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Use of smokeless tobacco (ST) and risk of cardiovascular disease (CVD): a systematic review and meta-analysis

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Abstract:	Objective: To assess the risk of Ischaemic Heart Disease (IHD) and stroke (non-fatal and fatal) among adult ever-users of smokeless tobacco (ST). Design: Systematic review and meta-analysis of observational studies. Methods: Data sources for the review included key electronic databases and reference lists. Studies were included based on design - cohort or case-control, exposure - exclusive use of ST or adjusted for smoking, and outcome - non-fatal and fatal IHD and stroke. Data extraction included reported measures of association (RRs or ORs) between ever use of ST (current or past) and CVD outcomes among non-smokers, and other study characteristics. Newcastle-Ottawa scale was used to assess study quality. Summary measures were estimated using random effects models. Results: Twenty studies were included in the meta-analyses. Overall, significantly increased risk of IHD deaths (1.15, 95% CI: 1.01-1.30) and stroke deaths (1.39, 95% CI: 1.29-1.49) was found among ever users of ST. We did not find an overall significant increased risk for IHD (1.14, 95% CI: 0.92-1.42) or stroke (1.01, 95% CI: 0.90-1.13). But geographical variations were marked for IHD, with significant positive association in Asian studies (1.40, 95% CI: 1.01-1.95), and the INTERHEART study, where ST data was mainly reported from Asia (2.23, 95% CI: 1.41-3.53). European studies did not show increased risk for non-fatal CVD. Conclusion: An association was found between ever use of ST and risk of fatal IHD and stroke, consistent with previous review. ST consumption also appears to significantly increase risk of non-fatal IHD among users in Asia, but not in Europe.

Use of smokeless tobacco (ST) and risk of cardiovascular disease (CVD): a systematic review and meta-analysis

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STRUCTURED ABSTRACT

Objective: To assess the risk of Ischaemic Heart Disease (IHD) and stroke (non-fatal and fatal) among adult ever-users of smokeless tobacco (ST).

Design: Systematic review and meta-analysis of observational studies.

Methods: Data sources for the review included key electronic databases and reference lists. Studies were included based on design – cohort or case-control, exposure – exclusive use of ST or adjusted for smoking, and outcome – non-fatal and fatal IHD and stroke. Data extraction included reported measures of association (RRs or ORs) between ever use of ST (current or past) and CVD outcomes among non-smokers, and other study characteristics. Newcastle-Ottawa scale was used to assess study quality. Summary measures were estimated using random effects models.

Results: Twenty studies were included in the meta-analyses. Overall, significantly increased risk of IHD deaths (1.15, 95% CI: 1.01-1.30) and stroke deaths (1.39, 95% CI: 1.29-1.49) was found among ever users of ST. We did not find an overall significant increased risk for IHD (1.14, 95% CI: 0.92-1.42) or stroke (1.01, 95% CI: 0.90-1.13). But geographical variations were marked for IHD, with significant positive association in Asian studies (1.40, 95% CI: 1.01-1.95), and the INTERHEART study, where ST data was mainly reported from Asia (2.23, 95% CI: 1.41-3.53). European studies did not show increased risk for non-fatal CVD.

Conclusion: An association was found between ever use of ST and risk of fatal IHD and stroke, consistent with previous review. ST consumption also appears to significantly increase risk of non-fatal IHD among users in Asia, but not in Europe.

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INTRODUCTION

Globally, there are more than 300 million estimated Smokeless Tobacco (ST) users, with numbers varying widely across geographical regions.[1] An overwhelming majority (nearly 89%) of these ST users live in the South Asian region, where approximately a third of all tobacco is consumed in smokeless forms.[2] ST is highly addictive[3] and its use is known to be associated with a range of adverse health effects including dental disease and precancerous oral lesions,[4] cancers of the oral cavity , oesophagus, and pancreas, [5] as well as negative reproductive outcomes such as stillbirth, pre-term birth, and low birth weight.[1, 6, 7] However, uncertainties exist in relation to CVD risks associated with the use of ST products, the link being only well established for exposure to tobacco in the form of cigarette smoking.[8]

The last systematic review and meta-analysis on this topic was published by Boffetta and Straif in 2009,[9] and found that while ST use was associated with an increased risk of fatal myocardial infarction (MI) and stroke, it was not associated with an increased risk of non-fatal CVD. However this review was geographically restricted to studies from Europe and North America. A subsequent meta-analysis of Asian studies on the risk of CVD from exposure to chewed substances was published in 2010, and found increased risks of IHD and stroke.[10] But exposure in this review was defined to include some products that did not necessarily contain tobacco. A further narrative review on ST use and coronary heart disease (CHD) was conducted in 2011.[11] But this review failed to include cerebrovascular outcomes and counted all observational study designs including cross-sectional studies, making it difficult to infer causality.

To address the lack of an up-to-date systematic review and meta-analysis on the risk of CVD from exposure to ST, which also included studies from Asia where the use of ST is most prevalent, we planned to undertake one without imposing any geographical restrictions. Also, given the differences in the type of ST products consumed in different geographical regions, which vary by composition, methods of preparation and consumption,[1] we hypothesised that the CVD risks associated with the use of these products might also be different. This paper presents the findings of a systematic review and a meta-analysis aimed to estimate the risk of CVD from exposure to ST, along with estimates for different geographical regions.

METHODS

The review protocol was not registered or published.

Search

Search period was from January 1946 to July 2014, and updated in September 2015. Search was not restricted by language or geographical region, and was carried out by combining an exhaustive list of terms denoting various ST products with terms for specific CVD outcomes (Appendix 1).

