Associations of erythrocyte fatty acids in the de novo lipogenesis pathway with risk of metabolic syndrome in a cohort study of middle-aged and older Chinese\textsuperscript{1–3}

Geng Zong, Jingwen Zhu, Liang Sun, Xingwang Ye, Ling Lu, Qianlu Jin, He Zheng, Zhijie Yu, Zhenni Zhu, Huaxing Li, Qi Sun, and Xu Lin

ABSTRACT

Background: Experimental studies suggest that elevated de novo lipogenesis (DNL) might be involved in the pathogenesis of metabolic disorders. Few prospective studies have been conducted, especially among populations with a high carbohydrate intake, to determine whether DNL fatty acids are associated with the risk of the metabolic syndrome (MetS).

Objective: We aimed to investigate associations of erythrocyte fatty acids in the DNL pathway—including myristic acid (14:0), palmitic acid (16:0), palmitoleic acid (16:1n-7), hexadecenoic acid (16:1n-9), stearic acid (18:0), vaccenic acid (18:1n-7), and oleic acid (18:1n-9)—with the risk of MetS in a Chinese population with an average carbohydrate intake of >60% of energy.

Design: A total of 1176 free-living Chinese men and women aged 50–70 y from Beijing and Shanghai were included in our analysis, giving rise to 412 incident MetS cases during 6 y of follow-up. Erythrocyte fatty acids and metabolic traits were measured in these participants.

Results: Erythrocyte fatty acids in the DNL pathway were correlated with a high ratio of carbohydrate-to-fat intake, less favorable lipid profiles, and elevated liver enzymes at baseline. In comparison with the lowest quartile, RR (95% CIs) of MetS in the highest quartile were 1.30 (1.04, 1.62; \textit{p}-trend = 0.007) for 16:1n-7, 1.48 (1.17, 1.86; \textit{p}-trend < 0.001) for 16:1n-9, 1.26 (1.01, 1.56; \textit{p}-trend = 0.06) for 18:1n-7, and 1.51 (1.19, 1.92; \textit{p}-trend < 0.001) for 18:1n-9 after multivariate adjustment for lifestyle factors and body mass index. Moreover, 16:0 and 16:1n-7 were associated with an elevated risk of diabetes.


INTRODUCTION

De novo lipogenesis (DNL)\textsuperscript{4} is the formation of fat from acetyl coenzyme A in the living body (1). In humans, DNL is low after consumption of a high-fat diet, but it can be upregulated by several physiologic or lifestyle factors, such as a high-carbohydrate diet (1–3). Although DNL is difficult to measure directly, its major products can be identified in blood components and adipose tissue (2–4). These products include an array of SFAs and MUFAs (5, 6), such as myristic acid (14:0), palmitic acid (16:0), palmitoleic acid (16:1n-7), hexadecenoic acid (16:1n-9), stearic acid (18:0), vaccenic acid (18:1n-7), and oleic acid (18:1n-9).

Studies in rodent models have shown that elevated DNL results in hypertriglyceridemia, hypercholesterolemia, insulin resistance, and obesity (7, 8), all of which are key component of the metabolic syndrome (MetS)\textsuperscript{9}. Correspondingly, several studies have reported that patients with MetS have significantly higher DNL fatty acids in the body than do control subjects (10–14).

In a previous study, we also found that erythrocyte 16:1n-7, a fatty acid that has rare dietary sources and can only be derived from DNL, was positively associated with MetS prevalence (15). However, most of these findings were cross-sectional, and whether DNL fatty acids are associated with risk of MetS has yet to be elucidated in well-designed prospective studies (16).

Current evidence from observational studies suggests that DNL fatty acids are associated with the risk of type 2 diabetes mellitus (T2DM) and cardiovascular diseases (17–23).

\textsuperscript{1}From the Key Laboratory of Nutrition and Metabolism, Institute for Nutritional Sciences, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences and Graduate University of the Chinese Academy of Sciences, Shanghai, China (GZ, JZ, LS, XY, LL, QJ, HZ, HL, and XL); the Department of Community Health Sciences, Brock University, St Catharines, Ontario, Canada (ZY); the Shanghai Municipal Center for Disease Control and Prevention, Shanghai, China (ZZ); the Department of Nutrition, Harvard School of Public Health, Boston, MA (QS); and the Channing Division of Network Medicine, Department of Medicine, Brigham and Women’s Hospital and Harvard Medical School, Boston, MA (QL).

