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S-Adenosylmethionine Is Associated with Fat Mass and Truncal Adiposity in Older Adults[1–3]

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Abstract

S-adenosylmethionine (SAM) is synthesized from methionine, which is abundant in animal-derived protein, in an energy-consuming reaction. SAM and *S*-adenosylhomocysteine (SAH) correlate with body mass index (BMI). Plasma total concentration of the SAM-associated product cysteine (tCys) correlates with fat mass in humans and cysteine promotes adiposity in animals. In a cross-sectional study of 610 participants, we investigated whether SAM and SAH are associated with BMI via lean mass or fat mass and dietary protein sources as determinants of SAM and tCys concentrations. Plasma SAM was not associated with lean mass, but mean adjusted fat mass increased from 24 kg (95% CI: 22.6, 25.1) to 30 kg (95% CI: 28.7, 31.3) across SAM quartiles ($P < 0.001$) and trunk fat:total fat ratio increased from 0.48 to 0.52 ($P < 0.001$). Erythrocyte SAM was also positively associated with fat mass and trunk fat:total fat ratio. The association of SAM with fat mass was not weakened by adjustment for serum tCys, lipids, creatinine, or dietary or lifestyle confounders. Concentrations of the SAM precursor, methionine, and the SAM product, SAH, were not independently associated with adiposity. Intake of animal-derived protein was not related to serum methionine but was positively associated with plasma SAM (partial $r = 0.11$) and serum tCys (partial $r = 0.13$; $P < 0.05$ for both after adjustment for age, gender, and total energy intake). In conclusion, plasma SAM, but not methionine, is independently associated with fat mass and truncal adiposity, suggesting increased conversion of methionine to SAM in obese individuals. Prospective studies are needed to investigate the interactions among dietary energy and animal protein content, SAM concentrations, and change in body weight and cardiometabolic risk. J. Nutr. 143: 1982–1988, 2013.

Introduction

S-adenosylmethionine (SAM)[13] is a high-energy compound that is synthesized from ATP and methionine (1), an essential amino acid abundant in animal-derived protein (2). *S*-adenosylhomocysteine (SAH), and subsequently homocysteine, are products of SAM-dependent methylation (3). Homocysteine is either remethylated to methionine or undergoes irreversible transsulfuration by cystathionine β synthase (CBS), which is regulated by SAM (4). Products of the transsulfuration pathway include cystathionine, cysteine, and glutathione.

Mouse CBS knockouts have substantial loss of fat mass (*5*). Likewise, humans with CBS deficiency are lean with decreased plasma total cysteine (tCys) (6). In contrast, high-plasma tCys is associated with increased BMI and fat mass in children and adults (7–9). Feeding cystine to mice induces lipogenic enzymes, lowers metabolic rate, and increases visceral adiposity (10). These observations suggest that cysteine or a related factor regulates body adiposity (11).

We previously explored the associations of plasma methionine, total homocysteine (tHcy), cystathionine, and total glutathione (tGSH) with fat mass. Apart from cystathionine, none showed positive associations (7,9). SAM and SAH have not, to our knowledge, been investigated in the same context. However, recently, plasma SAM was reported to increase across BMI categories (12) and BMI strongly correlated with plasma SAM

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[3] Supplemental Tables 1-3 are available from the "Online Supporting Material" link in the online posting of the article and from the same link in the online table of contents at http://nutrition.org.
[12] H.R. and J.M.D. are joint senior authors.
[13] Abbreviations used: CBS, cystathionine β synthase; MAT, methionine adenosyltransferase; SAA, sulfur amino acid; SAH, *S*-adenosylhomocysteine; SAM, *S*-adenoylemethionine; tCys, total cysteine; tGSH, total glutathione; tHcy, total homocysteine.
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and SAH in women (13). It is not known whether this is due to associations with fat mass or lean mass or whether the associations are independent of tCys.

As a product of methionine, the initiating amino acid in all eukaryotic protein synthesis (3), SAM might be expected to correlate with lean mass. SAM is also linked to lean mass via muscle creatine, which is partly supplied by SAM-dependent methylation (14). Yet SAM also lies at the intersection between sulfur amino acid (SAA) and fat metabolism. SAM provides methyl groups for synthesis of phosphatidylcholine (15), which is incorporated into VLDL, the "packaged" form of dietary fat that is exported from the liver (15). Low liver SAM disrupts VLDL assembly, leading to synthesis and secretion of lipid-poor VLDL particles (16).

