Erythrocyte odd-chain fatty acids and the risk of cardiometabolic diseases: a prospective study and updated meta-analysis

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Short title

Odd-chain fatty acids and cardiometabolic diseases

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Abbreviations

CMD: Cardiometabolic disease

CVD: Cardiovascular disease

CKB: China Kadoorie Biobank

HR: Hazard ratio

IHD: Ischemic heart disease

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IS: Ischemic stroke

ICH: Intracerebral hemorrhage

OCFA: Odd-chain fatty acid

RR: Relative risk

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2 Tables, 4 Figures, and 27 eTables/eFigures

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Abstract (252)

Aim: To determine dietary sources of odd-chain fatty acids (OCFAs) in Asians and their associations with cardiometabolic diseases (CMDs) and to compare these associations with other populations.

Methods: Erythrocyte fatty acids were profiled in 8,185 subjects (38% men, mean age 58.1 years) participating in the 2nd resurvey of the China Kadoorie Biobank (CKB) in 2013-14 using gas chromatography. Correlations of pentadecanoic (15:0) and heptadecanoic (17:0) acids with dietary factors, assessed via food frequency questionnaires, were examined by Spearman correlations. During about 5-year follow-up, 950 incident CMD were recorded, including 387 ischemic heart disease (IHD), 127 diabetes, and 459 stroke. Cox regression yielded adjusted hazard ratios (HRs) for CMDs associated with levels of 15:0. These results were further meta-analyzed with 33 additional prospective studies, involving 112,193 participants.

Results: OCFAs were significantly correlated with intakes of dairy products, wheat and coarse grains, and fish/seafood in the CKB. Both 15:0 and 17:0 were inversely associated with incident IHD, with adjusted HRs of 0.72 (95% CI 0.59-0.89) and 0.69 (0.56-0.86) for top vs. bottom tertile, respectively. Levels of 17:0 were also inversely associated with incident diabetes (0.41 [0.27-0.62]) and total CMDs (0.85 [0.74-0.97]). In the updated meta-analysis, both 15:0 and 17:0 levels showed inverse associations with diabetes, with pooled relative risks of 0.74 (0.68-0.80) and 0.65 (0.61-0.71) per 10th-90th percentile range, respectively. 17:0 was also inversely associated with incident IHD (0.87 [0.77-0.97]).

Conclusions: Our findings supported favorable associations between OCFAs and CMDs among populations with varied dietary sources and intake levels, which merits future intervention studies.

Keywords: *Fatty acid; Cardiometabolic diseases; Prospective Study; Meta-analysis; Diet*

Lay Summary (192)

This study underscores the potential for odd-chain fatty acids (OCFAs) 15:0 and 17:0 in cardiometabolic diseases, particularly in Asian populations where OCFAs were correlated with dietary fiber and fish besides dairy as indicated in Western populations with high dairy products. Clinically, these OCFAs could aid in risk stratification and dietary interventions, potentially guiding personalized nutrition to mitigate CMD risks. Key findings include the following:

- In Chinese with low dairy intake, our new evidence shows that OCFAs might serve as biomarkers of dietary fiber and fish intake besides dairy as indicated in Western studies with populations consumed high dairy products.
- Our findings suggest that erythrocyte 17:0 and/or 15:0 are associated with low risk of IHD and diabetes in the Asian population with varying dairy intake. OCFAs might serve as modifiable biomarkers for nutritional assessment, and their association with lower risk suggests their dietary sources are important to promote cardiometabolic health with diverse dietary sources.
- Meta-analysis supports the universal applicability of OCFAs as biomarkers, indicating their role in global health strategies. The modifiable features of OCFAs may offer a novel intervention strategy targeted raising their levels in high CMD risk population.

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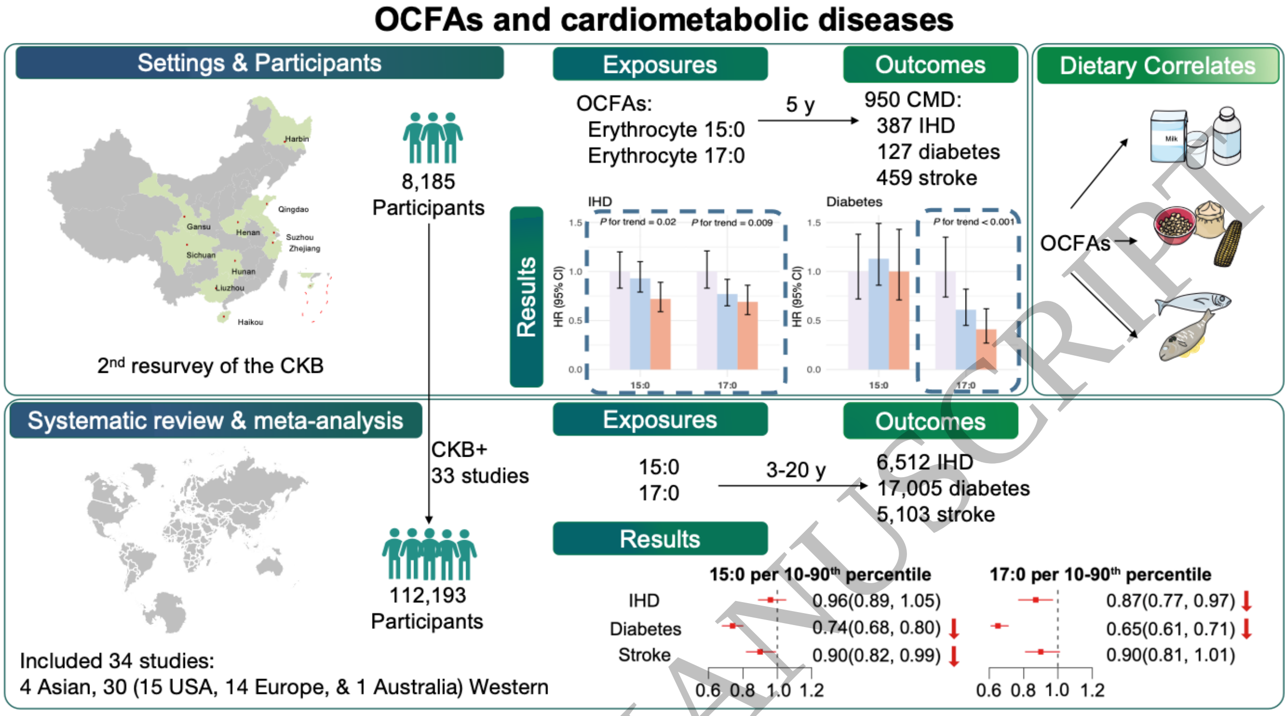
Graphical Abstract



Introduction

Cardiometabolic diseases (CMDs), including ischemic heart disease (IHD), diabetes, and stroke, are the leading causes of adult death and disability, and contribute to major disease burdens globally, including in China as well[1]. It was estimated that more than half of CMDs' deaths could be attributed to suboptimal dietary intake. However, defining optimal nutrition still remains a big challenge in nutritional epidemiology because traditional self-reported dietary questionnaires, which are still widely used, are subject to significant measurement errors and recall bias[2]. On the other hand, applications of biomarkers provide the valuable opportunity to capture specific signatures of dietary sources and intake levels in the context of dietary patterns[3]. Meanwhile, some of these dietary biomarkers may also reveal early trajectory of cardiometabolic dysregulation. Thus, discovering such biomarkers of food intakes is critically important to inform optimal nutritional recommendation or intervention policy relevant for prevention of CMDs and many other diseases.

