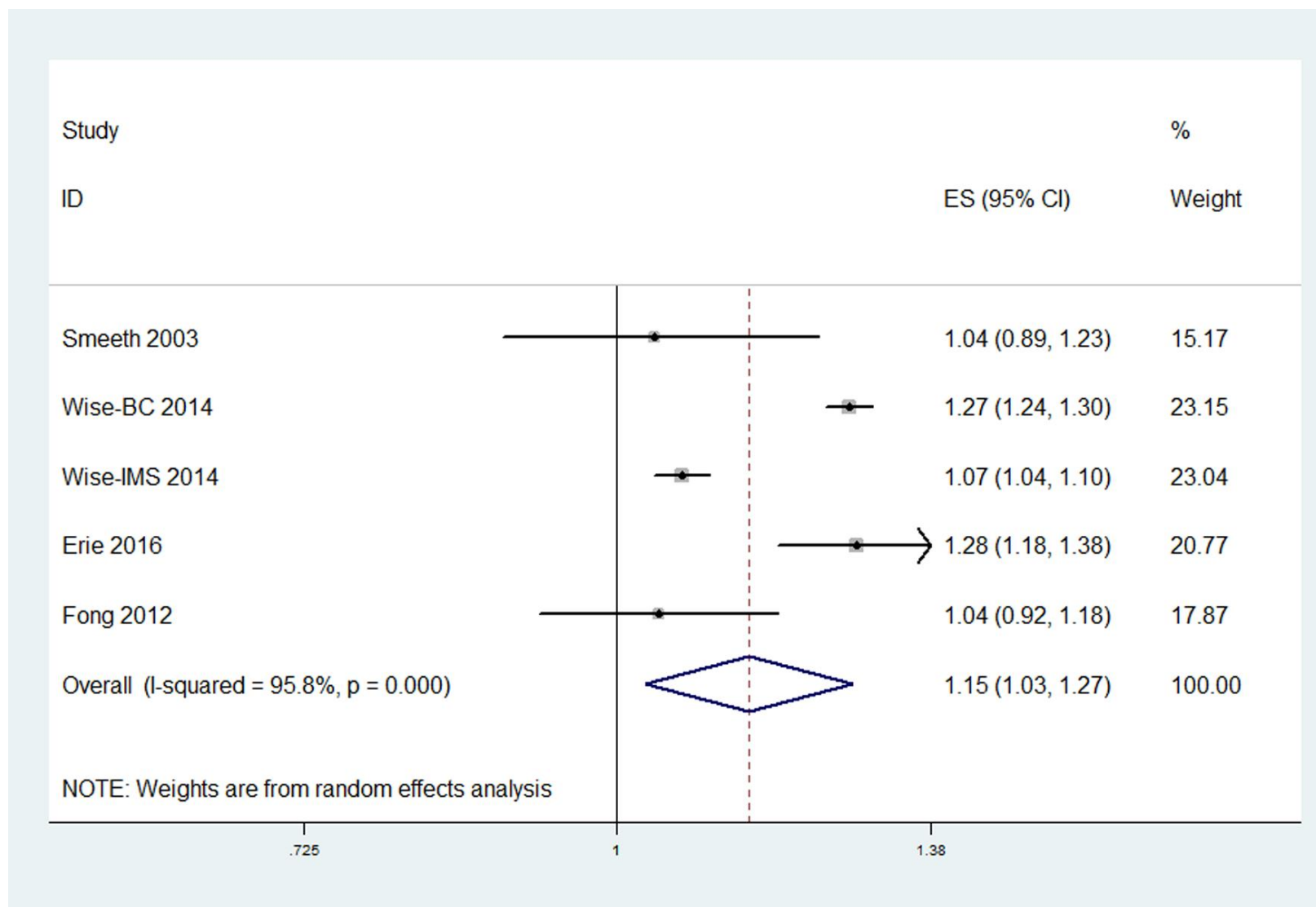
Figure S25.   Subgroup analysis of case-control by hypertension

A. Hypertension included

Study ID		ES (95% CI)	% Weight
Smeeth 2003		1.04 (0.89, 1.23)	18.56
Wise-BC 2014		1.27 (1.24, 1.30)	28.14
Wise-IMS 2014		1.07 (1.04, 1.10)	28.01
Erie 2016		1.28 (1.18, 1.38)	25.30
Overall (I-squared = 96.7%, p = 0.000)		1.17 (1.04, 1.32)	100.00
NOTE: Weights are from random effects analysis			

