Chewing substances with or without tobacco and risk of cardiovascular disease in Asia: a meta-analysis[*]

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Abstract: Objective: To assess whether people who ever use any form of chewing substance in Asia are at increased risk of cardiovascular disease (CVD). Methods: PubMed and ISI Web of Science were searched for relevant studies, with no limitation on language or study year. Studies were included if they provided quantitative estimate of the association between ever use of chewing substance and the occurrence of CVD. Two authors independently implemented inclusion criteria, abstracted study characteristics, and performed meta-analysis. Summary relative risks were estimated on the basis of a random effect model. We used *Q* statistic and Egger's test to examine heterogeneity across studies and potential publication bias, respectively. Results: Eight eligible studies were included. The relative risk of CVD for ever using chewing substances with or without tobacco was 1.26 (95% confidence interval (CI) 1.12–1.40), which was unchanged when restricted to cohort studies [1.25 (1.08–1.42)] or cohort studies in Taiwan [1.31 (1.12–1.51)]. The summary relative risk for ischemic heart disease was 1.27 (1.02–1.52), and was lowered to 1.26 (0.85–1.67) after exclusion of a cross-sectional study. The overall relative risk for cerebrovascular disease was 1.32 (1.08–1.56). On the basis of the Taiwan data, the summary relative risk of CVD for betel (*Areca catechu*) chewing was 1.30 (1.17–1.44). Data on dose-response were limited to betel chewing in Taiwan, suggesting a relationship between risk of CVD and cumulative exposure. Two large cohorts in Taiwan reported a greater risk of CVD with betel chewing than with smoking. Conclusions: An association was detected between betel chewing with or without tobacco and the risk of CVD. Betel chewing may impose a greater CVD risk than smoking. More effort is needed in developing betel chewing cessation programmes. The relationship between betel chewing and subgroups of CVD requires further investigation.

Key words: Cardiovascular disease, *Areca catechu*, Betel quid, Chewing tobacco, Relative risk, Meta-analysis
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1 Introduction

Various forms of smokeless tobacco, including chewing tobacco and paan, namely, *Areca catechu*/ betel quid with tobacco, have been used in Asia for centuries. Betel quid is made up of fresh betel leaves, areca nut, and slaked lime, and can be served with or without tobacco (Gupta and Ray, 2004). Preparation of betel quid varies from region to region, with the major difference being whether tobacco is added. To avoid a possible misnomer by classifying betel quid with some types of smokeless tobacco, while sometimes tobacco is actually absent, we herein employed the term "chewing substance" to refer to any type of chewing tobacco or betel quid with or without tobacco. Betel quid with tobacco is said to be one of the most commonly used forms of smokeless tobacco in South Asia (Gupta and Ray, 2003), whereas areca nut (usually incorporated in betel quid) ranks the fourth most common addictive substance in the world after

caffeine, tobacco, and alcohol (Gupta and Ray, 2004).

The complex nexus between chewing tobacco and betel quid is not easy to dissect. This, along with high prevalence of chewing tobacco and betel quid in South and Southeast Asia, exhibits a geographically unique scene of tobacco use, or more accurately, substance use other than the pandemic cigarette smoking (Rani *et al.*, 2003; Wen *et al.*, 2005; Teo *et al.*, 2006). Compared to cigarette smoking, which is a well established risk factor for cardiovascular disease (CVD), chewing tobacco and betel quid, though prevailing in many parts of Asia, are relatively less explored for their potential adverse effect on cardiovascular system. To date, few epidemiological studies have been conducted in Asia (Gupta *et al.*, 2005; Wen *et al.*, 2005; Teo *et al.*, 2006; Guh *et al.*, 2007; Lan *et al.*, 2007; Lin *et al.*, 2008; Rahman and Zaman, 2008; Yen *et al.*, 2008), investigating the relative risk of CVD related to chewing tobacco and betel quid, and the findings are not all comparable.

A recent meta-analysis indicated that smokeless tobacco users in Sweden and USA were at increased risk of CVD compared with nonusers (Boffetta and Straif, 2009). However, studies conducted in Asia were not included in view of heterogeneity between the contents of smokeless tobacco in Asia and those in Sweden and USA. Thus, the conclusion may not be readily applicable in the Asian context. Determining the roles of chewing tobacco and betel quid in CVD is important, given their high prevalence of usage and current high incidence and mortality of CVD in Asia. All these concerns prompted us to carry out a meta-analysis to summarize existing evidence, on the link between use of chewing substances and risk of CVD.

