




Association between erythrocyte fatty acids in de novo lipogenesis pathway and DXA-derived body fat and trunk fat distribution in Chinese adults: a prospective study

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Abstract

Purpose Higher levels of fatty acids (FAs) in the de novo lipogenesis (DNL) pathway might be associated with higher levels of fat mass (FM), while limited evidence is available from the general population. We aimed to examine the associations between DNL-FAs and body fat and fat distribution in a general population of Chinese adults.

Methods This community-based prospective cohort study included 3,075 participants (68% women) aged 40–75 years in urban Guangzhou, China. We measured erythrocyte DNL-FAs composition (including C16:0, C16:1n-7, C18:0, and C18:1n-9) at baseline and %FM over the total body (TB), trunk, limbs, android (A) and gynoid (G) regions after 3.2 years and 6.3 years of follow-up, respectively.

Results Generally, higher proportions of individual erythrocyte DNL-FAs and their combined index were positively associated with adipose indices in the multivariable cross-sectional and longitudinal analyses. The cross-sectional percentage mean differences in quartile 4 (vs. 1) of the DNL index were 3.43% (TB), 4.56% (trunk), and 2.67% (A/G ratio) (all *P* trends < 0.01). The corresponding values in longitudinal changes of adipose indices were 1.40% (TB), 1.78% (trunk), and 1.32% (A) (all *P* trends < 0.05). The above associations tended to be more pronounced in the trunk and android area than the limbs and gynoid area.

Conclusions Erythrocyte DNL-FAs may contribute to an increase in total body fat in Chinese adults, particularly FM distributed in trunk and abdominal regions.

Keywords Body fat · Chinese adults · De novo lipogenesis · Pathway · Erythrocyte fatty acids · Prospective study

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Introduction

In the past 50 years, obesity has become a global public health issue, which affects the quality of life, and raises health care costs [1]. Replacement of fat intake with carbohydrate intake has been suggested to prevent obesity and other chronic diseases for many years [2], but new controversies have arisen, including the suggestion that carbohydrate-rich diets might also have harmful effects on metabolic aspects of health [2].

De novo lipogenesis (DNL) is a carbohydrate catabolism pathway for fat synthesis, primarily in the liver and adipose tissue, in which acetyl-CoA from excess carbohydrate is converted into fatty acids (FAs), including palmitic acid (C16:0), palmitoleic acid (C16:1n-7), stearic acid (C18:0), and oleic acid (C18:1n-9). Except deriving from DNL pathway, DNL FAs can be also derived from dietary source, such

as C16:0 and C18:0 from animal products and C18:1n-9 from olive oil [3, 4]. Whereas dietary origin of 16:1n-7 is negligible because of oxidation shortly after absorption in the human body [5]. Thus, 16:1n-7 is a potential biomarker of hepatic DNL [6]. The FA products of DNL are key substrates for the formation of complex lipids such as phospholipids and triglycerides, and an accumulation of these FAs may result in fat deposition and obesity [7].

To date, population-based studies of the associations between tissue DNL FAs and obesity in general populations have been focused on anthropometric indices such as waist circumference (WC) and body mass index (BMI). Positive associations were observed in some studies [8–11], but not in others [12, 13]. The discrepant findings are possible because of different dietary or lifestyle habits (i.e., diet carbohydrate, and alcohol intake) which have been proposed to regulate DNL activity [8]. Although anthropometric indices are commonly used surrogates for obesity, these measures are prone to misclassification due to loss of lean muscle mass, especially in older populations [14]. Prior evidence suggested that abdominal fat increased with age, independent of BMI or WC [15]. Body FM indices have been proposed as more sensitive markers of the exact FM distribution and could be used to advance our understanding about the relationship between FM distribution and the risks of obesity [16, 17]. However, until now, no epidemiological study has addressed the relationship between DNL FAs and body FM and its distribution.

Therefore, we aimed to assess cross-sectional and prospective associations of four main erythrocyte FAs in the DNL pathway (C16:0, C16:1n-7, C18:0, and C18:1n-9) and their combined score with body fat and its distribution, determined by anthropometric measurements and by dual-energy X-ray absorptiometry (DXA), in a community-based cohort study of middle-aged and elderly Chinese subjects.

Methods

Study population

This study was based on the Guangzhou Nutrition and Health Study (GNHS), a community-based prospective cohort study designed to investigate risk factors for several chronic diseases, such as cardiovascular diseases and osteoporosis [18]. A total of 3,169 participants were initially recruited through advertisements, health talks, and referrals in urban Guangzhou, China, between July 2008 and June 2010, and were followed-up approximately every 2–3 years. Individuals between 40 and 75 years of age were eligible if they had lived in Guangzhou for more than 5 years. Participants were excluded if they were using weight-reducing aids or were confirmed to have serious chronic diseases, such

as diabetes, cardiovascular diseases, liver or renal failure, or cancers. In the first follow-up [2011–2013; mean (SD) duration of follow-up: 3.1 (0.4) years], 2,520 participants were successfully followed-up (79.5% follow-up rate) since their recruitment at baseline, and 879 new participants were recruited using the same methods as the original participants. In the second follow-up [2014–2017; mean (SD) duration of follow-up: 6.3 (0.4) years], 2977 (73.5%) participants were successfully followed. In the present study, all 3075 participants who completed the anthropometric and body FM distribution assessment, erythrocyte FA measurement, and the questionnaire interviews at the first follow-up were included in the cross-sectional analyses, and 2597 participants were included in the longitudinal analyses (from first to second follow-up). The flowchart of the study participants was shown in Fig. 1.

The study protocol was approved by the Ethics Committee of the School of Public Health at Sun Yat-sen University, and all participants provided written informed consent.