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Two major odd-chain fatty acids (OCFAs), pentadecanoic (15:0) and heptadecanoic (17:0) acids, have long been suggested as biomarkers of dairy fat[4–9]. Higher levels of 15:0 and 17:0 measured in various lipid compartments, including serum, plasma, erythrocyte, or adipose tissue, were found to be associated with lower risks of CMDs including diabetes and/or cardiovascular diseases (CVDs) in several population-based epidemiological studies, although inconsistent or even contradictory findings were reported in other studies[10,11]. In one meta-analysis - the Fatty Acids and Outcomes Research Consortium (FORCE) - of 63,682 participants from 16 prospective studies, higher levels of both 15:0 and 17:0 were significantly associated with lower risk of diabetes[12]. Similar inverse associations were also found for 17:0 with risks of IHD and stroke in another meta-analysis[13], although the stroke association was not identified in two recent meta-analyses[14,15]. Notably, the majority of studies included in previous meta-analyses of OCFAs involved Western populations, which can be characterized by high dairy consumption. In Asian populations such as Chinese where dairy consumption remained much lower than that in the Western populations[16], little is known about main dietary sources of OCFAs and their associations with CMDs. Evidence from a nested case-control Japanese study suggested a stronger association of OCFAs with fish/seafood than with dairy, but null association of OCFAs with diabetes incidence[17]; while a nested case-control study in China reported a positive association of 15:0 and 17:0 with risk of incident diabetes[18]. To date, no study has evaluated the associations between OCFAs and incidence of CVDs in Asian populations.

To fill the evidence gaps, we present detailed analyses of data in the prospective China Kadoorie Biobank (CKB). The main aims of the study were to (i) investigate the dietary correlates with erythrocyte 15:0 and 17:0 in Chinese adults, overall and across ten different study regions; (ii) examine the prospective associations of 15:0 and 17:0 with risks of incident CMDs (i.e. diabetes, IHD, and stroke) in Chinese; and (iii) compare and meta-analyze our study findings with those of previously published prospective studies.

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Materials and Methods

Study population

The CKB study recruited >512,000 adults aged 30-79 years (41% men) from ten geographical regions (five urban and five rural) across China in 2004-2008. Details of the study design, participants, data collection and follow-up were described previously[19]. During 2013-14, about 5% of the surviving participants were randomly selected to participate in the 2nd resurvey with new data and sample collection. Of the 24,996 participants with blood samples collected, 10,933 participants (approximately 1,100 persons per region on average) were randomly chosen to measure erythrocyte fatty acids.

At baseline and subsequent resurveys, international, national and local ethical approvals were obtained for the CKB. All participants provided written informed consent for linkages with their health records and for future unspecified research use of the stored biological samples.

Data collection

During the 2013-14 resurvey, information on dietary intake, sociodemographic status, lifestyle factors (i.e. diet, smoking, alcohol consumption, and physical activity), and medical history were collected by laptop-based questionnaires. Dietary information included intake frequency and amount (g/day) of major food groups (refined grains, coarse grains, red meat, poultry, fish/seafood, eggs, fresh vegetables, soy products, fresh fruits, soymilk, and dairy products, including cow's milk, yogurt, and other dairy products such as cheese and milk powder). Physical activity levels were calculated as daily metabolic equivalent tasks (MET)-hours, which summarized the MET-hours for various activities related to a person's occupation, commuting, housework, and non-sedentary leisure time activities.

Participants' standing and sitting height, weight, blood pressure, body composition (fat mass and fat-free mass), and heart rate were measured by trained health workers, using calibrated instruments with

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standard protocols. Non-fasting blood samples were collected (with recorded time from the last meal) using 10-mL EDTA tubes for immediate on-site tests of random blood glucose (Johnson & Johnson, New Brunswick, NJ, USA) and lipids (Mission Cholesterol Monitoring System, Acon Laboratories Inc, San Diego, CA), and for long-term storage.

Measurement of erythrocyte fatty acids

Blood samples collected were stored immediately in a 4°C refrigerator at study assessment centres for several hours before being transported to local laboratories for centrifugation and sub-aliquoting (mean time delay ~10 hours). After centrifuge and sub-aliquoting, the red cells were stored at -80 °C until analysis during 2016-2018. Erythrocyte fatty acids were measured by gas chromatography using an Agilent 6890 N GC with a flame ionization detector and a capillary column (SP-2560) as previously described[20]. The levels of fatty acids in erythrocytes were considered more stable and reflective of habitual dietary intakes than other circulating lipid fractions[21]. The relative proportion of each fatty acid was determined as a percentage of total detected 30 fatty acids, except for the internal standard[22]. The samples were analyzed randomly and quality controls were inserted every 11 samples for accuracy. The coefficients of variation were 11.5% for 15:0 and 8.5% for 17:0. Total OCFA in the current study was calculated by summing the levels of 15:0 and 17:0. Of the 10,933 samples measured, 10,563 (96.6%) had valid fatty acid data after the quality control process.

Follow-up for cardiometabolic diseases

The health status of the participants was monitored through linkage, *via* the participants' unique 18-digits national identification numbers, with local death and disease (for cancer, IHD, diabetes, and stroke) registries and with nationwide health insurance system, which covers >98% of study participants, on any episodes of hospitalization. To ensure the accuracy of participant survival status and minimize loss to follow-up (currently <1%), active follow-up was conducted annually to check

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against local residential and administrative records. All reported deaths and disease cases were coded according to the International Classification of Diseases, 10th Revision by the trained medical staff who were blinded to the study data.

The main outcome measures of the present study were CMDs, covering diabetes mellitus (E10-E14), IHD (I20-I25), and stroke (I60, I61, I63, and I64, with >93% of diagnoses confirmed by brain imaging) and its two main types (I63 for ischemic stroke and I61 for intracerebral hemorrhage). The follow-up was censored at death, occurrence of individual CMD, loss to follow-up, or to January 1 2019, whichever came the earliest. For the present study, participants who had developed diabetes, IHD, or stroke (n=2,369) before the 2nd resurvey in 2013-14 were excluded, along with those (n=9) with missing blood lipids data. After these exclusions, 8,185 participants were included in the main analyses.