B. Hypertension missing

Study ID		ES (95% CI)	% Weight
Schlienger 2001		1.00 (0.80, 1.20)	26.68
Fong 2012		1.04 (0.92, 1.18)	73.32
Overall (I-squared = 0.0%, p = 0.721)		1.03 (0.93, 1.15)	100.00
NOTE: Weights are from random effects analysis			
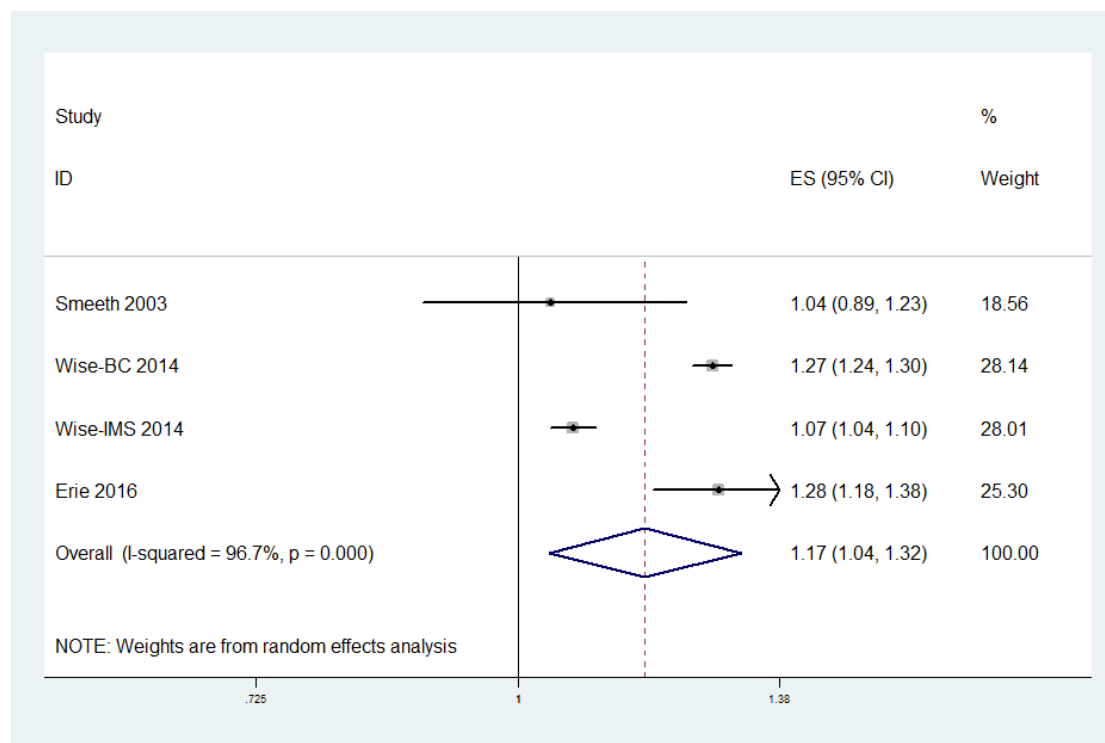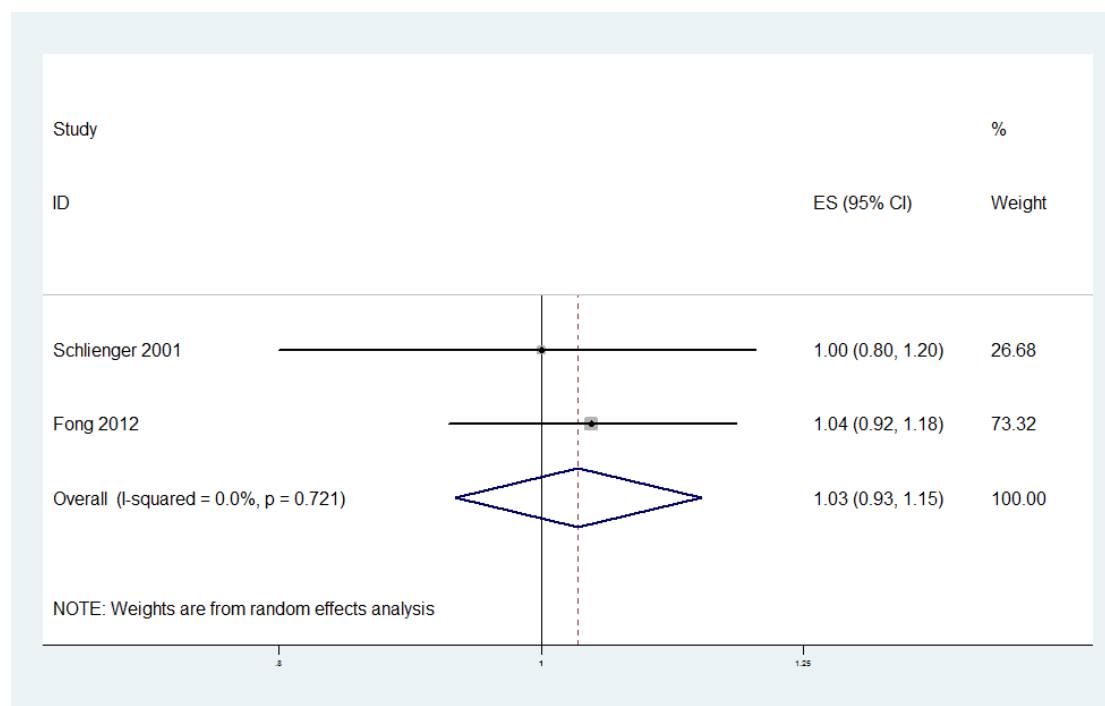
Figure S26. Subgroup analysis of case-control by age (Older than 60)