2 Methods

2.1 Searching strategy and selection criteria

The MOOSE guidelines for meta-analysis of observational studies in epidemiology were followed (Stroup *et al.*, 2000). We searched PubMed (up to July 2010), using the terms: ("cardiovascular diseases" [mesh] OR ("cardiovascular" [All Fields] AND "diseases" [All Fields]) OR "cardiovascular diseases" [All Fields] OR "cerebrovascular disorders" [mesh] OR ("cerebrovascular" [All Fields] AND "disorders" [All Fields]) OR "cerebrovascular disor-

ders" [All Fields] OR "stroke" [mesh] OR "stroke" [All Fields] OR mortality OR death*) AND ("betel quid" OR "betel-quid" OR "betel nut" OR "betel nuts" OR "areca nut" OR "areca nuts" OR "paan" OR "pan" OR snuff OR snus OR "gul" OR "gutka" OR "khaini" OR "loose leaf" OR "maras" OR "mawa" OR "mishri" OR "naswar" OR "*Areca catechu*" OR "tooth powder" OR "shammah" OR "tobacco chewing gum" OR "zarda" OR "tobacco, smokeless" [mesh] OR "smokeless tobacco" OR "chewing tobacco" OR "non-smoking tobacco") AND ("cohort studies" [mesh] OR "cross-sectional studies" [mesh] OR "case control studies" [mesh] OR ("cohort" [TI] AND stud* [TI]) OR (case* [TI] AND control* [TI]) OR prospective OR retrospective OR cross-sectional OR "cross sectional"), which yielded 1006 potentially relevant references. We adapted the searching strategy for a second search in ISI Web of Science (updated July 19, 2010), and found another 739 references. We identified all observational studies including cohorts, case-control studies, and cross-sectional studies, provided that they explored the association between ever using chewing substances and the occurrence (incidence or mortality) of CVD, and reported the strength of the associations with a quantitative risk estimate. There was no limitation on language, study year, or publication status.

After excluding duplicates, two authors independently reviewed all citations with titles and abstracts that appeared to fit the criteria for inclusion. We checked references of included studies and reviews to further identify other potentially eligible studies. The numbers of citations excluded and reason for exclusion were tracked.

2.2 Outcome measurement

We conducted the meta-analysis based on selected outcome measurements including cardiovascular disease (CVD), ischemic heart disease (IHD), and cerebrovascular disease (CBVD). The following sub section will describe in detail how these outcome measurements were identified.

2.3 Data extraction

Two authors independently extracted risk estimates and characteristics of each individual study. We followed the international classification code (ICD-9 and ICD-10) when grouping the extracted

outcome measurements. Accordingly, we regarded CVD as either 390–459 in ICD-9 or I00–I99 in ICD-10, IHD as either 410–414 in ICD-9 or I20–I25 in ICD-10, and CBVD as either 430–438 in ICD-9 or I60–I69 in ICD-10. When outcomes were not coded with an ICD number, we made assumptions according to the definition of diseases reported and how ascertainment was made. The extracted data were compared and any inconsistencies resolved. Wherever possible, data were extracted for fatal and non-fatal cardiovascular events.

If stratified results were presented from one study (for example, separate results for current and former use, for men and women), we combined them by carrying out a meta-analysis based on fixed effect model when Q statistic was not significant ($P>0.1$); otherwise we used a random effect model.

2.4 Data synthesis and statistical analysis

A meta-analysis was made of the selected primary endpoint outcomes based on a random effect model (DerSimonian and Laird, 1986). We examined heterogeneity across studies with the Q statistic ($P<0.1$ considered significant). Egger's test was used to detect possible publication bias. All of analyses were conducted with the statistical package STATA (Version 11.0; Stata Corp, College Station, TX, USA).