Statistical analysis

Spearman correlation coefficients (r) were used to assess the correlations of 15:0 and 17:0 with dietary factors, body mass index (BMI), body composition, systolic blood pressure (SBP), blood lipids, and random glucose, adjusting for age, sex, study regions, education, smoking, alcohol drinking, family history of cardiovascular diseases and diabetes, and physical activity. The correlations between different food groups and OCFAs were further adjusted for other food groups. Based on daily intake of OCFA-correlated food groups, including total dairy, coarse grains, wheat, red meat, and fish, the adjusted geometric mean values and 95% confidence intervals for 15:0, 17:0, and total OCFA were estimated with linear prediction adjusted for the same covariates.

Cox regression was used to examine the prospective associations of OCFA with CMD outcomes. A person-time for each participant was determined from the time of an FA assay to each end of follow-up. OCFA were analyzed as main exposure variables to estimate the adjusted hazard ratio (HRs) and 95% confidence intervals (CIs), across tertile categories and continuously with the top 10th compared to the

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bottom 10th percentiles after logarithm transformation due to skewed distribution. The analyses were adjusted for potential confounding factors as follows, including (i) *Model 1:* age (continuous variable), sex, study regions, education attainment (no formal education, primary school, middle school, or high school and above), (ii) *Model 2:* additionally adjusted for smoking status (never or occasional, ex-regular, current regular), alcohol drinking (never or occasional, ex-regular, current regular), family history of CMDs (yes/no for incident IHD and stroke; and yes/no for incident diabetes), and physical activity (MET-hr/day). In sensitivity analyses, additional adjustments were made: Model 3 further adjusted for SBP, BMI, low-density lipoprotein cholesterol (LDL-C), duration of fasting time; Model 4 further controlled for intake of major food groups and Model 5 further adjusted for erythrocyte levels of total monounsaturated, polyunsaturated, and other saturated FA. However, caution is warranted when interpreting the estimated effects from Models 4 and 5, since adjusting for dietary sources and other fatty acids may introduce overcontrol bias. The linear trend of HRs over tertiles was assessed by χ^2 test using these tertile numbers as continuous variables. We also conducted the Cox regression analysis to estimate the association between OCFA-correlated food groups and CMD outcomes.

The proportional hazards assumption in Cox regression was tested by Schoenfeld residuals method (which found no evidence of violation). For any exposure with more than two categories, a floating absolute-risk method was employed[23] to estimate the standard errors and confidence intervals (CIs) for each category, including the reference category. To ensure appropriate calculation of variances for the logarithm of relative risks (HRs in our analysis), "floated" variances were utilized, while preserving the integrity of HR values.

Furthermore, subgroup analyses were also conducted by age (30-49, 50-69, ≥70 y), sex (men/women), area of residence (rural/urban), family history of CVD/diabetes (yes/no), ever regular smoker/drinker (yes/no), physical activity (<10, 10-20, ≥20 MET hours/day), BMI (<24, 24-28, ≥28 kg/m^2), and dairy

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consumer (yes/no). In subgroup analysis by study regions, HRs were calculated per a region-specific standard deviation in erythrocyte OCFAs. To assess heterogeneity, χ^2 tests were applied to the logarithm of HRs and their corresponding standard errors.

The analyses were performed by R version 3.6 (http://R-project.org/). Two-sided $P<0.05$ was considered statistically significant.

Systematic review and meta-analysis

We undertook a systematic literature search in PubMed and Web of Science for relevant papers published in English before 31 May 2024 using a search strategy detailed in the **Supplementary Methods**. This study followed the PRISMA guidelines and was registered on PROSPERO [CRD42023442513].

For the literature search, we used the following criteria: (1) prospective cohort, case-cohort, or nested case-control studies among adults aged at >18 years old; (2) 15:0 or 17:0 measured as fatty acid (FA) profiles from lipid compartments including serum, plasma, erythrocyte, or adipose tissue; and (3) disease outcomes included IHD, diabetes, or stroke. Studies were excluded if: (1) they had a retrospective or cross-sectional design; or (2) standard errors for estimates were missing from the published papers. When we identified multiple publications from the same cohort or overlapping in participants across different studies (e.g. EPIC-InterAct included the participants from EPIC-Potsdam), we only included studies with a larger sample size.

For each identified article, two investigators (XX and QY) independently extracted relevant information from each study, including study-specific regression coefficients and standard errors for each OCFA published by FORCE with consent[12]. To assess the quality of studies included[4,10,11,13,18,24–34], we used the Newcastle-Ottawa Scale (NOS)[35], awarding up to nine points to each study, with four

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points for selection of participants and measurement of exposure, two for comparability of cohorts based on design or analysis, and three for assessment of outcomes and adequacy of follow-ups. We categorized NOS scores as follows: 0–3 for low quality, 4–6 for medium quality, and 7–9 for high quality. When a study presented estimates of OCFAs in multiple biological tissues, we evaluated data from lipid compartments that were more likely to reflect long-term dietary intakes as follows: adipose tissue > erythrocyte > phospholipids (plasma/serum) > cholesterol esters (plasma/serum) > total plasma/serum.

Pooled associations of 15:0 and 17:0 with specific CMD were estimated as continuous valuables (per study-specific 10th to 90th range) using fixed-effects meta-analysis stratified by continents (Details seen in the **Supplementary Methods**). For analyzing total IHD, the risk estimates in each study were selected in the following order: (1) total IHD/coronary heart disease (CHD); (2) acute myocardial infarction (AMI), if total IHD/CHD were not reported. I^2 statistics were used to evaluate the overall heterogeneity[36]. Moreover, subgroup analyses were conducted by (1) sex (women/men), (2) follow-up durations (<10, ≥10 y); (3) study populations (continents); and (4) lipid compartments (erythrocytes/others). *P* for interaction between subgroups was calculated by meta-analyzing study-specific risk estimates from each stratum, and was thereafter examined using meta-regression. To assess potential publication bias, Egger's test was conducted by using a linear regression approach and Begg's test by employing a rank correlation method. A *P*-value <0.10 was considered as having statistically significant small-study bias. In the sensitivity meta-analysis, we firstly stratified the studies by lipid compartment (per study-specific 10th to 90th range) using fixed-effects meta-analysis; then analyzed 15:0 and 17:0 within categorical terms (tertiles) by continents studies using fixed-effects meta-analysis; and finally stratified the studies by continents using random-effects meta-analysis.

Results

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Dietary correlates of OCFA in the CKB

Overall, the mean (SD) age of 8,185 study participants at 2013-14 resurvey was 58.1 (9.92), 62.0% were women, 52.9% resided in rural areas and 37.1% reported consuming dairy products regularly (i.e. milk, yoghurt, and other dairy products). The median (10^{th}-90^{th}) levels of erythrocyte as percentage (%) of total erythrocyte FA were 0.055 (0.033-0.090) for 15:0, 0.256 (0.199-0.340) for 17:0, and 0.313 (0.236-0.426) for total OCFA (**Table 1**). Participants with higher total OCFA levels generally exhibited healthier lifestyles, characterized by a higher proportion of non-smokers and non-drinkers, greater consumption of vegetables, fruits, and dairy products, and lower intake of red meat compared to those with lower total OCFA levels.

