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Case–control study of the association between kava use and pneumonia in eastern Arnhem Land Aboriginal communities (Northern Territory, Australia)

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SUMMARY

Pneumonia causes significant morbidity and mortality in Aboriginal populations in Australia's Northern Territory (NT). Kava, consumed in Arnhem Land since 1982, may be a risk factor for infectious disease including pneumonia. A case–control study ($n=115$ cases; $n=415$ controls) was conducted in 7001 Aboriginal people (4217 over 15 years). Odds ratios (OR) were calculated by conditional logistic regression with substance use and social factors as confounders. Pneumonia was not associated with kava use. Crude OR = 1·26 (0·74–2·14, $P=0·386$), increased after controlling for confounders (OR = 1·98, 0·63–6·23, $P=0·237$) but was not significant. Adjusted OR for pneumonia cases involving kava and alcohol users was 1·19 (0·39–3·62, $P=0·756$). In communities with longer kava-using histories, adjusted OR was 2·19 (0·67–7·14, $P=0·187$). There was no kava dose–response relationship. Crude ORs for associations between pneumonia and cannabis use (OR = 2·27, 1·18–4·37, $P=0·014$) and alcohol use (OR = 1·95, 1·07–3·53, $P=0·026$) were statistically significant and approached significance for petrol sniffing (OR = 1·98, 0·99–3·95, $P=0·056$).

INTRODUCTION

In the 1980s in Australia's Northern Territory (NT), Aboriginal people accounted for 77% of hospitalizations for pneumonia and influenza with around a tenfold risk of hospitalization compared with non-Aboriginal people [1]. Death rates reported since then were more than ten times the Australian rate for the period 1981–1995, with little change during that time [2].

Kava, the 'Intoxicating Pepper' (*Piper methysticum* Forst. f.), is a consciousness-altering muscle relaxant; a soporific with anaesthetic and analgesic properties [3]. In the Pacific islands region, where the kava plant was domesticated, people have used it for centuries in a manner consistent with local cultural practices primarily in the form of aqueous emulsions of the crushed fresh or dried roots or lower stems [3]. Kava powder mixed with water has been used by Aboriginal people in Arnhem Land since the early 1980s in eight settlements (isolated communities with from 200–1500 people) located along the 'Top End' coast of the NT [4]. Kava was brought to Arnhem Land in part to minimize the harmful effects of alcohol use [5, 6]. However, kava use has been associated with abnormal liver function tests reported in published studies in the region [7, 8]. There have also been concerns of an association in Arnhem Land populations between kava use and various infectious diseases such as melioidosis [9, 10].

Kava use in remote and isolated Aboriginal communities, which has continued despite NT Government efforts to restrict its use [11], is now part of what

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has become a global controversy about the health effects of kava use. Serious irreversible liver damage has been reported in people using herbal extracts that contain kava lactones in several countries since the late 1990s [12–14]. Consequently, manufactured kava-based products have become subject to medical alerts or bans on their sale in Europe, [15] North America [16, 17] and Australasia [18].

Amidst this broad international concern about kava's health effects, it is ironic that at the time of writing, the first kava legally available to Aboriginal communities under a licensing regime introduced by the NT Government [20] is being distributed in Arnhem Land. This study examined kava consumption as a potential independent risk factor for admission to hospital with pneumonia.

METHODS

Study base

A case–control study was conducted in a base population that comprised all Aboriginal residents over the age of 15 years in the region's communities (2005 males and 2212 females in 1996 [20]).

Ethics

Ethical approval was provided by the Joint Institutional Ethics Committee of the Royal Darwin Hospital and the Menzies School of Health Research which has an Aboriginal subcommittee and which works to National Health and Medical Research Council guidelines.

Cases

Data from Epidemiology Branch of Territory Health Services indicated that for ICD9 codes 4800–4879 'pneumonia and influenza', between 1994 and 1997 inclusive, there were 263 admissions (139 males and 124 females) to Gove District Hospital (GDH) or Royal Darwin Hospital (RDH) for Aboriginal people over the age of 15 years from the regions' communities. These admissions were for 226 individuals (117 males, 109 females) with 37 people admitted more than once during the study period. GDH is the only secondary referral centre for the east Arnhem health region and the one to which most relevant cases are admitted initially. Some were admitted directly to the RDH and these were included in the cases.