Study		ES (95% CI)	%
ID			Weight
Harris-1995		1.39 (0.70, 2.78)	24.41
Pederson-1996		0.80 (0.55, 1.17)	43.08
Bang-2015		0.56 (0.33, 0.96)	32.50
Overall (I-squared = 52.2%, p = 0.123)		0.82 (0.53, 1.26)	100.00

NOTE: Weights are from random effects analysis

.33   1   3.03
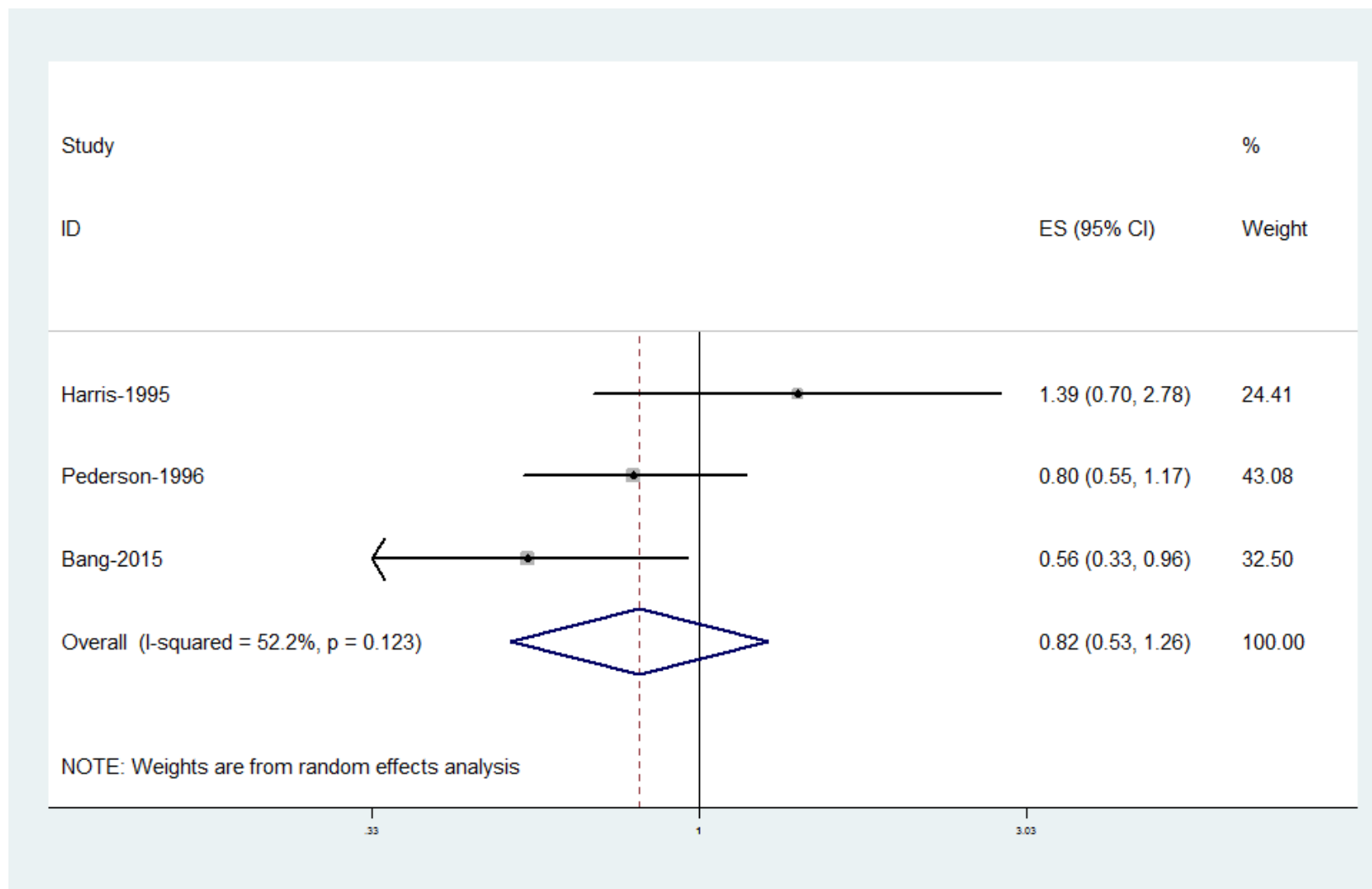
Figure S27. Subgroup analysis of case-control by age (including Spence's)

