Supplemental Material

A. The odds ratio regression offset variable applied to the Uruguay data

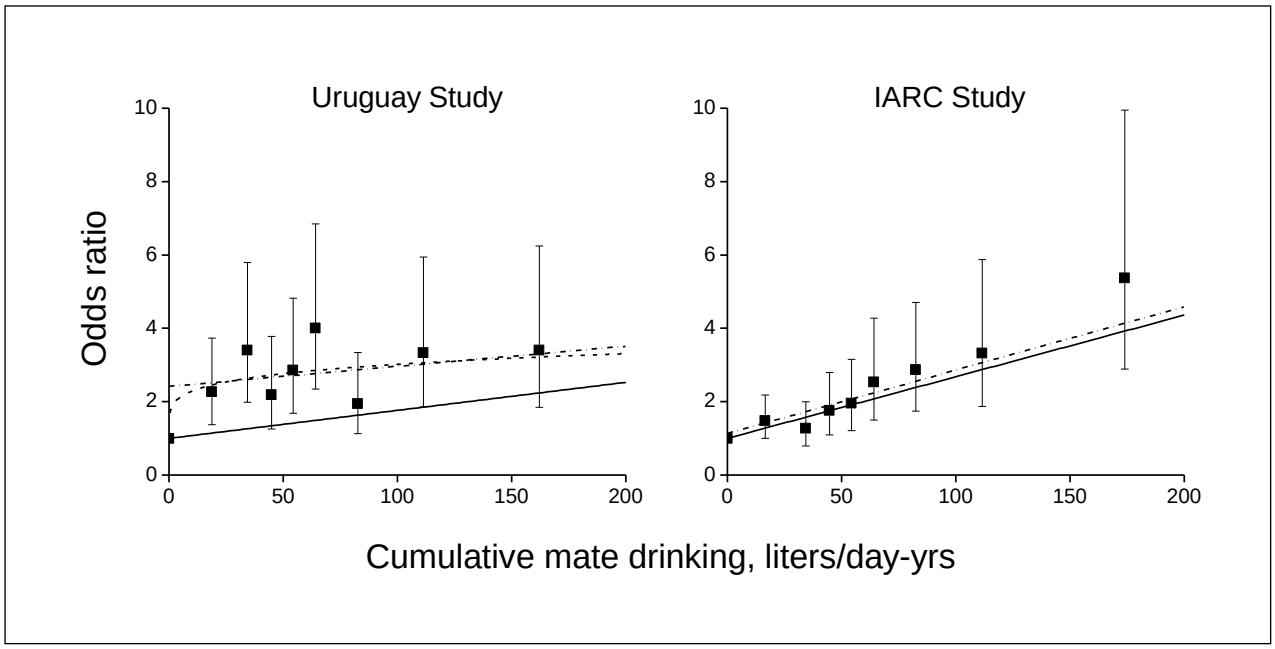
The Materials and Methods section briefly described the offset variable to adjust models for ORs by mate consumption (shown below in italics). This section provides additional details.

ORs by LPDY increased linearly in the IARC data and in the Uruguay data, but only among maté *drinkers in the latter. For Uruguay data, we defined a fixed offset to adjust for ever and never* maté *drinkers using the model* $OR(d) = \exp\{\alpha\, I(d)\} \times \{1 + \beta\, d\}$, *where I(d) equaled one for* $d>0$ *and zero otherwise. The estimate,* $\exp\{\alpha\}$, *was 2.42 (1.5, 2.9), and represented the LPDY-adjusted OR of ever relative to never consumed* maté. *A detailed examination identified a small subgroup responsible for the excess. The subgroup included male (3 cases and 53 controls) and female (1 case and 61 controls) urban residents who abstained from alcohol, with ORs for ever consumed* maté *of 4.24 (1.1, 16.7) and 13.8 (1.8, 105.8), respectively. The offset equaled* $-\ln(4.24)$ *and* $-\ln(13.8)$ *for Uruguay male and female urban residents who never consumed alcohol or* maté *and zero otherwise. The offset essentially replaced the observed case to control odds with the expected odds and eliminated the non-linearity.*