\textsuperscript{2}Supported by the National Basic Research 973 Program (2012CB524900), the National Natural Science Foundation of China (30930081 and 81021002), the Chinese Academy of Sciences (KSCX2-EW-R-10), Key Discipline of Shanghai Public Health-Food and Nutritional Sciences (12GWZX0702), and the China Postdoctoral Science Foundation (2011MS00027).

\textsuperscript{3}Address correspondence and reprint requests to Q Sun, Department of Nutrition, Harvard School of Public Health, Boston, MA 02115. E-mail: qisun@hsph.harvard.edu; or X Lin, Key Laboratory of Nutrition and Metabolism, Institute for Nutritional Sciences, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences, and Graduate University of the Chinese Academy of Sciences, Shanghai 20031, China. E-mail: xlin@sibs.ac.cn.

\textsuperscript{4}Abbreviations used: ALT, alanine aminotransferase; DNL, de novo lipogenesis; GGT, \gamma-glutamyl transpeptidase; GI, glycemic index; MetS, metabolic syndrome; \textit{r}, Spearman correlation coefficient; T2DM, type 2 diabetes mellitus.

Received February 21, 2013. Accepted for publication April 29, 2013. First published online June 26, 2013; doi: 10.3945/ajcn.113.061218.
which are common sequelae of MetS. However, most of these studies were conducted in Western populations, who typically eat a high-fat diet that may substantially suppress DNL (2, 3, 24). It is unknown whether DNL fatty acids are associated with metabolic disorders in people with a habitual high-carbohydrate diet.

The traditional Chinese diet is characterized by a high carbohydrate and low fat content (25), which may significantly upregulate liver DNL. Although this diet pattern has undergone changes over the past few decades, carbohydrate intake among Chinese is still much higher than that among Western populations, accounting for 60% of total energy according to a nationwide survey in 2004 (25). Meanwhile, the proportion of total carbohydrate intake contributed by refined carbohydrates has been increasing (26). To investigate whether DNL is prospectively associated with metabolic disorders in this population, we examined possible associations between erythrocyte fatty acids in the DNL pathway and risk of MetS in a cohort of middle-aged and older Chinese during 6 y of follow-up.

SUBJECTS AND METHODS

Baseline survey

The Nutrition and Health of Aging Population in China study is an ongoing population-based prospective study among 3289 Chinese aged 50–70 y living in Beijing and Shanghai. Details of the baseline survey were described elsewhere (27, 28). Briefly, study participants were randomly selected from March to June 2005 by using a multistage sampling method among residents living for >20 y in Beijing and Shanghai (2 urban districts and 1 rural district in each city). The study protocol was approved by the Institutional Review Board of the Institute for Nutritional Sciences. All participants provided written informed consent.

Data on demographic variables, health status, lifestyle, and physical activities were obtained by trained staff using a standardized questionnaire during a home interview. Educational attainment was categorized according to self-reported school years (0–6, 7–9, or ≥10 y). Current smoking and alcohol drinking were classified as yes or no. Physical activity data were collected by using the International Physical Activity Questionnaire (29) and categorized as low, moderate, or high according to the total metabolic equivalent time–minute/wk score. A subject was deemed to have a family history of chronic disease if he or she reported that a parent or sibling had coronary artery disease, stroke, T2DM, or hypertension. Dietary information was collected by using a 74-item food-frequency questionnaire inquiring about the frequency and amount of each food item consumed in the previous year. Dietary glycemic index (GI) was calculated as the weighted average GIs for all carbohydrate-containing foods with the use of the International Tables of Glycemic Index and Glycemic Load Values (30). Food intake was adjusted by total energy intake by using the residual model (31). After fasting overnight, all participants were required to undergo a physical examination and provide blood samples. Body weight, height, waist circumference, and blood pressure were measured by trained medical workers following a standard protocol (27). BMI was calculated as weight (in kg) divided by height (in m) squared.