The databases were selected to achieve a good balance of specialised databases, and grey literature resources. They included MEDLINE, EMBASE, PsycINFO, CINAHL Plus, Web of Science (including Conference Proceedings Citation Index, accessed via Web of Science™ Core Collection), Scopus, Cochrane Library, African Journals Online (AJOL), Latin American and Caribbean Health Sciences Literature (LILACS), WHO Index Medicus of the Eastern Mediterranean Region (IMEMR), WHO Index Medicus of the South-East Asian Region (IMSEAR), PakMediNet, IndMED, ProQuest Dissertations & Theses A&I, EThOS and Open Grey. Additionally, reference lists of all included studies were checked for any citations missed by electronic database searching.

Selection criteria

Cohort and case-control study designs were considered eligible for inclusion. Cross-sectional studies, case series and case reports were excluded. Exposure was defined as any use of ST (current or past), based on self-report or biochemical markers (cotinine in saliva, blood, urine, or hair). If an identified study included users of smoked and smokeless forms of tobacco, then it was only considered eligible if risks were reported for a subsample of exclusive ST users, or if smoking as a potential confounder was adjusted in the analysis. Studies reporting occurrence of non-fatal and/or fatal IHD or stroke, clearly defined according to a pre-existing diagnostic criteria were included. Studies that only reported 'intermediate' cardiovascular outcomes such as blood pressure or lipid levels were excluded.

Data extraction

Two researchers (AV, KS) independently carried out the first screening of titles and abstracts, and second screening of selected full texts to assess eligibility for inclusion. Data extraction was carried out using a pre-determined template by one researcher (AV), and verified by the second researcher (KS). The extracted information included estimates of risk (risk ratios, odds ratios) for each of the study outcomes, as well as other study characteristics, such as design, location, participants, duration, exposure and outcome definition, sample size, and adjustment for potential confounders. If several risk estimates were available from one study (for example, separate results for men and women, or for current and former ST use), we extracted these separately.

Quality assessment

Methodological quality of all included studies was assessed using the Newcastle-Ottawa Scale (NOS).[12] The scale allows a maximum score of 9, by allocating stars to judge each study on participant selection, comparability of groups, and ascertainment of exposure or outcome (Appendix 2). We did not exclude studies on the basis of quality assessment.

Data analysis

Meta-analyses were carried out separately for the four study outcomes using random effects models, on RevMan version 5.3.[13] Prior to analysis, all included studies were grouped by geographical region (Asia, Europe, and North America). The regions were selected on the basis of available studies and similarities in the types of ST products predominantly consumed within each region. The results of cohort and case-control studies were combined in the primary analyses and additional analyses were performed by grouping the included studies by study design for the four review outcomes (IHD and stroke – fatal and non-fatal). All findings were reported in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement (Appendix 3).[14]

RESULTS

A total of 20 studies reported in 19 publications were included in the meta-analyses (Table 1 & Figure 1). These included ten studies from Europe (all from Sweden),[15-24] three from the North America (all from United States of America),[25, 26] six from Asia (3 from Bangladesh, 2 from India and 1 from Pakistan),[27-32] and one large case-control study conducted in 52 countries worldwide (INTERHEART study).[33] All studies recruited adult participants, the youngest reported age being 20 years. Regarding gender, all European studies and two American studies were restricted to male participants, while the rest included both male and female participants.

Overall, there were 9 cohort and 11 case-control studies. While all three studies from North America used a cohort design, studies from Europe and Asia used both case-control and cohort designs. None of the included studies confirmed ST use through cotinine measurements. All relied on self-report, using a range of exposure definitions. Eighteen studies were restricted to never tobacco smokers, whereas two included former smokers, controlling for smoking in the analysis.[18, 29] Fifteen of the included studies used the International Classification of Disease [34] or a similar diagnostic standard to categorise disease outcomes. While a diagnostic standard was not explicitly

mentioned in the remaining five studies, these were all hospital-based, using registered data or clinical diagnosis by specialists for outcome classification.

The methodological quality of all included studies was assessed to be adequate using the NOS scale (Table 1), with scores ranging from 6 to 8. Four studies scored 6 points, 7 studies scored 7, and the highest score of 8 was given to 9 studies. All four studies that scored 6 were case-control studies, with the relatively lower scores resulting from inadequate description of non-response rates among participants.

Among the included studies, there were 15 independent estimates for IHD, 12 for IHD deaths, 4 estimates for stroke, and 12 for stroke deaths. The 15 independent risk estimates for IHD included 10 estimates from Europe, 4 from Asia and 1 from 52 countries. The analysis resulted in a summary relative risk of 1.14 (95% CI: 0.92 to 1.42) comparing ever use of ST to never use of tobacco (Figure 2). However, when estimated by geographical region, while studies from Sweden showed no significant association between ST use and risk of IHD (0.91, 95% CI: 0.83 to 1.01), studies from Asia showed a significantly increased risk of IHD among ST users as compared to non-tobacco users (1.40, 95% CI: 1.01 to 1.95). The reported increased risk was also significant in the INTERHEART study (OR=2.23, 95% CI: 1.41 to 3.53).

Among the studies reporting IHD deaths, the overall relative risk for ever use of ST was 1.15 (CI: 1.01 to 1.30), based on twelve risk estimates (Figure 3) - 2 from Asia, 5 from Europe and 5 from North America. However, by geographical subgroups, the increased risk of IHD deaths was only statistically significant for studies from Sweden (1.38, 95% CI: 1.13 to 1.67).

