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Plasma sulfur amino acids and stearoyl-CoA desaturase activity in two caucasian populations ☆

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ABSTRACT

In rats, dietary restriction of the cysteine precursor methionine suppresses hepatic stearoyl-CoA desaturase (SCD)-1 expression and activity, whereas cysteine supplementation reverses these effects. In 2 independent cohorts: Hordaland Health Study (HUSK; $N=2021$, aged 71–74 y), Norway, and Hoorn study ($N=686$, aged 50–87 y), Netherlands, we examined the cross-sectional associations of plasma sulfur-containing compounds (SCC; methionine, S-adenosylmethionine, S-adenosylhomocysteine, homocysteine, cystathionine, total cysteine (tCys), glutathione and cysteinylglycine) with SCD-16 index (16:1n-7/16:0), estimated from fatty acid profiles of total plasma or serum lipids. Only tCys was consistently associated with SCD-16 index after adjustments for sex and age (HUSK: partial $r=0.14$; Hoorn: partial $r=0.11$, $P<0.001$ for both), and after further adjustments for other SCC, body fat, diet, exercise and plasma lipids (HUSK: partial $r=0.07$, $P=0.004$; Hoorn: partial $r=0.12$, $P=0.013$). Together with animal data showing an effect of dietary cysteine on SCD1, our results suggest a role for cysteine in SCD1 regulation in humans.

1. Introduction

The enzyme stearoyl-CoA desaturase (SCD) is responsible for the synthesis of monounsaturated fatty acids and is closely associated with lipid and energy metabolism [1]. SCD1 is the major isoform present in lipogenic tissues including liver and adipose tissues, and in rodents as well as humans, high SCD1 activity is considered to be involved in development of obesity [2]. In epidemiological studies, SCD indices measured in plasma, serum or whole blood are often used as surrogate measures of tissue SCD enzyme activity. SCD indices are calculated as product/precursor ratios of individual fatty acids. The ratio of palmitoleic acid (16:1n-7) to palmitic acid (16:0) and the ratio of oleic acid (18:1n-9) to stearic acid (18:0) constitute the SCD-16 and SCD-18 indices respectively. Because 18:1n-9 is more prevalent in human diet than 16:1n-7, SCD-16 index and plasma 16:1n-7 have been suggested as preferred markers of SCD1 activity [3,4]. The SCD-16

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index in humans is strongly associated with fat mass [5], and prospectively predicts development of metabolic syndrome [6] and cardiovascular mortality [7].

Due to the role of SCD1 in pathogenesis of obesity [2], it is important to understand the factors that regulate SCD1 function in humans. Different dietary factors regulate SCD1 activity and expression, including dietary fatty acids and carbohydrates as previously reviewed [1]. In animal models, polyunsaturated fatty acids (PUFA) inhibit *Scd1* gene expression [8,9]; and at the population level, dietary PUFA [5] and plasma PUFA [10] show strong inverse associations with plasma SCD indices. Emerging evidence also suggests a role for sulfur amino acid metabolism in regulating SCD1 activity. Dietary restriction of the cysteine precursor methionine in rats decreases plasma total cysteine (tCys) [11], and suppresses hepatic *Scd1* expression [12], protein levels [12] and SCD indices [13], co-incident with hypermetabolism and a decrease in weight gain and body fat percent [12,14]. Cysteine supplementation in methionine-restricted rats enhances hepatic *Scd1* expression, activity indices and body fat gain, without restoring serum methionine [13]. This suggests that the effects of methionine restriction on SCD1 and adiposity are mediated by the reduced supply of cysteine. In humans, plasma tCys, but not methionine, is linearly associated with BMI and fat mass [15,16], but the relationship between cysteine and SCD1 function in humans has not been investigated.

The changes in tissue-specific *Scd1* expression profile in response to dietary methionine and cysteine in rats, with corresponding changes in estimated SCD activity [13], suggests that sulfur amino acid availability in humans may influence SCD1 function. In the present study, we investigated the association of plasma concentrations of methionine, tCys and related metabolites with estimated SCD activity in two Caucasian study populations from Norway and the Netherlands.

2. Methods

2.1. Study populations

The present study includes two separate study populations belonging to the Hordaland health Study (HUSK; Norway) or the Hoorn Study (Hoorn; the Netherlands). HUSK was the second round of the Hordaland Homocysteine Study conducted from 1997 to 1999 as a collaboration between the University of Bergen, the National Health Screening Service, local health services in the Bergen area and the University of Oslo. All subjects, recruited from the city of Bergen or its immediate surroundings in the county of Hordaland, Western Norway, underwent a brief health examination and provided a non-fasting blood sample. Self-administered questionnaires provided information on lifestyle factors including dietary habits [17].

The Hoorn Study is a population-based cohort study that started in 1989 in Hoorn in the Netherlands to study glucose tolerance [18]. In our present study, relevant data from the third follow-up in 2000–2001 were analyzed. The participants underwent a physical examination, provided a fasting blood sample, and completed questionnaires on their health status and lifestyle [19].