We classified studies on the basis of the chosen outcomes (CVD, IHD, CBVD). In addition, we also classified studies by geographical region of study and study design (cohort, case-control) in the subgroup analysis. We accounted for concurrent smoking as a confounding factor, if a risk estimate was neither restricted to non-smokers nor obtained after adjustment for smoking; we considered it for sensitivity analysis by repeating the meta-analysis after exclusion of the study. Similarly, we repeated the meta-analysis after removing cross-sectional studies, and studies in which we had made any assumption about the classification of diseases. To minimize the confounding due to presence or absence of tobacco in chewing substances, which may be characteristic of different regions, we repeated the meta-analysis after stratification by geographical region. The possible influence of study design was assessed by repeating the main analysis with cohort study data only. To disentangle the effect of geographical region from

that of study design, we carried out a further meta-analysis restricted to cohort studies from Taiwan.

3 Results

Fig. 1 shows details of study identification, inclusion, and exclusion. A total of 1599 publications were initially screened. Eight studies met the criteria for inclusion in the present study.
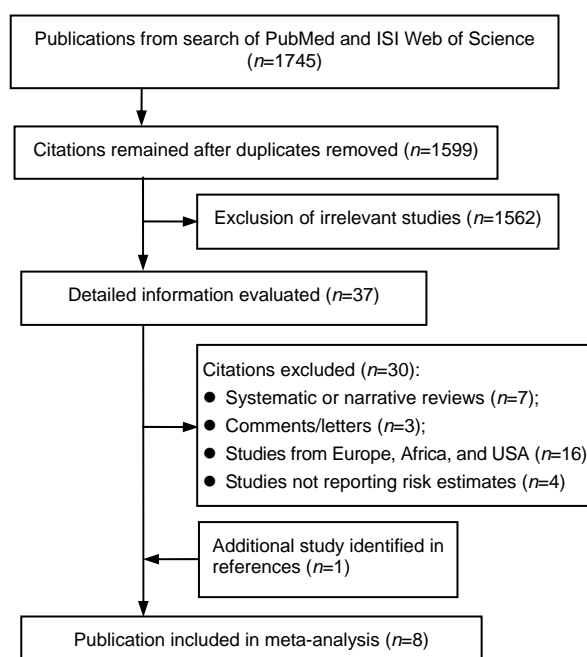

Fig. 1 Flow diagram of the study selection process

3.1 Characteristics of included studies

Table 1 shows the characteristics of the included studies. All of the epidemiological studies were undertaken in South and East Asia in recent years. Five cohort studies were from India and Taiwan (China) (Gupta *et al*., 2005; Wen *et al*., 2005; Lan *et al*., 2007; Lin *et al*., 2008; Yen *et al*., 2008), two used case-control design, one of which is a multi-center study (Teo *et al*., 2006; Rahman and Zaman, 2008), and another one used cross-sectional design (Guh *et al*., 2007). Of the eight studies included, four studies reported increased risk for use of chewing substance (Teo *et al*., 2006; Lin *et al*., 2008; Rahman and Zaman, 2008; Yen *et al*., 2008), two showed inconsistent results between women and men (Gupta *et al*.,

Table 1 Characteristics of included epidemiological studies on chewing substances and risk of CVD