On the basis of four risk estimates from Sweden, the overall relative risk of non-fatal stroke was 1.01 (95% CI: 0.90 to 1.13) (Figure 4). In the final meta-analysis, based on 12 estimates, including 4 from Asia, 3 from Europe, and 5 from North America (Figure 5), the overall risk of fatal stroke showed a significant positive effect in ST users as compared to non-users (1.39, 95% CI: 1.29 to 1.49). Grouping results by geographical regions, the effect sizes obtained were - Asia: 1.34 (95% CI: 1.18 to 1.52), Europe: 1.28 (95% CI: 0.98 to 1.68), and North America: 1.42 (95% CI: 1.29 to 1.57).

Results of additional analyses (Appendix 4) by study design showed no heterogeneity between subgroups for 3 of the 4 study outcomes. However, significant heterogeneity was observed for the non-fatal IHD outcome (test for subgroup differences: df = 1, P = 0.05).

DISCUSSION

This meta-analysis showed a significant increased risk of fatal IHD and stroke among ever users of ST compared to non-tobacco users. These conclusions were similar to Boffetta and Straif, [9] and did not differ much with magnitude of excess risk, despite the inclusion of two estimates from Asia for IHD deaths and four for stroke deaths. With regard to non-fatal outcomes, only one new study on risk of non-fatal stroke was identified since the previous review [15]. However, this study was also conducted in Sweden, and like previous studies from the Nordic region, did not show an increased risk of stroke among ever ST users. The analysis also showed no heterogeneity between included studies, thereby increasing the credibility of findings.

On the other hand, the meta-analysis of non-fatal IHD showed considerable heterogeneity (df = 14, P < 0.00001). However, this heterogeneity appeared to arise more from differences in the geographical setting of studies (test for subgroup differences: df = 2, P < 0.0001) rather than the differences between the two study designs (cohort and case-control), as no subgroup differences were noted in this analysis on removing the Asian studies. While results from Sweden showed no association between exposure and outcome, a 40% increased risk of IHD among ST users was calculated for studies from Asia, which was statistically significant (CI: 1.01 to 1.95). No studies from North America were found for this outcome category. We believe that the significant variations in the risk of non-fatal IHD seen by geographical regions highlight a truly increased risk among ST users in Asia, which is not found in Europe. We offer the following explanations to support this statement.

First, the methodological quality of all the studies that were used to arrive at this conclusion was assessed as being sound. Second, it is possible that the significantly increased risk of non-fatal IHD reported in the INTERHEART study[33] reflects our findings from Asia, because the use of ST was mainly reported from South Asia in that study. Third, reviews on the risk of cancer from ST use have also found significantly greater risk in Asia as compared to Western countries,[35] and this finding has been put down to geographical variations in the ST products consumed and their levels of chemical carcinogens. For example, while studies from India have reported high levels of tobacco-specific nitrosamines (TSNA) in locally available ST products,[36] much lower levels of TSNA have been detected in the moist snuff available in Swedish markets.[37]

Besides chemical carcinogens, the ST products in different settings are also known to vary by certain toxic constituents, additives, as well as methods of preparation and use,[38-40] which might explain some of the geographical differences noted in the risk of CVD associated with their use. Further research is needed to assess the composition of different ST products sold worldwide,[41] specifically examining the amount of toxins present in these products that are linked with cardiovascular risks. Locally prevalent ST manufacturing techniques and their consumption patterns may also contribute to the amount of toxic exposure and more research into this field could provide some explanation for the observed geographical differences.[42] Meanwhile, discussions around the biological plausibility of CVD risks associated with ST use[9, 17, 24] have tended to focus on the role of nicotine. However, with evidence from the use of nicotine patches in patients known to have CVD showing improvements in existing disease conditions,[43] it is likely that other chemical constituents of ST, in combination with nicotine, are responsible for increasing CVD risks among users.

A study published in 2012 showing increased of heart failure from two independent Swedish cohorts[44] was excluded after the second screening of full texts as the study outcomes did not match our inclusion criteria. We also excluded one study[45] from the previous meta-analysis on this topic, because exposure did not appear to be exclusive ST use, and smoking was not controlled in the analysis. Even within the included studies, our risk estimates were slightly different, due to differences in data extraction methods. While Boffetta and Straif[9] combined multiple risk estimates from a single study using a fixed-effect model, we extracted these as separate estimates, combining them finally in the meta-analyses based on random effect models. The most important difference however was that our analyses included studies from Asia, where ST use is most prevalent.

The strengths of this review include the thoroughness of the search strategy, the explicit criteria set out for inclusion of studies with regard to study design, exposure, outcome and control of confounding, and the robustness of the studies included in the meta-analysis. But several limitations have to be considered in interpreting the results. The conclusions on potentially higher cardiovascular risks associated with the use of ST products in Asia are based on a small number of studies showing considerable heterogeneity (df = 3, I^2 = 81%, P = 0.001). However publication bias did not appear substantial based on visual inspection of the funnel plot (Appendix 5), and the heterogeneity may largely be attributed to the 2012 study by Rahman et al,[27] which differed from the other studies by recruiting both community and hospital based controls. Although the authors controlled for hypertension in the analysis of this study, some potential for bias remains from

recruitment of hospital-based controls from a hypertension clinic, ST use being positively associated with risk of hypertension.[46]

The possibility of misclassification bias arising from differences in disease definitions cannot be entirely ruled out, considering diagnostic standards were not mentioned in three of the six Asian studies included in total. Misclassification could also have resulted from the absence of any biological measurement of ST exposure (e.g. cotinine test), as ST use was documented solely through self-report in all included studies.

