

Association of Monosodium Glutamate Intake With Overweight in Chinese Adults: The INTERMAP Study

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Animal studies indicate that monosodium glutamate (MSG) can induce hypothalamic lesions and leptin resistance, possibly influencing energy balance, leading to overweight. This study examines the association between MSG intake and overweight in humans. We conducted a cross-sectional study involving 752 healthy Chinese (48.7% women), aged 40–59 years, randomly sampled from three rural villages in north and south China. The great majority of participants prepared their foods at home, without use of commercially processed foods. Diet was assessed with four in-depth multipass 24-h recalls. Participants were asked to demonstrate MSG amounts added in food preparation. Amounts shaken out were weighed by trained interviewers. Overweight was defined as BMI ≥ 25.0 or ≥ 23.0 kg/m² (based on World Health Organization recommendations for Asian populations). Eighty-two percent of participants were MSG users. Average intake was 0.33 g/day (s.d. = 0.40). With adjustment for potential confounders including physical activity and total energy intake, MSG intake was positively related to BMI. Prevalence of overweight was significantly higher in MSG users than nonusers. For users in the highest tertile of MSG intake compared to nonusers, the multivariable-adjusted odds ratios of overweight (BMI ≥ 23.0 and ≥ 25.0) were 2.10 (95% confidence interval, 1.13–3.90, *P* for trend across four MSG categories = 0.03) and 2.75 (95% confidence interval, 1.28–5.95, *P* = 0.04). This research provides data that MSG intake may be associated with increased risk of overweight independent of physical activity and total energy intake in humans.

Obesity (2008) **16**, 1875–1880. doi:10.1038/oby.2008.274

INTRODUCTION

Obesity is a major health disorder for both men and women, comprising all age groups and all ethnic and socioeconomic backgrounds (1). There are diverse approaches for the control of body weight, but the fundamental key is energy balance. Previous studies suggest that diet composition may affect energy balance and/or energy-related metabolic pathways (2,3). Monosodium glutamate (MSG), the sodium salt of glutamic acid, is a food additive used as a flavoring agent for enhancing taste. It is frequently added to processed foods and shaken onto foods during preparation, particularly in Asian cuisine. Although evaluations by the US Food and Drug Administration and other organizations concluded that MSG

was a safe food ingredient for the general population (4), none of them answered the question: is MSG consumption healthy? Data from animal studies suggest a possible link between MSG and overweight/obesity (5–8). Weight gain was significantly greater in MSG-treated mice compared with controls even with consumption of similar amounts of food (5). A potential explanation for the MSG-obesity link is altered regulatory mechanisms that affect fat metabolism (9,10).

Worldwide MSG consumption has increased dramatically in recent decades (11,12). MSG has become a health concern with respect to epidemic overweight/obesity in addition to possible allergenic effects. However, we are unaware of published studies on MSG intake in relation to obesity or overweight in

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Received 7 July 2007; accepted 16 February 2008; published online 22 May 2008. doi:10.1038/oby.2008.274

humans, possibly due to difficulties in quantifying MSG intake, particularly in industrialized countries where it is widely added in commercial food processing.

In China, MSG is a common food additive. In the International Study of Macro-/Micro-nutrients and Blood Pressure (INTERMAP), MSG added by Chinese participants in home food preparation was quantitatively estimated in 1997. The primary purpose of collecting MSG data in INTERMAP was to study the association of sodium intake and blood pressure. Based on the suggestive findings from animal experimental studies, we used the INTERMAP data to examine the association between MSG intake and BMI in apparently healthy middle-aged Chinese adults.

METHODS AND PROCEDURES

Design and participants

INTERMAP is an international, cross-sectional basic epidemiologic investigation aiming to clarify unanswered questions on the role of dietary factors in the etiology of unfavorable blood pressure patterns prevailing for most middle-aged and older individuals of diverse ethnic-racial and sociodemographic backgrounds. INTERMAP recruited 4,680 men and women aged 40–59 years from 17 randomly selected diverse population samples in four countries (China ($n = 839$), Japan ($n = 1,145$), United Kingdom ($n = 501$), and United States ($n = 2,195$)). Three rural samples (two north, one south) were surveyed in China.