We confined the current cross-sectional study to 2021 HUSK participants (924 men and 1097 women) aged 71–74 years and to 686 Hoorn study participants (328 men and 358 women) aged 50–87 years, with data available on both fatty acid profile and sulfur-containing compounds (SCC). There were some differences between the two studies in data availability. The fatty acid profiles were analyzed in EDTA plasma in HUSK and in serum in the Hoorn study. In both the HUSK and Hoorn studies, data on total homocysteine (tHcy), tCys, methionine and cystathionine were available. In addition, data on cysteinylglycine (tCysGly) concentrations were available in HUSK, whereas data on S-adenosylmethionine (SAM), S-adenosylhomocysteine (SAH) and total glutathione (tGSH) were available in Hoorn.

All subjects gave their written, informed consent. The HUSK study protocol was approved by the Regional Committee for Medical Research Ethics of Western Norway, and the Hoorn study protocol was approved by the Ethical Review Committee of the VU University Medical Center, both based on directives in the Helsinki declaration.

2.2. BMI and body composition

In both cohorts, height and weight were measured in light clothing without shoes to nearest 1 cm and 0.5 kg, respectively, and BMI was calculated (kg/m^2). Fat mass was assessed by dual energy X-ray absorptiometry (DXA) [20] on a stationary fan-beam densitometer in both HUSK and Hoorn, using EXPERT-XL software (version 1.72-1.9; Lunar Corporation, Madison, WI) and QDR-2000 software (version 7.20D; Hologic, Brussels, Belgium), respectively.

2.3. Lifestyle and diet

Self-administered questionnaires provided information on diet (Food Frequency Questionnaire; FFQ) and lifestyle variables in both cohorts. In HUSK, the FFQ included 169 food items extensively validated [21,22]. Nutrient intakes were calculated using a food database and software system developed at the Institute for Nutrition Research, University of Oslo (KOSTBEREGNINGSSYSTEM, version 3.2: University of Oslo, Norway). Physical activity included two variables referring to heavy physical activity or light physical activity during the past year, where each variable comprised 4 categories: (1) none, (2) <1 h/wk, (3) 1–2 h/wk, and (4) ≥ 3 h/wk. The category numbers were replaced by a summary score estimated for each subject as previously described [5]. Smoking and coffee consumption were used as continuous variables comprising the number of cigarettes smoked per day or grams of coffee consumed per day.

In the Hoorn study, a 75-food item semi-quantitative FFQ was used. Nutrient intake was calculated using a computerized version of the Dutch Food Composition Table [23]. Physical activity was expressed in the number of hours of physical activity per day, and included activities such as sports, bicycling, gardening, walking, and housekeeping. Smoking status was categorized as current smoker or nonsmoker. Coffee consumption was calculated as gram/day.

2.4. Biochemical measurements

Non-fasting blood samples were collected for measurement of serum lipids and for preparation of EDTA plasma in HUSK [24]. Time since last meal was noted. In Hoorn, fasting blood samples were collected [25].

Serum HDL cholesterol, triacylglycerol, and total cholesterol were measured using enzymatic methods with reagents from Boehringer Mannheim (Roche, Basel, Switzerland) in both cohorts. In HUSK, plasma tHcy, tCys, and tCysGly were analyzed by high performance liquid chromatography (HPLC) with fluorescence detection (intra-assay CV $<4\%$) [26]. Liquid chromatography–tandem mass spectroscopy (LC–MS) was used for analyzing methionine and cystathionine [27]. In Hoorn, plasma SAM and SAH were determined with tandem LC–MS as previously described (intra-assay CV, 4% for both; inter-assay CV, 8 and 6%, respectively) [28]. Methionine, tHcy, cystathionine, tCys and tGSH were measured in serum in a single run using LC–MS with a modification of a previously described

method [29]. Inter-assay CV was $<4\%$ for tCys and tHcy, and $<8\%$ for methionine, cystathionine and tGSH.

Fatty acid profiles in total lipids in plasma (HUSK) and serum (Hoorn) were analyzed by gas liquid chromatography (GLC) with flame ionization detection by AS Vitas, Oslo Innovation Center, Norway (www.vitas.no) [5]. Fatty acid content was calculated based on the area % of peaks and response factors relative to 18:0. The SCD index was estimated as the ratio of 16:1n-7 to 16:0 in plasma (in HUSK) or serum (in Hoorn). For simplicity, we refer to the 16:1n-7/16:0 ratio in plasma or serum as the plasma SCD-16 index.

2.5. Statistical analyses

Due to skewed distributions of 16:1n-7, SCD-16 index and all SCC, except for tCys in HUSK, these variables were log-transformed for both study populations before parametric analysis. Population characteristics are summarized as median (25th–75th percentile). Group comparisons were conducted using Kruskal–Wallis ANOVA, followed by Mann–Whitney *U* test; or by Chi square test.

Using general linear models, we found no significant SCC × sex interactions for plasma SCD-16 index. Therefore we performed the analyses for the combined group adjusted for sex.