While potential confounding by active smoking was adequately controlled by restricting the analysis to never smokers or adjusted estimates of risk, most of the included studies did not report alcohol use among study participants. Given that the cardiovascular outcomes are varyingly associated with differing levels of alcohol use,[47] with the data available from included studies, we were unable to predict the effect of alcohol use on the overall results of analyses. A thorough ascertainment of other confounding effects such as those due to blood pressure, serum lipids, BMI, and diabetes, was also limited by a lack of uniformity within the included studies in adjusting for such variables during their analyses. For example, less than half of the studies (9 out of 20) have adjusted for the above classical biological risk factors. With regards to gender, most studies included in this review were conducted in men, with the exception of those conducted in Asia. However, sufficient data were not available to assess if the CVD risk conferred by ST use is different between men and women.

With the available data, we found consistent evidence for an increased risk of fatal IHD and fatal stroke associated with ever use of ST. Geographical variations for the risk of non-fatal IHD were noted, with significant positive association in studies from Asia, which may be attributed to the content and methods of use of ST products available in these settings. Although moderate, the cardiovascular health implication of these findings may be relevant to a significant number of ST users living in South Asia, as well as South Asian diaspora communities living elsewhere who also use similar ST products.[42, 48] Given that over three quarters of all CVD deaths take place in low- and middle-income countries,[49] more efforts should be made to regulate ST manufacturing and consumption in these settings to reduce CVD risks associated with the use of this modifiable risk factor.

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Authors' contributions:

AV: Contribution to the protocol, data collection, data analysis, data interpretation, drafting and approval of the manuscript

KS: Conceived the idea, contribution to the protocol, data collection, data interpretation, contribution to and approval of the manuscript

MK: Data analysis, data interpretation, contribution to and approval of the manuscript

All authors had full access to all of the data (including statistical reports and tables) in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Transparency declaration: The lead author affirms that the manuscript is an honest, accurate, and transparent account of the reported study; no important aspects of the study have been omitted; and any discrepancies from the study protocol have been explained.

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Table

Table 1: Characteristics of observational studies included in the meta-analyses

Country	Study period	Study design (no. of participants)	Age range of participants in years	Exposure status	Inclusion of smokers/ alcohol users	Outcome	ORs/RRs (95% CI)	Comments	Quality assessment (NOS)
INTERHEART Study - 52 countries									
52 countries[33]	1999-2003	Case-Control (Cases - 12461, Controls - 14637)	NA	Chewing tobacco	No/Yes	IHD	1·57 (1·24-1.99)	Adjusted for diabetes, abdominal obesity, HT, exercise, diet	Selection**** Comparability** Exposure*
Studies from Asia									
Pakistan[32]	2005-2011	Case-Control (Cases - 7905, Controls - 7458)	20 - 80	Dippers only Chewers only	No/NA	IHD	1.46 (1.20, 1.77) 1.71 (1.46, 2.00)	Adjusted for age, sex, region, ethnicity	Selection**** Comparability** Exposure**
Bangladesh[28]	2006-2007	Case-Control (Cases - 69, Controls - 138)	20 - 49	Ever ST users	No/NA	IHD	2.8 (1.1, 7.13)	Adjusted for age, sex, HT	Selection*** Comparability** Exposure*
Bangladesh[27]	2010	Case-Control (Cases - 302, Controls - 1510)	40 - 75	Ever ST users	No/NA	IHD	0.77 (0.52, 1.14)	Adjusted for age, HT, diabetes, acute psycho-social stress	Selection*** Comparability** Exposure*
Bangladesh[29]	2005-2008	Case-Control (Cases - 1250, Controls - 246)	20 - 100	Tobacco powder	Yes/NA	Stroke Deaths	1.15 (0.30, 7.64)	Adjusted for age, sex, HT, diabetes, betel nut, heart disease, smoking	Selection*** Comparability** Exposure*
India[30]	1992-1999	Cohort (5470)	> 35	Ever ST users	No/NA	IHD Deaths	Male - 0.89 (0.75, 1.05)	Adjusted for age, education	Selection**** Comparability**

						Stroke Deaths	Female - 1.25 (1.05, 1.49) Male - 1.32 (0.94, 1.84) Female - 1.15 (0.84, 1.59)		Outcome**
India[31]	1998-2001	Case-Control (Cases - 22000, Controls - 429000)	35 - 69	Ever ST users	No/No	Stroke Deaths	1.4 (1,2, 1.6)	Adjusted for age, sex, education, urban/rural	Selection**** Comparability** Exposure*
Studies from Europe									
Sweden[15]	1998-2005	Cohort (16642)	> 40	Current users Former users Current users Former users	No/NA	IHD Stroke	0.85 (0.51, 1.42) 1.07 (0.56, 2.04) 1.18 (0.67, 2.08) 1.35 (0.65, 2.82)	Adjusted for age, HT, diabetes, cholesterol	Selection*** Comparability** Outcome**
Sweden[16]	1998-2005	Case-Control (Cases - 1432, Controls - 1810)	45 - 70	Current users Former users Current users Former users	No/NA	IHD IHD Deaths	0.59 (0.25, 1.4) 1.2 (0.43, 3.2) 1.7 (0.48, 5.5) 1.7 (0.21, 13.6)	Exclusive ST users	Selection*** Comparability** Exposure**
Sweden[17]	1978-2004	Cohort (118395)	35 - 65	Ever ST users	No/NA	IHD IHD Deaths	0.91 (0.81, 1.02) 1.28 (1.06, 1.55)	Adjusted for age, BMI, region of residence	Selection** Comparability** Outcome***
Sweden[18]	1989-1991	Case-Control (Cases - 585, Controls - 589)	35 - 64	Regular ST users	Yes/NA	IHD	1.01 (0.66, 1.55)^	Adjusted for age, education, smoking	Selection*** Comparability** Exposure*
Sweden[19]	1991-	Case-Control	25 - 64	Former ST	No/NA	IHD	1.23 (0.54, 2.82)	Exclusive ST users	Selection****