Study	Geographical region, gender, recruitment, follow-up, No. of participants	Study design	Exposure	Outcome	Definition and ascertainment	No. of cases or deaths[#]	RR (95% CI)	Adjustment factors
Teo et al., 2006	Mainly South Asia, both sexes, 1999–2003, NR, 27098	Case-control	Chewing tobacco	Acute myocardial infarction	Characteristic manifestation and ECG (specific criteria available)	NA	2.23 (1.41–3.52)	Age, gender, diabetes, abdominal obesity, hypertension, exercise, diet
Wen et al., 2005	Taiwan (China), men, 1982–1992, 1982–2000, 19719	Cohort	Betel quid	CVD [390–459], IHD [410–414], stroke [430–438]	ICD-9, death registry system	275/ 39/ 86	1.1 (0.8–1.6), 1.0 (0.5–2.4), 1.3 (0.8–2.2)	Age, alcohol, education
Gupta et al., 2005	India, both sexes, 1992–1994, 1992–1999, 97244	Cohort	Betel quid, areca nut, mishri	CVD [100–199], IHD [110, 111, 113, 121, 124, 125, 146, 150], CBVD [161–164, 166, 167]	ICD-10, death registry system	1876/ 1372/ 386	1.06 (0.84–1.33)*, 1.05 (0.76–1.47)*, 1.23 (0.97–1.55)*	Age, education
Rahman and Zaman, 2008	Bangladesh, both sexes, 2006–2007, NR, 207	Case-control	Betel quid, dried tobacco leaf	Coronary heart disease (acute myocardial infarction and angina pectoris)	Clinical findings and ECG	NA	2.8 (1.1–7.3)	Gender, age, hypertension
Yen et al., 2008	Taiwan (China), men, 1999–2004, duration (2.81±1.50) years, 21906	Cohort	Betel quid	CVD [402, 410–414, 425–428, 430–438, 440–448]	ICD-9, incidence identified in hospital, mortality by registry system	3163	1.24 (1.11–1.39)	Age, education, occupation, smoking, alcohol, intake of fish, milk, coffee, physical activity, family history
Lan et al., 2007	Taiwan (China), both sexes, 1989–2003; 1996–2003, 6511	Cohort	Betel quid	CVD [390–459], IHD [410–414], CBVD [430–438]	ICD-9, death registry system	684/ 153/ 305	1.41 (1.12–1.77), 1.22 (0.73–2.04), 1.66 (1.19–2.30)	Gender, age, living area, hypertension, anemia, heart disease, liver disease, arthritis, physical difficulty, smoking, alcohol
Lin et al., 2008	Taiwan (China), men, 1998–1999, 998–2005, 56116	Cohort	Betel quid	CVD [390–459]	ICD-9, death registry system	309	1.77 (1.31–2.40)*	Age, BMI, diabetes, hypertension, cholesterol, triglyceride, alcohol, smoking, physical activity, income, education
Guh et al., 2007	Taiwan (China), both sexes, 1993–1996, NR, 1932	Cross-sectional	Betel quid	Heart disease	Questionnaires on self-report	NA	1.34 (1.12–1.62)*	Age, abdominal obesity, cholesterol, hypertension, diabetes, smoking, fruit intake

Number of cases or deaths from a certain outcome, cardiovascular disease (CVD), ischemic heart disease (IHD), cerebrovascular disease (CBVD), etc. (listed in order in the fifth column). Cases or deaths of non-chewing smokers were not included. The numbers are listed in the same order to accompany their corresponding outcomes. * Results of meta-analysis. RR: relative risk; CI: confidence interval; NR: not available; NA: not relevant; ECG: electrocardiograph, ICD: international classification code; BMI: body mass index

2005; Guh *et al.*, 2007), one found inconsistency between subtypes of CVD (Lan *et al.*, 2007), and still another one reported negative results (Wen *et al.*, 2005). Four studies (Gupta *et al.*, 2005; Teo *et al.*, 2006; Lin *et al.*, 2008; Rahman and Zaman, 2008) reported risk estimates of substance chewers restricted to never tobacco smokers, whereas the others all included cigarette smokers in both categories (Wen *et al.*, 2005; Lan *et al.*, 2007; Guh *et al.*, 2007; Yen *et al.*, 2008), and could not report the relative risk of chewing betel quid alone. In the latter, however, risk estimates were all adjusted for cigarette smoking, except in one study (Wen *et al.*, 2005).

Three studies (Wen *et al.*, 2005; Lan *et al.*, 2007; Lin *et al.*, 2008) mentioned that betel quid in Taiwan was generally chewed without tobacco. The betel quid was commonly used with added tobacco elsewhere in South Asia (Gupta and Ray, 2004), though it was not the case in the Mumbai cohort, where betel quid was chewed without tobacco (Gupta *et al.*, 2005). Meta-analyses of stratified results were performed for three studies to obtain a summary relative risk (Gupta *et al.*, 2005; Guh *et al.*, 2007; Lin *et al.*, 2008).

3.2 Chewing substances and risk of CVD

On the basis of six risk estimates, the overall relative risk of CVD (ICD-9: 390–459; ICD-10: I00–I99) for ever using chewing substances was 1.26 (95% confidence interval (CI) 1.12–1.40), with no evidence of heterogeneity among studies (Table 2, Fig. 2; test for publication bias $P=0.68$). Restricting the meta-analysis to cohort studies yielded a summary relative risk of 1.25 (1.08–1.42) based on five risk estimates. The summary relative risk of CVD for betel chewing was 1.30 (1.17–1.44) based on five studies from Taiwan. Data from cohort studies in Taiwan gave a summary relative risk of 1.31 (1.12–1.51) based on four risk estimates. An increased risk of death from CVD was present, 1.28 (1.00–1.56) based on four risk estimates. After removing one study that did not report a risk estimate after adjustment for smoking (Wen *et al.*, 2005), the positive direction of relative risks all persisted, except for the fatal form of CVD (data not shown).

