Relation between Cigarette Smoking and Sarcopenia–Meta Analysis

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Short title

Smoking and Sarcopenia

Summary

Background: Cigarette smoking is a risk factor for many diseases. It could be associated with sarcopenia.

Purposes: The aim of this meta-analysis was to determine whether smoking is an isolated risk factor for sarcopenia.

Methods: We searched PubMed, Web of Science, EBSCO, and Science Direct for articles addressing the relationship between cigarette smoking and sarcopenia. A total of 12 studies containing information on 22,515 participants were included in this meta-analysis. Odds ratio (OR) was calculated for each study group and for all studies together. An OR was also calculated separately for each sex. We used a fixed-effect model in overall estimation and in males, because results of small studies were significantly different from the results of large studies in those cases and in females where the estimation showed only moderate heterogeneity we used a random-effect model. According to proposes of the Cochrane Handbook for Systematic Reviews.

Results: The resulting OR in the fixed-effect model was 1.12 (95% CI 1.03 - 1.21), OR for each sex was in the fixed-effect model 1.20 (95% CI 1.06 - 1.35) in males and in the random-effect model 1.21 (95% CI 0.92 - 1.59) in females.

Conclusion: The results of this meta-analysis indicate that cigarette smoking as an isolated factor may contribute to the development of sarcopenia. However, the results of the individual studies were largely inconsistent due to different approaches of measuring the main variables which affected the results.

Key words

Smokers; Non-Smokers; Tobacco Smoke; Risk Factors

Introduction

Cigarette smoking is undoubtedly among the most serious health risk behaviors in today´s society. Cigarette smoking contributes to the development of many diseases; including perhaps, sarcopenia. Nevertheless, it is difficult on the basis of individual studies to confidently claim that smoking contributes to sarcopenia. Every age related condition or disease such as sarcopenia is associated with multiple causes. For the muscle wasting associated with sarcopenia, causes include chronic inflammation, stroke, rheumatism, fall-related injuries, and of course sedentary lifestyles (Evans 2010). The aforementioned notwithstanding, it is important to find out if cigarette smoking and sarcopenia are directly related as knowledge of each cause of this condition may lead to improving treatment. Although individual studies have shown that cigarette smoking should be counted among risk factors of sarcopenia (Landi et al. 2012; Lee et al. 2007), a comparative analysis of those studies has not been published, despite the fact that theoretical models of accelerated muscle loss by smoking cigarettes have been described previously. According to these models, metabolites that are assumed to be important in this process (eg, aldehydes, reactive oxygen species, and reactive nitrogen species), and are components of the cigarettes smoke, enter the bloodstream and reach the skeletal muscles of smokers and there accelerate muscle wasting (Rom et al. 2012b, 2013).

In this meta-analysis the relation between cigarette smoking and sarcopenia was investigated. The objective was to determine whether cigarette smoking as a separate factor may contribute to the progressive loss of muscle mass and contribute to or cause sarcopenia. The main finding could bring new information about association between smoking and sarcopenia.

Subjects and Methods

We searched PubMed, Web of Science, EBSCO, and Science Direct for articles addressing the relationship between cigarette smoking and sarcopenia. Specifically, we looked for case-control studies that provided information about the relationship. For the full text acquisition the databases Wiley Online Library, SpringerLink, Citation Linker SFX UK, Proquest, Ovid, and Scopus were used. The same search stream was used in all databases: the term sarcopenia was searched in the titles of articles as a first step, keywords: human, epidemiology, prevalence, association, retrospective, cohort study, cigarette, smoking, smoker, non-smoker, tobacco, and risk factor were searched in all fields as a second step, both results of searching were connected and searched together in a last step. Transparently presented data about persons suffering from sarcopenia as well as healthy persons and their connection with smoking status created the criteria for including studies into the meta-analysis.