Pearson correlation analysis and multivariate linear regression models were used to assess the associations of the plasma SCC with plasma concentrations of 16:1n-7, 16:0 and the SCD-16 index. The covariates were chosen based on their significant correlation with the independent and/or dependent variables. We examined various models with different covariates: Model 1, adjusted for age and sex (only sex in HUSK due to limited age range); Model 2, Model 1 plus adjustment for diabetes (Hoorn), body fat percent and reciprocally for all SCC; Model 3, Model 2 plus adjustment for triglycerides, cholesterol, intakes of total energy, fat, protein, alcohol (% of energy) and coffee, physical activity score, smoking and time since last meal (HUSK). Because both dietary PUFA [30] and carbohydrate [31] influence plasma SCD1 index, we also examined whether adjustments for intakes of PUFA and carbohydrate (% of energy) would alter the association of tCys with plasma
SCD-16 index.

We used Gaussian generalized additive regression models (RStudio foundation for Statistical Computing, version 0.97.173, Vienna, Austria) to create dose-response curves of the differences in plasma SCD-16 index by tCys. At approximately mean exposure of the independent variable (tCys), the model generates a reference value of zero for the dependent variable (plasma SCD-16 index). Models with different covariates are specified in the figure legends. *P* values were calculated from linear regression analyses.

Except for generalized additive models, all statistical analyses were performed with IBM SPSS Statistics for MAC OS (20.0; SPSS Inc., Chicago, IL, USA). Tests of significance were 2-tailed and *P*-values <0.05 were considered significant.

3. Results

3.1. Characteristics of the study populations

Selected population characteristics of the participants in the HUSK and Hoorn study populations are shown in Table 1. In both populations, median tHcy and methionine concentrations were significantly higher in men than in women, and there was no difference in tCys concentrations according to gender. Body composition and lipid variables by tertiles of plasma SCD-16 index in men and women are shown in Table 2. In HUSK, body fat percent, fat mass, BMI, waist circumference and waist-hip ratio increased significantly across tertiles of plasma SCD-16 index in both men and women. In Hoorn, men and women in the highest tertile of plasma SCD-16 index had significantly higher body fat percent and fat mass than those in the lowest tertile. Women in the highest tertile of plasma SCD-16 index also had significantly higher waist circumference compared with the lowest tertile. In HUSK, a significantly higher proportion of men and women in the highest plasma SCD-16 index tertile were overweight and obese compared with the lowest tertile whereas in Hoorn, prevalence of obesity was significantly increased only in men in the upper SCD-16 index tertile. Among the lipid variables, triglycerides, cholesterol, 16:0 and 16:1n-7 concentrations increased significantly across tertiles of plasma SCD-16 index in both men and women in HUSK. In Hoorn, triglycerides, 16:0 and 16:1n-7 concentrations were higher in the upper SCD-16 index tertile in both men and women compared with the lowest tertile, whereas cholesterol concentrations increased across tertiles only in men.

3.2. Associations of plasma sulfur-containing compounds with plasma concentrations of 16:0, 16:1n-7 and SCD-16 index

Of the SCC that were measured in Hoorn and HUSK, only tCys was positively associated with plasma SCD-16 index and with 16:1n-7 in both populations (Table 3; Model 1). These associations remained significant after controlling for body fat percent and the other SCC (Model 2), and after further adjustment for triglycerides, cholesterol, intakes of total energy, fat, protein, alcohol (% of energy) and coffee, physical activity score, smoking (and time since last meal in HUSK; partial $r=0.07$, $P=0.004$ in HUSK, and partial $r=0.12$, $P=0.013$ in Hoorn). Further adjustments for intakes of PUFA and carbohydrate (% of energy) did not alter the association of tCys with plasma SCD-16 index (data not shown). Plasma methionine showed inverse associations with 16:0, 16:1n-7, and SCD-16 index in HUSK, but these observations were not replicated in Hoorn.

To test whether the association of plasma tCys with SCD depends on methionine status as observed in animals [13] we repeated the analysis in two subgroups with low and high plasma methionine concentrations (below and above median). There was a tendency for the association between tCys and plasma SCD-16 index in Model 1 to be stronger in the low methionine group. The discrepancy was more apparent in Hoorn, in which the measurements were fasting (partial $r=0.20$, $P<0.001$ in the low methionine group, and partial $r=0.02$, $P=0.75$ in the high methionine group, $P_{interaction}=0.15$). Corresponding values in HUSK were partial $r=0.16$, $P<0.001$ and partial $r=0.09$, $P=0.002$, $P_{interaction}=0.40$. Similar patterns were also observed in Models 2 and 3 (data not shown).

Among the SCC that were available only in Hoorn, plasma SAM and SAH were not associated with plasma SCD-16 index in age- and sex-adjusted analysis (Model 1), but SAH was inversely associated with plasma SCD-16 index after further adjustment for other SCC, diabetes and body fat percent (Table 3; Model 2). SAH was inversely associated with 16:1n-7 in both models, whereas SAM was positively associated with 16:1n-7 only in Model 2. Plasma concentration of tGSH showed modest inverse associations with the plasma SCD-16 index and 16:1n-7 in Model 1 that disappeared in Model 2. CysGly, which was only available in HUSK, showed positive associations with plasma SCD-16 index and 16:1n-7 in Model 1 that became non-significant in Model 2.