Dose-response analysis for CVD was reported in three studies in Taiwan (Lan *et al.*, 2007; Lin *et al.*, 2008; Yen *et al.*, 2008), and significant trends in risk by cumulative exposure were detected in two studies

Table 2 Results of meta-analysis on risk of CVD and chewing substances with or without tobacco

Outcome and subgroups	No. of risk estimates	P^*	RR (95% CI)
CVD			
Overall	6	0.17	1.26 (1.12–1.40)
Cohort	5	0.13	1.25 (1.08–1.42)
Taiwan	5	0.29	1.30 (1.17–1.44)
Cohort Taiwan	4	0.19	1.31 (1.12–1.51)
Fatal	4	0.07	1.28 (1.00–1.56)
IHD			
Overall	6	0.29	1.27 (1.02–1.52)
Cohort	3	0.89	1.08 (0.78–1.38)
South Asia	3	0.07	1.64 (0.60–2.68)
Taiwan	3	0.77	1.31 (1.08–1.53)
Cohort Taiwan	2	0.71	1.15 (0.61–1.70)
Fatal	3	0.89	1.08 (0.78–1.38)
CBVD			
Overall	3	0.40	1.32 (1.08–1.56)
Taiwan	2	0.43	1.52 (1.09–1.96)

* P for heterogeneity. CVD: cardiovascular disease; IHD: ischemic heart disease; CBVD: cerebrovascular disease; RR: relative risk; CI: confidence interval
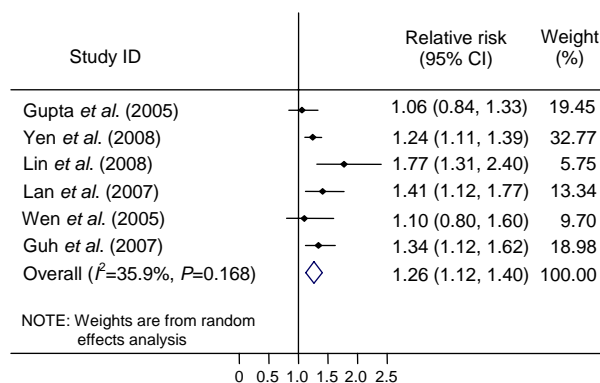
Fig. 2 Forest plot of risk estimates for CVD among users of chewing substances

(Lan *et al.*, 2007; Yen *et al.*, 2008). In the third study (Lin *et al.*, 2008), though the analysis for trend was not reported, the relative risk of fatal CVD was the highest in the groups of subjects using betel quid most often. In addition, two of these large cohorts (Lin *et al.*, 2008; Yen *et al.*, 2008) reported a greater risk of CVD caused by betel chewing than smoking. In Yen *et al.* (2008)'s study, the relative risks (95% CI) of CVD for betel chewing and smoking were 1.24 (1.11–1.39) and 0.96 (0.89–1.04), respectively. Lin *et al.* (2008) calculated that betel nut chewers had a higher risk of CVD mortality (relative risk 2.10; $P<0.05$) than did smokers.

3.3 Chewing substances and risk of IHD

An increased risk of IHD (ICD-9, 410–414; ICD-10: I20–I25) was observed, with a summary relative risk of 1.27 (1.02–1.52) on the basis of six risk estimates (Table 2; test for publication bias P=0.60). However, the relative risk effect became insignificant after the removal of the cross-sectional study of Guh *et al*. (2007), resulting in a summary risk estimate of 1.26 (0.85–1.67). The inconsistency between main analysis and subsequent sensitivity analysis indicated that a significant effect reached by main analysis may be heavily influenced by one single study. Thus, the result should be interpreted with caution. Restricting the meta-analysis to cohort studies (three risk estimates) or studies in South Asia (three risk estimates) did not show a marked increased risk, though the trend was toward positive (Table 2). Studies carried out in Taiwan revealed an increased risk of 1.31 (1.08–1.53), but again the effect appeared non-significant after exclusion of the same cross-sectional study where "heart disease" was recalled by patients rather than being diagnosed in hospital or classified with specific criteria (Guh *et al*., 2007).

