

Betel quid use and mortality in Bangladesh: a cohort study

Fen Wu,^a Faruque Parvez,^b Tariqul Islam,^c Alauddin Ahmed,^c Muhammad Rakibuz-Zaman,^c Rabiul Hasan,^c Maria Argos,^d Diane Levy,^b Golam Sarwar,^c Habibul Ahsan^d & Yu Chen^a

Objective To evaluate the potential effects of betel quid chewing on mortality. (A quid consists of betel nut, wrapped in betel leaves; tobacco is added to the quid by some users).

Methods Prospective data were available on 20033 individuals aged 18–75 years, living in Araihaazar, Bangladesh. Demographic and exposure data were collected at baseline using a standardized questionnaire. Cause of death was defined by verbal autopsy questionnaires administered to next of kin. We estimated hazard ratios (HR) and their 95% confidence intervals (CI) for associations between betel use and mortality from all causes and from specific causes, using Cox proportional hazards models. We adjusted for age, sex, body mass index, educational attainment and tobacco smoking history.

Findings There were 1072 deaths during an average of 10 years of follow-up. Participants who had ever used betel were significantly more likely to die from all causes (HR: 1.26; 95% CI: 1.09–1.44) and cancer (HR: 1.55; 95% CI: 1.09–2.22); but not cardiovascular disease (HR: 1.16; 95% CI: 0.93–1.43). These findings were robust to adjustment for potential confounders. There was a dose–response relationship between mortality from all causes and both the duration and the intensity of betel use. The population attributable fraction for betel use was 14.1% for deaths from all causes and 24.2% for cancer.

Conclusion Betel quid use was associated with mortality from all causes and from cancer in this cohort.

Abstracts in **عربي**, **中文**, **Français**, **Русский** and **Español** at the end of each article.

Introduction

Areca catechu nut (betel nut) is the fourth most commonly used addictive substance in the world, after caffeine, nicotine and alcohol.¹ Betel nut is consumed by chewing, either alone or in the form of a quid wrapped in betel leaves, slaked lime (calcium hydroxide) and different flavourings. Tobacco is added to the quid by some users. It is estimated that 600 million people worldwide chew betel regularly.^{1,2} Betel is widely used throughout central, south and south-east Asia, as well as in some South Pacific islands. With the growing number of immigrants from those areas, betel use is increasing in Africa, Australia, Europe and north America,¹ where betel use remains an under-recognized public health issue.

The International Agency for Research on Cancer has concluded that betel without tobacco causes oral cancer, while betel with tobacco causes upper aerodigestive tract cancers, including cancer of the oral cavity, pharynx and oesophagus.² Betel use has also been linked to metabolic syndrome,^{3,4} hypertension,^{5,6} diabetes mellitus,^{7,8} and obesity^{9,10} – diseases that are closely related to the development of cardiovascular disease (CVD). Recent evidence also suggests that betel use may play a role in CVD.^{11–13} Given that betel use has been related to an array of health outcomes, it is important to assess its impact on mortality.

Betel use has been a popular traditional habit in Bangladesh. According to a 2009 survey targeting all men and women aged 15 years or more in Bangladesh, betel was used by both men (23.5%) and women (25.2%).¹⁴ A study of the health effects of arsenic has recruited over 20 000 participants since the year 2000.¹⁵ This population-based cohort has also been used to assess other health issues.^{16,17} Here, we examine

the association of betel use with mortality from all causes and from specific causes in this cohort.

Methods

Study population

A population-based survey was used to enumerate the sampling frame and characterize residents of a 25 km² area in Araihaazar, Bangladesh. Between October 2000 and May 2002, we recruited 11 746 participants who met the following eligibility criteria: married (to reduce loss to follow-up); aged 18–75 years; user of a tube well as a primary water supply and living in the study area for at least five years before recruitment.¹⁵ During 2006–2008, the cohort was expanded to include an additional 8287 participants (the expansion cohort) in the same study area following the same methods.^{18–21} The overall participation rate was 97%.

The cohort has been followed up with in-person home visits at 2-year intervals.²² Participants who were not at home during the first visit were revisited and excluded if they were not reachable during any of the three attempted visits. A field clinic was established exclusively for the participants and their family members to passively follow-up the participants between their biennial visits.¹⁵ Since this rural population lacks basic health-care services from the existing health-care facilities, all participants and their family members come to the clinic for all health-care needs. Informed consent was obtained from the study participants and study procedures were approved by the Ethical Committee of the Bangladesh Medical Research Council and the Institutional Review Boards of

^a Department of Population Health, New York University School of Medicine, 650 First Avenue, New York, NY 10016, United States of America (USA).

^b Department of Environmental Health Sciences, Columbia University, New York, USA.

^c U-Chicago Research Bangladesh Ltd., Dhaka, Bangladesh.

^d Department of Health Studies, University of Chicago, Chicago, USA.

Correspondence to Yu Chen (email: yu.chen@nyumc.org).

(Submitted: 27 October 2014 – Revised version received: 24 May 2015 – Accepted: 29 May 2015 – Published online: 25 June 2015)

Columbia University and the University of Chicago.

Questionnaire data

Social and demographic data were collected at baseline using a standardized questionnaire. Physicians measured height, weight and blood pressure with standard equipment.^{23–25} We asked participants if they had been diagnosed with diabetes and compared their answers with results from glycosylated haemoglobin and glucosuria tests.²⁶ Questions on tobacco smoking included cigarettes and bidis (filterless, locally-produced cigarettes), smoked alone or together, past and current use and duration of tobacco smoking. To estimate the intensity of tobacco smoking, we calculated pack-years (the product of cigarettes or bidis smoked per day and years of smoking, divided by 20). Details of betel use were collected for both the original and expansion cohort, including information on past and current use, the number of times per day betel was used and years of betel use. Information on whether betel was chewed with smokeless tobacco was collected in the expansion cohort only. We did not collect information on the amount of smokeless tobacco that was used with betel. We also estimated the intensity of betel use (quid-years) as the product of times used per day and years of use.