Case definition

An admission was included as a case in the study if there were symptoms of pneumonia plus an X-ray report consistent with the principal diagnosis of pneumonia recorded in hospital discharge summaries by the medical officer and reported in epidemiological data during 1994–1997.

Controls

Controls were selected at random from rolls prepared for each community. Controls ($n=431$, up to four per case) were matched with 120 cases for home locality, sex and age, in 5-year groupings. The methods for selection of controls have been described elsewhere [21]. Each community health centre in the region maintains a paper record of the medical history of local patients which is stored in files held in the health centre. This paper record is usually accompanied by a community list compiled from these files. The active file set held by the local community clinic together with a community list (where available) were used to compile the rolls used to select the controls. Inactive files for deceased persons were also included in the roll for possible selection as controls, i.e. any individual who had died after 1994. A reference date for enumerating ages across the study at 1 October 1998 was used. Only those normally resident in the local community were eligible for selection as controls.

Data collection

For each case and control, consensus classification by health workers was used as already described [21]. Data collection faced peculiar constraints. In accordance with the wishes of Aboriginal community representatives and their community controlled health service, face-to-face interviewing was not carried out with cases or controls.

Additionally, a number of people were deceased among both cases ($n=10$) and controls ($n=34$). Furthermore, the status afforded kava, already highly stigmatized and controversial, which became an illegal substance shortly after the study commenced [11], also posed a significant challenge for data collection. These factors combined with the mobility of the region's population across the communities and nearby major centres in the 'Top End' of the NT, made interviewing of cases and controls infeasible. In order to overcome these difficulties, it was necessary to collect data by proxy using interviews with knowledgeable

Aboriginal health workers combined with documentary sources [21].

Aboriginal health workers in eastern Arnhem Land work in clinics in the communities in which they have lived for most of their lives and are held in high regard in those communities. They were often born in the communities where they work or in nearby communities that have close family and tribal affiliations. Most practising health workers in Arnhem Land are registered under the appropriate NT authority and have been trained on the job as well as through formal studies at an indigenous tertiary education institute at either diploma or certificate level. The senior health workers who provided information for this study have in some cases practised in the local clinic setting for 20 years.

For each case and control, consensus classification of kava use by health workers was compiled. Using their experience and knowledge without consulting clinic files and independently of each other, health workers evaluated whether cases or controls had ever used kava ('Yes' or 'No') and if they were using it during 1994–1997 ('Yes or 'No'). To assess the occurrences of heavy drinking, we also asked health workers to describe the estimated time in a week a subject usually spent drinking kava and the time spent in activities where kava was consumed. Chart review data using local community clinic files assisted to confirm health worker consensus for both cases and controls. Similar methods were used to estimate exposure to other substance use and other related data. These methods for assessing exposure to kava use have been validated in an earlier study [21] and the data collection procedures described in detail therein. To summarize, health workers concurred about an individual's history of kava use ($\kappa = 0{\cdot}83$), current use ($\kappa = 0{\cdot}43$) and also level of use ($\kappa = 0{\cdot}33$). We found good agreement between health workers' consensus and self-reported history of use ($\kappa = 0{\cdot}77$). Data from review of clinic patient notes and hospital discharge summaries supported agreement between consensus classification and self-reported history and level of use ($\kappa = 0{\cdot}39$) [21].

Data analysis

Analysis compared incident cases ($n = 115$, 60 males and 55 females) for whom kava use information was available with their matched controls ($n = 415$, 225 males and 190 females). Conditional logistic regression was used to calculate crude and adjusted odds ratios (with 95% confidence intervals) with variable numbers of controls per case. Analyses were performed with Stata 7.0 [22].