ORs for categories of cumulative mate consumption in liters/day-years (LPDY), adjusted for potential confounding variables, increased with increasing LPDY for each study (Figure A1). These ORs omitted any offset and so differed from the ORs in Table 2. ORs for the IARC Study followed a simple linear relationship with increasing LPDY, $OR(d) = 1 + \beta\, d$, while ORs for the Uruguay Study differed significantly from linearity ($p<0.01$) and were well described with the model (dash line):

$$OR(d) = 1 + \beta\, d \times \exp\{\, \theta \ln(d)\, \} = 1 + \beta\, d^{\,1+\theta}$$

Figure A1: ORs by cumulative mate consumption for each study (solid symbols), and fitted lines based on a linear model in LPDY, *d*, OR(*d*) = 1+β*d* (solid line), linear-power model, OR(*d*) = 1+ $\beta d^{1+\theta}$ (dash line) and linear model with intercept adjustment, OR(*d*) = exp{α I(*d*)}×{1+β*d*} (dot-dash line).



Our analysis could have fitted a linear model for the IARC data and the 2-parameter power model for the Uruguay data. However, simplicity is often a desirable (Occam's razor). For the Uruguay data, a linear model with a differential effect for never and ever mate drinkers, OR(*d*) = exp{α I(*d*)} × {1 + β *d*} significantly improved fit (P<0.01) and closely fitted the ORs (dot-dash line). The estimated intercept OR with 95% CI was 2.42 (1.5, 3.9). For the IARC data, the estimated intercept was 1.13 (0.7, 1.7). Thus, among exposed, ORs increase linearly for both studies.

The practice of mate drinking in Uruguay was widespread (only 12.6% of controls never consumed mate), which may signify marked differences in never and ever drinkers. One analytic option would identify reasons for differences by mate status in the Uruguay data, then adjust

models with a fixed offset variable. Variables for consideration included alcohol consumption, cigarette smoking and socio-economic related variables.

For the IARC data, intercept ORs for ever mate consumption did not significantly differ from one by alcohol use status, smoking status or educational level, and thus we did not further consider an offset. For the Uruguay data, we found differential ORs by mate status, 4.11 (1.6, 10.4) in never alcohol drinkers and 1.48 (0.8, 2.8) in ever alcohol drinkers, but similar ORs by cigarette smoking status, 2.26 (0.8, 6.1) in never smokers and 2.26 (1.3, 4.1) in ever smokers and by education, 2.97 (0.9, 9.5) for <6 years and 2.34 (1.4, 4.1) for ≥6 years (Figure A2). There was a suggestion of differential ORs by income level, 3.13 (1.3, 7.4) for <US$120 and 1.62 (0.8, 3.1) for ≥US$120, but the difference was less extreme than for alcohol status.