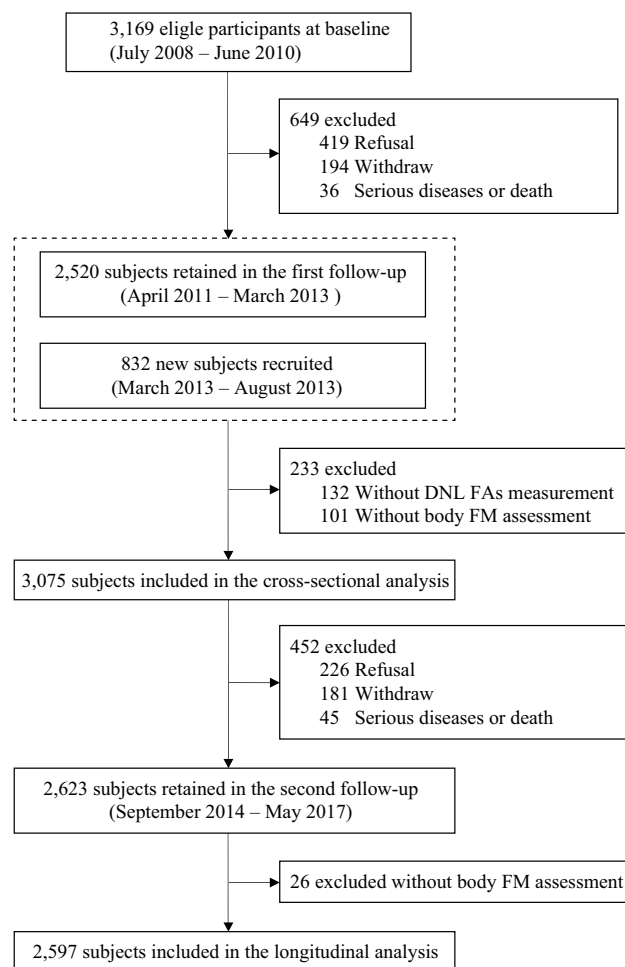


Fig. 1 Flow chart of the study participants. *DNL* de novo lipogenesis, *FAs* fatty acids, *FM* fat mass

Data collection

At each survey, the participants completed face-to-face interviews on socio-demographic characteristics, lifestyle habits, history of chronic diseases, medical history, and dietary habits over the past year. They also had physical measurements taken by trained and experienced interviewers and provided venous blood samples at each examination. Their physical activity was estimated as described previously [19]. A validated 79-item food frequency questionnaire (FFQ) was used to estimate intakes of total energy and nutrients [18]. Intakes of carbohydrate, protein, fat, saturated fatty acids (SFAs), and monounsaturated fatty acids (MUFAs) were adjusted for energy intake using the residual method [20].

Anthropometric measurements

Weight, height and WC of the participants were measured at each examination with light clothing. BMI was calculated as weight (kg) divided by height (m) squared.

Body FM assessment

At the first and second follow-up, total body and regional [trunk, limbs (arms and legs), android (abdominal), and gynoid (hip and thigh)] FM distributions were measured by trained professionals using DXA (Discovery W, Hologic Inc., Waltham, MA). The trunk, android, and gynoid regions were defined as previously described [18]. The percentage of FM, calculated as FM in kilograms divided by total mass in kilograms in the target region, was used as the primary measure. For example, the % FM for trunk region was calculated as FM in kilograms of trunk region divided by total mass in kilograms of trunk region; whereas the % FM for whole body was calculated as FM in kilograms of whole body divided by total mass in kilograms of whole body. The ratio of trunk area FM to limb area fat mass (% trunk/limbs) and android area FM ratio to gynoid area FM ratio (% A/G) were also calculated. Inter-individual coefficient of variations of 36 randomly selected duplicates were 1.60% for total FM, 4.7% for trunk FM, 4.5% for limb FM, 4.1% for android FM, and 4.0% for gynoid FM, respectively.

Measurement of erythrocyte FA composition

Red blood cells (erythrocyte) collected at baseline were separated. Erythrocyte FA methyl esters were obtained with methods previously described [21, 22] and used for measurement with gas chromatography (7890 GC, Agilent, California; DB-23 capillary column: 60 m × 0.25 mm internal diameter × 0.15 μm film, Agilent, California, USA). The area under the peak for each fatty acid represented the amount of target fatty acid which could be identified by the comparison

of retention time with commercially available standards (Nu-Chek Prep, Minnesota, USA). Relative amounts of each FA were expressed as the area under each peak of the FA as a percentage of total area under the peaks of all the fatty acids for each sample, and thus the unit for the fatty acids is percentage (%). All samples were analyzed in random order. Intra-assay coefficients of variation for 42 randomly selected duplicates were 2.5% for C16:0, 8.4% for C16:1n-7, and 5.0% for both C18:0 and C18:1n-9, respectively.

Statistical analysis

All statistical analyses were performed with SPSS 17.0 (SPSS, Inc., Chicago, IL). A two-tailed *P* value of less than 0.05 was considered statistical significance. The data were presented as means (standard deviation, SD) for the continuous variables and proportions (%) for the categorical variables. Spearman correlations were used to assess correlations among erythrocyte FAs in the DNL pathway and intakes of carbohydrate and fat controlled for age and gender. The participants were categorized into sex-specific quartiles according to each individual erythrocyte DNL FA and the combined association for DNL FAs (combined DNL index). The combined DNL index was calculated as the sum of quartile scores of the four DNL FAs. The scores on this index ranged from 4 to 16.

The body mass distribution variables were natural–log transformed before statistical analysis. Analysis of covariance (ANCOVA) was used to compare the mean differences in the body mass distribution variables at first follow-up (cross-sectional associations) and its changes (prospective associations) across quartiles of erythrocyte DNL FAs. The body mass distribution changes were adjusted for the corresponding baseline values with the residual method [20]. Two covariance models were used in all analyses, with model I adjusting for age (years), sex (men or women), and corresponding body composition variables at baseline (for longitudinal analyses), and model II further adjusting for marital status (married or single), education level (primary school or below, secondary school, or high school or above), household income (≤ 500, 501–2000, 2000–3000, or > 3000 Yuan/month/person), passive smoking status (yes or no), alcohol drinking status (yes or no), tea drinking status (yes or no), physical activity (MET·h/w), and energy intake (kcal/d) at baseline. We assessed *P* values for linear trend by treating quartiles as continuous variables.