Table 1. *Kava and alcohol use among cases and controls**

	Cases	Controls
Kava used but no alcohol	17% ($n = 19$)	16% ($n = 68$)
Kava and alcohol used	31% ($n = 35$)	29% ($n = 117$)
Alcohol used but no kava	27% ($n = 31$)	22% ($n = 90$)
No kava and no alcohol used	25% ($n = 28$)	33% ($n = 135$)

* Proportions based on 113 cases and 410 controls for whom kava and alcohol use information were both available.

RESULTS

There were 106 out of the 226 individuals who were admitted with pneumonia as a subsidiary diagnosis and/or for whom X-ray findings were inconclusive or unavailable. These were excluded. X-ray findings were consistent with the medical officer's diagnosis and pneumonia was the principle diagnosis in 120 cases (63 males, 57 females). Kava use information was available for 115 of these.

The median age among 120 cases was 38 years (men 38, $n = 63$ and women 39, $n = 57$). Ninety-one cases (76%) originated from communities within the region where kava had been used since the early 1980s with the remaining 29 (24%) from communities with little or no kava using history. Based on these numbers, pneumonia admission rates during 1994–1997 were 1845 and 243 per 100 000 in these communities respectively.

Kava use and pneumonia and the effects of alcohol and other substance use

Kava users comprised 49% (56) out of 115 cases and 46% (190) out of 415 controls. There were more males among the cases who used kava (63%, $n = 38$ males 33%, $n = 18$ females) as well as among the controls who used kava (58%, $n = 131$ males, 31%, $n = 59$ females).

There were similar proportions of kava and alcohol users among the cases and the controls (Table 1). In a regression model with just kava and alcohol, ORs

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Table 2*a*. *Crude odds ratios and 95% confidence intervals for the association between pneumonia and kava use and other substance use*

'a', reference category		Cases	Controls	OR	95% CI		*P*-value*
Kava – use before or during admission period 1994–1997							
Yes		56	190	1·26	0·74	2·14	0·386
a No		59	225	1·00			
Kava – level of use							
a None	None	59	225	1·00			
1 night/week for a few hours		6	8	3·01	0·95	9·58	
>1 night/week for a few hours	Occasional user	3	20	0·68	0·18	2·48	
about 2 nights a week		10	43	0·90	0·40	2·05	0·282
Drink kava during the day as well as at night	Regular user	9	25	1·52	0·60	3·83	
Sometimes drink for 24 h sessions	Heavy and regular user	23	82	1·23	0·64	2·38	
Alcohol – use before or during admission period 1994–1997							
Yes		66	207	1·95	1·07	3·53	0·026
a No		47	203	1·00			
Alcohol – level of use							
a None		47	203	1·00			
Light		14	31	2·51	1·09	5·79	
Moderate		9	53	1·11	0·44	2·78	0·043
Heavy		40	114	2·19	1·13	4·24	
Tobacco – use before or during admission period 1994–1997							
Yes		89	315	1·19	0·71	2·02	0·504
a No		25	95	1·00			
Tobacco – level of use							
a None		25	95	1·00			
Up to 15 sticks a day		3	11	0·96	0·22	4·25	
15–25 sticks a day		3	29	0·41	0·11	1·49	0·214
One pack a day		56	181	1·37	0·77	2·44	
More than 1 pack a day		22	85	1·06	0·50	2·22	
Petrol – use before or during admission period 1994–1997							
Yes		16	30	1·98	0·99	3·95	0·056
a No		96	370	1·00			
Cannabis – use before or during admission period 1994–1997							
Yes		26	57	2·27	1·18	4·37	0·014
a No		79	327	1·00			

* *P*-values reflect trend across categories.

for an association with pneumonia were 1·20 and 1·91 respectively but changed to 1·90 and 2·84 when the model included an interaction term for kava with alcohol (likelihood ratio test $K^2 = 2{\cdot}11$, $P = 0{\cdot}147$) which, while non-significant suggested, that interaction effects should be considered in the multivariate model. No interaction of kava was found with either tobacco or cannabis use or petrol sniffing.