INTERMAP design, data collection, and measurement procedures, and participant characteristics have been published previously (13–15). Briefly, participants were asked to attend the local research center four times: two visits on consecutive days, two visits again on average 3 weeks later. Dietary data were collected at each visit with the in-depth multipass 24-h recall method (14). All foods and drinks consumed in the previous 24 h, including dietary supplements, were recorded during a detailed interview by a trained and certified dietary interviewer. In countries other than the United States, dietary data were first entered onto standard forms, then coded and computerized (14). At the country level, coded recalls were logged into batches of 30, with a 10% random sample selected for recoding by the Country Nutritionist. Percent line error was calculated ((sum of lines with error/total lines of coding) \times 100). If this error rate exceeded 6%, the batch was recoded locally and subjected to this quality control procedure again until it passed. Nutrient data were derived from country-specific food tables standardized and enhanced by the Nutrition Coordinating Center, University of Minnesota (14,16). Dietary quality control procedures indicated generally high data quality (14).

Two 24-h urine specimens, timed at the research center, were collected on average 3 weeks apart (17). Measurements included 24-h urinary excretion of sodium, potassium, calcium, magnesium, and creatinine. Questionnaire data were obtained by interview on demographic and other possible confounding factors including physical activity, smoking, medical history, and medication use (13). Participants were asked whether they were on a special diet for weight loss, weight gain, vegetarianism, salt reduction, diabetes mellitus, fat modification, or other reasons. BMI was calculated as weight (kg)/height (m)² measured at visits one and three.

Of 839 Chinese participants, 28 were on a special diet, 42 had diabetes or cardiovascular disease, and 17 had diabetes or cardiovascular disease and were on a special diet. These participants were excluded from the main analyses. Cancer patients were excluded by design in INTERMAP. After these exclusions, a total of 752 apparently healthy Chinese men and women remained.

The study was approved by the Institutional Review Board at each center. All participants gave written informed consent.

MSG assessment

MSG is a common additive to Chinese food, shaken into foods during cooking. For most Chinese INTERMAP participants, who were from

rural areas, all foods were prepared in their households; they seldom ate processed or restaurant-prepared food. Thus the MSG measurements were reasonable estimates of total exposure to this additive. For INTERMAP Japanese, British, and American participants, MSG intake was more likely to be from commercially processed and restaurant foods, hence more difficult to quantify in these samples.

To assess MSG intake, Chinese INTERMAP participants were asked whether they used MSG in food preparation. MSG users were asked to demonstrate the amount added during food preparation, using actual MSG. For men, the wife was asked, if the food was prepared by her, to demonstrate amount of MSG added. Amounts shaken out were weighed by trained interviewers using a precise scale. For those who used soy sauce, the amount of MSG contained was derived from the labeling or recipes provided by the manufacturers. If participants reported that they had commercially processed foods during the survey, recipes were obtained by the interviewers from the grocery store or food booth. If participants ate restaurant foods, interviewers visited restaurants; chefs were interviewed and asked to demonstrate amounts of MSG added to the dishes. Average MSG intake from the four 24-h recalls per person was used in the analyses.

Overweight definition

In accordance with recommendations of the World Health Organization (18) and the International Association for the Study of Obesity for Asian populations (19), overweight was defined as BMI ≥ 23.0 kg/m² and BMI ≥ 25.0 .

Statistical analyses

To examine the association of MSG intake with overweight, we used logistic regression to estimate the odds ratios for overweight defined by BMI ≥ 23.0 and BMI ≥ 25.0 . MSG nonusers served as reference group; MSG users were divided into tertiles according to MSG intake. Odds ratios of overweight were calculated by comparing each MSG intake group with nonusers. Median MSG intake in each group was used as a continuous variable to test for trend across groups. In addition, multiple linear regression analysis was used to assess dose–response relationship between MSG intake and BMI. Gender-specific analyses were also performed.

Because of limited literature, dietary and nondietary potential confounders were identified based mainly on statistical tests. We calculated partial correlations between MSG and BMI, respectively, with individual nutrients and 24-h urinary excretions of sodium and potassium with adjustment for age, gender, and sample. Potential confounders were added sequentially to regression models to explore if odds ratios were substantially different with and without adding a particular variable. Adjustments were made with three successive models: model 1—adjustment for age, gender, sample; model 2—model 1 variables plus smoking status (never, former, current < 20 cigarettes/day, and current ≥ 20 cigarettes/day), physical activity (hours of moderate activity and hours of heavy activity per day, two variables), 24-h excretion of sodium, total energy intake; model 3—model 2 variables plus five nutrients, expressed as caloric density: animal protein, saturated fat, monounsaturated fat, total available carbohydrate, and fiber.