Definition of Sarcopenia

Sarcopenia, a geriatric syndrome, was first defined in 1989 by Rosenberg as a decrease of muscle mass and strength with aging. Since sarcopenia was initially defined so broadly, more specific criteria have since been developed. Basically, the criteria are divided into three areas. The first involves measuring muscle mass; the second involves measuring muscle strength and the third involves assessment of physical performance. The most commonly currently used method to measure muscle mass is dual energy X-ray absorptiometry (DEXA) (Pahor et al. 2009); nevertheless, measuring by the bioelectrical impedance analysis (BIA) has also been verified as a reliable tool (Janssen et al. 2000). Although there are alternative tools for measuring muscle strength (eg, Biodex or Cybex), hand grip seems to be a useful method for muscle strength measurement, because it is inexpensive and easily applicable (Rantanen et al.

2002). The usual gait speed and get up and go test could be counted among the basic methods for physical performance characterization. In 2011 the European Working Group on Sarcopenia in Older People (EWGSOP) proposed an algorithm for diagnosing sarcopenia (Cruz-Jentoft et al. 2010). All three of the criteria noted above were included into the algorithm. For the purposes of that meta-analysis, the EWGSOP algorithm and muscle mass measurement by DEXA or BIA were chosen as suitable methods of sarcopenia diagnosis. Each of these methods is respected by scientific community as a relevant in the diagnostic process of sarcopenia. Sarcopenia related health status was dichotomized in many studies as sarcopenia and non sarcopenia. In other studies where sarcopenia was divided into three categories - non sarcopenia, moderate sarcopenia and severe sarcopenia, moderate and severe sarcopenia were collapsed into a single sarcopenia category for the purposes of the meta-analysis.

Smoking Categories

Cigarette smoking status could be divided into a number of categories according to the amount number of cigarettes smoked daily, period of smoking in the subjects' lifetimes or current smoking habits. Therefore it was difficult in this work to find and establish optimal combination of categories. Different studies applied different method to quantify smoking status. An interview, a standardized questionnaire, an interviewer-administered questionnaire or self-report survey were done. Nevertheless, nearly every approach was based on the subjective evaluation of participants. Therefore, the assignment to categories of smokers and non-smokers could not be as objective as in the case of sarcopenia categories. We tried to find more precise data (e.g. - pack-years); nevertheless, it was not possible. For the purpose of this

meta-analysis, the smokers without the regard to the period or intensity of cigarette smoking were included in the exposed group.

Statistical Analysis

The quality rating of included articles was assessed using the Newcastle-Ottawa Quality Assessment Scale (Stang 2010). Odds ratios (OR) for the overall effect were first calculated thereafter, we calculated OR for each sex separately. In this case, OR was used to quantitatively describe the association between people exposed to smoking and sarcopenia. The Cochran Q statistic and I^2 statistic (Higgins et al. 2003) were conducted to find out if heterogeneity was present. We also performed a sensitivity analysis to select a suitable analysis method. Finally, there was used the Cochran–Mantel–Haenszel statistical method (Mantel and Haenszel 1959) and DerSimonian and Laird random-effects model (DerSimonian and Laird 1986). The Cochran–Mantel–Haenszel statistical method based on fixed-model effect values more large studies in contrast with DerSimonian and Laird random-effects model, which gives relatively the same worth to all the studies in the sample. All statistics were carried out in the Review Manager 5.3.

Results

Altogether, 988 papers were identified as potentially relevant. Of these, 12 papers (22,515 participants) were selected into the meta-analysis through a multiple-step selection procedure (Figure 1). The basic information about the studies included in the meta-analysis is presented in Table 1. In the overall estimation and in the male estimation the Q statistic and I^2 statistic indicated a high heterogeneity (Higgins et al. 2003). Because the results of the small studies

were different from the results of the large ones; this may happen as a result of publication bias (Egger et al. 1997). Therefore, we performed a sensitivity analysis. We tried to exclude small studies which could be affected by bias and we compared the results before and after excluding. Nevertheless, those analyses did not provide any significant changes in results. Finally, there was used the fixed-effect model which the Cochrane Handbook for Systematic Reviews suggests provided the results of small studies are significantly different from the results of large studies (Higgins and Green 2008). Unlike the overall and male estimate, the female estimation showed only moderate heterogeneity. Since the one of the biggest study's (KNHANES) estimate was substantially lower than OR = 1 and the other studies estimates were around OR = 1 or a little above, we used the random-effect model, which should be more sensitive in that case. The overall OR for every study in the fixed-effect model was 1.12 (95% CI 1.03 - 1.21), OR for each study separately are shown in Figure 2. In a detailed analysis for each gender in particular there were OR in the fixed-effect model 1.20 (95% CI 1.06 - 1.35) in male (Figure 3) and in the random-effect model 1.21 (95% CI 0.92 - 1.59) in female (Figure 4). All the OR increase above OR = 1, therefore, if results are OR > 1, it implies difference in effect. However, heterogeneity and objectionable publication bias were found in this case.