As shown in **Figure 1**, the total OCFA levels varied from 0.268% to 0.378% of total fatty acids across the ten regions, with Qingdao (coastal city) being the highest and Sichuan (inland rural area) being the lowest. The level of 15:0 was approximately one-fifth of 17:0, and both showed regional variations (medians ranging from 0.045% to 0.076% for 15:0 and from 0.223% to 0.302% for 17:0 of total fatty acids) (**Figure 1**). Notably, percentages of habitual (with daily dairy intake>0 within the past 12 months) dairy consumers (medians ranging from 20% to 75%), and subtypes and intake levels of dairy products differed across the ten regions (**Figure S1**). Dairy and non-dairy consumers differed in many aspects in the correlations between OCFAs and cardiometabolic traits, and other dietary intakes such as wheat, coarse grains, and fish/seafood, with absolute correlation coefficients ranging from 0 to 0.23 as shown in **Table S1-S2**. Overall, OCFAs were positively associated with total dairy (r=0.08~0.14) and wheat (r=0.11~0.21) and inversely associated with red meat (r=-0.19~-0.23) and rice (r=-0.08~-0.18) (**Table S2**). Participants who consumed over 200g/day dairy products had 15%, 5%, and 6% higher levels of 15:0, 17:0, and total OCFAs than those of non-dairy consumers; likewise, participants who consumed over 150g/day fish had 6%, 5% and 5% higher levels of 15:0, 17:0 and total OCFA levels

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than those of non-fish consumers (**Figure S2**-**S3**). In region-specific analyses, OCFAs showed different correlations with most of food groups (**Table S3**). For instance, OCFAs were primarily correlated positively with dairy intake in Harbin (north-eastern city); while they were mainly correlated positively with fish intake in Haikou (southern coastal city). On the other hand, in two inland rural areas (Gansu and Henan), OCFAs were inversely correlated with red meat intake.

Associations of OCFA with risks of CMDs in the CKB

During a median follow-up of 4.8 years, a total of 950 participants developed CMDs, including 387 IHD, 127 diabetes, and 459 stroke cases. In multivariable-adjusted models, a higher 15:0 level was significantly associated with a lower risk of IHD (adjusted HR=0.72 [95% CI, 0.59-0.89] for top *vs.* bottom tertile; P_{trend}=0.02), but not with diabetes (1.00 [0.71-1.43]), stroke (1.01 [0.85-1.20]), or stroke subtypes (**Table 2**). For 17:0, there was a significant inverse association with risks of both IHD (0.69 [0.56-0.86], P_{trend}=0.009) and diabetes (0.41 [0.27-0.62], P_{trend}< 0.001), but not with stroke (0.90 [0.74-1.08]) or stroke subtypes. For total OCFA, we found a significant inverse association with risks of IHD and diabetes. Similar results were also observed when using quintile categories for a combined outcome of diabetes and IHD (**Figure S4**).

These associations were not materially altered after further controlling for SBP, BMI, LDL-C, fasting hours, daily intakes of major food groups, and total monounsaturated, polyunsaturated, and other saturated fatty acids (**Table S4-S5**). Moreover, inverse association between 17:0 and incident diabetes also exhibited a linear dose-response manner (adjusted HR=0.66 [0.50-0.86], per 10th to 90th percentile; **Table 2**). However, we did not observe any significant associations of OCFAs-related food groups with CMD risks, except for a borderline significant inverse association between coarse grains and ischemic stroke (P_{trend}=0.04) (**Table S6**).

In subgroup analysis (**Figure S5-S7**), the association of 15:0 with IHD appeared more pronounced in

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women ($P_{\text{interaction}}<0.05$, **Figure S6**). However, subgroup analyses showed that neither geographical regions (**Figure S5**) nor dairy patterns (**Figures S6-S7**) significantly modified the associations between OCFAs and IHD or diabetes.

Systematic review and meta-analysis

In systematic review, we identified 33 prospective studies that met the inclusion criteria overall, including 16 from the FORCE consortium (**Figure S8**). Together with the CKB, only four were conducted in Asian populations and 30 (15 USA, 14 Europe, and one Australia) involved Western populations among these 34 studies. The present meta-analysis included a total of 112,193 participants, with a median follow-up ranging from 3 to 20 years, with 16 studies graded as high and two graded as moderate quality, and 16 studies from FORCE were not graded (**Table S7-S8**). The number of studies reporting different outcomes varied, with nine studies including IHD (nine for 15:0; five for 17:0), 21 including diabetes (21 for 15:0; 17 for 17:0), and eight including stroke (eight for 15:0; six for 17:0).

In the pooled analyses (**Figure 2-4**), 15:0 was inversely associated with risks of diabetes (n=17,005 cases; RR=0.74 [95% CI, 0.68-0.80] per 10th to 90th percentile) and stroke (5,103 cases; 0.90 [0.82-0.99]), but not with IHD (6,512 cases; 0.96 [0.89-1.05]). 17:0 was inversely associated with risks of diabetes (16,049 cases; 0.65 [0.61-0.71]) and IHD (4,298 cases; 0.87 [0.77-0.97]), but not with stroke (4,743 cases; 0.90 [0.81-1.01]). In further analyses stratified by lipid compartments, using study-specific tertiles of OCFA, or using random-effects model, similar results were obtained except for insignificant association between 15:0 and stroke in the random-effects meta-analysis (**Figure S9-S17**). In subgroup analyses, a stronger inverse association of 15:0 with IHD was observed in women compared to men ($P_{\text{interaction}}=0.02$, **Figure S18**), and stronger inverse associations of 15:0 with IHD/stroke were found in Europe compared to North America or East Asia, and with diabetes were found in Oceanian, European, and North American studies compared to East Asian studies, or in other

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lipid compartments compared to erythrocytes (all $P_{\text{interaction}}<0.05$, **Figure S18**). Although there were significant heterogeneities in risk estimates across different studies, there was no evidence of apparent publication bias upon visual examination of the funnel plots and both Begg's (P=0.13-0.65) and Egger's tests (P=0.25-0.93) (**Figure S19**).

Discussion

To the best of our knowledge, the analysis of the CKB data represented the largest prospective investigation to date in Asian populations about the dietary correlates and aetiologic role of OCFAs in CMDs. In this Chinese population with relatively low consumption of dairy products, there were regional variations in dietary correlates of OCFAs. In a few urban cities (i.e. Qingdao and Harbin) with high dairy intake, dairy products were predominantly correlated with erythrocyte OCFAs levels, while in other regions with low dairy intake, OCFA levels were positively correlated with fish intake (i.e. in Haikou) or dietary fiber intake (i.e. wheat and coarse grains) rather than with dairy intake. Higher levels of 15:0 and 17:0 were associated with lower risks of CMDs on average across the regions in China. The findings were confirmed in the global cohorts, robustly for diabetes in particular, as further demonstrated in our updated meta-analysis of the CKB and 33 other studies.