3.3. Dose-response relationship between plasma concentration of tCys and plasma SCD-16 index

Fig. 1 shows the dose-response relationships between plasma concentration of tCys and plasma SCD-16 index in the HUSK (Fig. 1, panels A and B) and Hoorn (Fig. 1, panels C and D) study

Table 1
Characteristics of the HUSK and Hoorn study populations[a].

	The HUSK study population		The Hoorn study population	
	Men (*n*=924)	**Women (*n*=1097)**	**Men (*n*=328)**	**Women (*n*=358)**
Variables				
Age, y	73 (72, 73)	73 (72, 73)	68 (63, 74)	68 (64, 74)
Body fat (%)	27.1 (22.1, 32.1)[b]	41.4 (35.5, 46.2)	28.1 (23.5, 32.2)[b]	42.2 (37.3, 46.3)
Fat mass (kg)	20.4 (15.5, 25.8)[b]	25.9 (20.2, 32.9)	22.6 (18.3, 27.7)[b]	29.3 (23.5, 36.4)
Lean mass (kg)	55.0 (51.0, 58.8)[b]	37.5 (34.7, 40.5)	54.7 (50.8, 59.0)[b]	39.2 (36.7, 42.6)
Waist circumference (cm)	95 (89, 101)[b]	84 (77, 92)	99 (94, 107)[b]	92 (84, 100)
Waist-hip ratio	0.95 (0.91, 0.99)[b]	0.83 (0.79, 0.88)	0.98 (0.94, 1.03)[b]	0.88 (0.82, 0.93)
BMI (kg/m^2)	25.9 (24.0, 27.8)	25.9 (23.2, 28.8)	27.1 (24.9, 29.4)	27.0 (24.7, 31.0)
Overweight, BMI ≥25, *n* (%)	578 (62.6)	643 (58.8)	242 (74.5)	254 (72.2)
Obesity, BMI ≥30, *n* (%)	80 (8.7)[b]	183 (16.7)	58 (18.0)[b]	107 (30.0)
Plasma/serum sulfur-containing compounds				
Methionine (μmol/L)	24.0 (20.2, 29.8)[b]	21.3 (17.8, 26.0)	27.2 (24.8, 30.0)[b]	24.4 (21.7, 26.4)
S-Adenosylmethionine (nmol/L)	–	–	90.3 (79.5, 103.5)	88.9 (77.4, 100.4)
S-Adenosylhomocysteine (nmol/L)	–	–	16.2 (13.7, 20.4)[b]	13.5 (11.1, 16.7)
Total homocysteine (μmol/L)	12.2 (10.4, 14.4)[b]	10.9 (9.0, 13.1)	13.1 (10.9, 16.5)[b]	11.7 (9.9, 14.0)
Total cysteine (μmol/L)	317 (295, 343)	319 (297, 342)	320 (294, 346)	316 (293, 348)
Cystathionine (μmol/L)	0.27 (0.19, 0.40)[b]	0.24 (0.17, 0.34)	0.24 (0.18, 0.35)	0.23 (0.17, 0.33)
Glutathione (μmol/L)	–	–	3.0 (2.6, 3.4)[c]	2.8 (2.5, 3.3)
Cysteinylglycine (μmol/L)	35.1 (31.4, 38.3)[b]	33.1 (30.1, 36.6)	–	–
Dietary intakes				
Energy (kJ/d)	8424 (7042, 9983)[b]	6442 (5030, 7942)	8623 (7440, 10044)[b]	7072 (6088, 8022)
Protein (% of energy)	15.8 (14.4, 17.4)[b]	16.2 (14.6, 18.0)	14.9 (13.3, 16.4)[b]	15.6 (13.9, 17.1)
Fat (% of energy)	31.0 (27.6, 34.4)[b]	29.7 (26.1, 33.3)	35.5 (31.5, 38.7)[c]	33.9 (30.6, 37.7)
Saturated fat	11.3 (9.8, 13.1)	11.4 (9.8, 13.1)	14.5 (12.9, 16.3)	14.5 (12.7, 16.1)
Monounsaturated fat	11.1 (9.7, 12.4)[b]	10.3 (9.0, 11.7)	13.3 (11.5, 15.1)[c]	12.7 (11.1, 14.5)
Polyunsaturated fat	5.7 (4.7, 6.9)[b]	5.1 (4.2, 6.3)	6.5 (5.2, 8.1)[c]	5.9 (4.9, 7.6)
Carbohydrates (% of energy)	50.8 (46.7, 54.7)[b]	53.3 (48.9, 57.2)	43.9 (39.7, 48.6)[b]	47.1 (42.5, 51.0)
Fiber	2.4 (2.0, 2.8)[b]	2.7 (2.2, 3.1)	2.3 (2.0, 2.7)[b]	2.5 (2.2, 2.9)

HUSK, Hordaland Health Study.