P values were two-sided with $P \leq 0.05$ considered statistically significant. SAS software (version 9; SAS Institute, Cary, NC) was used for analyses.

RESULTS

Of the 752 Chinese participants, 82.4% (84.2% men and 80.6% women) used MSG. Average intake of MSG was 0.33 g/day (s.d. = 0.40). Men had a slightly higher MSG intake than women (0.36 and 0.30 g/day). Average BMI was 22.3 (s.d. = 2.7) for men and 23.6 (3.6) for women. Age-, gender- and sample-adjusted characteristics of study participants are presented in **Table 1**. MSG users had higher BMI and were more likely to be overweight than nonusers. Also, MSG users generally had

Table 1 Age-, sex-, and sample-adjusted characteristics of study participants (752 healthy Chinese adults) by MSG intake

Characteristics	Nonusers of MSG	MSG users			P value
		Tertile 1	Tertile 2	Tertile 3	
Number of participants (%)	132 (17.6)	201 (26.7)	215 (28.6)	204 (27.1)	—
Education (years)	5.2 (0.23)	5.5 (0.20)	5.3 (0.17)	5.7 (0.20)	0.21
BMI (kg/m ²)	22.3 (0.28)	22.7 (0.24)	23.1 (0.21)	23.5 (0.25)	0.01
%BMI ≥ 23.0	34.5	40.0	46.1	54.4	0.01
%BMI ≥ 25.0	12.3	20.2	25.8	30.3	<0.01
Smoking status (%)					
Never	54.4	54.7	53.4	56.0	0.72
Former	5.7	5.3	10.8	8.2	
<20 cigarettes/day	12.1	11.2	10.6	9.2	
≥20 cigarettes/day	27.8	28.8	25.2	26.6	
Heavy activity (h/day)	1.9 (0.28)	2.0 (0.24)	2.3 (0.22)	2.0 (0.25)	0.73
Moderate activity (h/day)	4.2 (0.29)	4.2 (0.25)	4.2 (0.22)	4.0 (0.25)	0.98
Urinary sodium (mmol/24 h)	239 (6.79)	219 (5.82)	220 (5.21)	224 (6.02)	0.09
Urinary potassium (mmol/24 h)	39.6 (1.16)	38.2 (0.99)	36.7 (0.89)	39.0 (1.03)	0.14
Daily nutrient intake					
Glutamic acid (% kcal)	2.9 (0.04)	2.9 (0.03)	2.9 (0.03)	3.0 (0.03)	0.23
Alcohol (% kcal)	2.0 (0.53)	2.4 (0.46)	3.3 (0.41)	3.1 (0.47)	0.23
Total protein (% kcal)	12.1 (0.15)	12.3 (0.13)	12.5 (0.11)	12.7 (0.13)	0.08
Animal protein (% kcal)	1.9 (0.17)	2.3 (0.15)	2.7 (0.13)	3.1 (0.15)	<0.01
Vegetable protein (% kcal)	10.2 (0.11)	10.0 (0.09)	9.8 (0.08)	9.6 (0.10)	<0.01
Total fat (% kcal)	17.2 (0.51)	18.8 (0.44)	20.4 (0.39)	22.4 (0.45)	<0.01
SFA (% kcal)	4.0 (0.17)	4.7 (0.14)	5.2 (0.13)	5.9 (0.15)	<0.01
MFA (% kcal)	6.7 (0.24)	7.5 (0.20)	8.2 (0.18)	9.3 (0.21)	<0.01
PFA (% kcal)	5.4 (0.18)	5.5 (0.15)	5.9 (0.14)	6.1 (0.16)	0.03
n-3 fatty acids (% kcal)	0.47 (0.02)	0.53 (0.02)	0.53 (0.02)	0.54 (0.02)	0.10
n-6 fatty acids (% kcal)	5.0 (0.17)	5.0 (0.14)	5.4 (0.13)	5.6 (0.15)	0.04
Cholesterol (mg/1,000 kcal)	61.2 (7.46)	79.8 (6.40)	94.7 (5.72)	101.2 (6.62)	<0.01
Keys dietary lipid score	13.2 (0.88)	16.8 (0.75)	19.2 (0.67)	21.1 (0.78)	<0.01
Total available carbohydrate (% kcal)	68.7 (0.79)	66.4 (0.67)	63.7 (0.60)	61.8 (0.70)	<0.01
Starch (% kcal)	60.4 (0.84)	58.3 (0.72)	55.6 (0.64)	52.7 (0.74)	<0.01
Estimated total sugars (% kcal)	8.3 (0.47)	8.1 (0.40)	8.2 (0.36)	9.2 (0.41)	0.25
Calcium (mg/1,000 kcal)	144 (4.63)	145 (3.98)	151 (3.55)	152 (4.11)	0.49
Magnesium (mg/1,000 kcal)	166 (2.67)	154 (2.29)	155 (2.05)	152 (2.37)	<0.01
Phosphorus (mg/1,000 kcal)	457 (6.09)	437 (5.22)	441 (4.67)	441 (5.40)	0.06
Fiber (g/1,000 kcal)	16.0 (0.32)	14.1 (0.27)	13.6 (0.25)	13.5 (0.28)	<0.01
Total energy (kcal)	1,965 (42)	1,951 (36)	2,031 (33)	2,216 (38)	<0.01