Assessment of mortality

The vital status of the participants was assessed at each follow-up home visit. Details of the assessment of causes of death are described elsewhere.^{22,23,27} Briefly, we adapted a validated verbal autopsy procedure that was developed by the International Centre for Diarrhoea Disease Research, Bangladesh (ICDDR, B), in collaboration with the World Health Organization (WHO). The method has been used to ascertain causes of death since 1971²⁸ and has documented an overall 95% specificity, with an 85% sensitivity for deaths from cancer or CVD.²⁹ During follow-up, upon receipt of a death reported by family or neighbours, a study physician and a trained social worker administered the verbal autopsy questionnaire to the next of kin. Medical records and death certificates were collected and reviewed monthly by an outcome-assessment committee, consisting of physicians and consulting medical specialists. Causes of death were coded according to the

Table 1. **Underlying causes of death in the prospective study on betel use and mortality, Bangladesh, 2000–2014**

Cause of death (ICD–10 code)	No.
All causes	1072
Infectious and parasitic diseases (A00–B99)	66
Tuberculosis (A15–A19)	32
Other bacterial diseases (A35, A40, A41)	9
Viral hepatitis (B16, B18, B19)	5
Sequelae of infectious and parasitic diseases (B90)	13
Other (A08, A09, A82, A91, B01)	7
Cancer (C00–C97)	167
Lip, oral cavity and pharynx (C02, C03, C09, C10, C13)	7
Digestive organs (C15–C26)	64
Stomach (C16)	17
Liver (C22)	32
Gallbladder (C23)	8
Other (C15, C18–C21)	7
Respiratory and intrathoracic organs (C30–C39)	53
Lung (C34)	46
Larynx (C32)	7
Female genital organs (C53, C55, C56)	9
Urinary tract (C64, C66, C67)	11
Ill-defined, secondary and unspecified sites (C76–C79)	5
Lymphoid, haematopoietic and related tissue (C85, C91, C92)	7
Other (C43, C49, C50, C61, C69, C71, C73)	11
Diabetes mellitus (E10, E11, E14)	10
Diseases of the nervous system (G00–G99)	12
Inflammatory diseases of the central nervous system (G00, G02, G04, G06)	6
Other (G20, G41, G45, G61, G91, G95)	6
Cardiovascular diseases (I00–I99)	439
Chronic rheumatic heart diseases (I05, I06, I08)	12
Ischaemic heart diseases (I21, I24, I25)	181
Other forms of heart disease (I35, I42, I46, I47, I50)	51
Stroke (I60–I64, I69)	183
Other (I11, I27, I73)	12
Diseases of the respiratory system (J00–J99)	144
Other chronic obstructive pulmonary disease (J44)	106
Asthma (J45)	17
Status asthmaticus (J46)	10
Other (J22, J41, J69, J90, J95)	11
Diseases of the digestive system (K00–K93)	54
Oesophagus, stomach and duodenum (K22, K25, K27, K29, K31)	7
Liver (K70–K72, K74, K76)	39
Other (K56, K63, K65, K80, K92)	8
Diseases of the genitourinary system (N00–N99)	26
Renal failure (N17, N18)	21
Other (N05, N13, N83, N93)	5
Pregnancy, childbirth and the puerperium (O00–O99)	15
Eclampsia (O15)	5
Complications of labour and delivery (O64, O71, O72, O75)	8
Other (O07, O95)	2
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified (R00–R99)	72
General symptoms and signs (R50, R54, R57)	6
Ill-defined and unknown causes of mortality (R96, R99)	62
Other (R10, R14, R90)	4

(continues. . .)

(. . .continued)

Cause of death (ICD-10 code)	No.
External causes of morbidity and mortality (V01–Y98)	41
Pedestrian injured in transport accident (V02–V04)	10
Intentional self-harm (X68, X70)	7
Assault (X90, X91, Y05, Y09)	5
Other (V33, V34, V80, V89, W14, W30, W70, W74, W86, W87, Y21, Y83)	19
All other causes (D32, D37, D38, D43, D61, D64, D75, E64, E87, F20, L89, M51, M80, S06, T61, T82)	26

International Classification of Diseases, 10th Revision (ICD-10).³⁰

Statistical analyses

We computed person-years of follow-up from baseline to the date of death (for those who died) or to 21 April 2014. We estimated hazard ratios (HR) and 95% confidence intervals (CIs) for deaths from all causes, cancers and CVD using Cox proportional hazards models. History of betel use was classified as follows: never versus ever users; daily frequency (never, ≤ 3 times, 3–5 times and > 5 times); duration (never, ≤ 4 years, 4–12 years and > 12 years) and intensity (never, ≤ 12 quid-years, 13–60 quid-years and > 60 quid-years). We also estimated HRs for coronary heart disease, stroke and for cancer of the digestive or respiratory organs (these are the largest two categories of cancer deaths in the cohort).

We excluded 34 participants with missing data on betel use. Missing data on any of the covariates (8–281) were coded with dummy variables, allowing participants with missing data to be included in the analyses under a missing-at-random assumption. We first adjusted for sex and baseline age (model 1), we then adjusted for baseline body mass index (BMI; kg/m²), educational attainment (years) and smoking status (never, past and current), (model 2). The final model (model 3) was the same as model 2, except that we used intensity of tobacco smoking (pack-years) as the variable controlling for effects of tobacco.

Sensitivity analyses were conducted separately for mortality from all causes, cancers and CVD. We tested exclusion of deaths that occurred within two years of the baseline, under the assumption that individuals who are seriously ill at baseline are more likely to die in the first two years of follow-up. We conducted stratified analyses by sex, age, BMI, smoking status (never/

ever) and educational attainment, adjusted for the same covariates as in model 2. In these models, we included interaction terms between betel (never versus ever user) and the dichotomous strata variables.

In the expansion cohort ($n = 8287$), we assessed whether mortality from all causes differed depending on whether chewing tobacco was included in the betel quids used. Finally, we tested inclusion of additional variables for arsenic exposure, systolic blood pressure and diabetes status in the models. We calculated the population attributable fraction (PAF) of mortality from all causes and from cancer associated with use of betel (ever users versus never users) using the following equation¹⁷:

$$PAF = P_i \frac{HR_i - 1}{HR_i}$$

where P_i is the proportion of mortality within the exposure category i and HR_i is the adjusted HR of the i th category relative to the unexposed category. All analyses were done using SAS, version 9.3 (SAS Institute Inc., Cary, United States of America).