We also used logistic and linear regression analyses to calculate the odds ratios (ORs) and its 95% confidential intervals (95% CIs) to assess the effects of DNL FAs with those in the obese vs. non-obese categories with adjustment confounders as in the ANCOVA models. In accordance with the Chinese standard of BMI [23], the International Diabetes Federation Consensus Group's standard of WC [24],

and previous report standard of total body fat mass [25]: BMI ≥ 28 kg/m² for general obesity; WC ≥ 90 cm for men and ≥ 80 cm for women for central obesity; total body fat mass $\geq 25\%$ for men and $\geq 35\%$ for women for fat mass-derived obesity. We performed a series of sensitivity analyses for % total body FM and % trunk FM, stratified by sex, marital status, alcohol intake, and sex-specific dichotomies for age and physical activity. In addition, given that DNL FAs, especially C16:0, C18:0, and C18:1n-9, were also major dietary FAs [26], we performed subgroup analyses according to sex-specific dichotomies in dietary SFAs and MUFAs intakes to explore the possibility of confounding due to dietary intakes of FAs. Finally, we tested the potential interactions of DNL FAs with different population characteristics, by adding cross-product terms into the above main models.

Results

The sample consisted of 68.0% women. At baseline, the mean age was 58.5 ± 6.2 years (women: 57.5 ± 5.7 years; men: 60.7 ± 6.7 years); 60.0% of total energy was derived from dietary carbohydrate intake, 14.7% from protein intake, and 21.8% from fat intake; and the median percentages of baseline erythrocyte FAs in the DNL pathway were 27.5% for C16:0, 0.25% for C16:1n-7, 16.8% for C18:0, and 12.0% for C18:1n-9. Participants with higher combined DNL scores were more likely to have higher household income (Table 1).

The participants had a mean BMI and WC of 23.2 kg/m² and 82.1 cm at baseline and a mean percentage of total FM of 32.4% at first follow-up. The mean changes in the BMI and WC during the 6.3 years of follow-up were 0.391 kg/m² and 5.111 cm; and the mean change in the % total FM during the 3.2 years of follow-up was 0.387 (Supporting Information Table S1).

Spearman correlation analysis demonstrated that fat intake was inversely correlated with carbohydrate intake ($r_s = -0.785$, $P < 0.001$). FAs in DNL pathway were all significantly inter-correlated (Table 2). Furthermore, C16:0, C16:1n-7, and C18:0 was weakly and positively correlated with carbohydrate intake, whereas inversely correlated with fat intake (absolute r_s range 0.035–0.071, all P values < 0.05).

In the cross-sectional analyses ($n = 3075$), generally, the proportion of individual erythrocyte DNL FAs and their combined score had significant, dose-dependent positive association with both anthropometric and FM indices and with trunk/limb and A/G FM ratios, after adjusting for age and sex (Supporting Information Table S2). Similar associations remained after further adjustment for other potential confounders (Table 3, Supporting Information Table S4 and

Fig. 2). Among the DNL FA indices, the combined DNL score was the most sensitive index associated with adipose indices. The percentage mean differences between quartiles 4 and 1 of the combined DNL index were 2.93% (BMI), 1.38% (WC), 3.43% (% total body FM), 4.56% (trunk), 4.32% (android area), 2.5% (limbs), and 1.68% (gynoid area). For fat distribution, the associations tended to be more substantial at the trunk/android area than at the limbs and gynoid area. The percentage difference of quartile 4 and 1 for the four DNL FAs ranged from 1.7% (C18:0) to 3.93% (C18:1n-9) for trunk, 0.75% (C18:0) to 2.64% (C16:1n-7) for limbs, 1.69% (C18:0) to 4.26% (C18:1n-9) for android area, and 0.43% (C18:0) to 2.16% (C16:1n-7) for gynoid area, respectively. Logistic analyses also indicated that, compared with quartile 1, participants in the quartile 4 of combined DNL index had higher risk of BMI-derived obesity (OR = 1.69, 95% CI 1.19–2.41; P trend = 0.004), WC-derived obesity (OR = 1.27, 95% CI 1.03–1.57; P trend = 0.036), or body fat mass-derived obesity (OR = 1.38, 95% CI 1.14–1.68; P trend = 0.004) (Supporting Information Table S5).

In the longitudinal analyses ($n = 2597$), both minimally and maximally adjusted ANCOVA models showed similar (although attenuated) trends to the cross-sectional results in the associations between DNL FAs and changes in body FM indices (Table 4; Fig. 1 and Supporting Information Table S3 and S4). Similar with cross-sectional results, the trend for the combined DNL index was more remarkable than those for individual DNL FAs. A higher combined DNL score was significantly associated with increased changes in WC, % total body FM, % trunk FM, % android FM, and the ratios of A/G and trunk/limbs FM. The corresponding percentage mean differences in changes between quartiles 4 and 1 were 1.09%, 1.40%, 1.78%, 1.32%, 0.78%, and 0.89%, respectively. However, after excluding obesity cases at baseline (142 cases for BMI derived obesity, 1091 cases for WC derived obesity, and 1777 cases for whole body fat mass derived obesity) to assess the effect of DNA FAs on risk of incident obesity, significantly positive association was only observed between C16:1n-7 and risk of body fat mass-derived obesity (OR = 2.39, 95% CI 1.14–5.02; P trend = 0.021) (Supporting Information Table S5).

In stratified analyses, no significant interactions were observed between DNL FAs and % total and % trunk FM according to age, sex, marital status, alcohol intake, physical activity, or SFAs and MUFAs intake, with p interaction ranging from 0.069 to 0.993 (data not tabulated).