SAM is also a direct player in epigenetic regulation via DNA methylation. Along with other high-energy compounds, SAM may act as a sensor of cellular nutrient status that links nutrient availability with epigenetic regulation (17). Adiposity-related phenotypes resulting from diet changes in animals are linked to epigenetic modifications in genes influencing appetite, food selection, and glucose metabolism (18). Further, methylation of specific genes at birth was associated with later childhood fat mass (19). But despite the importance of SAM in VLDL formation and in methylation of metabolic genes, it is not known if SAM availability is associated with body fat mass at the population level. The role of diet in determining SAM concentration in humans is also not clear.

In this study, we investigated the associations of SAM and SAH in plasma and erythrocytes with lean mass and fat mass in older adults and explored different dietary protein sources as determinants of circulating SAM.

Methods

Subjects

The present study is a cross-sectional investigation using data from a single episode in the Hoorn Study, a prospective cohort of men and women aged 50–75 y (n = 2484) that started in 1989 (20). In the year 2000, all participants with type 2 diabetes (n = 176) and random samples of participants with normal (n = 705) and impaired (n = 193) glucose metabolism were invited (total n = 1074). A total of 648 (60%) participated and formed the basis for the present study. The analysis was limited to individuals with complete data on SAM, SAH, and body composition (n = 610). Of these, 551 participants had a complete serum SAA profile, including methionine, tHcy, cystathionine, tCys, and tGSH.

All participants provided written informed consent and the Ethics Committee of VU University Medical Center Amsterdam approved the study.

Study variables

Anthropometry and body composition. Weight and height were measured in participants wearing light clothing and BMI was calculated. Weight categories were defined using BMI cutoffs as follows: normal weight (BMI <25 kg/m^2), overweight (BMI = 25–29.9 kg/m^2), and obese (BMI ≥30 kg/m^2).

DXA was performed using fan beam technology (QDR-2000, software version 7.20D; Hologic). The software provides estimates of lean mass and fat mass, and bone mineral mass for total body and for standard body regions using specific anatomic landmarks (21). We used data on total fat mass, total soft tissue lean mass, and trunk fat mass. The ratio of trunk fat mass:total fat mass was used as an index of central (truncal) adiposity.

Health, lifestyle, and diet. Self-reported questionnaires provided information on health, physical activity (min/wk), caffeine consumption (mg/d), alcohol intake (g/d), and smoking (nonsmoker, ex-smoker, current smoker). Cardiovascular disease was defined as self-reported intermittent claudication, angina pectoris, or myocardial infarction (22) or a history of stroke or transient ischemic attack. Hypertension was defined as systolic blood pressure ≥160 mm Hg, a diastolic blood pressure ≥95 mm Hg, and/or the use of antihypertensives (23). Diabetes was defined according to revised WHO criteria 2011 (24).

A self-administered, validated FFQ developed for Dutch cohorts of the EPIC Study (25) was used to assess habitual dietary intakes. Intakes of energy and nutrients were calculated according to the extended version of the Dutch food composition table (NEVO) 1996 (26). Six food groups were used in the present study: red meat (the sum of beef, pork, and lamb intakes); poultry; fish (oily fish, lean fish, and shellfish); dairy (milk and milk products, including cheese and yoghurt of the whole, skimmed, and semi-skimmed varieties); whole grains (whole-grain cereals and brown rice); and legumes.

Biochemical analyses. Samples were processed within 30 min and stored at −80°C (except for lipids, −20°C). After collection, EDTA-blood was placed on ice for determination of SAM and SAH. Samples were immediately deproteinized and tandem MS was used for determination of SAM and SAH in plasma and whole blood, as previously described (inter-assay CV, 8% and 6%, respectively) (27). Erythrocyte concentrations were calculated by multiplying the difference between plasma and whole blood values by 100 × hematocrit^{-1}.