Discussion

Sarcopenia is the multi causal syndrome whose development is influenced by many factors. Besides those that are associated with the internal environment of the organism and are largely the result of endogenous influences such as hormonal changes, increasing of pro-inflammatory cytokines, increased insulin resistance with aging, mitochondrial impairment, loss of repair ability, reduction in the number of motor units (Burton and Sumukadas 2010; Di

Tano et al. 2005; Hollmann et al. 2007; Lang et al. 2010), there are also external risk factors which play an important role. External factors involved in the etiology of sarcopenia include poor nutrition, decreased physical activity, alcohol consuming, and also cigarette smoking (Cesari and Pahor 2008; Freiberger et al. 2011; Kamel 2003; Rom et al. 2012a, 2012b). There is no doubt that cigarette smoking contributes to the development of certain diseases and, it may even contribute to the development of sarcopenia which have been suggested in some studies.

The results of this meta-analysis suggest that if we followed only the relation between cigarette smoking and sarcopenia, the cigarette smoking may increase the chance of developing sarcopenia. However, the results could be particularly affected by a relatively small number of studies and their high heterogeneity. For example, the overall and males results were certainly affected by the Korean KNHANES studies (Park et al. 2013) mainly because the males estimation was significantly below OR = 1 (0.57; 95% CI 0.40 - 0.81). This means that smoking significantly decreases the risk of sarcopenia. In any case, this result could be influenced due to the design of the study, where smoking was not the main topic. However, it is still an interesting and hardly comprehensible result. On the other hand, the estimate of SPAH (Figueiredo et al. 2014) in males was significantly above OR = 1(4.62; 95% CI 2.42 - 8.80). Nevertheless, the study sample was relatively small and thus influences the overall estimate only slightly. It is even worth mentioning that the results of two American studies (NHANES 1988 - 1994 and NHANES 1999 - 2004) were different in males, which could have been caused by different approach in classification of sarcopenia and smoking status.

Perhaps the other problem of this meta-analysis is that there was not distinguished distinction between the races. The majority of the total sample consisted of Americans and Koreans, while Europeans were represented only by less than 10%. A few similar studies have been done in Europe - e.g. the Hertfordshire Cohort Study (HCS) (Patel et al. 2013), Mini-Finland Health Examination Survey in Finland - longitudinal study (Stenholm et al. 2012); European Male Ageing Study (EMAS) (Tajar et al. 2013) could be counted among these European studies which focus on the relation between cigarette smoking and sarcopenia. Nevertheless, their research design was unfortunately distinctively different to the one required for the inclusion to our meta-analysis.

Based on the results of this meta-analysis, it can be concluded that cigarette smoking could have relatively little impact on the development of sarcopenia. However, results are still inconclusive. There have not been many studies performed on the relation of sarcopenia and diverse health factors yet. Nevertheless, more than the above mentioned finding is the fact that there was not used a uniform assessing method of smoking status, even though a method had been developed, such as pack-year. That method was designed by World Health Organization (WHO) in 2008. This implies a need for more research on the relation of smoking and sarcopenia more properly designed studies.

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Table 1 The studies used in meta-analysis estimates