It is crucial to interpret our findings within the context of varying dairy consumption patterns. Though dairy consumption increased in last few decades, overall levels of habitual dairy intake in Chinese adults were only about one-third of that in typical Western populations[16]. In our CKB cohort, the mean dairy intake was 41.3 g/day that was comparable to the data from the China National Nutrition Surveys[37]. Notably, people living in ten regions of the CKB cohort exhibited significant heterogeneities, in terms of the proportion of dairy consumers (20-75% among ten regions), as well as levels of consumption (12–112 g/day). Though Chinese have different dietary patterns containing relatively lower dairy products (mainly milk) than Western populations, dairy products were still major

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dietary factors correlated with OCFAs in the CKB, which are the established dairy fat biomarkers in Western populations[4,6,8,9,38–40]. Moreover, the association between OCFAs and CMDs were not significantly modified when taking geographical regions into account. On the other hand, the relatively low dairy consumption in our population may allow us to identify other important dietary determinants of OCFAs that could be masked in those populations with high dairy consumption. For instance, fish rather dairy were positively correlated with 17:0 levels in participants living in Haikou, a coastal region with high fish consumption, similar to the findings from a Japanese study with high-fish-intake populations[31]. Moreover, intakes of fiber-rich food groups, including coarse grains and wheat in our study were found to be positively correlated with 15:0 and 17:0, which were reported to be correlated with fruits/vegetables in previous Western studies[40–42]. Despite differences in dietary sources and consumption levels, the beneficial association of OCFAs with CMDs remained remarkably consistent across cohort studies in diverse populations. Collectively, the favorable OCFA-CMD association could extend to populations with lower dairy intake and OCFA levels could be attributed to multiple food sources (i.e. coarse grains, fish, and dairy products) in populations with low dairy consumption.

To date, the associations between OCFAs and CMDs have been under-investigated in Asian populations, while existing evidence from Western populations remains inconclusive[4,11,13,24,25,32–34,40]. Notably, the magnitude of 15:0 association was comparable to that reported in a Swedish cohort[13] with the world's highest dairy consumption, although there could be large variation in dietary determinants of OCFAs and relatively lower levels of erythrocyte OCFAs in the CKB than in most Western studies[13,32–34]. Furthermore, women showed stronger 15:0-IHD associations than men in both the CKB and the meta-analysis, which merits further study. It is possible that sex hormones and prevalent "gynoid" type fat distribution may explain the more favorable cardiometabolic outcomes among women[43]. In our meta-analysis, a significant association between 15:0 and stroke was identified, contrasting with the null association observed in the CKB study. The discrepancy may be partially

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attributed to including different stroke subtypes with different etiologies[44]. There is evidence that Chinese tended to have higher rates of intracerebral hemorrhage and small vessel lacuna infarcts, whereas Western populations were more prone to ischemic stroke, especially large-vessel ischemic stroke[45]. In addition, there were also large differences in dietary patterns between Chinese and Western populations, which might also contribute to the observed variations.

As well as lower risk of IHD, high 17:0 levels were also significantly associated with a lower risk of diabetes in the CKB study, which was also confirmed by our updated meta-analysis. Previously, we found that high dairy intake, milk-related erythrocyte trans-18:1 isomers, or sphingomyelins were associated with lower incident diabetes or better fasting glucose in a population-based Chinese cohort[46,47]. Recently, in a nested case-control study based on the China Cardiometabolic Disease and Cancer Cohort (4C) Study (n=1,707 cases), the levels of milk-related 15:0 and 17:0, both at around 0.25% molar of total fatty acids in serum, showed inverse associations with incident diabetes, with ORs per SD of 0.85 (0.76-0.94) and 0.84 (0.76-0.92), respectively[18], which partially supported our findings, especially those related to 17:0 and diabetes. The reasons for discrepant associations of 15:0 with diabetes in the CKB *vs.* the 4C studies are not clear and may be due to difference in study power, levels of 15:0 and 17:0, as well as lipid compartments measured (serum free fatty acids in the 4C *vs.* erythrocyte fatty acids in the CKB).

Though potential biological mechanisms underlying the favorable associations between OCFAs and CMDs were not fully understood, there were several plausible explanations. Firstly, OCFAs were suggested to have anti-inflammatory property[48–51] and both higher 15:0 and 17:0 levels were associated with lower levels of plasma leptin and PAI-1 in a Japanese study of 484 participants[50]. In studies of rodent model and human cell culture, 15:0 attenuated inflammation, dyslipidemia, and fibrosis[51]. These beneficial effects of OCFAs may be mediated by binding key metabolic regulators like PPARs to repair

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mitochondrial function and ultimately to improve metabolisms by lowering blood glucose and cholesterol levels[51]. Secondly, OCFAs may improve insulin sensitivity and glucose homeostasis as suggested by the associations of higher OCFA levels with lower pro-insulin levels and better β-cell function in cohort studies among populations with high dairy consumption[49,52]. Indeed, feeding mice with propionate, a precursor of OCFAs, significantly suppressed insulin resistance[53]. Thirdly, OCFAs have bi-directional interactions with gut microbiota. Recently, in a randomized controlled trial with 88 participants, supplementation of 15:0 for 12 weeks significantly reduced LDL-C and induced favorable alterations in gut microbiome, including increased abundance of *Bifidobacterium adolescentis*[54]. Notably, high intake of dietary fiber increased yield of propionate by gut bacteria, the latter is then be absorbed and used as a precursor for hepatic de novo synthesis of OCFAs, especially 17:0. Additionally, as part of healthy dietary patterns, dairy, fish, dietary fiber, and their components might exert favorable impacts on cardiometabolic health, even though we failed to demonstrate significant associations between individual dietary factors and risks of CMDs using relatively crude assessment of dietary patterns in the CKB. Moreover, level of OCFAs may also reflect a general healthy dietary pattern as supported by the inverse correlation between red meat and OCFAs in our study.

By leveraging participants from ten regions with diverse diets in the CKB, we were also able to examine alternative dietary correlates with OCFAs beyond dairy, which might be critical for many countries with relatively low dairy consumption. Moreover, we measured erythrocyte OCFAs, which were expected to provide better objective assessment of long-term dietary exposures than plasma and serum. The null associations observed of the OCFAs-related food groups with CMDs also underscored the limitations of self-reported dietary studies, emphasizing the need for biomarkers to provide more

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precise and reliable insights into these complex relationships. Furthermore, the CKB findings were integrated into largest meta-analysis involving 34 cohort studies, further enhancing the reliability and generalizability of the study findings. However, our study also had limitations. Firstly, we could not fully avoid possible reverse causality due to the relatively short duration of follow-up, although participants with prior history of IHD, stroke, and diabetes were excluded from analyses. Secondly, we only measured OCFA once and were not able to estimate the mean usual exposure level during follow-up. Thirdly, although carefully collected following a standardized protocol in the CKB study, there were measurement errors in dietary intakes, other lifestyle factors, and cardiometabolic traits. Finally, we were not able to assess the causality of the observed associations due to lack of genetic instruments for OCFAs. To date, only one study[55] identified an infrequent SNP (rs13361131, major allele frequency=1.1%) within the *myosin X* gene for 17:0 (P=1.37×10^{-8}), with no significant genetic association reported for 15:0.