Methionine, tHcy, cystathionine, tCys, and tGSH were measured in serum using tandem-MS (28). The CV was <4% for tCys and tHcy and <8% for methionine, cystathionine, and tGSH. Serum folate and vitamin B-12 (CV ~5% for both) were measured by automated chemiluminescence (Chiron Diagnostics ASC:180 Automated Chemiluminescence System). Serum total cholesterol, HDL cholesterol, and TGs were assayed by enzymatic techniques. LDL cholesterol was calculated as the difference between total and HDL cholesterol. Serum creatinine was measured by modified Jaffé method (29).

Statistical methods

Population characteristics are summarized as median (25th, 75th percentile). The Kruskal-Wallis test was used for analysis of variance, and group comparisons were conducted using the Mann-Whitney U test. Skewed variables were log-transformed for parametric tests. $P < 0.05$ was considered significant for all tests.

Interactions. Univariate general linear models were used to test for interactions by gender, diabetes, or weight category on the associations of SAM, SAH, and SAA (as quartiles) with body composition variables (as continuous outcome variables) with adjustment for age (and gender in case of diabetes and weight category). Where meaningful significant interactions were detected, we stratified the analysis accordingly.

Correlation and linear regression analysis. Pearson correlations were used to explore: 1) the associations among SAM, SAH, SAA, and body composition; and 2) the relation of different dietary protein sources with SAM, methionine, and tCys concentrations after adjustment for age, gender, and energy intake.

Linear regression was used to determine independent predictors of fat mass and trunk fat:total fat ratio. Factors that are potentially related to body build or SAA metabolism were included as covariates, such as height, exercise, smoking, and serum lipids and B vitamins. The analysis was also adjusted for surrogate markers of the products of SAM-dependent methylation that are linked to lean mass or fat mass: *1*) creatinine, which comes from muscle creatine, a product of SAM-dependent methylation (14); and *2*) LDL-cholesterol, a constituent of lipoproteins that incorporate phosphatidylcholine, a phospholipid that is partly supplied by methylation (15).

To quantify the associations, adjusted means and 95% CIs of lean mass, fat mass, and trunk fat:total fat ratio were plotted by gender-specific quartiles of SAM, methionine, and tCys.

All analyses were done using PASW Statistics for Mac (18.0, SPSS).

Results

Population characteristics. The study included 304 men and 306 women with a median age of 69 y. Despite similar BMI, all body composition measures differed between men and women

TABLE 1 Characteristics of the study population according to gender[1]

	Men (n = 304)	Women (n = 306)
Age, *y*	69 (65, 74)	69 (65, 75)
BMI, *kg/m²*	26.7 (24.6, 28.9)	26.9 (24.5, 30.1)
Total lean mass, *kg*	54.7 (50.8, 59.0)	39.3 (36.7, 42.6)*
Total fat mass, *kg*	22.6 (18.3, 28.0)	29.3 (17.8, 47.0)*
Body fat, *%*	28.1 (18.2, 38.8)	42.1 (37.3, 46.3)*
Trunk fat mass, *kg*	12.0 (9.3, 15.8)	14.3 (10.0, 18.0)*
Trunk fat:total fat ratio	0.54 (0.50, 0.58)	0.48 (0.43, 0.52)*
Circulating variables[2]		
SAM, *nmol/L*	89 (80, 103)	89 (77, 100)
SAH, *nmol/L*	16.3 (13.7, 20.1)	13.4 (11.1, 16.4)*
Methionine, *μmol/L*	27.1 (24.8, 29.9)	24.6 (22.2, 26.4)*
Total homocysteine, *μmol/L*	13.3 (11.1, 16.6)	11.7 (9.8, 13.7)*
Cystathionine, *μmol/L*	0.23 (0.18, 0.34)	0.23 (0.17, 0.32)
tCys, *μmol/L*	319 (292, 346)	315 (294, 348)
Total glutathione, *μmol/L*	2.99 (2.60, 3.31)	2.83 (2.47, 3.27)*
Folate, *nmol/L*	14.1 (10.8, 18.2)	15.6 (12.3, 19.4)*
Vitamin B-12, *pmol/L*	270 (221, 326)	285 (232, 353)*
TGs, *mmol/L*	1.30 (1.00, 1.80)	1.30 (0.90, 1.70)
LDL-cholesterol, *mmol/L*	3.40 (2.80, 4.00)	3.80 (3.20, 4.40)*
Creatinine, *μmol/L*	102 (94, 112)	87 (80, 92)*
Erythrocyte SAM, *μmol/L*	3.71 (3.40, 4.12)	3.53 (3.09, 3.93)*
Erythrocyte SAH, *nmol/L*	136 (87, 211)	142 (85, 229)*
Health and lifestyle		
Alcohol intake, *g/d*	10.3 (2.1, 27.5)	2.9 (0.2, 11.1)*
Coffee intake, *mL/d*	450 (225, 563)	337(140, 450)*
Current smokers, *%*	19	12*
Physical activity, *h/d*	2.4 (1.3, 4.3)	3.1 (1.8, 3.6)*
Cardiovascular disease, *%*	54	52
Hypertension, *%*	47	54
Intake of lipid-lowering drugs, *%*	17	13
Intake of vitamin B supplements, *%*	4	4
Dietary intakes, *% of total energy*		
Total protein	14.8 (13.2, 16.1)	15.6 (14.0, 17.2)*
Animal protein	9.1 (7.8, 10.9)	10.1 (8.2, 11.9)*
Total fat	35.4 (31.2, 38.6)	33.9 (30.7, 37.5)*
Carbohydrate	44.1 (39.8, 48.6)	47.1 (42.8, 50.9)*