Results

Baseline characteristics

We observed 202 874 person-years during an average of 10 years of follow-up. There were 1072 deaths, of which 167 were from cancers and 439 were from CVD, together accounting for 56.5% of deaths. Among the deaths from CVD, 181 were from coronary heart disease and 183 were from stroke. Detailed causes of death and ICD-10 codes are shown in Table 1. Diabetes status as ascertained by questionnaire appeared valid, based on comparison with glycosylated haemoglobin and glucosuria

tests. The prevalence of diabetes at baseline in this lean population was under 2%.²⁶

The prevalence of past and current use of betel was 2.3% (465/19 999) and 32.7% (6535/19 999), respectively, in the overall study population. Given that the number of past users of betel was small, past and current users were combined as ever users in the analyses. While past and current use was significantly more frequent among men, women reported more frequent and intense use than men. Distributions of baseline variables by status of betel use are shown in Table 2. Past users were more likely to be men whereas more women were current users. Both past and current users tended to be older, less educated, past or current tobacco smokers and were more likely to have high BMI, high blood pressure or diabetes.

Betel use and mortality

Betel use was positively associated with all-cause and cancer-related mortality, after adjusting for age and sex (model 1). The associations did not change substantially when potential confounders (BMI, smoking status and educational attainment) were added to the model (model 2) or after adjusting for intensity of tobacco smoking (model 3, Table 3). Associations were significant for all causes of death (HR: 1.26; 95% CI: 1.09–1.44) and for cancer (HR: 1.55; 95% CI: 1.09–2.22); but not for CVD (HR: 1.16; 95% CI: 0.93–1.43).

The results were not appreciably altered by inclusion of arsenic exposure, systolic blood pressure or diabetes status in the models, or by exclusion of deaths reported in the first 2 years of follow-up (Table 3). The population attributable fraction for betel use was 14.1% for deaths from all causes and 24.2% for cancer-related deaths.

We observed a dose–response relationship between mortality from all causes and duration of betel use. Among participants who had used betel for less than 4 years, for 4–12 years and for more than 12 years, the HRs were 1.16 (95% CI: 0.96–1.40), 1.24 (95% CI: 1.03–1.49) and 1.37 (95% CI: 1.15–1.62) respectively (Table 3). Results for intensity of use were similar, though the central estimates of risk did not increase monotonically with intensity of use. A dose–response relationship was not evident for mortality from cancers or CVD (Table 3).

Betel use was associated with mortality from cancer of the digestive organs after adjustment for age and sex (HR: 1.92; 95% CI: 1.09–3.36). However, this association was attenuated and no longer significant after further adjusting for BMI, smoking status and educational attainment (HR: 1.70; 95% CI: 0.96–2.99). The risk of death from respiratory cancers was also increased among ever users, but not significantly (HR: 1.75; 95% CI: 0.96–3.18). There were no significant associations between betel use and the risk of death from coronary heart disease or stroke (data available from the corresponding author).

Subgroup analyses

The association between betel use and mortality from all causes was stronger in younger individuals as well as in individuals with a higher BMI; however, these interactions did not reach statistical significance (P for interaction = 0.06 and 0.09, respectively). Associations between betel use and mortality from all causes and from cancer did not differ substantially by sex or by smoking status. For instance, the HR for mortality from all causes was 1.24 (95% CI: 0.97–1.58) among never smokers and 1.19 (95% CI: 1.01–1.40) among ever smokers. Similarly, the HR for cancer mortality was 1.47 (95% CI: 0.78–2.76) among never smokers and 1.38 (95% CI: 0.92–2.07) among ever smokers.

In the expansion cohort, we had information on whether or not betel was chewed with tobacco. Among 2541 ever users, 2042 (80.4%) chewed betel with tobacco, while 499 (19.6%) chewed betel without tobacco. The association between betel use and mortality from all causes persisted and was marginally significant among individuals who chewed betel without tobacco (HR: 1.55; 95% CI: 0.99–2.44). Surprisingly, there was no significant association between betel use and mortality among those who chewed betel with tobacco (HR: 0.93; 95% CI: 0.65–1.32). There was a similar proportion of tobacco smokers among people who used betel alone and those who also used chewing tobacco (40.4% and 41.3%, respectively).

For mortality from CVD, there was a significant interaction between betel use and age ($P=0.01$) and between betel use and BMI ($P=0.02$), such that the risk was higher among younger individuals (HR: 1.88; 95% CI: 1.27–2.80) and those with a higher BMI (HR: 1.44; 95% CI:

Table 2. Characteristics of participants, Bangladesh, 2000–2014

Characteristic	No. (%)		
	Betel use		
	Never ($n=12\ 999$)	Past ($n=465$)	Current ($n=6\ 535$)
Sex			
Men	5 010 (38.5)	288 (61.9)	2 850 (43.6)
Women	7 989 (61.5)	177 (38.1)	3 685 (56.4)
Age, years			
18–29	5 199 (40.0)	25 (5.4)	426 (6.5)
30–39	4 590 (35.3)	106 (22.8)	1 754 (26.8)
40–49	2 260 (17.4)	138 (29.6)	2 529 (38.7)
≥ 50	950 (7.3)	196 (42.2)	1 826 (27.9)
BMI, kg/m²			
< 18.5	4 832 (37.6)	199 (43.5)	2 750 (42.8)
18.5–24.9	7 047 (54.9)	224 (49.0)	3 266 (50.8)
> 24.9	958 (7.5)	34 (7.4)	410 (6.4)
Education, years			
None	4 837 (37.2)	230 (49.5)	3 647 (55.8)
1–5	4 114 (31.7)	136 (29.2)	1 849 (28.3)
6–9	2 346 (18.1)	59 (12.7)	611 (9.4)
≥ 10	1 694 (13.0)	40 (8.6)	425 (6.5)
Cigarette/bidi use			
Never	9 793 (75.4)	179 (38.5)	3 519 (53.9)
Past	273 (2.1)	75 (16.1)	906 (13.9)
Current	2 929 (22.5)	211 (45.4)	2 109 (32.3)
SBP, mm/Hg			
< 140	11 938 (92.9)	388 (84.5)	5 727 (89.0)
≥ 140	907 (7.1)	71 (15.5)	711 (11.0)
DBP, mm/Hg			
< 90	11 707 (91.2)	402 (87.8)	5 787 (89.9)
≥ 90	1 133 (8.8)	56 (12.2)	649 (10.1)
Diabetes			
Yes	178 (1.4)	21 (4.7)	144 (2.2)
No	12 619 (98.6)	428 (95.3)	6 290 (97.8)

BMI: body mass index; DBP: diastolic blood pressure; SBP: systolic blood pressure.