Discussion

In this community-based prospective study, we examined the associations between erythrocyte DNL FAs (C16:0, C16:1n-7, C18:0, C18:1n-9, and combined DNL index)

Table 1 Baseline characteristics of study participants according to quartile of combined DNL index by gender (*n* = 3075)

| | Quartile of baseline combined DNL index | | | | <i>P</i> trend |
|---|---|----------------|--------------------|--------------------|----------------|
| | Quartile 1 (4–8) | Quartile 2 (9) | Quartile 3 (10–11) | Quartile 4 (12–16) | |
| <i>n</i> | 888 | 465 | 890 | 832 | |
| Age at baseline (years) | 58.0 ± 6.04 | 58.7 ± 6.62 | 58.7 ± 6.38 | 58.7 ± 6.19 | 0.693 |
| Gender | | | | | 0.421 |
| Men | 295 (33.2) | 134 (28.8) | 287 (32.2) | 268 (32.2) | |
| Women | 593 (66.8) | 331 (71.2) | 603 (67.8) | 564 (67.8) | |
| Marital status | | | | | 0.736 |
| Married | 787 (89.4) | 415 (90.2) | 803 (90.9) | 742 (89.7) | |
| Single | 93 (10.6) | 45 (9.8) | 80 (9.1) | 85 (10.3) | |
| Education level | | | | | 0.454 |
| Primary school or below | 247 (28.1) | 124 (27.0) | 259 (29.3) | 246 (29.8) | |
| Secondary school | 418 (47.5) | 213 (46.3) | 381 (43.1) | 387 (46.9) | |
| High school or above | 215 (24.4) | 123 (26.7) | 243 (27.5) | 193 (23.4) | |
| Household income (Yuan/month/person) | | | | | 0.003 |
| ≤ 2000 | 246 (28.3) | 103 (22.9) | 247 (28) | 219 (26.8) | |
| 2000–3000 | 429 (49.4) | 201 (44.7) | 379 (42.9) | 366 (44.9) | |
| > 3000 | 193 (22.2) | 146 (32.4) | 257 (29.1) | 231 (28.3) | |
| Passive smokers ^a | 244 (27.8) | 124 (27) | 219 (24.8) | 226 (27.4) | 0.500 |
| Alcohol drinkers ^b | 73 (8.3) | 24 (5.2) | 52 (5.9) | 59 (7.1) | 0.103 |
| Tea drinkers ^c | 455 (51.7) | 222 (48.3) | 487 (55.2) | 451 (54.5) | 0.067 |
| Physical activity (MET × h/week) ^d | 19.9 ± 7.30 | 20 ± 7.59 | 19.4 ± 7.41 | 19.9 ± 7.60 | 0.613 |
| Energy intake (kcal/day) | 1822 ± 636 | 1753 ± 540 | 1772 ± 553 | 1792 ± 679 | 0.468 |
| Carbohydrate intake (g/day) ^e | 227.6 ± 41.0 | 229 ± 40.8 | 228.7 ± 40.6 | 230.7 ± 48.7 | 0.185 |
| Protein intake (g/day) ^e | 70.9 ± 17.4 | 69.5 ± 12.6 | 70.8 ± 16.3 | 69.9 ± 13 | 0.515 |
| Fat intake (g/day) ^e | 56.1 ± 15.7 | 54.3 ± 13.2 | 54.9 ± 14.5 | 55.1 ± 14 | 0.269 |
| SFA intake (g/day) ^e | 14.4 ± 3.70 | 14.0 ± 3.50 | 14.2 ± 3.67 | 14.4 ± 3.83 | 0.693 |
| MUFA intake (g/day) ^e | 19.6 ± 5.45 | 19.1 ± 5.13 | 19.5 ± 5.65 | 19.8 ± 5.77 | 0.307 |
| PUFA intake (g/day) ^e | 15.2 ± 5.28 | 15.0 ± 5.45 | 15.0 ± 5.65 | 15.2 ± 5.69 | 0.998 |

P value in bold indicates statistical significance

Continuous variables were described by means ± SDs and categorical variables were described by *N* (%)

DNL de novo lipogenesis, *FAs* fatty acids, *MET* metabolic equivalent task

^aPassive smokers were defined as having been exposed to other people’s tobacco smoking for at least 5 min daily in the previous 5 years

^bAlcohol drinkers were defined as having had wine at least once daily for at least 6 consecutive months

^cTea drinkers were defined as drinking at least one cup of tea per week in the previous 6 months

^dPhysical activity included daily occupational, leisure-time, and household-chores, evaluated by MET hours per day

^eEnergy adjusted intake

Table 2 Spearman’s correlation coefficients among baseline erythrocyte fatty acids in the de novo lipogenesis pathway and energy-adjusted intakes of carbohydrate, energy and fat

| | Carbohydrate | Fat | C16:0 | C16:1n-7 | C18:0 | C18:1n-9 |
|--------------|--------------|----------|-----------|-----------|-----------|----------|
| Carbohydrate | 1.000 | | | | | |
| Fat | −0.785*** | 1.000 | | | | |
| C16:0 | 0.048** | −0.071* | 1.000 | | | |
| C16:1n-7 | 0.067*** | −0.062** | 0.072*** | 1.000 | | |
| C18:0 | 0.035* | −0.038* | 0.513*** | −0.195*** | 1.000 | |
| C18:1n-9 | 0.002 | 0.001 | −0.049*** | 0.126*** | −0.284*** | 1.000 |

Spearman’s correlation coefficients were calculated with adjustment for age and gender; Individual erythrocyte fatty acids were expressed as % of total fatty acids