[1] Data presented as medians (25th, 75th percentiles). *Different from men by Mann-Whitney U test, $P < 0.05$. SAH, *S*-adenosylhomocysteine; SAM, *S*-adenosylmethionine; tCys, total cysteine.
[2] Measured in serum or plasma unless otherwise indicated.

(**Table 1**). Women also had higher concentrations of B vitamins and lower serum methionine, SAH, tHcy, and tGSH, whereas serum tCys and SAM were similar in men and women. Around one-half of the participants had a history of cardiovascular disease and/or hypertension (Table 1). The population characteristics according to weight category are shown in **Supplemental Table 1**. Overweight and obese men and women had higher plasma SAM, SAH, and tCys compared with normal-weight participants.

Type 2 diabetes was present in 28% of men and 26% of women. There were several differences between diabetic and nondiabetic individuals in adiposity measures and circulating sulfur compounds (**Supplemental Table 2**). Plasma SAM, SAH, cystathionine, and tCys were higher in participants with diabetes and tGSH was lower. Diabetic individuals also had significantly higher intakes of total protein and animal protein and higher prevalence of cardiovascular disease and hypertension (Supplemental Table 2).

Interactions. There was no effect modification by diabetes on the associations of SAM, SAH, methionine, or tCys with fat mass or lean mass (P-interaction = 0.18–0.89) apart from interactions in case of plasma SAH as a predictor of fat mass (P-interaction = 0.047) and methionine as a predictor of lean mass (P-interaction = 0.06). The association patterns were essentially similar, so participants with and without diabetes were pooled for the present analysis. There were also no interactions by gender and therefore men and women were combined for analysis. There was, however, a significant effect modification by weight category on the association of SAM with fat mass as detailed below.

Associations of SAM and SAH with related compounds. Using Pearson correlations adjusted for age and gender, SAM and SAH in plasma were strongly correlated (partial $r = 0.70$; $P < 0.001$), whereas SAM and SAH in erythrocytes were not. SAM and SAH in plasma, but not in erythrocytes, positively correlated with serum cystathionine and tCys (partial $r = 0.20$–0.42; $P < 0.001$ for all). Plasma SAH was also associated with serum tHcy (partial $r = 0.34$; $P < 0.001$). Plasma and erythrocyte SAM concentrations were not related to serum folate or vitamin B-12 (data not shown).

SAM, SAH, related metabolites, and body composition. Plasma SAM and SAH, serum tCys, and erythrocyte SAM correlated with BMI, fat mass, body fat percentage, and trunk fat:total fat ratio after adjustment for age and gender (**Supplemental Table 3**). The strongest correlations were for plasma SAM and tCys with fat mass and body fat percentage (partial $r = 0.25$–0.27; $P < 0.001$ for all). Erythrocyte SAM was more strongly associated with trunk fat:total fat ratio (partial $r = 0.21$; $P < 0.001$) than with other measures. Plasma SAM was associated with serum creatinine but not with LDL-cholesterol.