A crude odds ratio that those admitted for pneumonia were kava users was 1·26 (0·74–2·14, $P = 0{\cdot}386$) (Table 2*a*). In those who used no alcohol, after adjusting for the effects of tobacco and cannabis use, petrol sniffing as well as body size, location of usual residence and a residual effect of age, the OR for kava use increased to 1·98 (0·63–6·23, $P = 0{\cdot}237$) (Table 3*a*). In those who used alcohol the OR for kava use was 1·19 (0·39–3·62, $P = 0{\cdot}756$). In a multivariate model that included confounders and an interaction term between kava and alcohol, OR for kava use was 2·22 and changed to 1·42 without the

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Table 2*b*. *Crude odds ratios and 95% confidence intervals for the association between pneumonia and social and demographic characteristics*

'a', reference category		Cases	Controls	OR	95% CI		*P*-value*
Employment							
a Paid employment (not including CDEP)	In labour force	16	57	1·00			
CDEP	In labour force (CDEP)	31	146	0·62	0·30	1·29	
Supporting parent							0·049
Pension							
Unemployment benefit	Not in labour force	58	176	1·23	0·63	2·40	
No money							
Time spent on outstations or community							
a Mostly on community		67	250	1·00			
Divided between community and outstations		19	93	0·70	0·38	1·28	
							0·145
Mostly on outstations		9	28	1·06	0·45	2·47	
Live outside of the area		11	20	2·04	0·92	4·54	
Condition of house							
a Good		64	263	1·00			
Fair		11	47	1·32	0·58	2·99	0·693
Poor		11	25	2·41	0·99	5·83	
People living in the house							
More than 10		38	128	0·80	0·37	1·74	0·024
6–10		27	139	0·47	0·23	0·99	
a 5 or less		20	60	1·00			
Goes hunting regularly							
Yes		60	229	1·04	0·62	1·77	0·872
a No		34	127	1·00			
Diet includes bush food							
Yes		68	289	0·67	0·37	1·18	0·168
a No		24	71	1·00			
Active person							
a Yes		62	291	1·00			
No		32	47	3·86	1·94	7·71	<0·001
Body size							
Overweight		8	41	1·00	0·42	2·37	
a About right		65	295	1·00			0·143
Underweight		37	74	2·33	1·42	3·82	

* *P*-values reflect trend across categories.

interaction (likelihood ratio test, $K^2 = 1{\cdot}76$, $P = 0{\cdot}184$) indicating no significant interaction between kava and alcohol. There was no dose–response relationship (Table 2*a*, Tables 3*a*, *b*).

Among the cases normally resident in communities with a longer kava using history and who did not use alcohol, 19 were kava users and 13 were non-users with 68 users and 76 non-users among the controls. A crude OR for an association with kava use of 1·75 (0·65–4·72, $P = 0{\cdot}264$) in those who did not use alcohol in the kava using communities increased to 2·19 (0·67–7·14, $P = 0{\cdot}187$) in the multivariate analysis, i.e. little different from the OR using data for all communities.

There were crude associations between pneumonia admission and alcohol use (OR = 1·95, 1·07–3·53, $P = 0{\cdot}026$), cannabis use (OR = 2·27, 1·18–4·37, $P = 0{\cdot}014$) and a tendency for an association with petrol sniffing (OR = 1·98, 0·99–3·95, $P = 0{\cdot}056$) (Table 2*a*).

Social and contextual data

Published data for 1996 for the region, showed that an average of between 8 and 9 people lived in each of

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Table 3*a*. *Adjusted odds ratios and 95% confidence intervals for the association between pneumonia and kava use in those who do not use alcohol.* (*Adjusted for a history of petrol sniffing, tobacco and cannabis use, usual residence, body size and age.*)

'a', reference category		Cases	Controls	OR	95% CI		*P*-value*
Kava – use before or during admission period 1994–1997							
Yes		19	68	1·98	0·63	6·23	0·237
a No		28	135	1·00			
Kava – level of use							
a None	None	28	135	1·00			
1 night/week for a few hours		4	4	6·14	0·69	54·44	
>1 night/week for a few hours	Occasional user	1	6	0·81	0·05	12·70	
† about 2 nights a week		2	14	—	—	—	0·165
Drink kava during the day as well as at night	Regular use	4	7	9·61	0·79	117·98	
Sometimes drink for 24 hour sessions	Heavy and regular user	7	28	2·51	0·45	13·95	

* *P*-values reflect trend across categories.
† No information about effect because of sparse data.