Note: Data were missing on betel use for 34 subjects; on BMI for 281 subjects; on education for 11 subjects; on cigarette/bidi smoking for 8 subjects; on systolic blood pressure for 260 subjects; on diastolic blood pressure for 268 subjects; and on diabetes status for 321 subjects.

1.08–1.91) relative to older individuals or those with a lower BMI (Fig. 1).

Discussion

Betel use was significantly associated with all-cause and cancer-related mortality in this south Asian cohort. Two studies in India reported mixed results for chewing of betel quid or betel nut (without tobacco added).^{31,32} One study³¹ reported no significant effect of chewing betel quid, while the other reported increased all-cause mortality with age-adjusted relative risks of 1.19 among women and 1.11 among men,³² but confidence intervals were not reported. In China, a study reported increased all-

cause mortality associated with betel nut chewing and smoking.³³ Betel use was associated with all-cause mortality in two other studies, with relative risks of 1.19 and 1.40, respectively.^{12,13} Mortality increased with higher frequency of betel use,¹³ longer duration of use¹² or greater intensity of use (quid-years).¹² Increased risk was predominantly seen in users who had chewed betel for 25 years or for 350 quid-years or longer.¹²

We report increased mortality with longer duration and intensity of use, but not with higher frequency of use. In our cohort, the median duration and intensity of betel use were seven years and 30 quid-years, respectively. It is possible that the dose–response relationship is

Table 3. Betel use and mortality, Bangladesh, 2000–2014

Variable	Person-years		All causes		Cancers		CVD	
	No.	HR (95% CI)	No.	HR (95% CI)	No.	HR (95% CI)	No.	HR (95% CI)
Betel use								
Never	130 808	1.00	422	1.00	62	1.00	174	1.00
Ever	71 669	1.26 (1.09–1.44)	646	1.26 (1.09–1.44)	105	1.55 (1.09–2.22)	265	1.16 (0.93–1.43)
Excluding deaths in 1–2 years of follow-up	71 572	1.30 (1.12–1.51)	560	1.30 (1.12–1.51)	89	1.59 (1.08–2.33)	236	1.18 (0.94–1.48)
Frequency of use								
Never	130 808	1.00	422	1.00	62	1.00	174	1.00
≤ 3 times/day	29 990	1.38 (1.17–1.63)	292	1.38 (1.17–1.63)	48	1.67 (1.10–2.53)	129	1.40 (1.09–1.80)
3–5 times/day	19 645	1.17 (0.96–1.43)	156	1.17 (0.96–1.43)	27	1.53 (0.94–2.50)	63	1.06 (0.77–1.45)
> 5 times/day	21 787	1.16 (0.96–1.40)	196	1.16 (0.96–1.40)	30	1.42 (0.89–2.29)	72	0.92 (0.68–1.25)
Duration of use								
Never	130 808	1.00	422	1.00	62	1.00	174	1.00
≤ 4 years	28 130	1.16 (0.96–1.40)	177	1.16 (0.96–1.40)	35	1.73 (1.11–2.70)	67	1.05 (0.77–1.43)
4–12 years	22 311	1.24 (1.03–1.49)	186	1.24 (1.03–1.49)	32	1.59 (1.00–2.52)	75	1.16 (0.87–1.55)
> 12 years	20 708	1.37 (1.15–1.62)	278	1.37 (1.15–1.62)	38	1.38 (0.87–2.19)	120	1.22 (0.93–1.58)
Intensity of use								
Never	130 808	1.00	422	1.00	62	1.00	174	1.00
≤ 12 quid-years	24 617	1.24 (1.02–1.51)	158	1.24 (1.02–1.51)	28	1.64 (1.02–2.64)	62	1.21 (0.88–1.65)
13–60 quid-years	26 077	1.19 (0.99–1.41)	237	1.19 (0.99–1.41)	44	1.51 (1.05–2.49)	97	1.10 (0.83–1.44)
> 60 quid-years	20 442	1.35 (1.13–1.62)	246	1.35 (1.13–1.62)	33	1.44 (0.90–2.29)	103	1.17 (0.89–1.54)

CI: confidence interval; CVD: cardiovascular disease; HR: hazard ratio.

Note: Cox proportional hazards models, adjusting for sex, baseline age, educational attainment, body mass index and pack-years of tobacco smoking.