Serum cystathionine had significant but weaker positive associations with BMI, fat mass, and body fat percentage, whereas tGSH was inversely correlated with these variables and with trunk fat:total fat ratio. Neither SAM nor SAH nor any of the SAAs or B vitamins was associated with lean mass, apart from methionine (partial $r = 0.14$; $P = 0.001$). Serum folate, vitamin B-12, and tHcy, and erythrocyte SAH, as well as the SAM:SAH ratio in plasma and erythrocytes were not associated with BMI or body composition (data not shown).

Mean fat mass, adjusted for age, gender, and lean mass, increased from 24 to 30 kg across quartiles of plasma SAM (P-trend < 0.001) and the trunk fat:total fat ratio increased from 0.48 to 0.52 (P-trend < 0.001; **Fig. 1***B*). The associations were equally strong for tCys (Fig. 1*C*) and slightly less so for plasma SAH (not shown). Methionine was unrelated to fat mass but remained modestly associated with lean mass after adjustment for fat mass (~2 kg difference; P-trend = 0.01) (Fig. 1*A*).

Independent associations of SAM, SAH, and SAA with adiposity. Preliminary regression analysis showed that the associations of plasma SAH with fat mass and the trunk fat:total fat ratio were abolished by adjustment for plasma SAM. Thus, plasma SAH was excluded from subsequent analysis due to strong collinearity with plasma SAM. The other plasma metabolites that were associated with fat mass (Supplemental Table 3) were simultaneously entered into a linear regression model to determine their independent associations with fat mass after controlling for age, gender, lean mass, diabetes, and serum folate and vitamin B-12. Plasma SAM and serum tCys were independently associated with fat mass, whereas cystathionine was not