Study Name	Subjects	Definition of Sarcopenia	Definition of Smoking Categories
Chinese Hong Kong (Lau et al. 2005)	n = 345 173 men and 172 women ≥ 70years	Appendicular skeletal muscle mass (ASM) two standard deviations or more below the normal mean for young Asian men and women in this study body composition by DEXA	A standardized, structured interview questionnaire never and current or ex-smoker
CRIME Study (Vetrano et al. 2014)	n = 770 56% women 80.8±7 years	EWGSOP algorithm (Cruz-Jentoft et al. 2010) body composition by BIA (Janssen et al. 2000)	A standardized questionnaire smoker (actual/former)
EPIDOS (Rolland et al. 2009)	n = 837 women >75 years	SMI of < 5.45 kg/m^2 as cut off points (Baumgartner et al. 1998; Heymsfield et al. 1990) body composition by DEXA	Self-reporting smoking, former or current
InCHIANTI (Volpato et al. 2013)	n = 538 250 men and 288 women ≥ 65 years	EWGSOP algorithm (Cruz-Jentoft et al. 2010) body composition by BIA (Janssen et al. 2004)	Survey questions never and former/current
KNHANES (Park et al. 2013)	n = 5,263 2,258 men and 3,005 women >50 years	Skeletal muscle index (SMI) values in KNHANES 2009-2010 participants aged 18-39 years corresponding to two standard deviations below the mean levels were used to identify sarcopenia (Janssen et al. 2000; Sanada et al. 2010) body composition by DEXA	A health interview never-smokers < 100 cigarettes in their lifetimes, ≥100 cigarettes were classified as past or current smokers
NHANES 1988 – 1994 (Beavers et al. 2009)	n = 7,544 3663 men and 3881 women >40 years	Skeletal muscle mass (SMM) when is within 1 and 2 resp. 2 standard deviations or more below the SMM mean of a young reference group that is Class I resp. Class II (Janssen et al. 2002) body composition by BIA	Self-report survey never/former /current
NHANES 1999 – 2004 (Goodman et al. 2013)	n = 2,747 1,387 men and 1,360 women ≥ 65 years	SMI of 1.0 SD below the mean SMI of the reference population (adults aged 20–40) calculated separately for males and females (Heymsfield et al. 1990) body composition by DEXA	Self-reporting current smoking
Rancho Bernardo Study (Castillo et al. 2003)	n = 1,700 694 men and 1006 women 55–98 years	Fat free mass (FFM) that is 2.0 standard deviations or more below the mean of a young reference group (Pichard et al. 2000) body composition by BIA	A standardized, self-administered questionnaire current/not current
ROAD study (Akune et al. 2013)	n = 1,000 349 men and 651 women ≥ 65 years	EWGSOP algorithm (Cruz-Jentoft et al. 2010) SMI of <7.0 kg/m^2 in males and <5.8 kg/m^2 in females as cut off points (Tanimoto et al. 2012) body composition by BIA	An interviewer-administered questionnaire smoking/no smoking

SPAH (Domiciano et al. 2013; Figueiredo et al. 2013)	n = 1,010 399 men 72.71±5.06 and 611 women 73.22± 5.21 years	SMI of <7.26 kg/m^2 in males and <5.45 kg/m^2 in females as cut off points (Baumgartner et al. 1998; Newman et al. 2003) body composition by DEXA	A standardized questionnaire current smoking
Taiwan (Lin et al. 2013)	n = 761 407 men and 354 women ≥ 65 years	EWGSOP algorithm (Cruz-Jentoft et al. 2010) body composition by DEXA	Self-reporting never/current/ former