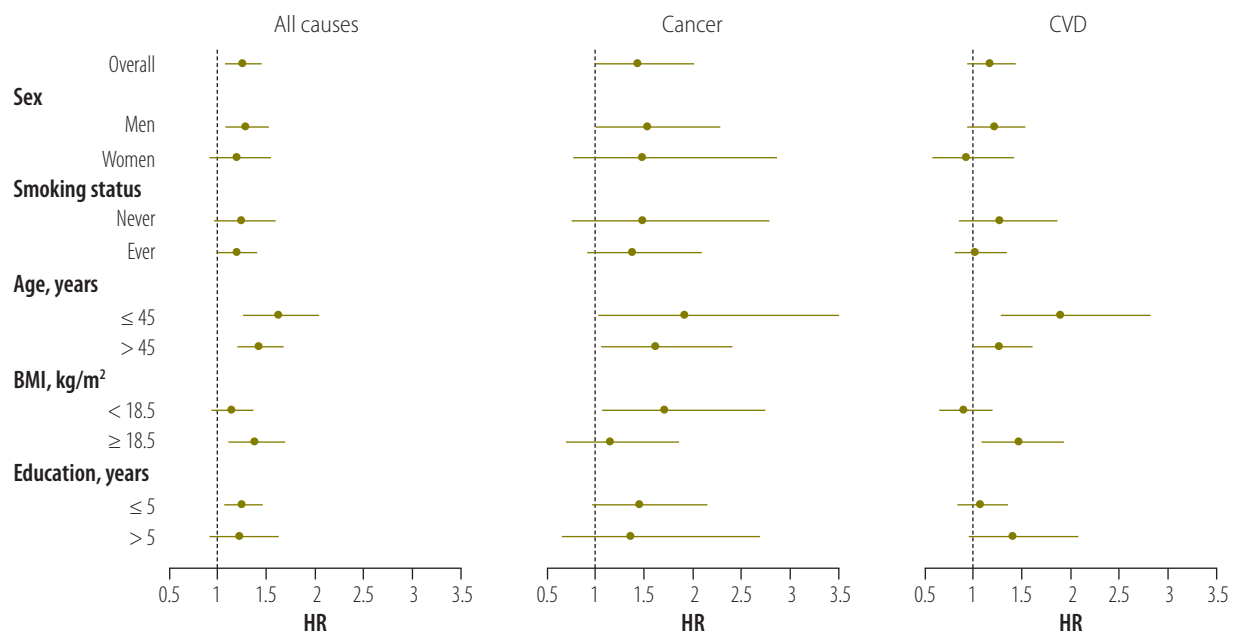
not apparent at lower intensity of use, or that this cohort has too limited a range of exposure to detect a dose–response relationship. In China, it was reported that betel was mostly used by men and rarely by women and almost all users were smokers,³³ in contrast to our study population in which men and women had a similar prevalence of betel use and less than half of betel users were also smokers.

Several previous studies investigated the effects of betel use on the risk of death from all cancers or cancer of the oral cavity and other upper-digestive organs. There was increased mortality from cancer of the oral cavity, nasopharynx, liver and lung associated with betel nut chewing and smoking in China.³³ In another study, betel use without chewing tobacco was associated with a significant increase in deaths from all cancers and cancer of the oesophagus, liver, pancreas, larynx and lung but despite the fact that 90% of the betel users were also smokers, the authors did not control for smoking status.³⁴ Another cohort study in an elderly population found no association between betel use and cancer-related mortality.¹²

In our study, we controlled for smoking and found a significantly higher risk of cancer-related mortality in participants who had ever used betel. The effect estimates did not differ substantially by smoking status. Only seven deaths in the cohort were reportedly due to cancer of the oral cavity and other upper digestive organs and analyses excluding these cases did not change the effect estimates. The associations with cancer were similar in men and women, although not significant in women. Taken together, our data add to the growing body of evidence of the influence of betel use on cancer and suggest that the effect may be independent of tobacco smoking.

Several prospective studies have suggested an overall positive association between betel use and CVD risk,^{11–13} although some other studies found no association when CVD subtypes were considered.^{12,33} In a prospective cohort of 6511 men older than 50 years, users of betel nut were at a higher risk of mortality from overall CVD and stroke but not coronary heart disease.¹² In a cohort of 56 116 men, betel nut chewing was independently associated with a greater risk of CVD mortality.¹³ Similarly, in a

Fig. 1. Betel use and mortality, Bangladesh, 2000–2014



BMI: body mass index, CVD: cardiovascular disease; HR: hazard ratio.

Note: Cox proportional hazards models were adjusted for baseline age, sex, body mass index, smoking status (never, past and current) and educational attainment. For the stratified models, we included an interaction term between betel use and the dichotomous strata variable.

prospective registry-based cohort study of 21 906 men followed for 2.7 years, an independent dose–response effect of betel use on risk of incident CVD cases and deaths was observed.¹¹ Although we found no significant association between betel use and CVD mortality overall, CVD mortality was significantly increased among younger people and those with a higher BMI. In our previous analyses of betel use and blood pressure in the same cohort, we found that betel use without tobacco was associated with higher blood pressure.⁵

Betel contains four arecal alkaloids (primarily arecoline, along with arecaine, guvacine and guvacoline), all of which have been shown to produce nitrosamine derivatives that have potential carcinogenic effects.² Betel components can induce both local and systemic release of inflammatory biomarkers^{35–37} thereby provoking oxidative stress³⁸ and chronic inflammation related to the development of systemic diseases. Betel chewing also causes periodontal disease,^{39,40} a risk factor for cancer and CVD.^{41,42}

Our study represents a large population from south Asia that has received

little epidemiologic attention. Other strengths of the present study include the population-based prospective study design with a high response rate (97%) and the extensive data on betel use and potential confounders, including smoking status and the intensity of smoking.

Several potential limitations, however, should also be noted. First, this cohort was not established to focus on betel use and thus is lacking information on changes in use over time. Also the population was relatively young, with a mean age of 36 years at baseline and the overall average duration of use was relatively short. The relatively small number of cases for subtypes of cancer or CVD may explain the insignificant effect estimates on these outcomes.

Second, we did not have comprehensive data on chewing tobacco use, either alone or with betel. Research on the effects of chewing tobacco (in the absence of betel nut) on mortality has been inconclusive.^{43,44} In one study, no association was observed between chewing betel either with or without tobacco and mortality.³¹ In our cohort, the positive association for all-cause mortality remained among individuals who did

not use smokeless tobacco together with betel, but no significant association was observed among those who chewed betel with tobacco. However, a limited number of subjects had data on whether chewing tobacco was used together with betel and larger studies are needed. Lastly, we cannot rule out the possibility of residual confounding by tobacco smoking in our findings.

Our data suggest that betel has a small-to-moderate impact on mortality from all causes and from cancer in this Bangladeshi population. Future larger studies are warranted to investigate the effects of betel use on subtypes of cancer and CVD. ■

Acknowledgements

Habibul Ahsan and Yu Chen contributed equally to this work.

Funding: Supported by New York University (14-A0-00-002282) and the National Institutes of Health (R01 ES017541, P30 ES000260 and R01 CA107431).

Competing interests: None declared.