Conclusions

In conclusion, the present study provided new evidence that OCFAs might serve as good biomarkers reflecting consumption of dairy and other food in populations with low dairy consumption. Moreover, irrespective of the main dietary correlates, higher levels of OCFAs were associated with lower risks of CMDs. Future intervention trials are necessary to establish the causality and dose-response relationships of OCFAs with various foods and to clarify the specific biological mechanisms linking OCFAs with CMD outcomes.

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Ethics approval and consent to participate

The study protocol was approved by the Ethics Review Committee of the Chinese Center for Disease Control and Prevention (Beijing, China) and the Oxford Tropical Research Ethics Committee, University of Oxford (UK). All participants provided written informed consent before taking part in the study.

Consent for publication

None.

Author Contribution

XL, ZC, LL, and Yan Chen contributed to the conception or design of the work. Yiping Chen, PP, HY, LY, GZ, CY, QC, JL, PZ, DS, JC, and XG provided administrative, technical, or material support. XX and SL conducted formal analysis. XX and QY performed meta-analysis. SL, XX, FI, HD, ZC, and XL developed methodology. SL, HD, LL, ZC, and XL provided supervision. XX, SL, and XL wrote the original draft. ZC, HD, and FI critically revised the manuscript. All gave final approval.

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Competing interests

The authors declare that they have no conflict of interest.

Data availability statement

Data will be made available upon request pending application and approval. Details are available from www.ckbiobank.org/site/Data+Access.

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Figure Legends

Figure 1. Median concentrations (10^{th} - 90^{th}) (% total fatty acids) of 15:0, 17:0, and total odd-chain fatty acid across ten CKB study regions

Correlation between total odd-chain fatty acid and total dairy intake was adjusted for age, sex, study regions, education, smoking, alcohol drinking, family history of cardiovascular diseases and diabetes, physical activity, and other food groups.

Figure 2. Associations of 15:0 and 17:0 per 10^{th} to 90^{th} percentiles with incident risk of IHD in the updated meta-analysis of the CKB and other prospective studies

Study-specific estimates for risk ratios (RRs) and 95% CIs per 10^{th} to 90^{th} percentiles were showed,

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grouped by continents, and were pooled into risk estimates for overall risks. The dots indicated individual studies and the diamonds represented summary risk estimates from the pooled meta-analysis. The size of grey-shaded square reflected study weights and the results were sorted by the order of each study's effect size.

Abbreviations: CE=cholesteryl ester; CHS=Cardiovascular Health Study; CKB=China Kadoorie Biobank Study; EPIC-Norfolk=European Prospective Investigation Norfolk; HPFS=Health Professionals' Follow-up Study; MESA=Multi-Ethnic Study of Atherosclerosis; NHS=Nurses' Health Study; NSHDS=Northern Sweden Health and Disease Study; WHI-OS=Women's Health Initiative Observational Study; 60YO=the Stockholm Cohort of 60-year-olds.

Figure 3. Associations of 15:0 and 17:0 per 10th to 90th percentiles with incident risk of diabetes in the updated meta-analysis of the CKB and other prospective studies

Study-specific estimates for risk ratios (RRs) and 95% CIs per 10th to 90th percentiles were showed, grouped by continents, and were pooled into risk estimates for overall risks. The dots indicated individual studies and the diamonds represented summary risk estimates from the pooled meta-analysis. The size of grey-shaded square reflected study weight and the results were sorted by the order of each study's effect size.

Abbreviations: AGESR=Age, Genes, Environment Susceptibility Study (Reykjavik); AOC=Alpha Omega Cohort; CCCC=Chin-Shan Community Cardiovascular Cohort Study; CHS=Cardiovascular Health Study; CKB=China Kadoorie Biobank Study; EPIC-InterAct=European Prospective Investigation InterAct; FHS=Framingham Heart Study; HPFS=Health Professionals' Follow-up Study; IRAS=Insulin Resistance Atherosclerosis Study; MCCS=Melbourne Collaborative Cohort Study; MESA=Multi-Ethnic Study of Atherosclerosis; METSIM=Metabolic Syndrome in Men Study; NHS=Nurses' Health Study; PIVUS=Prospective Investigation of the Vasculature in Uppsala Seniors;

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Three C=Three City Study; ULSAM=Uppsala Longitudinal Study of Adult Men; VIP=Vasterbotten Intervention Program; WHIMS=Women's Health Initiative Memory Study; 4C=China Cardiometabolic Disease and Cancer Cohort.

Figure 4. Associations of 15:0 and 17:0 per 10th to 90th percentiles with incident risk of stroke in the updated meta-analysis of the CKB and other prospective studies

Study-specific estimates for risk ratios (RRs) and 95% CIs per 10th to 90th percentiles were showed, grouped by continents, and were pooled into risk estimates for overall risks. The dots indicated individual studies and the diamonds represented summary risk estimates from the pooled meta-analysis. The size of grey-shaded square reflected study weights and the results were sorted by the order of each study's effect size.

Abbreviations: ARIC=Minneapolis field center of Atherosclerosis Risk in Communities Study; CE=cholesteryl ester; CHS=Cardiovascular Health Study; CKB=China Kadoorie Biobank Study; HPFS=Health Professionals' Follow-up Study; MONICA=Monitoring of Trends and Determinants in Cardiovascular Disease Study; NHS=Nurses' Health Study; VIP=Vasterbotten Intervention Program; WHI-OS=Women's Health Initiative Observational Study; 60YO=Stockholm Cohort of 60-year-olds.

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Table 1. Characteristics of participants by tertiles of odd-chain fatty acids in the CKB*