Follow-up

In 2011, all study participants were contacted by public health staff from local Centers for Disease Control and Prevention and community hospitals. Possible migration and updated contact information was provided by the local family register office. Deaths were reported by next of kin. People who could not attend because of disabilities or changes in living arrangements were invited to complete a short questionnaire inquiring about onset of diabetes, cardiovascular disease, and cancer. For participants who were unable to answer the questions because of cognitive deficits or severe illness, a family member was asked to fill out the questionnaire.

A home interview was conducted by trained staff to update medical history, lifestyle, and other information. The standardized questionnaire used in the baseline survey was also used in the follow-up visit with minor modifications. All participants were required to have a physical examination conducted by trained medical professionals using the same protocol as used for the baseline examination. At the follow-up visit, a total of 2268 participants underwent a physical examination and provided blood samples.

Laboratory measurements

Fasting venous blood samples were collected with EDTA used as the anticoagulant and centrifuged at 3000 rpm for 15 min. Plasma and erythrocytes were stored at −80°C before analysis (27). Plasma fasting glucose, triglycerides, HDL cholesterol, total cholesterol, alanine aminotransferase (ALT), and γ-glutamyl transpeptidase (GGT) were measured by using an automatic analyzer (model 7080; Hitachi) with reagents purchased from Wako Pure Chemical Industries (27).

Erythrocyte fatty acids were measured by using gas chromatography coupled with positive chemical ionization (Agilent 6890 GC-5975B) (15). The CVs for fatty acid assays ranged from 0.34% for 18:1n−9 to 9.8% for 16:1n−7.

Definition of incident MetS

MetS was defined according to the updated National Cholesterol Education Program Adult Treatment Panel III criteria for Asian Americans (32). Participants with any 3 of the 5 following items were identified as having MetS: 1) waist circumferences ≥90 cm in men or ≥80 cm in women, 2) triglycerides ≥1.7 mmol/L, 3) HDL cholesterol ≤1.03 mmol/L in men or ≤1.30 mmol/L in women, 4) blood pressure ≥130/85 mm Hg or current use of antihypertensive medications, and 5) fasting plasma glucose ≥5.6 mmol/L or use of oral antidiabetic agents or insulin.

A total of 760 (23.1%) participants were lost to follow-up because of a lack of updated contact information (n = 554) or refusal to participate (n = 206). Of the 2529 who remained, 122 died and another 84 completed only the short questionnaire. Participants who took part in follow-up visits were excluded if they met any of the following criteria: 1) had MetS or diabetes at baseline, 2) lacked baseline erythrocyte fatty acid data, 3) had an extreme total energy intake (<800 or >4000 kcal/d for men and <500 or >3500 kcal/d for women), or 4) lacked sufficient data to define incident MetS. After exclusions, data for 1176 participants were available for the current analysis.
Statistical analysis

Baseline characteristics were compared by using a t test for continuous variables and a chi-square test for categorical variables between participants lost to follow-up and those who remained, and between participants with and without MetS. Distributions of fatty acids according to quartiles of macronutrient intake were compared by ANOVA. Spearman correlation coefficients ($r$) were calculated to evaluate intercorrelations among DNL fatty acids and their correlations with blood lipids and markers of liver dysfunction at both baseline and follow-up after adjustment for age, sex, region, and residence. Participants were categorized according to quartiles of DNL fatty acids to estimated RRs and CIs of MetS. Because of the high risk of metabolic disorders among our participants, RRs were estimated by using log-binomial regression (33, 34). However, because the models for MetS did not converge in such a model, we used log-Poisson models instead, which provide consistent but not fully efficient estimates of RRs and CIs (35). The following covariates were adjusted for: age, sex, region (Beijing or Shanghai), residence (urban or rural), physical activity, educational attainment, smoking, alcohol drinking, family history of chronic diseases (family history of diabetes was used when modeling T2DM), total energy intake, adjusted dietary GI, and BMI. We also analyzed the associations of DNL fatty acids with risk of MeS after excluding participants with incident diabetes. All analyses were performed with Stata version 9.2 (StataCorp). Two-sided P values <0.05 were considered statistically significant.