Резюме

Употребление бетелевой жвачки и смертность в Бангладеш: когортное исследование

Цель Оценить потенциальное воздействие жевания бетеля на смертность. Бетелевая жвачка состоит из ядра семени пальмы арека, завернутого в листья бетеля. Также к нему может добавляться табак.

Методы Были изучены проспективные данные 20 033 лиц в возрасте от 18 до 75 лет, проживающих в г. Араихазар, Бангладеш. Базовые демографические данные и сведения об употреблении бетеля были получены из стандартизированной анкеты. Причина смерти определялась с помощью анкетирования, основанного на вербальной аутопсии, вопросы из которого предьявлялись ближайшим родственникам покойного. Нами были оценены относительные риски (ОР) и их доверительные интервалы (ДИ) в 95%. Это позволило выявить взаимосвязь между жеванием бетеля и смертностью по любым причинам и по конкретным причинам. Для оценки использовалась пропорциональная модель рисков Кокса. Результаты были откорректированы с учетом возраста, пола, индекса массы тела (ИМТ), уровня образования и наличия

табакокурения в анамнезе.

Результаты На протяжении 10 лет наблюдения умерли 1072 участника исследования. Участники, жевавшие бетель или хотя бы пробовавшие его, имели значительно более высокую вероятность умереть по какой-либо причине (ОР: 1,26; 95% ДИ: 1,09–1,44), в том числе от рака (ОР: 1,55; 95% ДИ: 1,09–2,22), но не от сердечно-сосудистых заболеваний (ОР: 1,16; 95% ДИ: 0,93–1,43). Эти выводы оказались устойчивыми к корректировке по всем потенциальным искажающим факторам. Между смертностью по какой-либо причине и длительностью, а также интенсивностью употребления бетеля наблюдалась зависимость «доза-эффект». Доля представителей населения, употребляющих бетель, составила 14,1% для смертей по всех остальных причинам и 24,2% для смертей от рака.

Вывод В данном когортном исследовании употребление бетелевой жвачки ассоциируется со смертностью от рака и по всем остальным причинам.

Resumen

El uso de mascada de betel y la mortalidad en Bangladesh: un estudio de cohortes

Objetivo Evaluar los posibles efectos de mascar mascada de betel en la mortalidad. (Una mascada consiste de una nuez de betel envuelta en hojas de betel; algunos usuarios le añaden tabaco).

Métodos Se disponía de datos prospectivos de 20.033 individuos de entre 18 y 75 años que habitaban en Araihasar, Bangladesh. Se recogieron datos demográficos y de exposiciones al inicio del estudio mediante un cuestionario normalizado. Se definió la causa de mortalidad a través de cuestionarios de autopsia verbales administrados a los familiares. Se estimó el cociente de riesgos y su intervalo de confianza (IC) del 95% para asociaciones entre el uso de betel y la mortalidad por todas las causas, y las causas específicas mediante el uso de modelos de Cox de riesgos proporcionales. Se ajustó en cuanto a edad, sexo, peso medio, nivel educativo e historial de consumo de tabaco.

Resultados Hubo 1.072 muertes en un periodo medio de seguimiento de 10 años. Los participantes que nunca habían utilizado betel tenían más posibilidades de morir por todas las causas (cociente de riesgos: 1,26; IC del 95%: 1,09–1,44) y cáncer (cociente de riesgos: 1,55; IC del 95%: 1,09–2,22); pero no enfermedades cardiovasculares (cociente de riesgos: 1,16; IC del 95%: 0,93–1,43). Estos resultados fueron sólidos para un ajuste de los factores potenciales de confusión. Hubo una relación de respuesta a la dosis entre la mortalidad de todas las causas y la duración e intensidad del uso de betel. La fracción atribuible de la población por el uso de betel fue del 14,1% de las muertes por todas las causas y del 24,2% por cáncer.

Conclusión El uso de mascada de betel estaba asociado a la mortalidad por todas las causas y por cáncer en este cohorte.

References

- Gupta PC, Warnakulasuriya S. Global epidemiology of areca nut usage. *Addict Biol.* 2002 Jan;7(1):77–83. doi: <http://dx.doi.org/10.1080/13556210020091437> PMID: 11900626
- IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Betel-quid and areca-nut chewing and some areca-nut derived nitrosamines. *IARC Monogr Eval Carcinog Risks Hum.* 2004;85:1–334. PMID: 15635762
- Guh JY, Chuang LY, Chen HC. Betel-quid use is associated with the risk of the metabolic syndrome in adults. *Am J Clin Nutr.* 2006 Jun;83(6):1313–20. PMID: 16762942
- Yen AM, Chiu YH, Chen LS, Wu HM, Huang CC, Boucher BJ, et al. A population-based study of the association between betel-quid chewing and the metabolic syndrome in men. *Am J Clin Nutr.* 2006 May;83(5):1153–60. PMID: 16685060
- Heck JE, Marcotte EL, Argos M, Parvez F, Ahmed A, Islam T, et al. Betel quid chewing in rural Bangladesh: prevalence, predictors and relationship to blood pressure. *Int J Epidemiol.* 2012 Apr;41(2):462–71. doi: <http://dx.doi.org/10.1093/ije/dyr191> PMID: 22253307
- Tseng CH. Betel nut chewing is associated with hypertension in Taiwanese type 2 diabetic patients. *Hypertens Res.* 2008 Mar;31(3):417–23. doi: <http://dx.doi.org/10.1291/hypres.31.417> PMID: 18497460
- Tseng CH. Betel nut chewing and incidence of newly diagnosed type 2 diabetes mellitus in Taiwan. *BMC Res Notes.* 2010;3(1):228. doi: <http://dx.doi.org/10.1186/1756-0500-3-228> PMID: 20716326
- Tung TH, Chiu YH, Chen LS, Wu HM, Boucher BJ, Chen TH; Keelung Community-based Integrated Screening programme No. 2. A population-based study of the association between areca nut chewing and type 2 diabetes mellitus in men (Keelung Community-based Integrated Screening programme No. 2). *Diabetologia.* 2004 Oct;47(10):1776–81. doi: <http://dx.doi.org/10.1007/s00125-004-1532-2> PMID: 15517150
- Lin WY, Pi-Sunyer FX, Liu CS, Li TC, Li CL, Huang CY, et al. Betel nut chewing is strongly associated with general and central obesity in Chinese male middle-aged adults. *Obesity (Silver Spring).* 2009 Jun;17(6):1247–54. PMID: 19247275
- Chang WC, Hsiao CF, Chang HY, Lan TY, Hsiung CA, Shih YT, et al. Betel nut chewing and other risk factors associated with obesity among Taiwanese male adults. *Int J Obes.* 2006 Feb;30(2):359–63. doi: <http://dx.doi.org/10.1038/sj.ijo.0803053> PMID: 16116491
- Yen AM, Chen LS, Chiu YH, Boucher BJ, Chen TH. A prospective community-population-registry based cohort study of the association between betel-quid chewing and cardiovascular disease in men in Taiwan (KCIS no. 19). *Am J Clin Nutr.* 2008 Jan;87(1):70–8. PMID: 18175739
- Lan TY, Chang WC, Tsai YJ, Chuang YL, Lin HS, Tai TY. Areca nut chewing and mortality in an elderly cohort study. *Am J Epidemiol.* 2007 Mar 15;165(6):677–83. doi: <http://dx.doi.org/10.1093/aje/kwk056> PMID: 17204513