[a] Data presented as median (25th, 75th percentiles).
[b] Significantly different from women in the same population at $P<0.001$.
[c] Significantly different from women in the same population at $P<0.05$.

populations after adjusting for age (only in Hoorn) and sex (Fig. 1A and C) and further adjustments for body fat percent (HUSK) and body fat percent and diabetes (Hoorn). In HUSK, the positive association between plasma concentration of tCys and plasma SCD-16 index was weakened after adjusting for body fat percent, whereas in the Hoorn study, the association was essentially not affected by such adjustment (Fig. 1). Similar dose–response relationships were observed for plasma concentration of tCys versus 16:1n-7 (data not shown).

4. Discussion

We investigated the associations of SCC with plasma SCD-16 index, 16:1n-7 and 16:0 in participants of two European cohorts, HUSK [17] and Hoorn [18]. Of all SCC, only tCys showed a consistent positive association with plasma SCD-16 index and 16:1n-7 in both populations, and the associations remained significant after adjustments for potential confounders. Given that plasma concentration of tCys also correlates positively with fat mass [15], our findings together with animal data detailed below, suggest that SCD activity may be one mechanism linking tCys to fat accumulation.

The effect of dietary intake of several SCC on SCD1 has been tested in rodents. Both the methionine-restricted diet [13] and the methionine-choline deficient diet [32] cause profound suppression of hepatic *scd1* expression, suggesting that adequate methionine intake is needed for normal *scd1* expression. Homocysteine supplementation of methionine-choline deficient rats raised *scd1* expression [33]. Furthermore, supplementing methionine-restricted rats with cysteine [13] or n-acetylcysteine [34], but not taurine [34] rescued their weight gain and enhanced *scd1* expression and activity indices. Thus, availability of methionine appears to influence SCD1 at least partly via supplying cysteine. Mice with deficient cysteine synthesis due to homozygous deletion of cystathionine beta synthase have low plasma tCys levels, and marked inhibition of hepatic *scd1* expression despite elevated plasma concentration of methionine [35]. Mice with a genetic block in glutathione synthesis also feature low plasma cysteine and glutathione levels and down regulated *scd1* gene expression [36].

In accordance with observations in rodents, plasma concentration of methionine did not show consistent associations with plasma SCD-16 index in our present study. However, there was a tendency for the association between plasma concentration of tCys and plasma SCD-16 index to be stronger in subjects with lower plasma methionine. This parallels our observation that cysteine supplementation influences SCD activity only in methionine-restricted but not in methionine-replete rats [13]. The importance of our finding in humans is difficult to interpret. If not due to chance, it may suggest that cysteine is more relevant for regulation of SCD activity when methionine supply is limited, as in those on vegan diets [37].

We observed no consistent associations of plasma SAH, tHcy, cystathionine, tGSH or its dipeptide product, CysGly, with plasma SCD-16 index. Epidemiological studies show a positive linear association of plasma concentration of tCys with BMI and fat mass; this is not observed with methionine, tHcy, cystathionine, taurine, tGSH, or CysGly [15,16]. Similar to tCys, plasma SAM strongly positively correlated with BMI [38] and fat mass [39]. However, SAM was unrelated to the SCD-16 index in our present study,

Table 2
Anthropometric and lipid variables by tertiles of plasma SCD-16 index.