Of note, there were two case-control studies that investigated the incidences of "coronary heart disease" and "acute myocardial infarction" (one of them being a multi-center study), and both showed marked increase of risk in tobacco chewers in South Asia (Teo *et al*., 2006; Rahman and Zaman, 2008).

3.4 Chewing substances and risk of CBVD

Only three estimates (Gupta *et al*., 2005; Wen *et al*., 2005; Lan *et al*., 2007) were available for CBVD (ICD-9: 430–438; ICD-10: I60–I69; all in fatal form), resulting in an overall relative risk of 1.32 (1.08–1.56) (Table 2; test for publication bias P=0.76). No heterogeneity was observed. Given the limited number of studies, we did not perform further subgroup analysis.

4 Discussion

Our meta-analysis showed an increased risk of CVD among users of chewing substances with or without tobacco compared with non-users. Study data from Taiwan indicated significantly increased CVD risk in relation to betel chewing. When meta-analyses were confined to cohort studies or cohort studies in Taiwan, the positive effects remained significant. This was further confirmed by subsequent sensitivity analysis by removing the studies that either did not report an adequately adjusted risk estimate (Wen *et al*., 2005) or defined the outcome measurement less clearly (Guh *et al*., 2007). The magnitudes of the excess risks for CVD and CBVD were both small, but the results were produced on the basis of several studies with large numbers of participants. The consistency of results among studies, and their robustness for study design and quality also added to their credibility. The meta-analysis for IHD, however, showed inconsistency, when a sensitivity analysis was undertaken. Further grouping the meta-analysis by study design or geographical region did not show the evidence of excess risk for IHD.

Several explanations may be given for the discrepancy in results between CVD in total and subtypes of CVD, such as IHD. First of all, numbers of IHD cases included may be relatively small. For example, four out of six studies had included no more than 200 IHD cases or deaths in each (Wen *et al*., 2005; Lan *et al*., 2007; Guh *et al*., 2007; Rahman and Zaman, 2008). Small study population may be underpowered to detect a possible association. However, this was not the case in the Mumbai cohort study (Gupta *et al*., 2005), which documented a total of 1372 IHD deaths (631 men and 741 women), though an increased risk was found only in women. Gupta *et al*. (2005) reasoned that cause-specific death rates could be underestimated, since nearly a quarter of total deaths could not be matched. Of note, identification of IHD deaths in this cohort showed a wider range than those in the other studies (Table 1), which might be a source of inconsistent results among studies. Furthermore, it was also noted that misclassification for the cause of death may well be possible even within a high quality death registering system (Gupta *et al*., 2005). It is unclear, however, how misclassification of fatal IHD could generate a false negative result in cohort studies, since misclassification would most likely be non-discriminatory for the exposure status (Rothman and Greenland, 1998). In

any case, misclassification could have little influence on the identification of CVD in total. Since diseases of other systems were much less likely to be classified as circulatory diseases, while various diseases within the group of recognized CVD may be mistaken for each other.

Moreover, the meta-analysis for the risk of CVD in total was largely based on four cohort studies in Taiwan (Wen *et al*., 2005; Lan *et al*., 2007; Lin *et al*., 2008; Yen *et al*., 2008) where betel quid was chewed without tobacco (Wen *et al*., 2005). Meta-analysis based on Taiwan data showed increased risk of CVD for betel chewing, relative risk 1.30 (1.17–1.44) based on five risk estimates. When it was confined to cohort studies in Taiwan, the positive direction persisted, and was not swerved by exclusion of the very study in which risk estimate was not adjusted for cigarette smoking (Wen *et al*., 2005). In addition, two large cohorts in Taiwan (Lin *et al*., 2008; Yen *et al*., 2008) reported a greater risk of CVD from betel chewing than from smoking. The consistency between main analysis and sensitivity analysis, together with dose-response effect in several of these studies, attested to the evidence that betel chews free of tobacco can be harmful to cardiovascular system, though further classified subtypes of CVD were less studied for betel chewing. On the other hand, however, concerning chewing substances with tobacco, only one cohort study (Gupta *et al*., 2005) was available for the risk estimate of CVD in total, where increased relative risk was found only in women. In contrast, the two case-control studies including both sexes (Teo *et al*., 2006; Rahman and Zaman, 2008) have explored exclusively the relationship between coronary heart disease and use of chewing tobacco, which supported a positive link. Given these concerns, more investigations are needed to explore the risks for specific subgroups of CVD in relation to the use of betel chews with or without tobacco, but this would have to rely on specific and accurate classification of specific CVD forms and of specific CVD events.