A. Older than 60
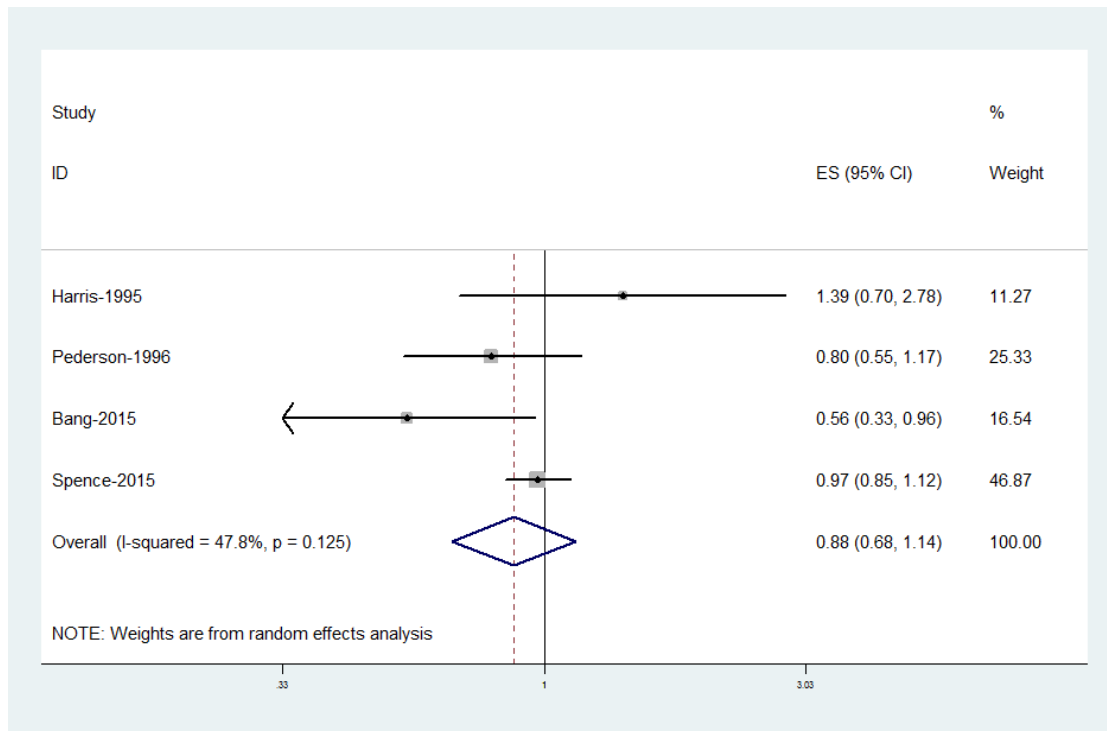
B. Younger than 60
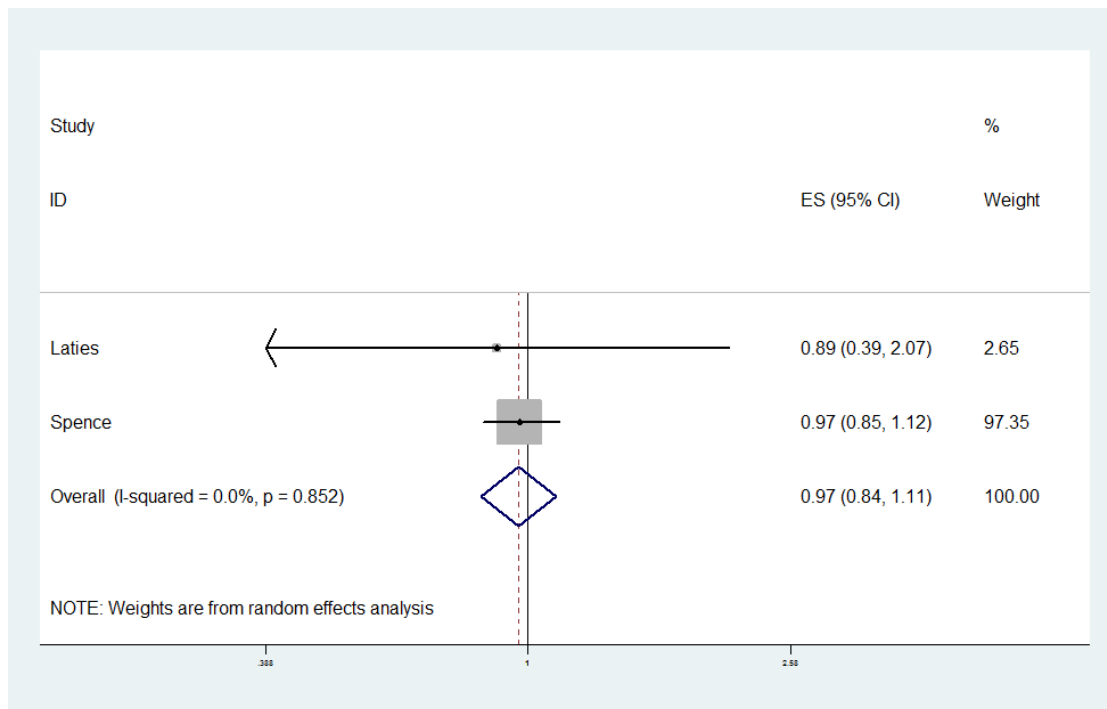
Figure S28. Subgroup analysis of case-control by follow-up duration