	The HUSK study population			The Hoorn study population		
	Tertiles of plasma SCD-16 index					
	T1	T2	T3	T1	T2	T3
Men						
Body fat (%)	24.8 (20.0, 29.0)	26.7 (22.2, 31.3)[b]	30.1 (24.6, 34.9)[b]	27.1 (22.7, 31.3)	27.2 (23.7, 31.4)	29.9 (23.7, 33.7)[a]
Fat mass (kg)	17.9 (13.5, 23.4)	20.4 (15.5, 24.7)[b]	23.5 (17.6, 29.6)[b]	21.1 (16.7, 26.5)	21.1 (18.1, 26.2)	24.0 (18.9, 29.8)[a]
Lean mass (kg)	55.4 (50.5, 59.1)	54.7 (50.8, 59.1)	54.9 (51.5, 58.7)	54.6 (50.8, 58.1)	54.3 (50.7, 58.4)	54.8 (50.8, 60.8)
Waist circumference	93 (87, 99)	95 (90, 100)[a]	99 (92, 104)[b]	98 (91, 105)	98 (93, 105)	100 (94, 107)
Waist-hip ratio	0.94 (0.90, 0.98)	0.95 (0.91, 0.99)[a]	0.97 (0.92, 1.01)[b]	0.99 (0.93, 1.03)	0.97 (0.94, 1.02)	0.99 (0.94, 1.03)
BMI (kg/m^2)	25.3 (23.3, 27.1)	25.7 (23.9, 27.7)[a]	26.8 (24.6, 28.7)[b]	26.7 (24.9, 28.9)	26.8 (24.6, 28.9)	27.3 (25.0, 29.5)
Overweight, BMI $\geq$25, n (%)	172 (55.8)	182 (59.3)	224 (72.7)[b]	86 (74.8)	81 (69.8)	88 (75.2)
Obesity, BMI $\geq$30, n (%)	12 (3.9)	20 (6.5)	48 (15.6)[b]	17 (14.8)	19 (16.4)	25 (21.7)[b]
Triglycerides (mmol/L)	1.5 (1.1, 2.0)	1.6 (1.2, 2.2)[a]	1.8 (1.5, 2.5)[b]	1.3 (0.9, 1.7)	1.3 (1.0, 1.8)	1.5 (1.1, 2.2)[a]
Total cholesterol (mmol/L)	5.7 (5.0, 6.4)	5.8 (5.1, 6.5)	6.0 (5.3, 6.7)[b]	5.2 (4.6, 5.9)	5.2 (4.6, 5.8)	6.1 (5.3, 6.8)[a]
Palmitic acid (16:0)	20.8 (20.0, 21.7)	21.8 (21.0, 22.6)[b]	23.0 (22.1, 24.1)[b]	21.8 (21.0, 22.7)	22.7 (21.6, 23.5)[b]	23.7 (22.7, 24.5)[b]
Palmitoleic acid (16:1n-7)	1.3 (1.1, 1.5)	1.8 (1.7, 1.9)[b]	2.4 (2.2, 2.9)[b]	1.5 (1.3, 1.6)	2.1 (1.9, 2.2)[b]	2.9 (2.5, 3.4)[b]
SCD-16 index (16:1n-7/16:0)	0.06 (0.06, 0.07)	0.08 (0.08, 0.09)[b]	0.11 (0.10, 0.12)[b]	0.07 (0.06, 0.07)	0.09 (0.09, 0.10)[b]	0.12 (0.11, 0.14)[b]
Polyunsaturated fat (% of energy)	6.5 (5.4, 7.7)	5.9 (4.7, 6.8)[b]	5.1 (4.2, 5.9)[b]	7.1 (5.9, 9.0)	6.5 (5.2, 7.8)[a]	5.7 (4.5, 7.4)[b]
Carbohydrates (% of energy)	50.6 (47.0, 54.0)	50.8 (46.7, 54.8)	51.0 (46.5, 54.8)	44.3 (41.0, 49.0)	44.1 (38.8, 48.7)	43.6 (38.9, 48.4)
Women						
Body fat (%)	38.8 (33.6, 43.6)	41.2 (34.9, 45.8)[b]	44.1 (38.2, 48.6)[b]	39.3 (34.4, 45.7)	43.2 (36.8, 46.4)	43.0 (39.2, 46.7)[a]
Fat mass (kg)	23.7 (18.7, 29.3)	25.9 (20.0, 32.8)[b]	29.7 (23.3, 36.0)[b]	26.3 (22.1, 36.5)	30.5 (23.5, 35.0)	30.5 (24.4, 37.9)[a]
Lean mass (kg)	37.1 (34.2, 40.1)	37.7 (34.6, 40.6)	37.7 (35.1, 40.7)	39.3 (37.0, 42.7)	38.6 (36.5, 41.9)	39.6 (36.3, 43.2)
Waist circumference	81 (75, 88)	82 (76, 92)[a]	87 (80, 94)[b]	89 (81, 98)	92 (82, 99)	95 (87, 102)[a]
Waist-hip ratio	0.82 (0.79, 0.88)	0.82 (0.77, 0.88)	0.84 (0.80, 0.89)[a]	0.87 (0.81, 0.92)	0.88 (0.81, 0.92)	0.88 (0.84, 0.93)
BMI (kg/m^2)	24.8 (22.6, 27.3)	25.7 (23.1, 28.8)[b]	27.5 (24.1, 30.1)[b]	26.0 (24.0, 29.9)	27.3 (24.7, 30.6)	28.3 (25.3, 32.1)[b]
Overweight, BMI $\geq$25, n (%)	176 (48.2)	216 (59.2)[b]	251 (69.0)[b]	77 (64.2)	87 (71.3)	99 (80.5)
Obesity, BMI $\geq$30, n (%)	26 (7.1)	59 (16.2)[b]	98 (26.9)[b]	30 (24.6)	34 (27.4)	44 (35.5)
Triglycerides (mmol/L)	1.5 (1.1, 2.0)	1.5 (1.1, 2.0)	1.7 (1.3, 2.4)[b]	1.1 (0.9, 1.7)	1.3 (1.0, 1.7)[a]	1.6 (1.1, 2.0)[b]
Total cholesterol (mmol/L)	6.5 (5.8, 7.2)	6.5 (5.7, 7.4)	6.8 (5.9, 7.5)[a]	5.7 (5.2, 6.6)	6.1 (5.5, 6.8)	6.1 (5.3, 6.8)
Palmitic acid (16:0)	20.8 (20.0, 21.7)	21.4 (20.6, 22.5)[b]	22.2 (21.2, 23.2)[b]	21.3 (20.5, 22.3)	22.1 (21.2, 23.0)[b]	22.8 (22.0, 24.0)[b]
Palmitoleic acid (16:1n-7)	1.6 (1.5, 1.8)	2.2 (2.0, 2.3)[b]	2.8 (2.6, 3.2)[b]	1.8 (1.6, 2.1)	2.4 (2.3, 2.6)[b]	3.2 (2.9, 3.7)[b]
SCD-16 index (16:1n-7/16:0)	0.08 (0.07, 0.08)	0.10 (0.09, 0.10)[b]	0.13 (0.12, 0.14)[b]	0.09 (0.08, 0.10)	0.11 (0.10, 0.12)[b]	0.14 (0.13, 0.15)[b]
Polyunsaturated fat (% of energy)	5.7 (4.8, 7.0)	5.0 (4.2, 6.0)[b]	4.7 (3.8, 5.6)[b]	6.7 (5.7, 8.7)	5.8 (4.8, 7.6)[a]	5.2 (4.5, 6.6)[b]
Carbohydrates (% of energy)	51.9 (48.2, 56.0)	53.5 (49.5, 57.4)[a]	54.1 (49.6, 57.9)[b]	46.3 (42.6, 50.2)	47.1 (42.7, 50.8)	48.1 (42.0, 51.6)