	Total OCFA			15:0			17:0			Overall [‡] (n=8185)
	Tertile 1[†]	Tertile 2[†]	Tertile 3[†]	Tertile 1[†]	Tertile 2[†]	Tertile 3[†]	Tertile 1[†]	Tertile 2[†]	Tertile 3[†]	
Age, yrs	57.6	57.8	59.0	57.6	57.7	59.1	57.7	57.7	59.0	58.1
Men, %	46.1	33.9	33.9	48.0	35.2	30.7	44.3	34.3	35.3	38.0
Urban residence, %	39.1	50.0	52.1	41.5	49.8	50.0	39.3	48.9	53.0	47.1
≥Middle school, %	49.2	49.4	51.7	49.6	50.2	50.4	48.7	49.6	52.0	47.5
Ever regular	35.2	23.6	21.4	35.7	24.5	20.1	34.1	23.9	22.3	26.8
Ever regular	26.7	16.6	12.3	27.1	16.8	11.8	26.3	16.1	13.3	18.5
Physical activity,	19.5	18.7	18.5	19.2	19.3	18.2	19.5	18.7	18.5	18.9
BMI, kg/m^2	24.3	23.8	23.9	23.9	24.0	24.1	24.3	23.8	23.8	24.0
SBP, mmHg	136	135	134	136	134	134	136	135	134	135
RBG, mmol/l	5.50	5.40	5.47	5.45	5.42	5.50	5.50	5.41	5.45	5.45
HDL-C, mmol/l	1.27	1.29	1.22	1.32	1.26	1.19	1.26	1.29	1.23	1.26
LDL-C, mmol/l	2.05	1.98	1.78	2.07	2.02	1.72	2.03	1.97	1.81	1.94
TG, mmol/l	1.52	1.41	1.39	1.41	1.42	1.50	1.54	1.43	1.36	1.44
TC, mmol/l	3.99	3.88	3.58	4.01	3.90	3.54	3.96	3.88	3.61	3.82
Dietary intakes, g/day										
Refined grains	308	300	310	306	307	305	307	301	310	306
Rice	231	211	165	227	220	160	229	210	168	202
Wheat	77.4	88.7	145	79.4	86.8	145	78.1	91.2	142	104
Coarse grains	29.0	35.3	37.1	30.4	35.1	36.0	29.0	35.4	37.0	33.8
Fresh vegetables	233	235	253	236	235	251	233	235	254	241
Fresh fruits	75.7	87.6	101	78.0	83.8	103	75.5	88.7	100	88.1
Red meat	69.7	56.2	40.8	66.8	58.1	41.8	69.4	55.6	41.7	55.6
Fish	24.0	30.3	28.3	24.6	29.2	28.9	24.2	30.0	28.5	27.6
Dairy products										
Milk	19.8	28.7	43.0	19.6	25.6	46.3	20.8	29.5	41.1	30.5
Yoghurt	6.02	8.57	14.7	7.22	7.44	14.6	6.22	8.79	14.3	9.76
Others[§]	0.87	1.02	1.36	0.71	0.96	1.58	0.97(7.7	0.97	1.30	1.08

[*] Means (standard deviations) were presented across categories for each continuous variable.

[†] Total OCFA, 15:0, and 17:0 were presented as percentages (%) of total fatty acids, median (10th - 90th).

[‡] The median and range of erythrocyte as percentage (%) of total fatty acids from 10th to 90th percentiles were 0.055% (0.033%-0.090%) for 15:0, 0.256% (0.199%-0.340%) for 17:0, and 0.313% (0.236%-0.426%) for total OCFA (15:0+17:0).

[§] Other dairy products included cheese, milk powder, and butter.

Abbreviations: BMI=body mass index; HDL-C=high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol; MET=metabolic equivalent tasks; OCFA=odd-chain fatty acid; TC=Total cholesterol; TG=Triglycerides; SBP=systolic blood pressure.

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Table 2. Adjusted HRs for incident cardiometabolic disease associated with levels of odd-chain fatty acids in the CKB

	Model 1					Model 2				
	Tertile 1	**Tertile 2**	**Tertile 3**	P_{trend}	**HR (95% CI) per 10th-90th**	**Tertile 1**	**Tertile 2**	**Tertile 3**	P_{trend}	**HR (95% CI) per 10th-90th**
IHD										
N cases/person-years	145/12,984	120/12,854	122/12,546			145/12,984	120/12,854	122/12,546		
15:0	1.00 (0.84-1.20)	0.97 (0.82-1.15)	0.76 (0.62-0.93)	0.05	0.89 (0.72,1.11)	1.00 (0.83-1.20)	0.93 (0.79-1.10)	0.72 (0.59-0.89)	0.02	0.87 (0.70-1.09)
17:0	1.00 (0.83-1.21)	0.78 (0.66-0.93)	0.71 (0.58-0.87)	0.01	0.95 (0.76,1.19)	1.00 (0.83-1.21)	0.77 (0.65-0.92)	0.69 (0.56-0.86)	0.009	0.94 (0.75-1.18)
Total OCFA	1.00 (0.83-1.21)	0.84 (0.71-0.99)	0.72 (0.58-0.89)	0.02	0.92 (0.72,1.16)	1.00 (0.83-1.21)	0.82 (0.70-0.97)	0.70 (0.56-0.86)	0.01	0.90 (0.71-1.15)
Diabetes										
N cases/person-years	54/13,214	44/13,060	29/12,780			54/13,214	44/13,060	29/12,780		
15:0	1.00 (0.72-1.38)	1.13 (0.86-1.49)	1.02 (0.72-1.45)	0.90	0.95 (0.63,1.43)	1.00 (0.72-1.38)	1.13 (0.86-1.49)	1.00 (0.71-1.43)	0.96	0.93 (0.61-1.40)
17:0	1.00 (0.74-1.35)	0.61 (0.45-0.82)	0.42 (0.28-0.63)	<0.001	0.65 (0.49,0.86)	1.00 (0.74-1.35)	0.61 (0.45-0.82)	0.41 (0.27-0.62)	<0.001	0.66 (0.50-0.86)
Total OCFA	1.00 (0.73-1.37)	0.78 (0.59-1.03)	0.52 (0.35-0.77)	0.01	0.62 (0.43,0.89)	1.00 (0.73-1.37)	0.77 (0.59-1.01)	0.51 (0.34-0.76)	0.01	0.62 (0.43-0.89)
Total stroke										
N cases/person-years	145/12,964	162/12,749	152/12,490			145/12,964	162/12,749	152/12,490		
15:0	1.00 (0.84-1.19)	1.08 (0.93-1.26)	1.00 (0.84-1.19)	0.99	1.06 (0.86,1.31)	1.00 (0.84-1.20)	1.08 (0.92-1.25)	1.01 (0.85-1.20)	0.97	1.07 (0.86-1.32)
17:0	1.00 (0.83-1.20)	1.21 (1.05-1.39)	0.89 (0.74-1.07)	0.40	1.01 (0.83,1.23)	1.00 (0.83-1.20)	1.20 (1.04-1.38)	0.90 (0.74-1.08)	0.44	1.02 (0.83-1.26)
Total OCFA	1.00 (0.84-1.20)	1.07 (0.92-1.23)	0.85 (0.71-1.03)	0.24	1.04 (0.84,1.29)	1.00 (0.83-1.20)	1.05 (0.91-1.22)	0.86 (0.72-1.04)	0.28	1.06 (0.85-1.31)
IS										
N cases/person-years	116/13,004	136/12,803	128/12,520			116/13,004	136/12,803	128/12,520		
15:0	1.00 (0.82-1.22)	1.10 (0.93-1.30)	1.05 (0.88-1.27)	0.71	1.10 (0.87,1.39)	1.00 (0.82-1.22)	1.09 (0.92-1.29)	1.06 (0.88-1.28)	0.67	1.11 (0.87-1.41)
17:0	1.00 (0.82-1.22)	1.22 (1.05-1.43)	0.91 (0.74-1.12)	0.54	1.04 (0.83,1.30)	1.00 (0.81-1.23)	1.20 (1.03-1.40)	0.91 (0.74-1.12)	0.53	1.05 (0.84-1.32)
Total OCFA	1.00 (0.82-1.22)	1.10 (0.94-1.29)	0.91 (0.74-1.11)	0.52	1.09 (0.86,1.38)	1.00 (0.82-1.23)	1.08 (0.92-1.26)	0.91 (0.74-1.12)	0.53	1.10 (0.87-1.40)
CMD										
N cases/person-years	330/12,575	319/12,463	301/122,00			330/12,575	319/12,463	301/122,00		
15:0	1.00 (0.89-1.13)	1.03 (0.92-1.14)	0.88 (0.78-1.00)	0.17	0.97 (0.84,1.13)	1.00 (0.87-1.15)	1.02 (0.90-1.16)	1.00 (0.88-1.13)	0.20	0.97 (0.83-1.12)
17:0	1.00 (0.89-	0.93 (0.84-	0.73 (0.64-	<0.001	0.93	1.00 (0.87-	1.01 (0.89-	0.85 (0.74-	0.003	0.93