RESULTS

Participants lost to follow-up were more likely to be men and to live in an urban area than were their counterparts. In addition, they had higher educational attainment and family income and less optimal blood lipids at baseline (see Supplementary Table 1 under “Supplemental data” in the online issue). Characteristics of participants with and without incident MetS are shown in Table 1. The mean age of all participants was 58.0 y, and 45.5% of them were men. On average, the population derived 60.8% of its energy intake from dietary carbohydrate and 27.0% from fat. After 6 y of follow-up, 412 (35.0%) participants developed MetS, who were more likely to be female and nonsmokers, to live in urban areas, to have a family history of chronic diseases, and to have higher BMI at baseline. The mean percentages of DNL fatty acids in the study population were 22.2% for 16:0, 0.38% for 16:1n−7, 0.128% for 16:1n−9, 1.03% for 18:1n−7, 0.37% for 14:0, 14.8% for 18:0, and 10.9% for 18:1n−9. Participants with incident MetS had higher 16:1n−7, 16:1n−9, and 18:1n−9 but lower 18:0 at baseline. Meanwhile, triglycerides at baseline and ALT, GGT, and triglycerides at follow-up were higher, whereas HDL cholesterol and the HDL:total cholesterol ratio at both baseline and follow-up were lower in participants with incident MetS than in MetS-free participants. During the follow-up period, ALT, GGT, and triglycerides increased, whereas HDL cholesterol and the HDL:total cholesterol ratio decreased in our study population (P-trend < 0.01 for all; data not shown).

Mean consumption of refined grains (including white rice and white flour) and whole grains were 358 and 14 g/d, respectively.

### Table 1

<table>
<thead>
<tr>
<th>Without incident metabolic syndrome (n = 764)</th>
<th>With incident metabolic syndrome (n = 412)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (y)</strong></td>
<td>58.0 ± 6.0</td>
</tr>
<tr>
<td><strong>Men [n (%)]</strong></td>
<td>383 (50.1)</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td>22.1 ± 2.6</td>
</tr>
<tr>
<td><strong>Northern residents [n (%)]</strong></td>
<td>295 (38.6)</td>
</tr>
<tr>
<td><strong>Urban residents [n (%)]</strong></td>
<td>277 (36.3)</td>
</tr>
<tr>
<td><strong>Current drinking [n (%)]</strong></td>
<td>226 (29.6)</td>
</tr>
<tr>
<td><strong>Current smoking [n (%)]</strong></td>
<td>244 (31.9)</td>
</tr>
<tr>
<td><strong>Physical activity [n (%)]</strong></td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>High</td>
</tr>
<tr>
<td><strong>Education [n (%)]</strong></td>
<td>0–6 y</td>
</tr>
<tr>
<td></td>
<td>7–9 y</td>
</tr>
<tr>
<td></td>
<td>≥10 y</td>
</tr>
<tr>
<td><strong>Family history of chronic disease [n (%)]</strong></td>
<td>361 (47.3)</td>
</tr>
<tr>
<td><strong>Total energy intake (kcal/d)</strong></td>
<td>2305 ± 650</td>
</tr>
<tr>
<td><strong>Refined grain (g/d)</strong></td>
<td>360 ± 102</td>
</tr>
<tr>
<td><strong>Whole grain (g/d)</strong></td>
<td>13 ± 24</td>
</tr>
<tr>
<td><strong>Total carbohydrate (g/d)</strong></td>
<td>348 ± 59</td>
</tr>
<tr>
<td><strong>Protein (g/d)</strong></td>
<td>68 ± 15</td>
</tr>
<tr>
<td><strong>Fat (g/d)</strong></td>
<td>67 ± 21</td>
</tr>
<tr>
<td><strong>Erythrocyte fatty acids (%)</strong></td>
<td>16:0</td>
</tr>
<tr>
<td></td>
<td>16:1n−7</td>
</tr>
<tr>
<td></td>
<td>16:1n−9</td>
</tr>
<tr>
<td></td>
<td>18:1n−7</td>
</tr>
<tr>
<td></td>
<td>14:0</td>
</tr>
<tr>
<td></td>
<td>18:0</td>
</tr>
<tr>
<td></td>
<td>18:1n−9</td>
</tr>
<tr>
<td><strong>Liver enzyme and blood lipids at baseline</strong></td>
<td></td>
</tr>
<tr>
<td><strong>ALT (IU/L)</strong></td>
<td>18.94 ± 14.48</td>
</tr>
<tr>
<td><strong>GGT (IU/L)</strong></td>
<td>28.35 ± 42.27</td>
</tr>
<tr>
<td><strong>Triglycerides (mmol/L)</strong></td>
<td>0.85 ± 0.44</td>
</tr>
<tr>
<td><strong>HDL cholesterol (mmol/L)</strong></td>
<td>1.45 ± 0.34</td>
</tr>
<tr>
<td><strong>HDL:total cholesterol ratio</strong></td>
<td>0.33 ± 0.07</td>
</tr>
<tr>
<td><strong>Liver enzyme and blood lipids at follow-up</strong></td>
<td></td>
</tr>
<tr>
<td><strong>ALT (IU/L)</strong></td>
<td>20.61 ± 11.22</td>
</tr>
<tr>
<td><strong>GGT (IU/L)</strong></td>
<td>30.15 ± 31.59</td>
</tr>
<tr>
<td><strong>Triglycerides (mmol/L)</strong></td>
<td>1.14 ± 0.46</td>
</tr>
<tr>
<td><strong>HDL cholesterol (mmol/L)</strong></td>
<td>1.65 ± 0.43</td>
</tr>
<tr>
<td><strong>HDL:total cholesterol ratio</strong></td>
<td>0.31 ± 0.07</td>
</tr>
</tbody>
</table>