A More than 5 years

Study		
ID	ES (95% CI)	Weight (%)
Pederson	0.80 (0.55, 1.17)	11.78
Heart Protection Study	0.97 (0.85, 1.12)	88.22
Overall (I-squared = 0.0%, p = 0.347)	0.95 (0.83, 1.08)	100.00

NOTE: Weights are from random effects analysis

.55   1   1.82

B No more than 5 years

Study		
ID	ES (95% CI)	Weight (%)
Laties	0.89 (0.39, 2.07)	26.74
Harris	1.39 (0.70, 2.78)	32.70
Bang	0.56 (0.33, 0.96)	40.55
Overall (I-squared = 53.0%, p = 0.119)	0.86 (0.48, 1.51)	100.00

NOTE: Weights are from random effects analysis

.33   1   3.03
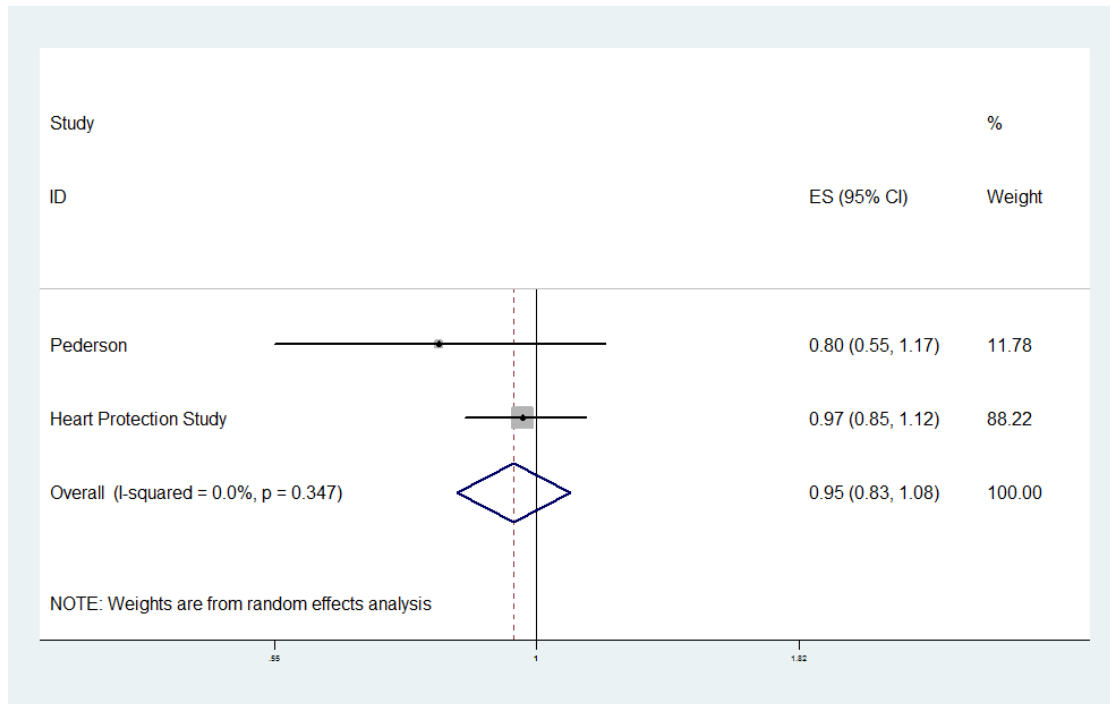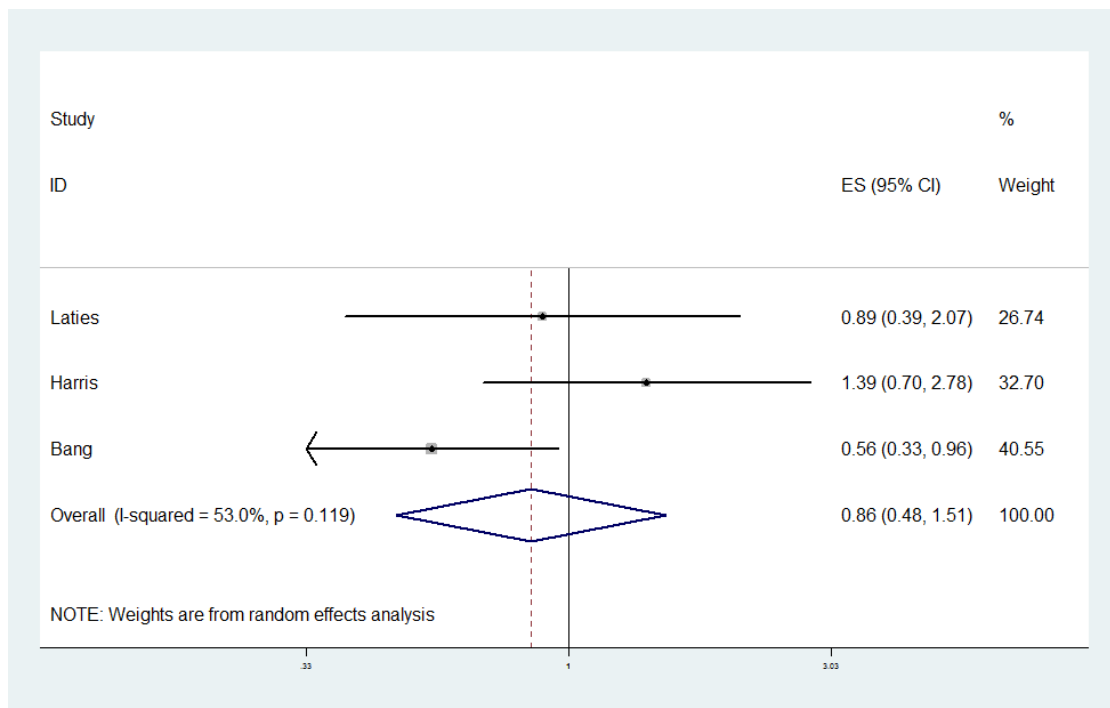
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