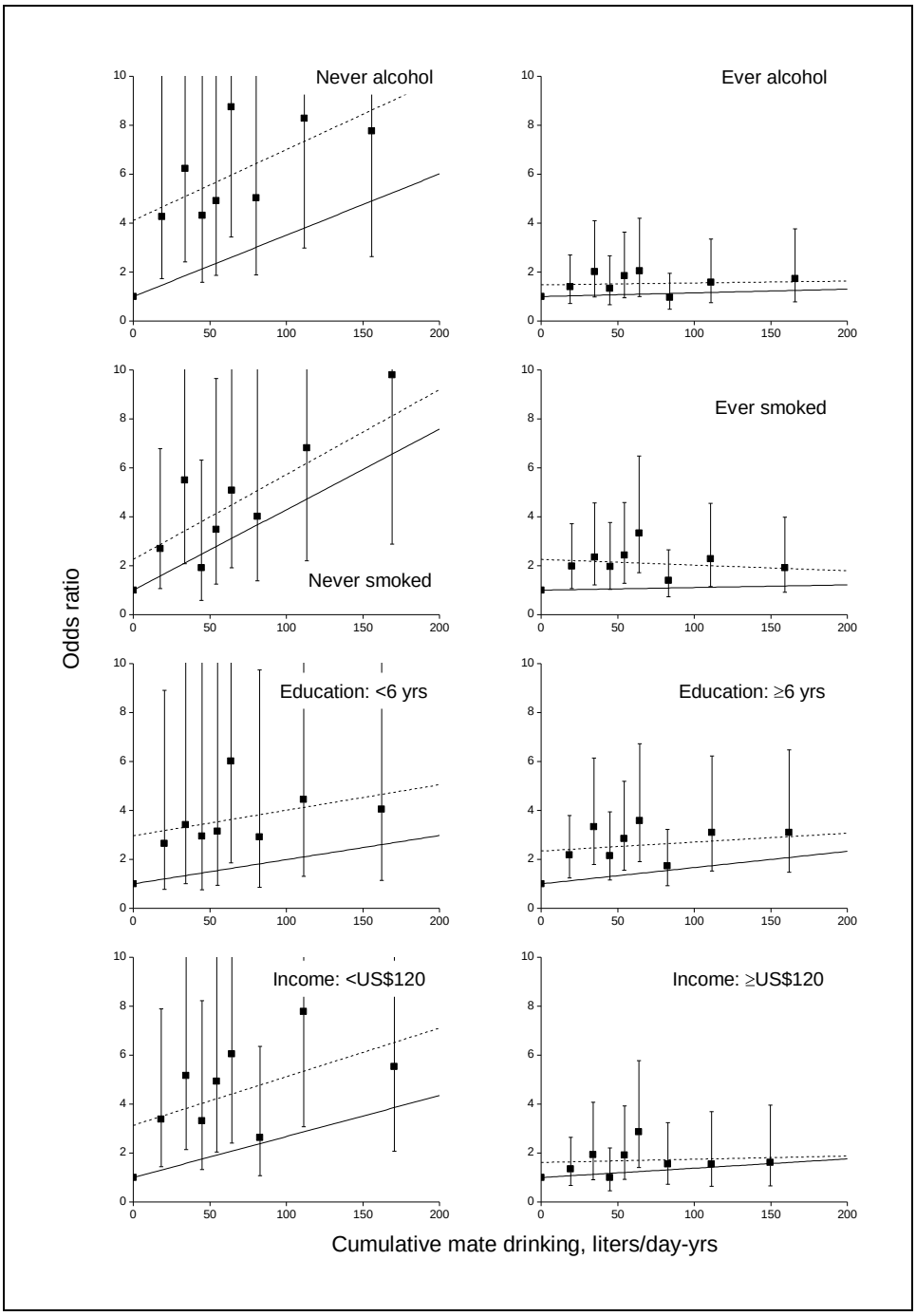


Figure A2: ORs for cumulative mate consumption by alcohol consumption, cigarette smoking status, education and income and and fitted lines based on a linear model in LPDY, d, $OR(d) = 1+\beta d$ (solid line) and linear model with intercept adjustment, $OR(d) = \exp\{\alpha\, I(d)\}\times\{1+\beta d\}$ (dash line). Data from Uruguay Study only.

Figure A2 suggested that never alcohol drinkers were the likely source of the differential ORs by mate status. We further partitioned never alcohol drinkers by residency (urban or rural),

educational level or income. While numbers of never alcohol drinkers were limited, ORs by mate status were comparable within lower and higher educational level, 5.56 (1.1, 27.3) and 6.12 (2.1, 17.7), respectively, and lower and higher income, 5.10 (1.1, 24.4) and 2.82 (0.8, 9.9). In contrast, ORs for urban and rural residence were 6.78 (2.3, 20.0) and 0.22 (0.0, 45.7), suggesting the subgroup of urban, never alcohol drinkers was an important contributor to the significant intercept of Figure A1.