Data are mean (s.e.), unless otherwise specified. Keys dietary lipid score = 1.35 (2SFA–PFA) + 1.5 Cholesterol^{1/2}. MFA, monounsaturated fatty acids; PFA, polyunsaturated fatty acids; SFA, saturated fatty acids.

higher intakes of animal protein, fats, cholesterol and calories, and lower intakes of vegetable protein, total carbohydrate, starch, fiber, and magnesium than nonusers.

With adjustment for potential confounders, MSG intake was positively related to BMI. With 1 g higher MSG intake, the estimate of BMI was higher by 0.61 kg/m² ($P = 0.08$). Prevalence of overweight was significantly higher for MSG users than

nonusers: with BMI ≥ 23.0 as criterion for overweight, the multivariable odds ratio (model 3) for MSG users in the highest tertile of MSG intake compared with nonusers was 2.10 (95% confidence interval, 1.13–3.90, P for trend across the four MSG categories = 0.03); with BMI ≥ 25.0, it was 2.75 (95% confidence interval, 1.28–5.95, P for trend = 0.04) (Table 2). Positive associations between MSG intake and overweight prevailed for men

Table 2 Odds ratio and 95% confidence interval for overweight by MSG intake

	Nonusers of MSG	MSG users			P value
		Tertile 1	Tertile 2	Tertile 3	
Number of participants	132	201	215	204	—
Median MSG intake (range), g/d	0.00 (0.00–0.00)	0.08 (0.01–0.15)	0.28 (0.15–0.45)	0.70 (0.45–3.23)	—
BMI ≥ 23.0					
No. of participants with BMI ≥ 23.0	56	98	97	85	—
Model 1	1.0	1.27 (0.80–2.00)	1.67 (1.03–2.72)	2.50 (1.43–4.38)	<0.01
Model 2	1.0	1.42 (0.88–2.30)	1.84 (1.10–3.06)	2.51 (1.40–4.52)	<0.01
Model 3	1.0	1.30 (0.80–2.12)	1.59 (0.94–2.72)	2.10 (1.13–3.90)	0.03
BMI ≥ 25.0					
No. of participants with BMI ≥ 25.0	25	55	52	42	—
Model 1	1.0	1.61 (0.92–2.82)	2.33 (1.28–4.25)	3.37 (1.68–6.75)	<0.01
Model 2	1.0	1.83 (1.03–3.25)	2.59 (1.39–4.83)	3.21 (1.55–6.65)	<0.01
Model 3	1.0	1.77 (0.98–3.20)	2.36 (1.23–4.52)	2.75 (1.28–5.95)	0.04

Model 1, adjustment for age, gender, and sample; model 2, model 1 with additional adjustment for smoking status, heavy activity, moderate activity, total energy intake, and 24-h excretion of sodium; model 3, model 2 with additional adjustment for intakes (expressed as caloric density) of animal protein, saturated fatty acids, monounsaturated fatty acids, total carbohydrate, and fiber. P value is test for trend across four categories.