HUSK, Hordaland Health Study; SCD, stearoyl-coenzyme A desaturase.
Significance of difference between tertiles was tested by chi-square tests, or Kruskal–Wallis ANOVA followed by Mann–Whitney U test for group-wise comparisons with the lowest tertile as reference.
Tertiles are sex-specific.
Data presented as median (25th, 75th percentiles) or number (%).

[a] $P < 0.05$ compared with first tertile.
[b] $P < 0.001$ compared with first tertile.

suggesting different mechanisms for the associations of SAM and tCys with adiposity. These results suggest that SCD1 may be one factor linking plasma cysteine concentration with fat mass in humans. Enhanced SCD1 activity may influence energy expenditure via regulation of enzymes in the fat oxidation pathway, such as hepatic AMP-activated protein kinase [2,13]. High SCD1 activity may also increase body fat accumulation by incorporation of monounsaturated fatty acids into triglycerides, with subsequent VLDL packaging, secretion, and transport to peripheral tissues and storage [1].

Several authors have reported that reduced hepatic *scd1* expression protects against liver steatosis [40,41]. Yet rodents fed a methionine-choline-deficient diet develop fatty liver despite having reduced hepatic *scd1* expression and activity [32,42]. Notably, Cabarello et al. [43] investigated the individual contribution of the lack of methionine and choline in liver steatosis. They showed that although methionine restriction promoted liver damage, steatosis was mainly due to deficiency of choline rather than methionine. Furthermore, a recent study by Malloy et al. [44] showed that dietary restriction of methionine alone may protect against hepatic steatosis in ob/ob mice; the suggested mechanism included down-regulation of hepatic *scd1* expression, upregulation of genes associated with fatty acid oxidation, and increased export of lipids.

The present report represents the first evidence in humans linking a single amino acid to SCD function, but several caveats should be noted. Due to the age-range of the participants (71–74 y in HUSK and 50–87 in Hoorn), the data may not be generalizable to younger adults and children. The positive correlation between plasma concentration of tCys and plasma SCD-16 index, although consistent, is weaker than the correlation of tCys with obesity [15], suggesting that SCD may not be the only factor linking tCys to fat mass. Estimated SCD activity was based on fatty acid profile in total plasma lipids, which introduces uncertainty concerning the relative contribution of the liver and other tissues. However, we observed in rats that this index tends to reflect changes in hepatic *scd1* expression [13]. Our findings show an association between plasma cysteine and SCD activity index but the cross-sectional design of the study precludes conclusive inference on causality. One alternative interpretation is that plasma tCys reflects a broader factor regulating SCD activity, such as methionine availability or nitrogen balance. However, we did not observe any significant associations between protein intake and SCD indices [5]. Furthermore, animal data showing a direct positive effect of dietary cysteine [13] and N-acetylcysteine [34] on *scd1* expression and activity indices independent of plasma methionine, suggest that cysteine or a related factor may be involved in regulation of SCD activity.

Table 3
Partial correlation coefficients for plasma sulfur-compounds with plasma SCD-16 index, palmitoleic acid (16:1n-7), and palmitic acid (16:0) in the HUSK and Hoorn populations[a].