Table 3*b*. *Adjusted odds ratios and 95% confidence intervals for the association between pneumonia and kava use in those who use alcohol.* (*Adjusted for a history of petrol sniffing, tobacco and cannabis use, usual residence, body size and age.*)

'a', reference category		Cases	Controls	OR	95% CI		*P*-value*
Kava – use before or during admission period 1994–1997							
Yes		35	117	1·19	0·39	3·62	0·756
a No		31	90	1·00			
Kava – level of use							
a None	None	31	90	1·00			
† 1 night/week for a few hours		2	4	—	—	—	
† >1 night/week for a few hours	Occasional user	2	14	—	—	—	
about 2 nights a week		8	27	1·18	0·26	5·34	0· 146
Drink kava during the day as well as at night	Regular user	5	18	1·19	0·20	7·03	
Sometimes drink for 24 hour sessions	Heavy and regular user	15	51	0·94	0·24	3·76	

* *P*-values reflect trend across categories.
† No information about effect because of sparse data.

the 839 available dwellings [20]. The modal category in our data was from 6 to 10 persons per dwelling among controls (Table 2*b*). Those living on outstations (smaller living areas with up to 120 people) were around 18% in 1996 [20]. In our data 7% ($n=28$) of controls were outstation residents with another 24% ($n=93$) spending time in both communities and outstations. Five per cent ($n=20$) were normally resident in the community but also resided in a town or major regional centre during the study period. Fifty-four per cent ($n=203/379$) of controls were in paid employment or CDEP (Community Development Employment Program) with the balance not in the labour force at the time of the survey (Table 2*b*), somewhat higher than in the published data for 1996 (37%) [20]. In our data, no people relied totally on a diet of 'bush food', while those who were active and who had superior diets were also regular hunters (Table 2*b*).

While the direction of the association is not clear, pneumonia admission appears to be associated with both participation in the labour force and the number

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of people living in the house where the case or control resided (Table 2*b*). There is an association of pneumonia admission with people who were regarded as 'inactive' by health workers (crude OR = 3·86, 1·94–7·71, $P < 0·001$).

DISCUSSION

To our knowledge, this is the first controlled study to consider kava use as an independent risk factor for pneumonia in any population. Admission for pneumonia was not associated with kava use.

Confounding effects

A dynamic substance use complex exists in eastern Arnhem Land Aboriginal populations involving changing patterns of cannabis use, petrol sniffing, tobacco and alcohol use as well as kava [23]. Kava is usually consumed in the home community with groups of between 2 and 11 drinkers participating and with varying numbers of casual drinkers. Alcohol is consumed periodically in the home community, but usually in the nearby large towns or in one of two regional centres, where it is more freely available and where heavy drinking is a common pattern of consumption [24]. Petrol sniffing occurs sporadically with periodic resurgences [23]. Cannabis use (14%, $n = 57$ controls) and a high prevalence of a history of tobacco use (77%, $n = 315$ controls) was seen (Table 2*a*). The prevalence of cannabis use has increased rapidly over the past 5 years [23].

The multivariate analysis adjusted for confounders including tobacco, a known risk factor for pneumonia [25, 26]. A weak interaction between kava and alcohol use, also a known risk factor for pneumonia [27–29], was considered but found to be non-significant. Effects of alcohol use, if they exist, were controlled in the stratified analysis (Tables 3*a*, *b*). Body size, age and place of usual residence (a likely surrogate for heavy alcohol use) were also adjusted for in the multivariate model.