	1993	(Cases - 687, Controls - 687)		users					Comparability** Exposure**
Sweden[20]	1988-2000	Cohort (3120)	30 - 75	Daily ST users	No/NA	IHD	1.41 (0.61, 3.28)	Adjusted for BMI, physical activity, diabetes, HT	Selection**** Comparability** Outcome**
Sweden[21]	1985-1999	Case-Control (Cases - 525, Controls - 1798)	30 - 60	Current users Former users	No/NA	IHD	0.82 (0.46, 1.46) 0.66 (0.32, 1.36)	Adjusted for BMI, physical activity, education, cholesterol	Selection**** Comparability** Exposure**
Sweden[22]	1974-1985	Cohort (135036)	35 - 65	ST users	No/NA	IHD Deaths Stroke Deaths	35 – 54 years - 2.0 (1.4, 2.9) 55 – 65 years - 1.2 (1.0, 1.5) 35 – 54 years - 1.9 (0.6, 5.7) 55 – 65 years - 1.2 (0.7, 1.8)	Adjusted for age, region of origin	Selection** Comparability** Outcome***
Sweden[23]	1985-2000	Case-Control (Cases - 276, Controls - 551)	25 - 74	Regular ST users	No/NA	Stroke	0.87 (0.41, 1.83)	Adjusted for diabetes, HT, education, marital status, cholesterol	Selection**** Comparability** Exposure**
Sweden[24]	1978-2003	Cohort (118465)	35 - 65	Ever ST users	No/NA	Stroke Stroke deaths	1.00 (0.89, 1.11) 1.27 (0.92, 1.76)	Adjusted for age, BMI, region of residence	Selection** Comparability** Outcome***
Studies from North America									
USA[25]	1971-1992	Cohort (6805)	25 - 74	Ever ST users	No/NA	IHD Deaths	Male - 0.6 (0.3, 1.2)	Adjusted for age, race, poverty index	Selection*** Comparability**

						Stroke Deaths	Female - 1.4 (0.8, 2.2) Male - 0.7 (0.2, 2.0) Female - 1.0 (0.3, 2.9)	ratio, alcohol, physical activity, fruit/veg intake, HT, cholesterol, BMI	Outcome***
USA[26]	1959-1972	Cohort CPS-I (77407)	> 35	Current ST users	No/Yes	IHD Deaths Stroke Deaths	1.12 (1.03, 1.21) 1.46 (1.31, 1.64)	Adjusted for age, race, education, alcohol, BMI, physical activity, fruit/veg intake, fat intake, aspirin	Selection*** Comparability** Outcome***
USA[26]	1982-2000	Cohort CPS-II (114809)	> 35	Current users Former users Current users Former users	No/Yes	IHD Deaths Stroke Deaths	1.26 (1.08, 1.47) 0.70 (0.52, 0.95) 1.40 (1.10, 1.79) 1.21 (0.83, 1.76)	Adjusted for age, race, education, employment, alcohol, physical activity, fruit/veg intake, fat intake, BMI, aspirin use	Selection*** Comparability** Outcome***

Abbreviations:

OR, Odds Ratio; RR, Risk Ratio; CI, Confidence Interval; NOS, Newcastle-Ottawa Scale; IHD, Ischaemic Heart Disease; HT, Hypertension; NA, Not Available; ST, Smokeless Tobacco; BMI, Body Mass Index; CPS, Cancer Prevention Study