The subgroup of urban subjects, who consumed neither alcohol nor mate, included four cases (3 males and 1 female) and 114 controls (53 males and 61 females). We defined a preliminary offset with value -ln(6.78) for this subgroup and zero otherwise. In a final examination, we divided this subgroup by sex and found significant intercept ORs of 4.24 (1.1, 16.7) and 13.8 (1.8, 105.8) for males and females, respectively (Figure A3). We defined a final offset variable with values -ln(4.24) and -ln(13.8) for males and females, respectively, in never alcohol and never mate drinkers and zero otherwise.

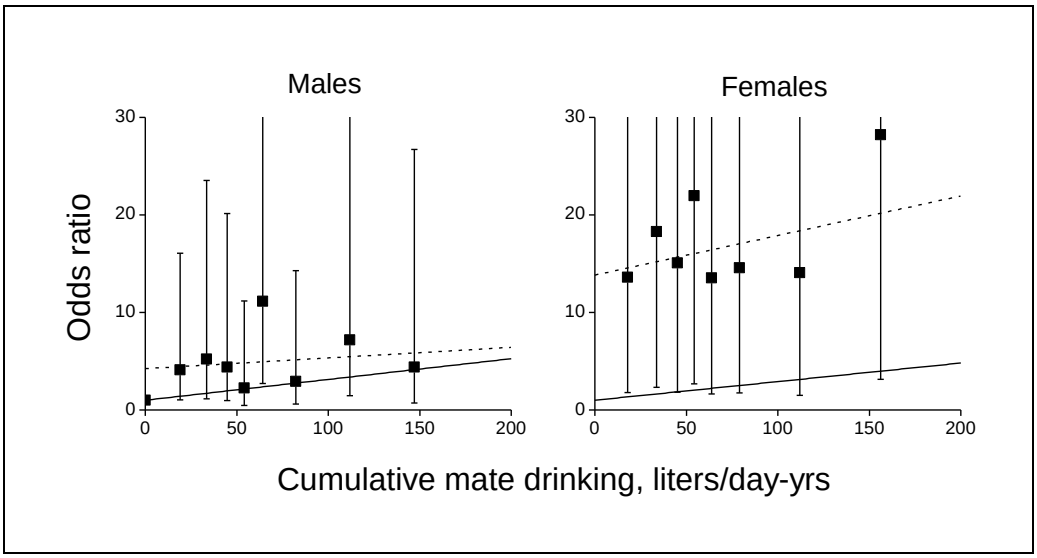


Figure A3: ORs for cumulative mate consumption by sex and fitted lines based on a linear model in LPDY, d, $OR(d) = 1+\beta d$ (solid line), and linear model with intercept adjustment, $OR(d) = \exp\{\alpha\, I(d)\}\times\{1+\beta d\}$ (dash line). Data limited to urban, never alcohol drinkers in the Uruguay Study.

With a fixed offset, the ORs by LPDY increased linearly (Figure A4, solid symbol and line), with no evidence of a deviation from linearity (P=0.76) or differential effect by mate consumption status, OR=1.19 (0.9, 1.7). This contrasted with the ORs without adjustment (Figure A4, open symbol and dash-dot line). Results were similar using the offset with (shown in figure) or without additional adjustment for sex. The EOR/LPDY estimate was 0.009 (0.005, 0.014).