Petrol sniffing, which is known to have occurred widely in the region for upwards of 30 years [30], and cannabis use which may lead to respiratory abnormalities similar to those among tobacco users [31] perhaps by compromising the lung's immune system [32] were also included in the multivariate analysis. No comprehensive data were available describing the presence or absence of chronic obstructive pulmonary disease or other chronic diseases in the cases or controls and so these variables could not be included in the analysis.

Strengths and weaknesses of the study

This study uses data for all cases of pneumonia admitted from eastern Arnhem Land for a defined period where the majority of kava users in the Aboriginal population reside and for whom diagnosis could be confirmed. It is possible that information bias [21] occurred in this study because health workers may have known not only the kava using status of individuals in the study but also their hospital admission history and perhaps unwittingly reported substance use status for those known to have been admitted to hospital more readily than for those they knew had not been admitted. This prospect was minimized; except for appropriate identifiers, health workers were blinded to any information about cases and controls during interview. We have assessed the level of agreement that health workers demonstrated about kava using status of individuals known to them [21]. It seems highly unlikely that all health workers who provided information would show the same pattern of information bias and that this bias would also occur between health worker consensus and self-reported data.

The higher admission rates for pneumonia in kava using communities compared with those with little or no kava use history may be due to a difference in the social and environmental factors affecting disease rates in each subregion. It is also possible, however, that these differences are due more to differential treatment regimes; clinics in one part of the region tending to treat pneumonia cases in the community rather than evacuating them to the regional hospital. There are also major cultural and historical differences between kava using communities, Yolngu communities [33], and those with little or no kava using history, Anindilyakwa and Nunggubuyu communities [34], which may be reflected in the differential use of health services.

Imprecise measures of the level of kava use was an unavoidable weakness in this study, in part a consequence of the lack of reliable supply and consumption data given kava's illegal or stigmatized status throughout the course of the data collection and study periods [11]. Kava supply and consumption had likely reached its apogee in 1996 and 1997 under the pervasive influence of an informal trade, but reliable supply information does not exist from 1994

onwards because the regulatory regime operating at that time was dismantled [4] and not reinstated. For this reason, it is unlikely that more precise determination of consumption levels during the study period can be made. Future monitoring of kava's health effects may benefit from the availability of reliable community supply information with which to compare usage levels reported by proxy.

Plausibility of a history of kava use as a cause for pneumonia

There may be an immune system abnormality in kava users. In an earlier study heavy kava use was found to be associated with decreased lymphocytes [7]. In a recent study we also found decreased lymphocytes (with 51% of kava users having levels below the normal reference range) along with a tendency for higher IgE antibody levels among kava users [8]. It is likely that decreased lymphocyte levels return to normal upon ceasing kava use, as do elevated liver enzymes with abstinence from kava [8, 35]. Lymphocyte levels in past kava users ($1{\cdot}8 \times 10^9$/l, S.D. $= 0{\cdot}6$) tended to be higher than in current users ($1{\cdot}6 \times 10^9$/l, S.D. $= 0{\cdot}6$) [8] although this was not statistically significant ($|t| = 1{\cdot}26$, $P = 0{\cdot}213$).

Despite the possibility of an immune abnormality, this study has shown that kava use alone is not clearly an independent risk factor for pneumonia as it appears to be for other serious infectious disease such as melioidosis [10, 36]. Information bias, incorrect diagnosis, and differential treatment regimes across the region may have confounded kava's effect if it exists.

The statistically significant associations between pneumonia admission and alcohol use, pneumonia admission and cannabis use and the tendency for an association with petrol sniffing (Table 2*a*), suggest that the effects of other substances, or combinations of substances, may also be important or may compound kava's effects in ways not yet understood. These should be further examined as risk factors for pneumonia, and other serious infectious disease.

Environmental and biological processes that may increase pneumonia risk, such as lack of employment opportunities, poor nutrition and poor community living conditions, are likely to persist alongside the complex of substance use in Arnhem Land and its legacy. If Aboriginal people continue to drink kava in this context, it would be prudent to moderate consumption even though an association with pneumonia has not been shown.

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