13. Lin WY, Chiu TY, Lee LT, Lin CC, Huang CY, Huang KC. Betel nut chewing is associated with increased risk of cardiovascular disease and all-cause mortality in Taiwanese men. *Am J Clin Nutr*. 2008 May;87(5):1204–11. PMID: 18469240
14. Global adult tobacco survey Bangladesh report. Geneva: World Health Organization; 2009. Available from: http://www.who.int/tobacco/surveillance/global_adult_tobacco_survey_bangladesh_report_2009.pdf [cited 2009 Dec].
15. Ahsan H, Chen Y, Parvez F, Argos M, Hussain AI, Momotaj H, et al. Health Effects of Arsenic Longitudinal Study (HEALS): description of a multidisciplinary epidemiologic investigation. *J Expo Sci Environ Epidemiol*. 2006 Mar;16(2):191–205. doi: <http://dx.doi.org/10.1038/sj.jea.7500449> PMID: 16160703
16. Chen Y, McClintock TR, Segers S, Parvez F, Islam T, Ahmed A, et al. Prospective investigation of major dietary patterns and risk of cardiovascular mortality in Bangladesh. *Int J Cardiol*. 2013 Aug 20;167(4):1495–501. doi: <http://dx.doi.org/10.1016/j.ijcard.2012.04.041> PMID: 22560940
17. Wu F, Chen Y, Parvez F, Segers S, Argos M, Islam T, et al. A prospective study of tobacco smoking and mortality in Bangladesh. *PLoS ONE*. 2013;8(3):e58516. doi: <http://dx.doi.org/10.1371/journal.pone.0058516> PMID: 23505526
18. Wu F, Jasmine F, Kibriya MG, Liu M, Cheng X, Parvez F, et al. Interaction between Arsenic Exposure from Drinking Water and Genetic Polymorphisms on Cardiovascular Disease in Bangladesh: A Prospective Case-Cohort Study. *Environ Health Perspect*. 2015 May;123(5):451–7. PMID: 25575156
19. Wu F, Jasmine F, Kibriya MG, Liu M, Cheng X, Parvez F, et al. Interaction between arsenic exposure from drinking water and genetic susceptibility in carotid intima-media thickness in Bangladesh. *Toxicol Appl Pharmacol*. 2014 May 1;276(3):195–203. doi: <http://dx.doi.org/10.1016/j.taap.2014.02.014> PMID: 24593923
20. Chen Y, Wu F, Graziano JH, Parvez F, Liu M, Paul RR, et al. Arsenic exposure from drinking water, arsenic methylation capacity, and carotid intima-media thickness in Bangladesh. *Am J Epidemiol*. 2013 Aug 1;178(3):372–81. doi: <http://dx.doi.org/10.1093/aje/kwt001> PMID: 23788675
21. Wu F, Jasmine F, Kibriya MG, Liu M, Wójcik O, Parvez F, et al. Association between arsenic exposure from drinking water and plasma levels of cardiovascular markers. *Am J Epidemiol*. 2012 Jun 15;175(12):1252–61. doi: <http://dx.doi.org/10.1093/aje/kwr464> PMID: 22534204
22. Chen Y, Graziano JH, Parvez F, Liu M, Slavkovich V, Kalra T, et al. Arsenic exposure from drinking water and mortality from cardiovascular disease in Bangladesh: prospective cohort study. *BMJ*. 2011;342(may05 2):d2431. doi: <http://dx.doi.org/10.1136/bmj.d2431> PMID: 21546419
23. Pierce BL, Kalra T, Argos M, Parvez F, Chen Y, Islam T, et al. A prospective study of body mass index and mortality in Bangladesh. *Int J Epidemiol*. 2010 Aug;39(4):1037–45. doi: <http://dx.doi.org/10.1093/ije/dyp364> PMID: 20032266
24. Chen Y, Factor-Litvak P, Howe GR, Graziano JH, Brandt-Rauf P, Parvez F, et al. Arsenic exposure from drinking water, dietary intakes of B vitamins and folate, and risk of high blood pressure in Bangladesh: a population-based, cross-sectional study. *Am J Epidemiol*. 2007 Mar 1;165(5):541–52. doi: <http://dx.doi.org/10.1093/aje/kwk037> PMID: 17164464
25. Chen Y, Factor-Litvak P, Howe GR, Parvez F, Ahsan H. Nutritional influence on risk of high blood pressure in Bangladesh: a population-based cross-sectional study. *Am J Clin Nutr*. 2006 Nov;84(5):1224–32. PMID: 17093178
26. Chen Y, Ahsan H, Slavkovich V, Peltier GL, Gluskin RT, Parvez F, et al. No association between arsenic exposure from drinking water and diabetes mellitus: a cross-sectional study in Bangladesh. *Environ Health Perspect*. 2010 Sep;118(9):1299–305. doi: <http://dx.doi.org/10.1289/ehp.0901559> PMID: 20813654
27. Argos M, Kalra T, Rathouz PJ, Chen Y, Pierce B, Parvez F, et al. Arsenic exposure from drinking water, and all-cause and chronic-disease mortalities in Bangladesh (HEALS): a prospective cohort study. *Lancet*. 2010 Jul 24;376(9737):252–8. doi: [http://dx.doi.org/10.1016/S0140-6736\(10\)60481-3](http://dx.doi.org/10.1016/S0140-6736(10)60481-3) PMID: 20646756