P* < 0.05, *P* < 0.01, ****P* < 0.001

Table 3 Cross-sectional associations of proportion of baseline erythrocyte DNL fatty acids and total body FM and FM distribution variables ($n = 3075$)

| | Quartile of baseline erythrocyte DNL fatty acids | | | | %Difference ^a | <i>P</i> difference | <i>P</i> trend |
|---------------------------------------|--|---------------|---------------|---------------|--------------------------|---------------------|----------------|
| | Quartile 1 | Quartile 2 | Quartile 3 | Quartile 4 | | | |
| Combined DNL index^b | | | | | | | |
| Median | 7 | 9 | 10 | 13 | | | |
| Total body | 31.14 ± 0.155 | 31.55 ± 0.219 | 31.68 ± 0.156 | 32.22 ± 0.165 | 3.43 | < 0.001 | < 0.001 |
| Trunk | 32.06 ± 0.191 | 32.54 ± 0.270 | 32.87 ± 0.194 | 33.55 ± 0.206 | 4.56 | < 0.001 | < 0.001 |
| Limbs | 31.17 ± 0.168 | 31.60 ± 0.236 | 31.51 ± 0.168 | 31.96 ± 0.177 | 2.50 | 0.015 | 0.004 |
| Android area | 33.51 ± 0.222 | 33.98 ± 0.313 | 34.41 ± 0.225 | 34.99 ± 0.238 | 4.32 | < 0.001 | < 0.001 |
| Gynoid area | 32.56 ± 0.144 | 32.92 ± 0.202 | 32.84 ± 0.144 | 33.11 ± 0.151 | 1.68 | 0.066 | 0.019 |
| %Trunk/limbs | 1.03 ± 0.004 | 1.03 ± 0.006 | 1.04 ± 0.004 | 1.05 ± 0.005 | 2.12 | 0.002 | < 0.001 |
| C16:0 | | | | | | | |
| Median (% of total FAs) | 23.8 | 26.6 | 28.3 | 31.2 | | | |
| Total body | 31.19 ± 0.171 | 31.53 ± 0.169 | 31.87 ± 0.173 | 32.00 ± 0.171 | 2.55 | 0.005 | < 0.001 |
| Trunk | 32.13 ± 0.211 | 32.68 ± 0.210 | 33.04 ± 0.215 | 33.21 ± 0.213 | 3.28 | 0.002 | < 0.001 |
| Limbs | 31.20 ± 0.184 | 31.36 ± 0.181 | 31.76 ± 0.185 | 31.85 ± 0.183 | 2.04 | 0.044 | 0.005 |
| Android area | 33.66 ± 0.245 | 34.13 ± 0.243 | 34.45 ± 0.248 | 34.71 ± 0.246 | 3.08 | 0.02 | 0.002 |
| Gynoid area | 32.75 ± 0.159 | 32.63 ± 0.155 | 32.94 ± 0.158 | 33.04 ± 0.156 | 0.86 | 0.271 | 0.106 |
| %Trunk/limbs | 1.03 ± 0.005 | 1.04 ± 0.005 | 1.04 ± 0.005 | 1.04 ± 0.005 | 1.28 | 0.201 | 0.087 |
| C16:1n-7 | | | | | | | |
| Median (% of total FAs) | 0.141 | 0.209 | 0.291 | 0.404 | | | |
| Total body | 31.14 ± 0.167 | 31.67 ± 0.170 | 31.76 ± 0.169 | 32.02 ± 0.172 | 2.79 | 0.003 | < 0.001 |
| Trunk | 32.16 ± 0.207 | 32.83 ± 0.211 | 32.91 ± 0.210 | 33.15 ± 0.214 | 3.02 | 0.007 | 0.001 |
| Limbs | 31.11 ± 0.180 | 31.50 ± 0.182 | 31.63 ± 0.182 | 31.94 ± 0.185 | 2.64 | 0.014 | 0.001 |
| Android area | 33.70 ± 0.240 | 34.36 ± 0.245 | 34.32 ± 0.243 | 34.58 ± 0.247 | 2.58 | 0.065 | 0.017 |
| Gynoid area | 32.49 ± 0.154 | 32.85 ± 0.156 | 32.83 ± 0.155 | 33.20 ± 0.158 | 2.16 | 0.017 | 0.003 |
| %Trunk/limbs | 1.03 ± 0.005 | 1.04 ± 0.005 | 1.04 ± 0.005 | 1.04 ± 0.005 | 0.40 | 0.616 | 0.627 |
| C18:0 | | | | | | | |
| Median (% of total FAs) | 15.5 | 16.4 | 17.3 | 19.3 | | | |
| Total body | 31.42 ± 0.168 | 31.59 ± 0.170 | 31.79 ± 0.170 | 31.80 ± 0.170 | 1.21 | 0.333 | 0.077 |
| Trunk | 32.42 ± 0.208 | 32.69 ± 0.211 | 32.97 ± 0.212 | 32.98 ± 0.211 | 1.70 | 0.189 | 0.038 |
| Limbs | 31.39 ± 0.181 | 31.52 ± 0.183 | 31.64 ± 0.183 | 31.63 ± 0.182 | 0.75 | 0.757 | 0.310 |
| Android area | 33.77 ± 0.240 | 34.14 ± 0.244 | 34.69 ± 0.247 | 34.35 ± 0.244 | 1.69 | 0.06 | 0.035 |
| Gynoid area | 32.79 ± 0.155 | 32.80 ± 0.156 | 32.85 ± 0.156 | 32.93 ± 0.156 | 0.43 | 0.918 | 0.501 |
| %Trunk/limbs | 1.03 ± 0.005 | 1.04 ± 0.005 | 1.04 ± 0.005 | 1.04 ± 0.005 | 0.98 | 0.404 | 0.100 |
| C18:1n-9 | | | | | | | |
| Median (% of total FAs) | 10.7 | 11.7 | 12.5 | 14 | | | |
| Total body | 31.33 ± 0.167 | 31.72 ± 0.170 | 31.48 ± 0.168 | 32.07 ± 0.173 | 2.36 | 0.013 | 0.009 |
| Trunk | 32.27 ± 0.207 | 32.56 ± 0.208 | 32.68 ± 0.209 | 33.56 ± 0.217 | 3.93 | < 0.001 | < 0.001 |
| Limbs | 31.35 ± 0.181 | 31.94 ± 0.184 | 31.27 ± 0.180 | 31.62 ± 0.184 | 0.85 | 0.039 | 0.872 |
| Android area | 33.69 ± 0.239 | 34.05 ± 0.241 | 34.09 ± 0.242 | 35.15 ± 0.251 | 4.26 | < 0.001 | < 0.001 |
| Gynoid area | 32.66 ± 0.155 | 33.14 ± 0.157 | 32.66 ± 0.155 | 32.91 ± 0.157 | 0.76 | 0.086 | 0.705 |
| %Trunk/limbs | 1.03 ± 0.005 | 1.02 ± 0.005 | 1.05 ± 0.005 | 1.06 ± 0.005 | 3.17 | < 0.001 | < 0.001 |