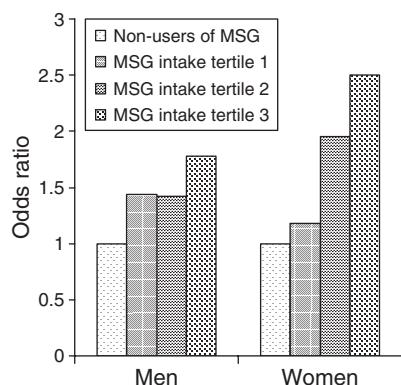


Figure 1 Odds ratio of overweight (BMI ≥ 23.0 kg/m²) by gender according to monosodium glutamate (MSG) intake. Adjustment for age, gender, and sample, smoking status, heavy activity, moderate activity, total energy intake, 24-h excretion of sodium, and intakes (expressed as caloric density) of animal protein, saturated fatty acids, monounsaturated fatty acids, carbohydrates, and fiber.

and women, slightly more pronounced in women (Figure 1), but the interaction test between MSG intake and gender was statistically nonsignificant.

In sensitivity analyses including all 839 INTERMAP Chinese participants, the associations of MSG intake with BMI were somewhat attenuated (data not shown). Also, because 7% (n = 54) participants reported in at least one visit that they ate commercially processed foods or restaurant foods, we excluded those participants in further sensitivity analyses; associations between MSG intake and BMI remained (data not shown).

DISCUSSION

This cross-sectional study is, to the best of our knowledge, the first to examine the association between MSG intake and overweight in human population samples. A positive relation

prevailed with control for physical activity, total energy intake, and other possible confounders. Although animal studies have indicated for decades that MSG intake may cause overweight or obesity, data on humans have been lacking, possibly because MSG is widely used in commercially processed foods; hence it is difficult to measure intake, particularly in economically developed countries. INTERMAP Chinese participants were from rural areas in China. In 1997 when the population-based INTERMAP field surveys were done, most foods eaten by Chinese participants were prepared in their households (by themselves or by their spouses). Thus, they lent themselves particularly to the investigation of MSG intake in relation to overweight/obesity.

These positive associations between MSG intake and overweight are generally consistent with data from animal studies. In 1969, it was first reported that weight gain in 4 months was significantly greater in both male and female mice with large-dose MSG administration immediately after birth compared to controls, even though the controls had slightly larger food consumption (5). Hypothalamic lesions were found in the MSG-treated animals. The investigator suggested that a regulatory mechanism affecting fat metabolism in the mouse, other than appetite disturbance, should be considered as linking MSG intake with obesity. Recently, the MSG-obesity hypothesis has been reformulated, i.e., chronic MSG intake may intoxicate arcuate nucleus neurons and disrupt the hypothalamic signaling cascade of leptin action, causing leptin resistance related to overweight/obesity (9,10).

MSG ingestion as a cause of hypothalamic damage has been debated for decades. Some animal studies suggest that injection of MSG may induce neuronal necrosis in several brain regions including the hypothalamus (5,20–25). Because destruction of hypothalamic neurons in animals results in a complex neuroendocrine deficiency syndrome, concern has

arisen that ingestion of MSG by humans may contribute to occurrence of neuroendocrinopathies (26,27). Most of the evidence on hypothalamic lesions and appetite regulation was provided from laboratory animals that were injected with MSG at neonatal age. Although the deleterious effects of MSG injection on hypothalamic neuronal circuitries have been well documented, limited studies have been published on the effects of orally administered MSG (12,28). Some researchers are unconvinced that oral MSG affects appetite regulation (29). Further studies are clearly needed. Nevertheless, the findings from our study support the judgment against MSG supplementation of human foods.

In addition, studies have indicated an important role for leptin in regulating food intake and energy balance (30,31). Leptin receptor mRNA is present in the hypothalamus, postulated as a potential site of action for leptin (32). Leptin production is increased in animal models of obesity associated with experimentally induced hypothalamic damage, including the MSG-treated model (33). One study found that leptin suppressed body weight gain in controls but did not suppress weight gain in MSG-treated rats (6). This finding suggests that destruction of neurons in the hypothalamus by MSG can attenuate the actions of leptin. Another study reported that leptin significantly inhibited food intake and caused weight loss in control rats whereas MSG-treated rats were unresponsive to leptin treatment (7). The authors suggested that the hypothalamic arcuate nucleus is essential for mediating the anorectic effects of leptin influencing energy balance. Hypothalamic obesity has been reported in humans due to hypothalamic damage from tumor (34,35), as well as in animals after neonatal administration of MSG (5,36). A recent study reported that MSG maintains its toxicity in animals when administered orally, and that MSG at concentrations only slightly surpassing those found in everyday human food has potential for damaging hypothalamic regulation of appetite (12).