Figure 1

FIGURE 1: SELECTION OF STUDIES IN META-ANALYSIS

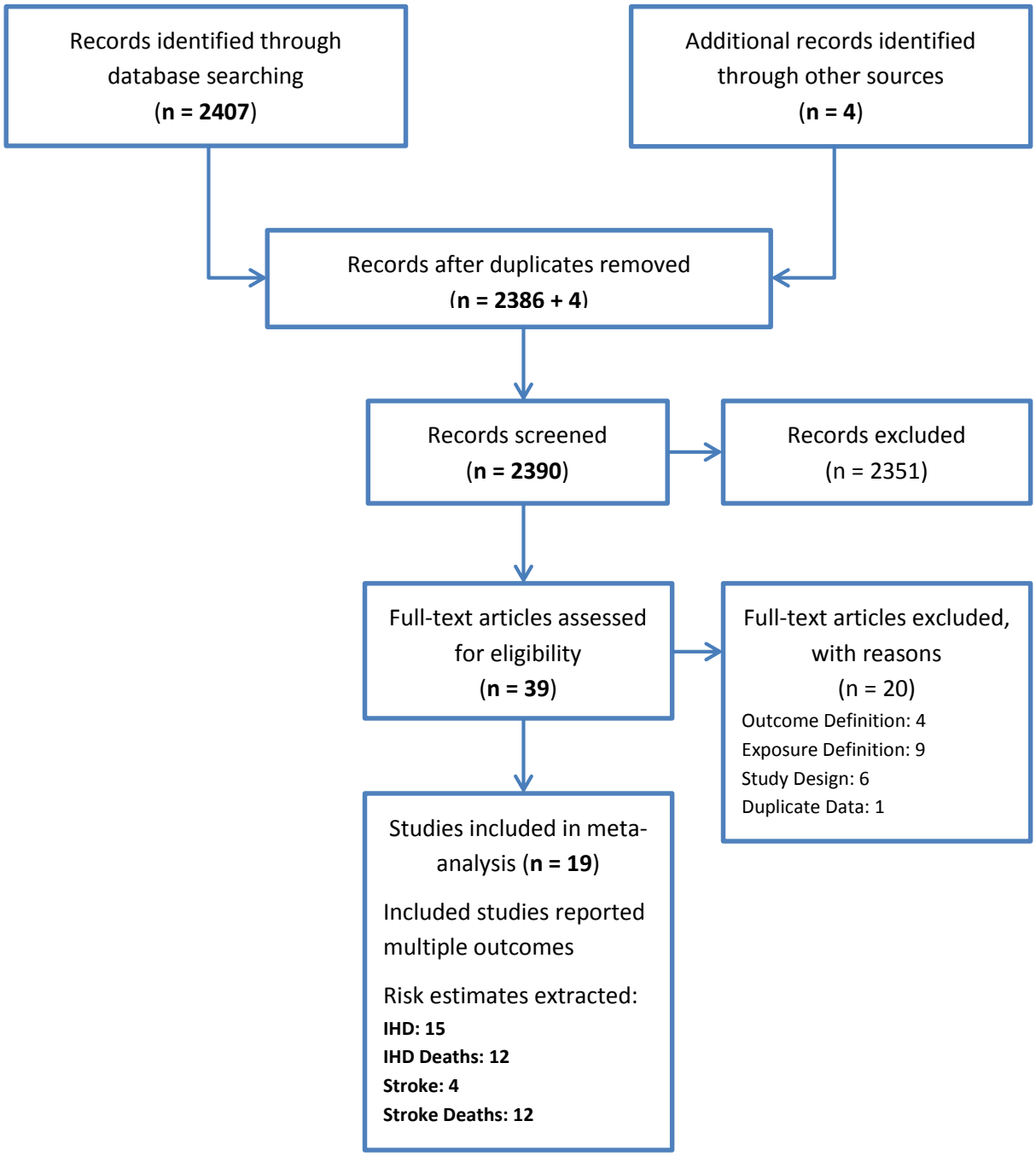
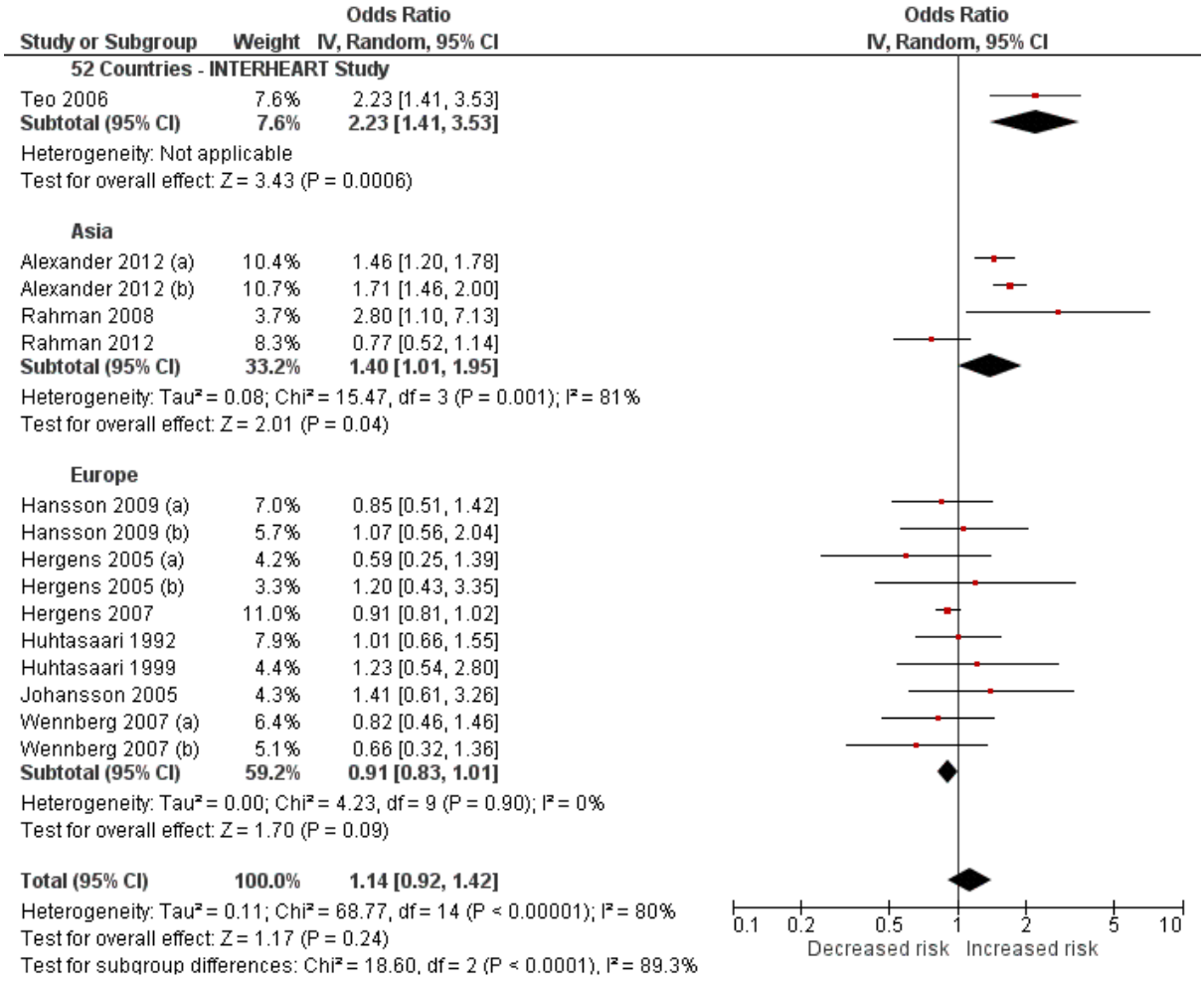