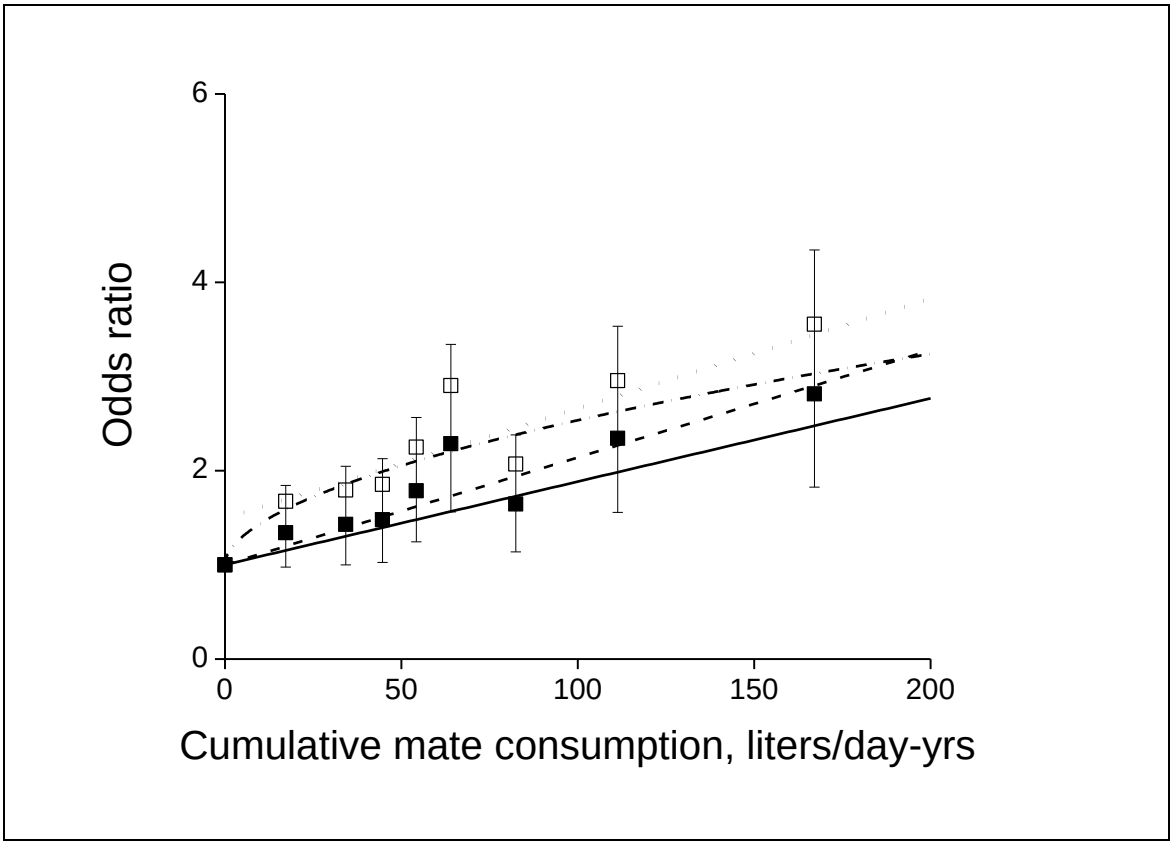


Figure A4: ORs for cumulative mate intake for all data with (solid symbol) and without (open symbol) a fixed offset. Without a fixed offset, fitted lines include a linear model in LPDY, d, $OR(d) = 1+\beta d$, (dash line), a linear model with estimated intercept, $OR(d) = \exp\{\alpha\, I(d)\}\times(1+\beta d)$, (dot line) and a linear-exponential model, $OR(d) = 1+\beta d\times\exp\{\theta \ln(d)\}$ (dash-dot line). With a fixed offset, the fitted line includes a linear model (solid line).

B. Comparisons by study/components

Comparison of results across study components showing general homogeneity of the exposure response and patterns of effect modification. The only significant difference occurred for age at first *maté* use.

Table B1: Percentages of mate drinkers and mate intake metrics, including liters/day, duration of use in years and cumulative mate consumption in liters/day-years (LPDY) for the Uruguay Study and the IARC Study and its components.