	The HUSK study population						The Hoorn study population					
	SCD-16		16:1n-7		16:0		SCD-16		16:1n-7		16:0	
	Partial *r*	*P*	Partial *r*	*P*	Partial *r*	*P*	Partial *r*	*P*	Partial *r*	*P*	Partial *r*	*P*
Model 1[b]												
Methionine	−0.08	<0.001	−0.09	<0.001	−0.07	0.003	0.05	0.23	0.06	0.10	0.10	0.007
S-Adenosylmethionine	–	–	–	–	–	–	0.04	0.28	0.09	0.027	0.22	<0.001
S-Adenosylhomocysteine	–	–	–	–	–	–	−0.06	0.10	−0.02	0.62	0.16	<0.001
Total homocysteine	0.06	0.004	0.06	0.011	0.01	0.67	<−0.01	0.99	0.02	0.68	0.07	0.067
Cystathionine	−0.02	0.45	−0.01	0.69	0.04	0.10	−0.09	0.018	−0.06	0.11	0.08	0.031
Total cysteine	0.14	<0.001	0.13	<0.001	0.06	0.005	0.11	0.004	0.13	0.001	0.13	0.001
Glutathione	–	–	–	–	–	–	−0.07	0.080	−0.08	0.032	−0.11	0.005
Cysteinylglycine	0.05	0.018	0.05	0.016	0.02	0.33	–	–	–	–	–	–
Model 2[c]												
Methionine	−0.06	0.006	−0.07	0.002	−0.06	0.004	0.06	0.15	0.09	0.047	0.14	0.001
S-Adenosylmethionine	–	–	–	–	–	–	0.08	0.067	0.10	0.029	0.12	0.008
S-Adenosylhomocysteine	–	–	–	–	–	–	−0.12	0.007	−0.10	0.019	0.003	0.95
Total homocysteine	0.04	0.100	0.03	0.21	−0.001	0.67	0.05	0.27	0.06	0.21	0.06	0.20
Cystathionine	−0.02	0.46	−0.01	0.77	0.03	0.16	−0.10	0.028	−0.10	0.03	−0.06	0.17
Total cysteine	0.06	0.008	0.05	0.019	0.001	0.97	0.12	0.005	0.11	0.010	0.03	0.48
Glutathione	–	–	–	–	–	–	−0.02	0.60	−0.04	0.35	−0.09	0.032
Cysteinylglycine	0.03	0.16	0.03	0.16	0.02	0.37	–	–	–	–	–	–

HUSK, Hordaland Health Study; SCD, stearoyl-coenzyme A desaturase.

[a] Linear regressions analysis using log-transformed values for SCD-16, 16:1n-7, S-Adenosylmethionine and S-Adenosylhomocysteine.
[b] Model 1: adjusted for sex (in HUSK) and age and sex (in Hoorn).
[c] Model 2: adjusted for sex, body fat percent and reciprocally for all plasma sulfur-compounds (in HUSK) in addition to age and diabetes in Hoorn.

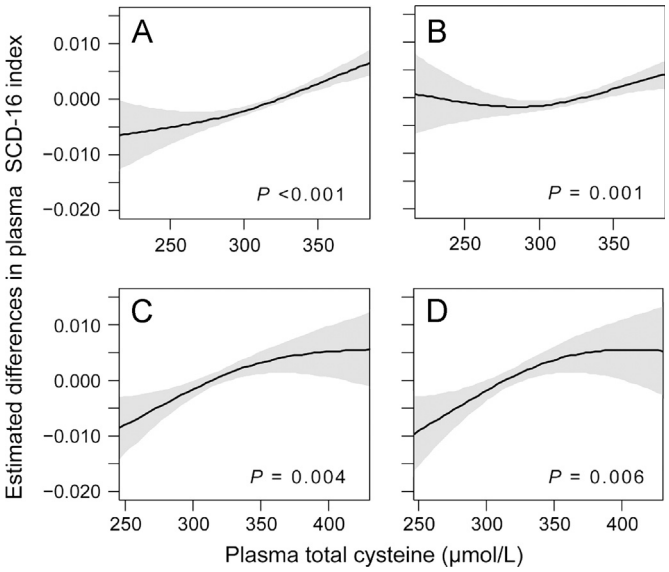

Fig. 1. Associations between plasma total cysteine (tCys) and plasma stearoyl-CoA desaturase-16 (SCD-16) index in the HUSK (panels A and B) and Hoorn (panels C and D) study populations. Dose–response curves (solid lines) were obtained by generalized additive models, and shaded areas represent 95% confidence intervals. Panels A and C to the left show simple models adjusted for sex (and age in Hoorn), whereas panels B and D show models further adjusted for body fat percent (and diabetes in Hoorn). *P*-values were obtained from corresponding linear regression analysis. Data are shown only for the 2.5th–97.5th percentiles of tCys for each group.

The main strength of the present study is that our findings are based on two distinct cohorts, thus allowing identification of consistent associations. The two populations were large and recruited from the general population, and the fatty acid profile was measured by the same method in both cohorts. Available data enabled adjustment for several potential confounders associated with estimated SCD activity, including lipid variables, lifestyle, dietary factors, and fat mass measured by DXA [5].

In conclusion, we explored the relation of plasma markers of the sulfur amino acid metabolic pathway with estimated SCD activity in two large cohorts, and observed that plasma concentration of tCys shows independent and positive associations with plasma SCD-16 index and the SCD product, 16:1n-7, in line with the relation of tCys with human obesity. This finding indicates that the effects of dietary [13,33,34,45] and transgenic [35,36] manipulation of sulfur amino acid metabolism on SCD and fat deposition in rodents may be relevant to humans, and points to sulfur amino acids as possible targets for control of human obesity.

Author contributions

KJV, AKE, and HR: designed and conducted the research; JMD, TT, CDAS, CAD, GST, SEV, HR, GN: data collection; KJV, AKE, and HR: performed statistical analyses; KJV and AKE: wrote the paper; CAD supervised development of the FFQ in HHS; JMD, TT, CDAS, AKE, EN, CAD, GST, ON, SE: critically revised manuscript for important intellectual content; and KJV and AKE: had primary responsibility for final content.

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