Figure 2

FIGURE 2: FOREST PLOT OF RISK ESTIMATES FOR IHD AMONG EVER ST USERS

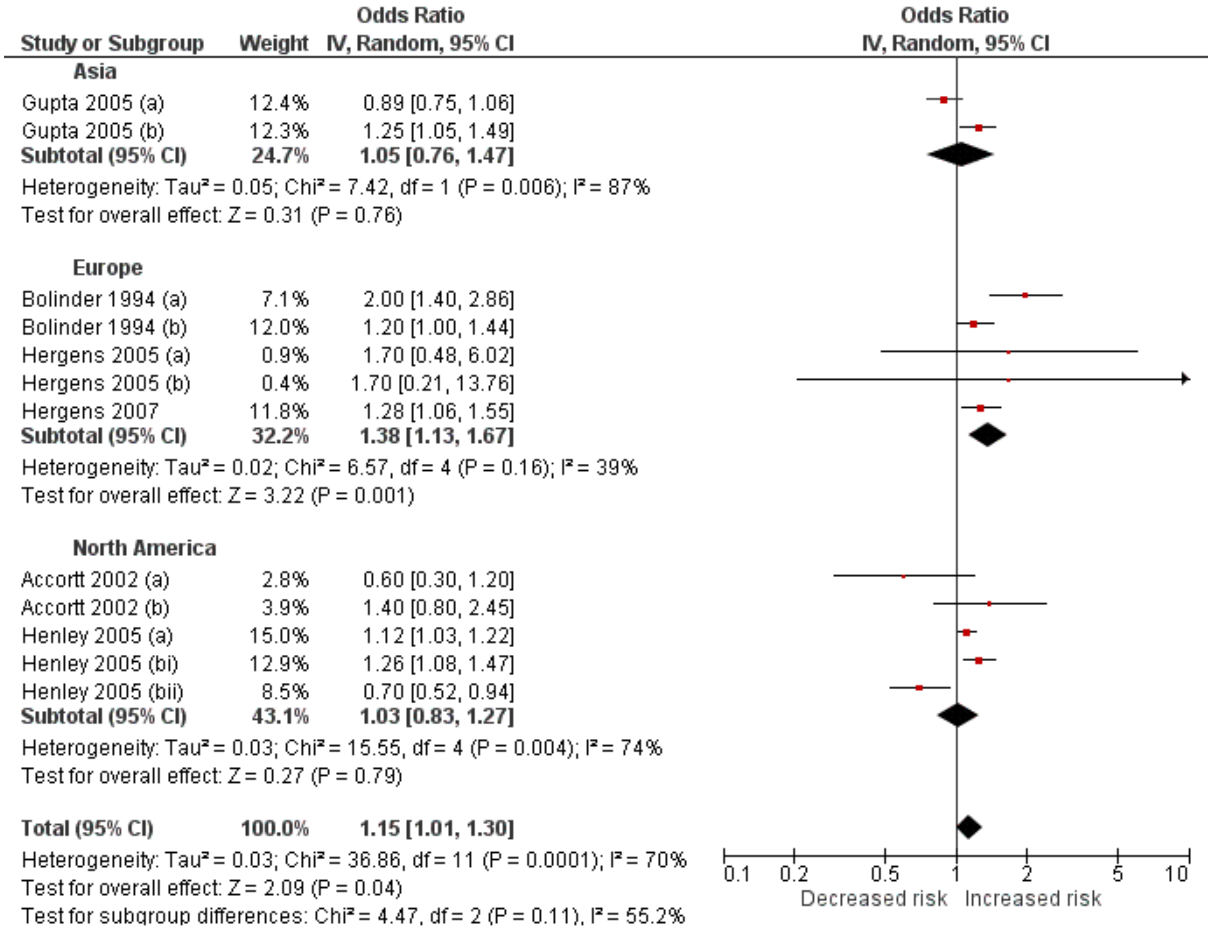


Alexander 2012 (a): Dippers, Alexander 2012 (b): Chewers,
Hansson 2009 (a): Current users, Hansson 2009 (b): Former users,
Hergens 2005 (a): Current users, Hergens 2005 (b): Former users
Wennberg 2007 (a): Current users, Wennberg 2007 (b): Former users