1. Continuous variables are shown as means ± SDs and were compared by t test, whereas categorical variables are shown as numbers (percentages) and were compared by chi-square test. *P < 0.05, **P < 0.01, ***P < 0.001. ALT, alanine aminotransferase; GGT, γ-glutamyl transpeptidase.

2. Includes coronary artery disease, stroke, hypertension, and diabetes of a parent or a first-degree sibling.

3. Includes white rice and white flour.

4. Data are missing for 2 participants.
Higher carbohydrate intake and lower fat intake was associated with increased erythrocyte 16:0, 16:1n7, 18:1n7, 14:0, and 18:0 (Table 2). These fatty acids increased by 4–36% in the fourth quartile of the carbohydrate:fat ratio compared with the first quartile (P ≤ 0.005 for all). Meanwhile, 16:1n9 was associated with protein intake, and proportions of this fatty acid were 0.127%, 0.125%, 0.128%, and 0.133% from the first to the fourth quartiles of protein intake at baseline, respectively (P-trend = 0.07; data not shown).

The r values among DNL fatty acids and between the fatty acids and markers of liver dysfunction and blood lipids, at study baseline are shown in Table 3. MUFA s were intercorrelated, and pairwise r values ranged from 0.07 (between 16:1n9 and 18:1n7) to 0.46 (between 16:1n9 and 16:1n7). Similarly, 16:0 was associated with 14:0 and 18:0. Erythrocyte 16:1n7, 16:1n9, 14:0, and 18:1n9 were statistically significantly associated with ALT (r ≥ 0.08, P < 0.01), GGT (r ≥ 0.08, P < 0.01), HDL cholesterol (r ≤ −0.09, P < 0.001), the HDL:total cholesterol ratio (r ≥ −0.11, P < 0.001), and triglycerides (r ≥ 0.24, P < 0.001) at baseline. Similar associations were found between baseline erythrocyte fatty acids and both markers of liver function and blood lipids at follow-up, but the correlation coefficients were smaller than those at baseline.

Erythrocyte 16:1n7, 16:1n9, and 18:1n9 were positively associated with risk of incident MetS (Table 4) after 6 y of follow-up. Compared with the first quartiles of these fatty acids, RRs of MetS ranged from 1.45 to 1.56 in the fourth quartiles (P-trend < 0.05) after adjustment for age, sex, region, and residence (model 1). These associations were only slightly attenuated after adjustment for BMI in model 3. Risks of developing MetS were still 30–51% higher in the fourth quartiles of these fatty acids. Furthermore, participants in the highest quartile of 18:1n7 had a 26% greater risk of MetS than did those in the first quartile (P-trend = 0.06) in model 3. Among the components of MetS (see Supplementary Table 2 under “Supplemental data” in the online issue), elevated hypertriglyceridemia was positively associated with 16:1n7, 16:1n9, and 18:1n9.