The underlying mechanisms for the link between chewing substance and CVD may be multiple. Nicotine and arecoline, the predominant alkaloids that were found, respectively, in tobacco and betel quid (*Areca catechu*), are recognized for their short-term effects in causing increased heart rate and blood pressure (Benowitz and Gourlay, 1997; Boucher and Mannan, 2002). Recent studies both in India and Taiwan have found that tobacco chewers and betel chewers were more prone to have dyslipidemia and hypertension (Khurana *et al*., 2000; Chung *et al*., 2006; Gupta *et al*., 2007; Tseng, 2008), which are traditional risk factors of CVD. It may well raise the suspicion that some chemicals from these chewing substances may trigger specific biochemical reactions related to dyslipidemia and hypertension, which in turn lead to cardiovascular events. In addition, chewing itself may lead to susceptibility to periodontal diseases, which are potentially associated with cardiovascular malfunction (Ling *et al*., 2001; Janket *et al*., 2003). The detailed mechanism by which these processes are involved in the development of CVD remains unclear and merits further investigation.

Our findings extend the conclusion reached by a previous meta-analysis which indicated an association between smokeless tobacco and risk of CVD based on studies carried out in the United States and Sweden (Boffetta and Straif, 2009). To explore the associations of tobacco/betel chewing and CVD risks in Asia, we carried out a meta-analysis based on explicit criteria for inclusion of studies, extraction, and pooling of results. By summarizing the existing evidence quantitatively, we obtained a more precise risk estimate with a narrowed confidence interval, and thus increased the power to detect a link between use of betel quid and risk of CVD. The results included in the meta-analysis were adjusted for other known risk factors of CVD, such as hypertension, obesity, and education level.

Our study also has some limitations. First, it was unclear whether substance chewers would change their habit during follow-up in the cohort study. It might generate a false positive effect if chewers shifted to smoking. However, evidence supporting chewing tobacco or betel quid as a "gateway" to smoking was lacking in Asia. In fact, Taiwan data indicated that smoking appeared a "gateway" for betel quid chewing while smokers rarely started chewing first (Wen *et al*., 2005). Second, confounding by cigarette smoking might be a potential source of bias. Still this meta-analysis has very few studies suitable to use, and not all studies reported the relative risk confined to non-smokers. However, the numbers

of participants in most of these studies were large, and in three of the four studies (Guh *et al.*, 2007; Lan *et al.*, 2007; Yen *et al.*, 2008) where smokers were included, risk estimates were all reported after adjustment of smoking status. The other study (Wen *et al.*, 2005) was removed in the sensitivity analysis, without altering the findings. Third, we did not perform meta-analysis stratified by gender, given lack of data. Very few women in Taiwan use betel quid (Wen *et al.*, 2005; Lin *et al.*, 2008), and in fact, three large cohorts in Taiwan investigated male participants exclusively (Wen *et al.*, 2005; Lin *et al.*, 2008; Yen *et al.*, 2008). Furthermore, only one large cohort (Gupta *et al.*, 2005) and another two studies (Guh *et al.*, 2007; Rahman and Zaman, 2008) reported relative risk for females separately. However, the latter two included far less cases compared to other studies, making it meaningless to stratify the data by gender. Finally, in consideration of possible heterogeneity, we used a random effect model which may result in wider confidence intervals, and thus a more conservative estimate of effect.

In conclusion, a meta-analysis was carried out on studies of betel chewing in Asia, with and without tobacco, in relation to CVD risks. A direct association was detected, though the results on subgroups of CVD were less convincing. Furthermore, betel chewing may impose a greater CVD risk than smoking. More effort on developing betel chewing cessation programmes is urgently warranted. Further studies are needed to elucidate whether a similar effect is present for different subgroups of CVD and to clarify the mechanisms of the effect of chewing tobacco and betel quid on the occurrence of CVD.

5 Acknowledgements

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