28. Ronsmans C, Vanneste AM, Chakraborty J, Van Ginneken J. A comparison of three verbal autopsy methods to ascertain levels and causes of maternal deaths in Matlab, Bangladesh. *Int J Epidemiol*. 1998 Aug;27(4):660–6. doi: <http://dx.doi.org/10.1093/ije/27.4.660> PMID: 9758122
29. Sohel N, Persson LA, Rahman M, Streatfield PK, Yunus M, Ekström EC, et al. Arsenic in drinking water and adult mortality: a population-based cohort study in rural Bangladesh. *Epidemiology*. 2009 Nov;20(6):824–30. doi: <http://dx.doi.org/10.1097/EDE.0b013e3181bb56ec> PMID: 19797964
30. Manual of the international classification of diseases, injuries and causes of death. Geneva: World Health Organization; 2007.
31. Gupta PC, Pednekar MS, Parkin DM, Sankaranarayanan R. Tobacco associated mortality in Mumbai (Bombay) India. Results of the Bombay Cohort Study. *Int J Epidemiol*. 2005 Dec;34(6):1395–402. doi: <http://dx.doi.org/10.1093/ije/dyi196> PMID: 16249218
32. Gupta PC, Mehta HC. Cohort study of all-cause mortality among tobacco users in Mumbai, India. *Bull World Health Organ*. 2000;78(7):877–83. PMID: 10994260
33. Wen CP, Tsai SP, Cheng TY, Chen CJ, Levy DT, Yang HJ, et al. Uncovering the relation between betel quid chewing and cigarette smoking in Taiwan. *Tob Control*. 2005 Jun;14 Suppl 1:i16–22. doi: <http://dx.doi.org/10.1136/tc.2004.008003> PMID: 15923442
34. Wen CP, Tsai MK, Chung WS, Hsu HL, Chang YC, Chan HT, et al. Cancer risks from betel quid chewing beyond oral cancer: a multiple-site carcinogen when acting with smoking. *Cancer Causes Control*. 2010 Sep;21(9):1427–35. doi: <http://dx.doi.org/10.1007/s10552-010-9570-1> PMID: 20458529
35. Chang LY, Wan HC, Lai YL, Kuo YF, Liu TY, Chen YT, et al. Areca nut extracts increased expression of inflammatory cytokines, tumor necrosis factor- α , interleukin-1 β , interleukin-6 and interleukin-8, in peripheral blood mononuclear cells. *J Periodontol Res*. 2009 Apr;44(2):175–83. doi: <http://dx.doi.org/10.1111/j.1600-0765.2008.01104.x> PMID: 18973534
36. Timms PM, Mannan N, Hitman GA, Noonan K, Mills PG, Syndercombe-Court D, et al. Circulating MMP9, vitamin D and variation in the TIMP-1 response with VDR genotype: mechanisms for inflammatory damage in chronic disorders? *QJM*. 2002 Dec;95(12):787–96. doi: <http://dx.doi.org/10.1093/qjmed/95.12.787> PMID: 12454321
37. Shafique K, Mirza SS, Vart P, Memon AR, Arain MI, Tareen MF, et al. Areca nut chewing and systemic inflammation: evidence of a common pathway for systemic diseases. *J Inflamm (Lond)*. 2012;9(1):22. doi: <http://dx.doi.org/10.1186/1476-9255-9-22> PMID: 22676449
38. Lai KC, Lee TC. Genetic damage in cultured human keratinocytes stressed by long-term exposure to areca nut extracts. *Mutat Res*. 2006 Jul 25;599(1-2):66–75. doi: <http://dx.doi.org/10.1016/j.mrfmmm.2006.01.005> PMID: 16488451
39. Ling LJ, Hung SL, Tseng SC, Chen YT, Chi LY, Wu KM, et al. Association between betel quid chewing, periodontal status and periodontal pathogens. *Oral Microbiol Immunol*. 2001 Dec;16(6):364–9. doi: <http://dx.doi.org/10.1034/j.1399-302X.2001.160608.x> PMID: 11737660
40. Javed F, Vohra F, Al-Kheraif AA, Malmstrom H, Romanos GE. Comparison of periodontal inflammatory conditions among habitual gutka chewers and betel quid chewers. *Oral Dis*. 2015 May;21(4):437–42. doi: <http://dx.doi.org/10.1111/odi.12295> PMID: 25297062
41. Meyer MS, Joshipura K, Giovannucci E, Michaud DS. A review of the relationship between tooth loss, periodontal disease, and cancer. *Cancer Causes Control*. 2008 Nov;19(9):895–907. doi: <http://dx.doi.org/10.1007/s10552-008-9163-4> PMID: 18478344
42. Beck JD, Offenbacher S. Systemic effects of periodontitis: epidemiology of periodontal disease and cardiovascular disease. *J Periodontol*. 2005 Nov;76(11) Suppl:2089–100. doi: <http://dx.doi.org/10.1902/jop.2005.76.11-S.2089> PMID: 16277581
43. Boffetta P, Hecht S, Gray N, Gupta P, Straif K. Smokeless tobacco and cancer. *Lancet Oncol*. 2008 Jul;9(7):667–75. doi: [http://dx.doi.org/10.1016/S1470-2045\(08\)70173-6](http://dx.doi.org/10.1016/S1470-2045(08)70173-6) PMID: 18598931
44. Accortt NA, Waterbor JW, Beall C, Howard G. Chronic disease mortality in a cohort of smokeless tobacco users. *Am J Epidemiol*. 2002 Oct 15;156(8):730–7. doi: <http://dx.doi.org/10.1093/aje/kwf106> PMID: 12370161