Of the 7 fatty acids in the DNL pathway, erythrocyte 16:0 and 16:1n7 were associated with an increased risk of T2DM. From the first to the fourth quartiles, RRs (95% CIs) of T2DM were 1 (reference), 1.08 (0.87, 1.34), 1.30 (1.02, 1.62), and 1.29 (1.02, 1.63; P-trend = 0.01) for 16:0, and RRs (95% CIs) were 1 (reference), 1.15 (0.92, 1.43), 1.30 (0.92, 1.43), and 1.38 (1.12, 1.71; P-trend = 0.005) for 16:1n7 after adjustment for age, sex, region, residence, physical activity, educational attainment, current smoking, current drinking, family history of diabetes, total energy intake, percentage of energy intake from carbohydrate, and energy-adjusted dietary GI (α = 2066). Further adjustment for BMI, in a comparison of extreme quartiles, attenuated the associations for 16:1n7 (RR: 1.23; 95% CI: 1.00, 1.53; P-trend = 0.07), but did not materially change the association for 16:0 (RR: 1.26; 95% CI: 1.00, 1.58; P-trend = 0.02).

In a sensitivity analysis for MetS, the associations remained largely unchanged after all participants with incident diabetes were excluded. RRs (95% CIs) were 1.36 (1.04, 1.78; P-trend = 0.005) for 16:1n7, 1.50 (1.14, 1.98; P-trend = 0.003) for 16:1n9, 1.35 (1.05, 1.73; P-trend = 0.03) for 18:1n7, and 1.42 (1.08, 1.88; P-trend = 0.003) for 18:1n9 in a comparison of extreme quartiles of these fatty acids in the final model. Other fatty acids were not significantly associated with MetS.
DISCUSSION

In the current study, we found that erythrocyte fatty acids in the DNL pathway were associated with a higher carbohydrate intake, a lower fat intake, and less favorable blood lipids and liver enzymes. Furthermore, 16:1n-9, 16:1n-7, and 18:1n-9 were independently associated with an increased risk of MetS, whereas 16:0 and 16:1n-7 were associated with a higher risk of T2DM.

To our knowledge, this was the first prospective study to document positive associations between DNL fatty acids and risk of MetS in people with a high habitual intake of carbohydrate. Previous cross-sectional studies showed that individuals with MetS had higher DNL fatty acids than did those without MetS (10–14). In a study of 706 Swedish men, Warensjö et al (16) reported that baseline 16:0, 16:1n, 18:0, and 18:1n fatty acids were higher in those who developed MetS after 20 y of follow-up. In addition, they found that a higher ratio of 16:1n to 16:0 predicted incident MetS in late DNL and lead to unfavorable changes in metabolic traits in humans (6, 38). In our study, 5 of 7 DNL fatty acids were associated with a higher intake of carbohydrate, whereas none was correlated with fat intake, which suggests that most of these fatty acids are derived from the DNL pathway. This inference is further supported by positive associations between DNL fatty acids and unfavorable blood lipids, which are commonly found in DNL induced by a high carbohydrate intake (6, 38) and with elevated liver enzymes, which may partly reflect liver fat accumulation and liver dysfunction (39, 40).

In the current study, hypertriglyceridemia was apparently the major factor underlying the associations between DNL fatty acids and risk of MetS. This might be explained by the fact that MUFA's produced by DNL are important substrates for triglyceride synthesis (7). Notably, a high-carbohydrate diet could lead to elevated triglycerides and reduced HDL cholesterol through pathways other than stimulating DNL (41, 42). However, when carbohydrate intake and dietary GI were further adjusted, we did