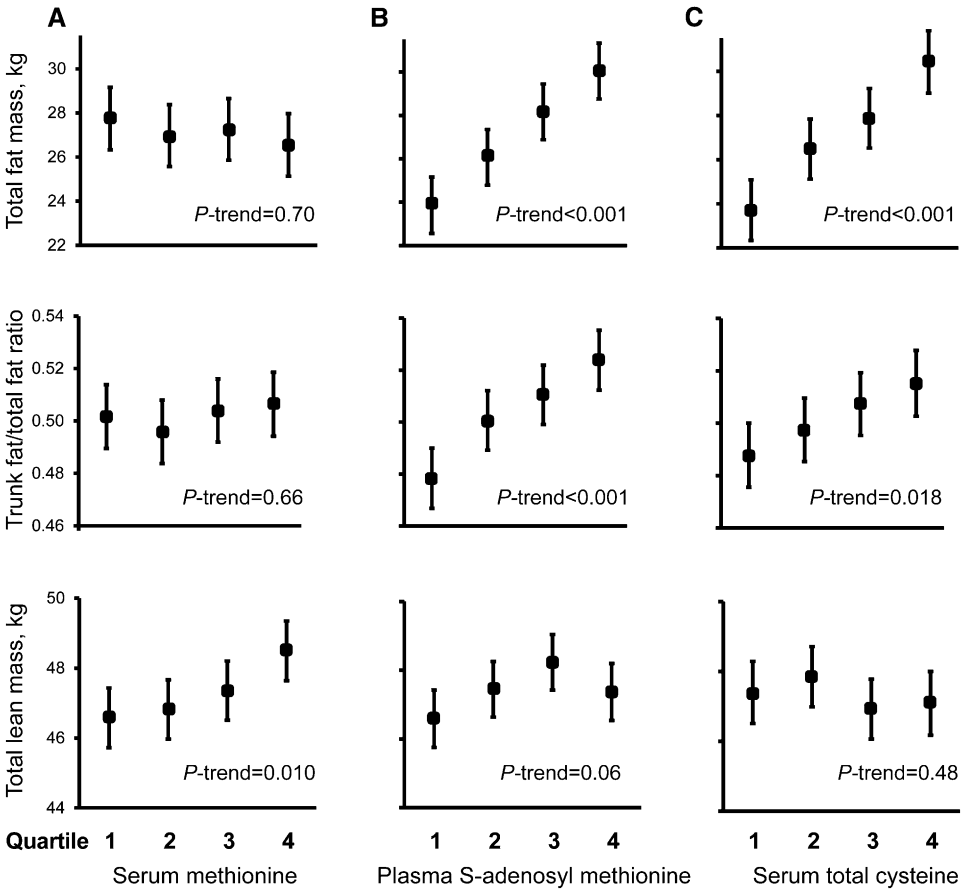

FIGURE 1 Fat mass, trunk fat: total fat ratio, and lean mass by quartiles of serum methionine (*A*), plasma SAM (*B*), and serum tCys (*C*) in the total study population. Values are means and 95% CIs, adjusted for age and gender, n = 551–610. Fat mass estimates are also adjusted for lean mass, and lean mass estimates are adjusted for fat mass. The second, third, and fourth quartiles of serum methionine begin at 24.7, 27.1, and 29.0 μmol/L in men and 22.2, 24.6, and 26.4 μmol/L in women. The second, third, and fourth quartiles of plasma SAM begin at 79.3, 89.1, and 103.0 nmol/L in men and 76.8, 88.6, and 99.3 nmol/L in women. The second, third, and fourth quartiles of serum tCys begin at 291, 318, and 345 μmol/L in men and 294, 315, and 347 μmol/L in women. SAM, *S*-adenoylemethionine; tCys, total cysteine.

(**Table 2**, model 1). Serum tGSH was inversely associated with fat mass. When erythrocyte SAM replaced plasma SAM in the same model, it was associated with fat mass (β = 0.11; P = 0.007), with little change in other predictors (data not shown). Adjustment for height, physical activity, smoking, coffee and alcohol intakes, and serum TGs, LDL-cholesterol, and creatinine did not weaken the associations for serum tCys (β = 0.19; P < 0.001) or plasma SAM (β = 0.17; P < 0.001).

Using a similar approach as above but with the trunk fat:total fat ratio as the outcome variable, SAM and to a lesser extent tCys were positively associated, whereas tGSH was inversely related to truncal adiposity (Table 2, model 2). The associations changed minimally after multiple adjustments (data not shown). When erythrocyte SAM replaced plasma SAM in model 2, it was the strongest predictor (β = 0.19; P < 0.001) but did not weaken the other predictors.

TABLE 2 Independent predictors of fat mass and trunk fat:total fat ratio in the total population and in the normal-weight and overweight/obese subgroups[1]

		Standardized regression coefficient (β)[3]			
Outcome	Predictor[2]	Total population (n = 551)	Normal-weight participants (n = 173)	Overweight/obese participants (n = 378)	P-interaction
Fat mass (model 1)	SAM[4]	0.19**	0.04	0.20**	0.020
	Cysta[4]	0.02	—	—	—
	tCys[4]	0.18**	0.15§	0.12*	0.12
	tGSH	−0.13**	−0.14§	−0.09*	0.70
Trunk fat:total fat ratio (model 2)	SAM[4]	0.16**	−0.02	0.21**	0.030
	tCys[4]	0.11*	0.08	0.06	0.27
	tGSH	−0.14*	−0.07	−0.15**	0.59

[1] Using linear regression with fat mass (model 1) or trunk fat:total fat ratio (model 2) as outcome variables. Both models are adjusted for age, gender, diabetes, and serum folate and vitamin B-12. Model 1 is additionally adjusted for lean mass. Normal-weight participants had a BMI <25 kg/m^2; overweight/obese participants had a BMI ≥25 kg/m^2. Cysta, cystathionine; SAM, *S*-adenosylmethionine; tCys, total cysteine; tGSH, total glutathione.

[2] The variables simultaneously entered as predictors are those for which results are shown and refer to serum or plasma variables. For the total population, predictors were selected based on significant (P < 0.05) correlations with the outcome variables (Supplemental Table 3). Only significant (P < 0.05) predictors in the total population were entered into analysis stratified by weight.

[3] Regression coefficients with P < 0.10 are marked as *P < 0.05, **P ≤ 0.001, §P ≤ 0.06.