P values in bold indicate statistical significance

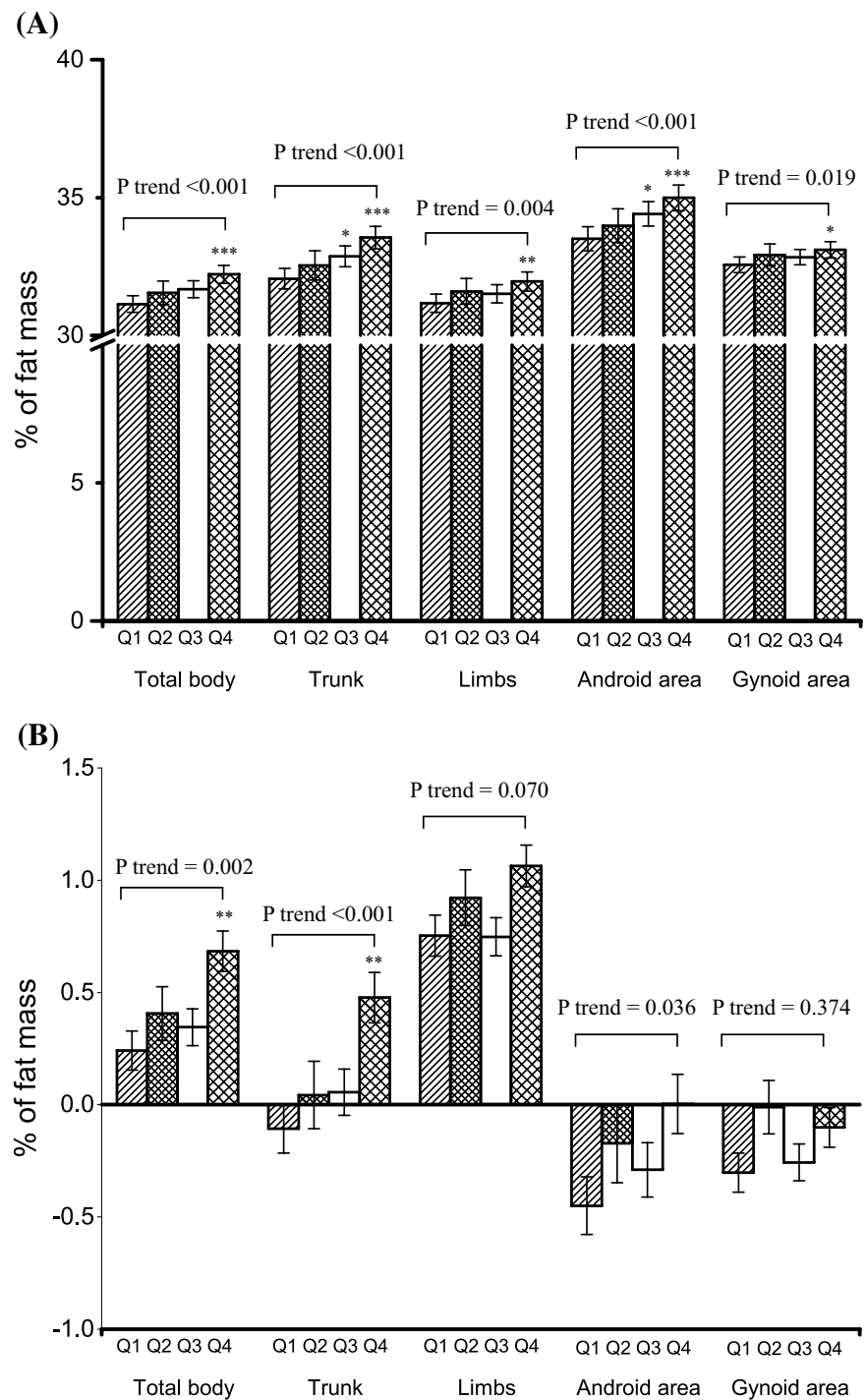
DNL de novo lipogenesis, FM fat mass, %Trunk/limbs ratio of trunk area fat mass ratio to limbs area fat mass ratio

All values are means ± SEMs; categories based on quartiles of fatty acids by gender; Covariates included age, gender, marital status, education level, household income, passive smoking, alcohol drinking, tea drinking, physical activity, and energy intake

^aPercentage difference between Q4 and Q1 = $(Q4 - Q1)/Q1 \times 100$

^bCombined DNL index was calculated as sex-specific sum of quartile score of the four DNL fatty acids. The score of the index range from 4 to 16

Fig. 2 Percentage mean (change) differences and its standard errors for indices of body fat and fat distribution by quartiles of combined DNL index. The combined DNL index was calculated as the sum of quartile scores of the four DNL fatty acids. Quartile 1 was used as the reference. The results are from an analysis of covariance test. The covariates adjusted for are listed in Tables 2 and 3 (a cross-sectional results; b longitudinal results)



and body composition indices and their changes in middle-aged and older Chinese subjects. DNL FAs were positively associated with the cross-sectional values and longitudinal changes of anthropometric and DXA-derived FM indices, particularly in the trunk and abdominal regions. The combined DNL FA score showed more remarkable associations than those for individual DNL FA.