A further mechanism for the possible linkage of MSG to obesity is that MSG may regulate adiponectin and thereby change body composition. Adiponectin is synthesized and secreted by adipocytes. Depressed adiponectin expression has been associated with obesity in animal models (37). Mice treated with MSG had 50% lower serum adiponectin and more than twofold higher percentage of body fat than lean controls (38).

A positive association between MSG intake and overweight may be a result of greater voracity because MSG or leptin resistance can stimulate appetite. In the INTERMAP Chinese samples, participants with higher MSG intake tended to have higher total energy intake. However, our findings are independent of total energy intake. Presumably, overweight independent of total energy intake and physical activity was due to decreased nonexercise energy expenditure, e.g., thermogenesis (39,40).

Our findings are unlikely to be due to chance. The multivariable-adjusted positive associations are statistically significant, and prevailed for men and women. Also, the associations were present using either the international standardized cutoff (BMI \geq 25.0) or the World Health Organization recommendation (BMI \geq 23.0) for overweight for Asian populations.

One concern is the accuracy of the MSG measurement. Similar to other food additives such as salt (NaCl), MSG intake is difficult to quantify accurately with existing dietary assessment instruments. However, our estimation of MSG intake in INTERMAP is unlikely to be substantially biased. First, all foods eaten by the great majority of INTERMAP Chinese participants were exclusively prepared in their households. Second, the amounts of MSG added to foods during preparation appear to be habitual and were demonstrable by participants in the diet assessment. Third, although estimates of absolute intake of MSG may have been limited in precision, we apparently were able to identify MSG users and nonusers. In fact, the prevalence of overweight among MSG users was significantly higher compared with MSG nonusers, in addition to the positive trend for relation of amount of MSG intake to BMI. Finally, measurement error is likely to be nondifferential, tending to dilute any observed association.

Another relevant question is: why are Asian populations relatively lean even though MSG use is popular in Asian cuisine? A possible explanation is that an adverse effect of MSG intake on body weight may be attenuated by lower caloric density of foods and other lifestyle factors such as greater physical activity in Asian populations compared to Western populations. For example, the average amount of heavy activity per day for INTERMAP rural Chinese participants was 2.4 h (s.d. = 3.7) for men and 1.7 h (3.2) for women, indicating relatively higher energy expenditure in this group.

In this study, our ability to examine the relationship of MSG intake and obesity was limited by the small number of persons (3%) with BMI \geq 30.0. However, the partial correlation between MSG intake and BMI approached significance. Hence it is reasonable to infer that MSG intake is also associated with higher prevalence of obesity. This study is also limited by lack of data on leptin and adiponectin concentrations. In addition, the INTERMAP findings are cross-sectional, but nevertheless unique; this topic has not been previously pursued in human population samples.

In conclusion, we found a positive relation of MSG intake to BMI that persisted with control for physical activity and total energy intake among apparently healthy Chinese adults. MSG intake was significantly related to prevalence of overweight. This study is of public health interest because MSG is increasingly used worldwide. This study also provides the first data in humans on this issue and raises a concern about MSG use and body weight in addition to allergenic effects. Further studies are needed to determine reproducibility of these findings, elucidate their etiopathogenetic pathway, and amass the evidence needed to assess whether the relation between MSG intake and body weight is causal.

ACKNOWLEDGMENTS

This work was supported by National Institutes of Health grants 2-R01-HL50490 and R21DK073812; the Chicago Health Research Foundation; and national and local agencies in China, Japan, and the United Kingdom. We thank our colleagues from Beijing, Shanxi Province, and Guangxi Zhuang Autonomous Region, and colleagues at other INTERMAP research facilities. A partial listing of these colleagues is given in ref. 13.

DISCLOSURE

The authors declared no conflict of interest.

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