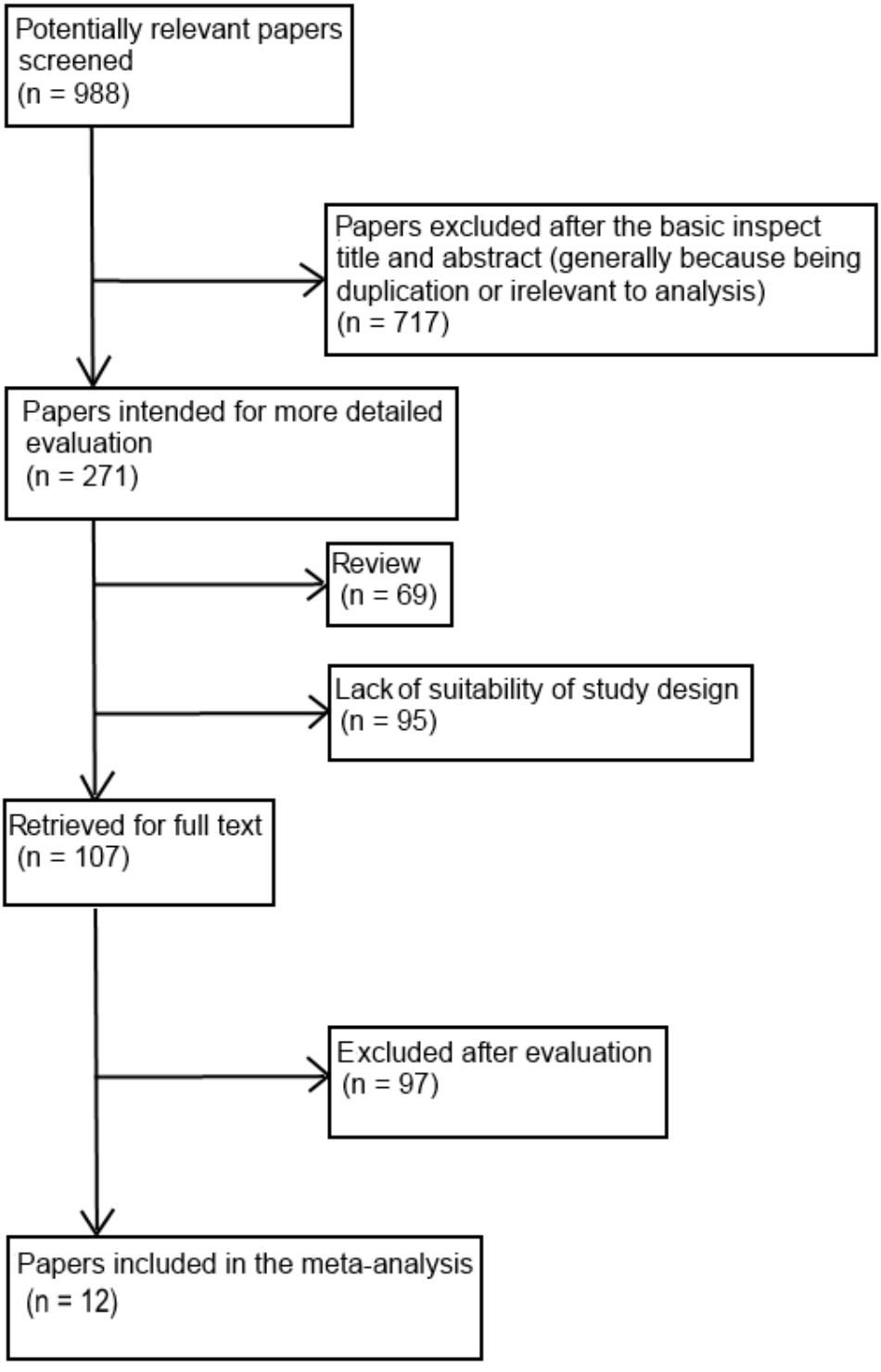

Figure 1 Flow of information through the different phases of a systematic review.