To the best of our knowledge, this is the first prospective study to document the associations between blood DNL FAs and DXA-derived body FM indices in the general population. We also found that DNL FAs were positively associated with anthropometric indices (BMI and WC), similar to the findings for C16:1n-7 of two large-scale cross-sectional studies [8, 9]. In a study of 3,630 US participants,

Table 4 Prospective longitudinal associations between erythrocyte fatty acids and 3-year change of body FM and FM distribution variables ($n = 2597$)

| 3-year changes of FM indices ^a | Quartile of baseline erythrocyte DNL fatty acids | | | | %Difference ^b | <i>P</i> difference | <i>P</i> trend |
|---|--|----------------|----------------|----------------|--------------------------|---------------------|----------------|
| | Quartile 1 | Quartile 2 | Quartile 3 | Quartile 4 | | | |
| Combined DNL index ^c | | | | | | | |
| Total body FM | 0.241 ± 0.087 | 0.406 ± 0.120 | 0.345 ± 0.082 | 0.683 ± 0.090 | 1.40 | 0.004 | 0.002 |
| Trunk FM | −0.107 ± 0.109 | 0.043 ± 0.150 | 0.056 ± 0.103 | 0.477 ± 0.112 | 1.78 | 0.002 | < 0.001 |
| Limbs FM | 0.753 ± 0.091 | 0.922 ± 0.124 | 0.748 ± 0.085 | 1.063 ± 0.093 | 0.98 | 0.044 | 0.070 |
| Android area FM | −0.450 ± 0.128 | −0.172 ± 0.176 | −0.290 ± 0.121 | 0.003 ± 0.132 | 1.32 | 0.094 | 0.036 |
| Gynoid area FM | −0.302 ± 0.087 | −0.011 ± 0.119 | −0.257 ± 0.082 | −0.101 ± 0.089 | 0.61 | 0.136 | 0.374 |
| %Trunk/limbs FM | −0.030 ± 0.002 | −0.032 ± 0.003 | −0.026 ± 0.002 | −0.021 ± 0.002 | 0.89 | 0.023 | 0.003 |
| C16:0 | | | | | | | |
| Total body FM | 0.218 ± 0.098 | 0.383 ± 0.095 | 0.438 ± 0.089 | 0.586 ± 0.090 | 1.16 | 0.053 | 0.006 |
| Trunk FM | −0.170 ± 0.122 | 0.075 ± 0.118 | 0.235 ± 0.111 | 0.288 ± 0.112 | 1.40 | 0.032 | 0.004 |
| Limbs FM | 0.747 ± 0.101 | 0.852 ± 0.098 | 0.766 ± 0.092 | 1.055 ± 0.093 | 0.98 | 0.082 | 0.056 |
| Android area FM | −0.367 ± 0.144 | −0.247 ± 0.139 | −0.230 ± 0.130 | −0.134 ± 0.132 | 0.68 | 0.700 | 0.249 |
| Gynoid area FM | −0.285 ± 0.098 | −0.190 ± 0.094 | −0.123 ± 0.088 | −0.188 ± 0.090 | 0.30 | 0.683 | 0.394 |
| %Trunk/limbs FM | −0.032 ± 0.003 | −0.029 ± 0.003 | −0.020 ± 0.002 | −0.027 ± 0.002 | 0.50 | 0.004 | 0.030 |
| C16:1n-7 | | | | | | | |
| Total body FM | 0.329 ± 0.090 | 0.395 ± 0.091 | 0.477 ± 0.093 | 0.464 ± 0.096 | 0.43 | 0.646 | 0.242 |
| Trunk FM | −0.003 ± 0.113 | 0.048 ± 0.114 | 0.236 ± 0.116 | 0.214 ± 0.120 | 0.66 | 0.364 | 0.107 |
| Limbs FM | 0.802 ± 0.093 | 0.885 ± 0.094 | 0.874 ± 0.096 | 0.874 ± 0.099 | 0.23 | 0.920 | 0.633 |
| Android area FM | −0.398 ± 0.132 | −0.314 ± 0.133 | −0.168 ± 0.136 | −0.055 ± 0.140 | 1.00 | 0.290 | 0.054 |
| Gynoid area FM | −0.286 ± 0.089 | −0.157 ± 0.090 | −0.110 ± 0.092 | −0.212 ± 0.095 | 0.23 | 0.557 | 0.518 |
| %Trunk/limbs FM | −0.029 ± 0.002 | −0.030 ± 0.002 | −0.024 ± 0.002 | −0.025 ± 0.003 | 0.40 | 0.208 | 0.081 |
| C18:0 | | | | | | | |
| Total body FM | 0.195 ± 0.092 | 0.456 ± 0.093 | 0.461 ± 0.095 | 0.543 ± 0.090 | 1.10 | 0.041 | 0.010 |
| Trunk FM | −0.117 ± 0.114 | 0.136 ± 0.117 | 0.141 ± 0.118 | 0.311 ± 0.112 | 1.31 | 0.064 | 0.011 |
| Limbs FM | 0.648 ± 0.095 | 0.928 ± 0.097 | 0.934 ± 0.098 | 0.925 ± 0.093 | 0.88 | 0.088 | 0.047 |
| Android area FM | −0.468 ± 0.134 | −0.200 ± 0.137 | −0.053 ± 0.138 | −0.226 ± 0.131 | 0.71 | 0.187 | 0.142 |
| Gynoid area FM | −0.405 ± 0.091 | 0.014 ± 0.093 | −0.086 ± 0.094 | −0.275 ± 0.089 | 0.40 | 0.006 | 0.472 |
| %Trunk/limbs FM | −0.028 ± 0.002 | −0.028 ± 0.002 | −0.029 ± 0.003 | −0.023 ± 0.002 | 0.50 | 0.363 | 0.194 |
| C18:1n-9 | | | | | | | |
| Total body FM | 0.269 ± 0.093 | 0.458 ± 0.089 | 0.432 ± 0.095 | 0.495 ± 0.093 | 0.71 | 0.325 | 0.117 |
| Trunk FM | −0.045 ± 0.116 | 0.137 ± 0.112 | 0.154 ± 0.118 | 0.233 ± 0.116 | 0.85 | 0.381 | 0.101 |
| Limbs FM | 0.728 ± 0.096 | 0.959 ± 0.092 | 0.846 ± 0.098 | 0.889 ± 0.096 | 0.51 | 0.375 | 0.391 |
| Android area FM | −0.327 ± 0.136 | −0.233 ± 0.131 | −0.246 ± 0.139 | −0.155 ± 0.136 | 0.50 | 0.847 | 0.408 |
| Gynoid area FM | −0.235 ± 0.092 | −0.238 ± 0.089 | −0.148 ± 0.094 | −0.142 ± 0.092 | 0.28 | 0.803 | 0.374 |
| %Trunk/limbs FM | −0.027 ± 0.002 | −0.031 ± 0.002 | −0.026 ± 0.003 | −0.024 ± 0.002 | 0.30 | 0.289 | 0.284 |