[4] Using log-transformed data.

The associations of SAM with adiposity were stronger in overweight and obese participants than in normal-weight individuals (Table 2). The interaction was significant for the association of plasma SAM with fat mass ($\beta = 0.04$ $P = 0.55$ in normal-weight individuals; vs. $\beta = 0.20$, $P < 0.001$ in overweight/obese individuals; P-interaction = 0.020) and with trunk fat:total fat ratio (Table 2). There were no significant differences in the associations of SAM with adiposity in overweight compared with obese individuals (P-interaction ≥ 0.74) and no significant interactions by weight category for the associations of tCys, tGSH, or cystathionine with adiposity.

Dietary macronutrient intakes as determinants of methionine, SAM, and tCys. Animal-derived protein intake was a positive predictor of plasma SAM and serum tCys, but not serum methionine, after adjustment for age, gender, and total energy intake. In contrast, intake of plant-derived protein was inversely associated with plasma SAM and serum tCys (**Table 3**). Adjusting for intake of plant-derived protein did not weaken the associations of animal-derived protein with plasma SAM (partial $r = 0.11$; $P = 0.014$) or with serum tCys (partial $r = 0.13$; $P = 0.004$; adjusted for age, gender, energy intake, and plant-derived protein intake in g/d). Among the food groups rich in animal protein, only red meat was associated with plasma SAM (partial $r = 0.13$; $P = 0.003$), and dairy products were associated with serum tCys (partial $r = 0.10$; $P = 0.033$).

Discussion

SAM and SAH are associated with BMI (13) and are precursors of cysteine, a SAA strongly associated with obesity (11). We show that the SAM concentration in plasma and erythrocytes is unrelated to lean mass but positively correlates with fat mass independent of serum tCys. Intake of animal-derived protein, in particular from red meat, was a positive predictor of plasma SAM. Neither methionine nor SAH was independently associated with adiposity or animal protein intake. These data suggest that SAM, a high-energy compound, may be a marker of high animal protein intake and positive energy balance, both of which are associated with obesity as detailed below.

Our data are supported by previous reports that SAM is associated with BMI (12,13,30). We also observed that SAM was linked to truncal adiposity. This finding contradicts the view that increased SAM underlies the benefit of therapies that prevent liver fat accumulation (31) and that rate of SAM synthesis is decreased in patients with fatty liver (32). However, transgenic models show that not only SAM deficiency but also excess SAM promotes liver steatosis (33).

TABLE 3 Dietary protein types and sources as determinants of circulating methionine, SAM, and tCys in the total study population[1]

	Serum methionine	Erythrocyte SAM	Plasma SAM[2]	Serum tCys[2]
Total protein, *kcal/d*	−0.01	0.01	0.06	0.09*
Animal protein, *kcal/d*	0.02	0.02	0.11*	0.13*
Red meat, *g/d*	0.03	0.06	0.13*	0.06
Poultry, *g/d*	−0.01	0.10*	0.01	0.01
Fish, *g/d*	−0.01	−0.05	−0.01	0.05
Dairy, *g/d*	−0.02	−0.02	0.05	0.10*
Plant protein, *kcal/d*	−0.08	−0.03	−0.12*	−0.11*
Grains, *g/d*	0.08	−0.01	−0.04	−0.01
Legumes, *g/d*	−0.03	−0.10*	−0.04	0.03

[1] Partial correlation coefficients adjusted for age, gender, and total energy intake, $n = 503–571$. *$P < 0.05$. SAM, *S*-adenosylmethionine; tCys, total cysteine.
[2] Using log-transformed data.

Possible explanations for the association of SAM with adiposity. Elevation of SAM in overweight and obese individuals could indicate changes in SAM synthesis, catabolism, or compartmentalization or could be related to the role of SAM in VLDL production. Decreased SAM uptake and increased SAM export into the plasma are unlikely to be the only explanations, because erythrocyte SAM was also associated with adiposity. Alternatively, obesity may be associated with decreased SAM breakdown, similar to BCAAs that accumulate in obesity due to downregulation of their catabolic enzymes (34). Against this possibility is that cystathionine and cysteine, which are products of SAM catabolism via transsulfuration, are elevated rather than decreased in obesity (8).