<table>
<thead>
<tr>
<th>TABLE 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spearman correlation coefficients between baseline erythrocyte fatty acids in the de novo lipogenesis pathway and plasma markers of liver function and lipids&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>16:1n-7</td>
</tr>
<tr>
<td>16:1n-9</td>
</tr>
<tr>
<td>18:1n-7</td>
</tr>
<tr>
<td>14:0</td>
</tr>
<tr>
<td>18:0</td>
</tr>
<tr>
<td>18:1n-9</td>
</tr>
</tbody>
</table>

Baseline:
- ALT<sup>2</sup>
- GGT<sup>3</sup>
- Triglycerides
- HDL cholesterol
- HDL:total cholesterol ratio

Follow-up:
- ALT<sup>2</sup>
- GGT
- Triglycerides
- HDL cholesterol
- HDL:total cholesterol ratio

<sup>1</sup>Spearman correlation coefficients were calculated after adjustment for age, sex, region, and residence. **p < 0.01, ***p < 0.001. ALT, alanine aminotransferase; GGT, γ-glutamyl transpeptidase.
<sup>2</sup>No significant association observed.
<sup>3</sup>Data are missing for 2 participants.
not detect substantial changes in the associations of DNL fatty acids with MetS and T2DM. Another plausible explanation could be that DNL fatty acids competitively suppress the integration of PUFAs into cell membranes and reduce membrane fluidity, which is essential to cell function (43).

The specific roles of DNL fatty acids in the etiology of metabolic disorders are unclear. Previous studies in animal models found that 16:0 can cause endoplasmic reticulum stress, endothelial dysfunction, and activation of an inflammatory response (44–46). MUFAs in the DNL pathway (16:1n-7, 16:1n-9, 18:1n-7, and 18:1n-9) can all be derived from 16:0 through the DNL pathway, which may explain their putative pathogenic role in metabolic disorders (19). Consistent with this notion, the Physicians’ Health Study and Cardiovascular Health Study have shown that 18:1n-7 or 16:1n-9 in the body was associated with a higher risk of cardiovascular disease (19, 47). Meanwhile, serum cholesterol ester 16:1n-7 was associated with insulin resistance in 767 participants from the Uppsala Longitudinal Study of Adult Men (48). In the same cohort, 16:1n-7 and 18:1n-9 were positively associated with serum C-reactive protein (49).

One strength of the current investigation lies in the study population, whose diet was consistently high in carbohydrate and
LIPOGENESIS, FATTY ACIDS, AND METABOLIC SYNDROME

low in fat. This not only provides a unique opportunity for investigating possible associations between the elevated DNL fatty acids induced by a high carbohydrate intake and the development of metabolic abnormalities, but also reduces possible confounding from a high fat intake common in Western populations. Another strength of our study is that we carefully controlled for established risk factors and other possible confounding factors.

However, our study has certain limitations. First, we had a moderate loss to follow-up (21%), and we found somewhat different characteristics between those who were lost to follow-up and all eligible participants. Second, middle-aged and elderly persons have a higher incidence of MetS and T2DM than the general population, although none of these fatty acids in erythrocytes was associated with total fat intake.

In conclusion, our findings suggest that fatty acids in the DNL pathway are independently associated with a higher risk of MetS in a Chinese population with a high habitual carbohydrate intake. Further studies are needed to confirm our findings in other populations.

We sincerely thank Yunhua Zhou, Shaojie Ma, Yiqin Wang, Danxia Yu, and Geng Zhang for their contributions at various stages of this study. We further appreciate the strong commitment shown by Shurong Zhou, Xinghuo Pang, and all staff members from the local Center for Disease Control and hospitals during field work in Beijing and Shanghai. We especially thank the participants involved in this study.

The authors’ responsibilities were as follows: GZ: conducted the research, performed the statistical analysis, and wrote the manuscript; JZ: performed the statistical analysis and wrote the manuscript; LS and XY: conducted the research and wrote the manuscript; JZ: performed the statistical analysis, and wrote the manuscript; LL, QJ, HZ, ZY, ZZ, and HL: designed the research, conducted the research, and wrote the manuscript; LL, QJ, HZ, ZY, ZZ, and HL: designed the research, conducted the research, and wrote the manuscript; JZ: designed the research, conducted the research, and had primary responsibility for the final content. All authors read and approved the final manuscript. None of the authors declared a conflict of interest.

REFERENCES