IV, Inverse Variance; CI, Confidence Interval

Figure 3

FIGURE 3: FOREST PLOT OF RISK ESTIMATES FOR IHD DEATHS AMONG EVER ST USERS

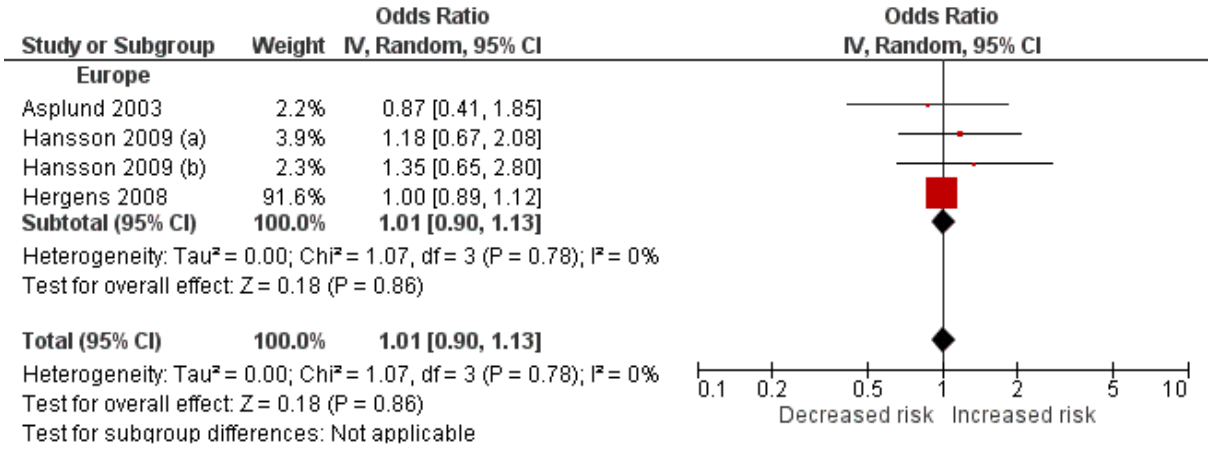


Gupta 2005 (a): Men, Gupta 2005 (b): Women
Bolinder 1994 (a): 35-54 years, Bolinder 1994 (b): 55-65 years
Hergens 2005 (a): Current users, Hergens 2005 (b): Former users
Accortt 2002 (a): Men, Accortt 2002 (b): Women
Henley 2005 (a): CPS-I, Henley 2005 (bi): CPS-II, Current users, Henley 2005 (bii): CPS-II, Former users

IV, Inverse Variance; CI, Confidence Interval

Figure 4

FIGURE 4: FOREST PLOT OF RISK ESTIMATES FOR STROKE AMONG EVER ST USERS

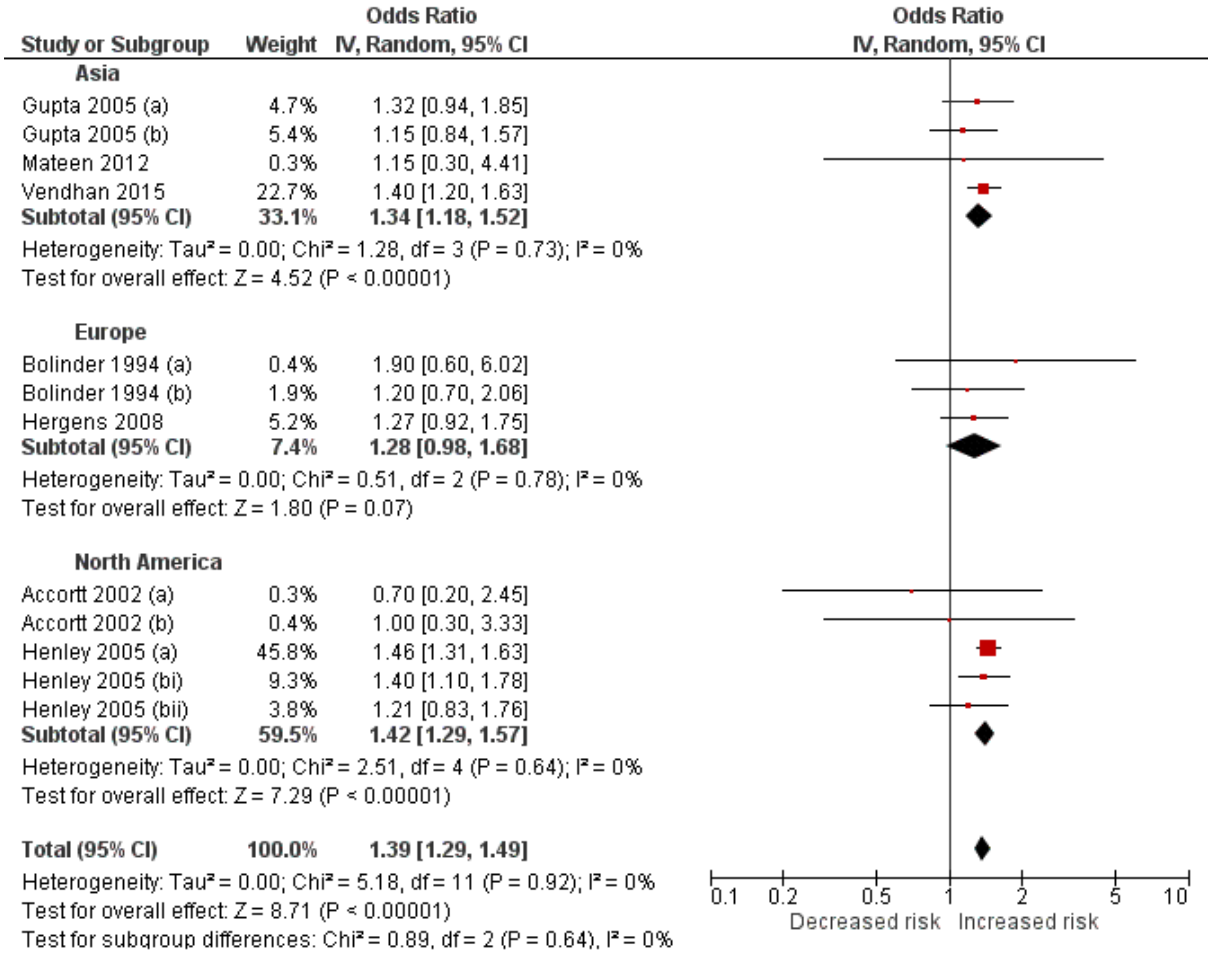


Hansson 2009 (a): Current users, Hansson 2009 (b): Former users

IV, Inverse Variance; CI, Confidence Interval

Figure 5

FIGURE 5: FOREST PLOT OF RISK ESTIMATES FOR STROKE DEATHS AMONG EVER ST USERS



Gupta 2005 (a): Men, Gupta 2005 (b): Women
Bolinder 1994 (a): 35-54 years, Bolinder 1994 (b): 55-65 years
Accortt 2002 (a): Men, Accortt 2002 (b): Women
Henley 2005 (a): CPS-I, Henley 2005 (bi): CPS-II, Current users, Henley 2005 (bii): CPS-II, Former users

IV, Inverse Variance; CI, Confidence Interval

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