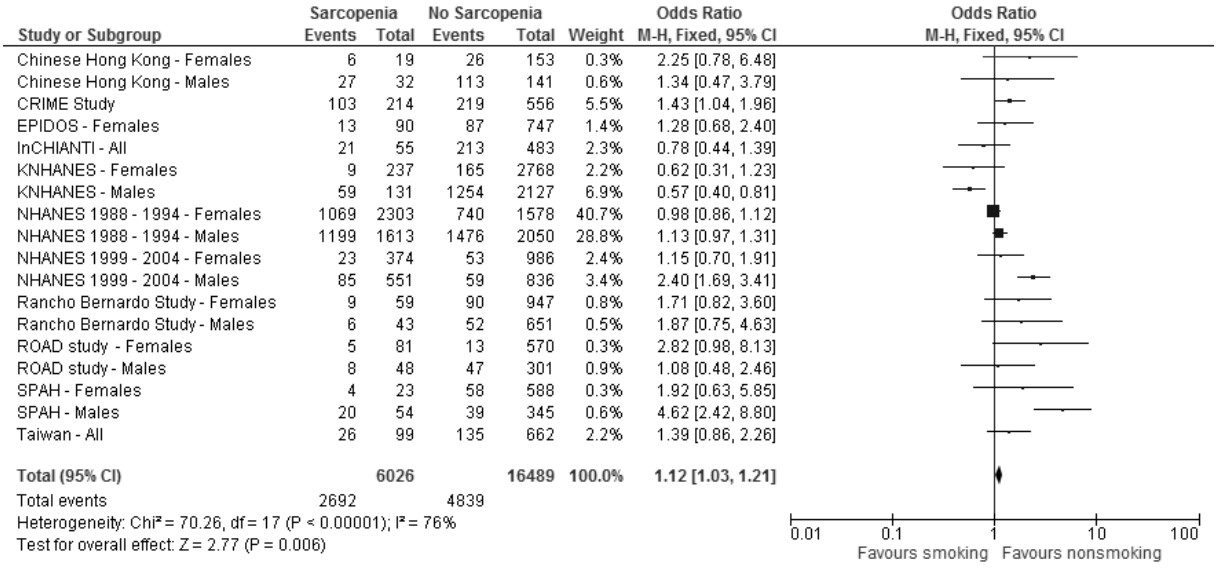

Figure 2 A forest plot for estimating OR, the fixed-effect model and 95% CI for males and females together.

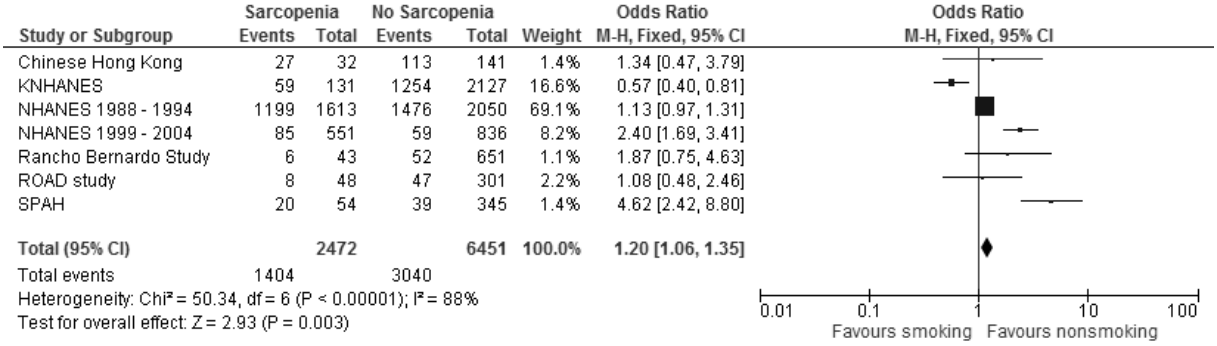

Figure 3 A forest plot for estimating OR, the fixed-effect model and 95% CI for males.

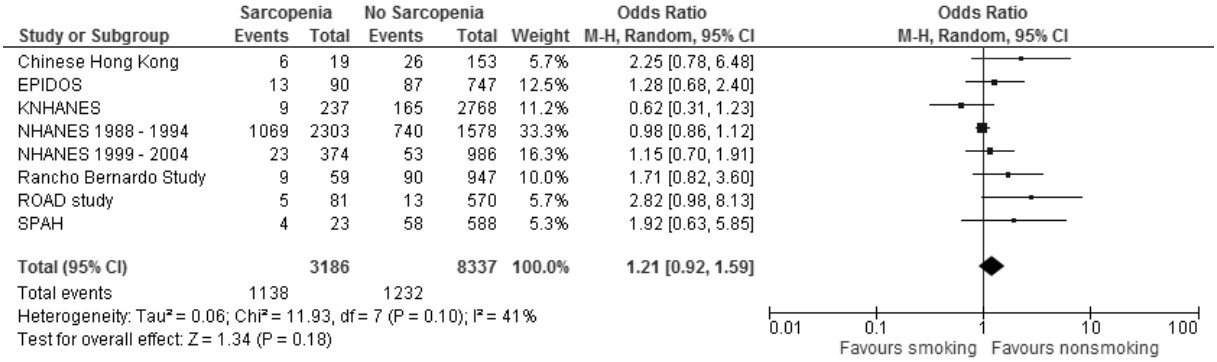

Figure 4 A forest plot for estimating OR, the random-effect model and 95% CI in females.