The link between SAM and fat mass could be related to SAM's role in the production of phosphatidylcholine, a constituent of lipoproteins that exports lipids from the liver (15). However, the association was not attenuated by adjustment for the surrogate marker of lipoproteins, LDL-cholesterol, and SAM was not associated with this marker. Also, if the association of SAM with fat mass is explained by its role as a methyl donor, then the SAM:SAH ratio, an index of methylation potential (35), might correlate with fat mass. This was not the case in our study. Further, concentrations of other methyl donors, folate and vitamin B-12, were unrelated to adiposity.

Our observation that SAM, but not the precursor methionine, closely tracked fat mass is in line with the possibility that SAM synthesis increases in obesity. SAM is synthesized by methionine adenosyltransferase (MAT) in an energy-consuming process that hydrolyses all 3 phosphodiester bonds of ATP (1). MAT activation requires both methionine and ATP (36). Overexpression of liver-specific MAT1a in vitro resulted in a 50% depletion of ATP (37), implying that SAM is a quantitatively important consumer of ATP. In vitro, glucose increased MAT activity and SAM concentration (38). Thus, the positive energy balance that underlies fat deposition in obesity may also drive SAM synthesis. This interpretation fits with our observation that SAM correlates with fat mass only in overweight individuals.

If SAM formation increases with positive energy balance, then SAM should increase in animals fed obesogenic diets. A problem is that high-fat diets often induce liver injury, which is associated with SAM reduction (1). Indeed, hepatic MAT1a was downregulated and SAM concentrations were lower in mice fed a steatohepatitis-inducing diet (39), and hepatic SAM decreased after 3 wk of a high-fat diet (40). Notably, in these 2 studies, weight gain did not increase beyond that of the control. On the other hand, 2 similar studies of longer duration reported MAT1a upregulation (41,42) concomitant with increased fat gain. Zucker fatty rats, in which a leptin receptor mutation produces hyperphagia and obesity, have increased hepatic SAM (43). Thus, diet-induced obesity appears to be associated with MAT upregulation and high SAM concentrations.

In view of the above findings, we postulate that elevation of plasma SAM in proportion to fat mass reflects increased SAM formation in obesity. Methionine availability is an obvious limiting factor in this paradigm. Notably, high methionine intake is associated with BMI (44,45). Furthermore, high intake of methionine-rich animal protein is linked to obesity (46) and was associated with SAM and tCys in the present study. Thus,

elevated SAM may reflect excess intake of both energy and methionine. Whether SAM is an active player in the ensuing weight gain is an intriguing question that deserves investigation. The abundance of SAM and other high-energy metabolites is thought to be a marker of nutrient status that can influence the phenotype via epigenetic mechanisms (17,18). SAM also drives the synthesis of cysteine (4), which in turn promotes adiposity in animals (10,47) and correlates with fat mass in humans (7,9). Thus, the SAM-cysteine pathway may act as an interface for the cross-talk between protein/nutrient availability and fat storage.

Strengths and limitations. The study benefits from several strengths, including immediate sample treatment to control for instability of SAM and SAH, and regional DXA data, which enabled accurate assessment of truncal adiposity. Participants were selected based on glucose status, so the study included more individuals with diabetes than are found in the general population. However, adjusting for diabetes did not influence the results; and results agree with findings from a population-based cohort (12). The cross-sectional design makes it difficult to determine causality, but we hope that our findings will stimulate prospective studies to investigate the interaction between SAM concentrations and loss or gain of body fat.

In conclusion, we observed positive associations of plasma and erythrocyte SAM with fat mass and trunk fat:total fat ratio in 610 participants. The associations were independent of tCys and other confounders and extend previous reports that SAM and BMI are correlated (12,13). Intake of methionine-rich animal protein was a positive predictor of SAM and tCys concentrations. Methionine (44,45) and animal protein (46) intakes are associated with obesity. We propose that nutrient oversupply, facilitated by high methionine intake, drives the ATP-dependent conversion of methionine to SAM, concomitant with increased fat deposition. Studies of changes in SAM in response to caloric restriction, overfeeding, or change in protein intake are needed to confirm or refute this interpretation.

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