Abbreviations as in Table 1

P values in bold indicate statistical significance

All values are means ± SEMs; categories based on quartiles of fatty acids by gender; Covariates included age, gender, marital status, education level, household income, passive smoking, alcohol drinking, tea drinking, physical activity, energy intake, and corresponding body composition variable at baseline

^aChange of fat mass (ratio) = fat mass (ratio) at the 6.3-year (second) follow up—fat mass (ratio) at the 3.1-year (first) follow up

^bPercentage difference between Q4 and Q1 = (Q4 − Q1)/corresponding Q1 value at cross-sectional analysis × 100.

^cCombined DNL index was calculated as sex-specific sum of quartile score of the four DNL fatty acids. The score of the index range from 4 to 16

Mozaffarian et al. [8] reported that higher plasma phospholipid C16:1n-7 was independently associated with both higher BMI and greater WC ($P < 0.001$). Gong et al. [9] also observed that adipose C16:1n-7 had positive association with BMI among 1926 US adults. Our present findings, together with the prior evidence suggest that DNL FAs might be associated with FM, particularly FM in the trunk/abdominal regions. A few observational studies suggested that DNL FAs were positively associated with risk of sudden cardiac arrest [14], metabolic syndrome [27], and diabetes [12], which are close associated with obesity. Further studies are needed to clarify whether the associations between DNL FAs and the above-mentioned chronic diseases are mediated by the trunk/abdominal fat.

Our findings were inconsistent with another cross-sectional survey of 3,107 Chinese adults by Zong et al. [12]. They found that the significant positive association between central obesity and C16:1n-7 after adjustment for age, sex, region, and residence (Q4 vs. Q1: odds ratio, 1.90; 95% confidence interval, 1.53 to 2.35; P trend < 0.001), but this association was abolished after further adjustment for other covariates such as drinking, smoking, educational level, and physical activity. The discrepant findings are possibly because of differences in dietary intake (i.e., dietary carbohydrate or fat intake) and lifestyle factors (e.g., alcohol intake), which have been proposed to regulate DNL [28].

In humans, DNL is suppressed with a high-fat diet, but it could be regulated by other dietary intake and lifestyle factors such as high-carbohydrate meals and alcohol consumption [8, 28]. In adult men fed a high-carbohydrate and low-fat meal, postprandial DNL was significantly increased and was positively associated with body fat mass and triacylglycerol [29]. Although it is generally thought that the DNL pathway does not contribute to the increased fat balance in general populations who do not follow the extreme diets of intervention studies [30], there is increasing concern that the DNL pathway may play a more significant role in the general increase of fat synthesis at a population level because of the increased proportion of refined carbohydrates in the diet [30, 31]. In our study, the fat intake was low compared with Western Countries (21% of total energy vs. $> 35\%$ in many US or European countries) possibly because traditional Chinese foods contain lower fat, and the contents of nutrients in the China Food Composition Tables were based on un-cooked food material. Our findings showed that the DNL FAs, especially dietary fat source fatty acids C16:0 and C18:0, were positively associated with obesity, which indicated that the DNL pathway might be activated under high carbohydrate intake. Although alcohol consumption has been considered as the most important stimulator for DNL pathway [32], the proportion of alcohol consumption in our study was low (6.8%) and the influence of alcohol needs further confirmation.

Of note, the FAs in the DNL pathway tended to be more closely correlated to fat distribution in the trunk and android areas than in the limbs and gynoid region, which indicates that the DNL FAs are closely associated with the FM distribution, in addition to the FM content. Increasing evidence suggested that fat accumulation in the abdominal area produced the most profound risk of developing future cardiovascular events and diabetes [17].

Strengths and limitations

The strengths of this study include the prospective study design, objective measurement of DNL FAs with gas chromatography, and precise assessment of total and regional FM using DXA-based whole-body scans.

There are several limitations. First, the small mean change of the FM in a short duration of follow-up (only 3.2 years for FM), in addition to random errors in the FM measurements, would significantly attenuate the FA–FM associations in the longitudinal studies. Second, non-random sampling may lead to selection bias. However, we did not observe any significant interactions between DNL FA indices and the factors of age, education, household income, physical activity, or alcohol consumption on body composition indices. Third, only one measurement was taken for erythrocyte FA biomarkers, which may be susceptible to regression dilution bias. Fourth, in addition to synthesis through the DNL pathway, the DNL FAs C16:0, C18:0, and C18:1n-9 were also significantly correlated with dietary intake. We cannot completely rule out the effect of dietary fat intake, although we performed stratified analyses according to SFA and MUFA intakes and no interaction was found. Finally, as with any observational study, residual confounding cannot be ruled out, despite our attempts to control for the major potential confounders.

In conclusion, the results of this community-based prospective cohort study suggest that erythrocyte FAs in the DNL pathway may contribute to the increased body FM, especially in the trunk/abdominal regions, in a Chinese population. Further prospective studies with longer follow-up duration are needed to confirm our findings.

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Compliance with ethical standards

Conflict of interest None of the authors reported a conflict of interest related to the study.

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