		IARC Study				
Mate use	Uruguay Study	Argentina	Brazil	Paraguay	Uruguay-I	Uruguay-II
			Case subjects			
No.	612	125	159	122	247	135
Ever (%)	95.6	88.8	85.5	92.6	98.0	96.3
			Control subjects			
No.	1518	254	323	368	497	269
Ever (%)	87.5	91.7	77.1	86.1	91.1	87.7
			Mate drinkers: case subjects			
No.	585	111	136	113	242	130
Liters/day	1.24	0.66	0.94	0.95	1.46	1.31
Duration (yr)	52.3	49.5	40.1	36.9	51.0	53.1
LPDY	64.8	33.4	37.4	35.3	74.5	69.0
			Mate drinkers: control subjects			
No.	1328	233	249	317	453	236
Liters/day	1.09	0.63	0.89	0.75	1.04	1.04
Duration (yr)	50.8	51.8	38.3	37.9	47.3	50.2
LPDY	55.3	33.8	36.0	29.0	49.6	51.8

TABLE B2. Estimated excess odds ratio (EOR) per liter/day-year (LPDY) of mate consumption with 95% confidence limits, overall and by levels of potential effect modifiers [a]. Data from the Uruguay and IARC Multinational Case-Control Studies.

	Uruguay Study		IARC Study		Pooled data		
Modifier	EOR/LPDY	P [b]	EOR/LPDY	P [b]	EOR/LPDY	P [b]	**P [c]**
None	0.003		0.015		0.009		0.01
	(0.000,0.009)		(0.008,0.025)		(0.005,0.014)		
Temperature							
Warm	-0.004		0.012		0.004		
Hot	0.002		0.011		0.007		
Very hot	0.006	0.01	0.034	0.01	0.016	<0.01	0.10
Years since last mate							
0	0.004		0.015		0.009		
1-4	0.011		0.028		0.020		
5+	-0.001	0.31	0.017	0.43	0.005	<0.01	0.49
Age 1st mate							
<12	0.014		0.010		0.012		
12-16	-0.001		0.024		0.005		
≥17	0.005	<0.01	0.013	0.02	0.008	<0.01	<0.01
Sex							
Males	0.003		0.012		0.007		
Females	0.004	0.80	0.026	0.18	0.013	0.29	0.74
Attained age							
<65	0.006		0.024		0.015		
65-74	0.001		0.009		0.006		
≥75	0.003	0.39	0.011	0.13	0.006	0.14	0.78
Smoking status							
Never	0.012		0.024		0.018		
Former	0.004		0.014		0.009		
Current	0.002	0.02	0.008	0.20	0.003	0.02	0.12
Tobacco type [d]							
Never	0.010		0.012		0.011		
Blond	-0.002		-0.003		-0.002		
Mixed/black	0.005	0.06	0.024	<0.01	0.014	<0.01	0.62
Alcohol status							
Never	0.007		0.038		0.017		
Former	0.002		0.015		0.004		
Current	0.007	0.41	0.008	0.04	0.008	0.12	0.24

[a] Estimates from a linear odds ratio model for LPDY relative to never-drinkers within categories: $OR(d) = 1 + \sum_s \beta_s d_s$ where β_s and d_s denoted the EOR/LPDY and LPDY, respectively, at level s of the modifier. Models adjusted for study, cigarette smoking (pack-years, cigarettes/day), alcohol consumption (drink-years, ml ethanol/day), age, sex, sex by education and for Uruguay income and urban/rural residence. Models included a sex-specific fixed offset variable to account for differential effects of mate consumption in urban, never alcohol consumers for the Uruguay data.
[b] P-value for test of homogeneity of EOR/LPDY within study population.
[c] P-value for test of homogeneity of effect modification of EOR/LPDY across study populations, adjusting for study differences in EOR/LPDY, from χ^2distribution with number of levels minus 1 degrees of freedom.
[d] Data restricted to males.