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	1.13)	1.03)	0.83)		(0.80,1.06)	1.15)	1.14)	0.97)		(0.81-1.07)
Total OCFA	1.00 (0.88-1.13)	0.93 (0.84-1.03)	0.75 (0.66-0.85)	<0.001	0.93 (0.80,1.08)	1.00 (0.87-1.15)	0.98 (0.86-1.11)	0.86 (0.75-0.98)	0.003	0.93 (0.80-1.09)

Model 1 was adjusted for age, sex, study regions, and education. Model 2 was further adjusted for smoking, alcohol drinking, family history of cardiovascular diseases (for IHD and stroke) and diabetes (for diabetes), and physical activity. Cox regression was used to estimate hazard ratios and 95% confidence intervals. The range from 10th to 90th percentiles were 0.033%-0.090% for 15:0, 0.199%-0.340% for 17:0, and 0.236%-0.426% for 15:0+17:0.

N cases/person-years are according to the total OCFA tertile.

Abbreviations: ICH=intracerebral hemorrhage; IHD=ischemic heart disease; IS=ischemic stroke; CMD=cardiometabolic disease; OCFA=odd-chain fatty acid.

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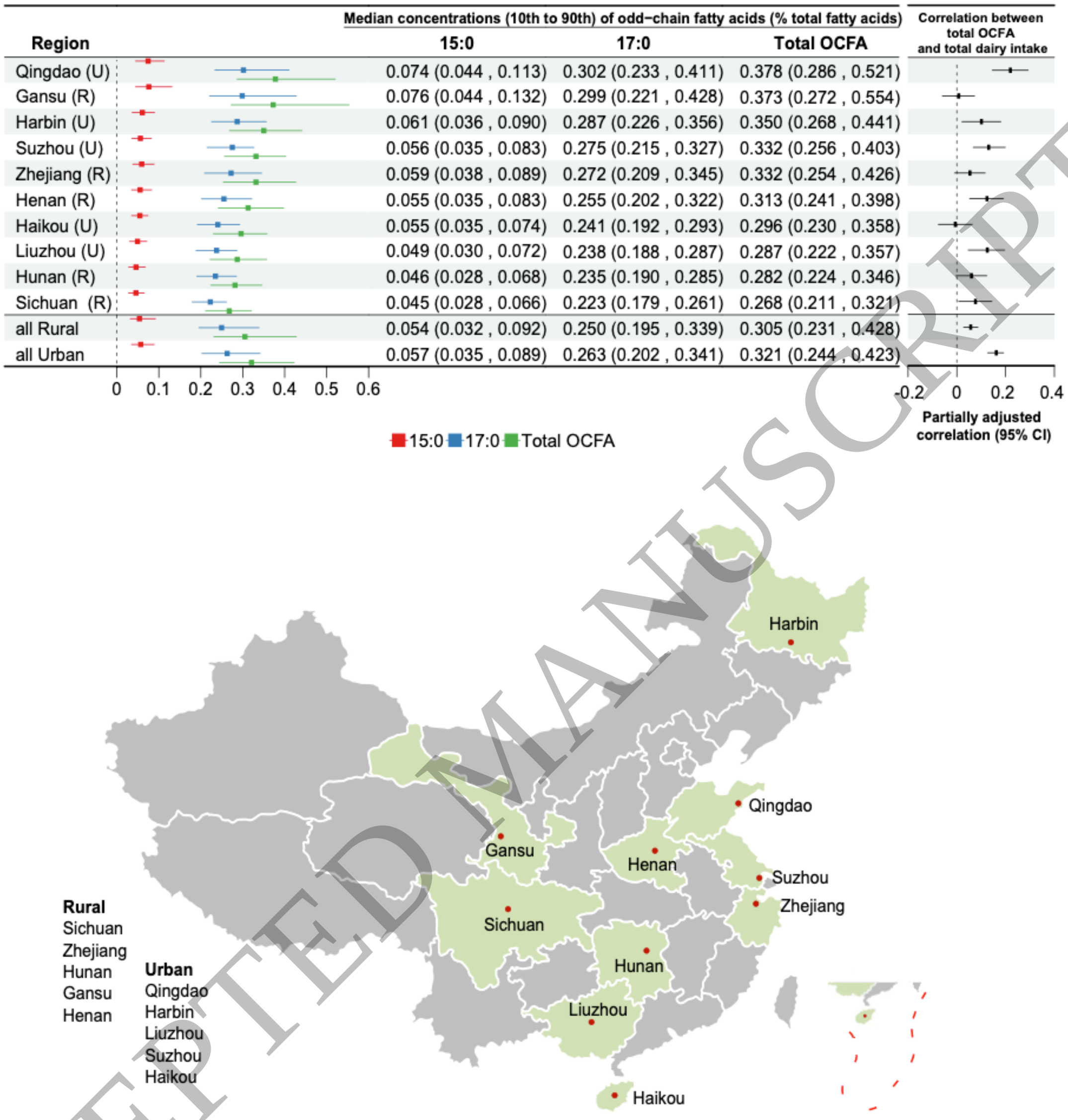

Region	Median concentrations (10th to 90th) of odd−chain fatty acids (% total fatty acids) 15:0	17:0	Total OCFA
Qingdao (U)	0.074 (0.044 , 0.113)	0.302 (0.233 , 0.411)	0.378 (0.286 , 0.521)
Gansu (R)	0.076 (0.044 , 0.132)	0.299 (0.221 , 0.428)	0.373 (0.272 , 0.554)
Harbin (U)	0.061 (0.036 , 0.090)	0.287 (0.226 , 0.356)	0.350 (0.268 , 0.441)
Suzhou (U)	0.056 (0.035 , 0.083)	0.275 (0.215 , 0.327)	0.332 (0.256 , 0.403)
Zhejiang (R)	0.059 (0.038 , 0.089)	0.272 (0.209 , 0.345)	0.332 (0.254 , 0.426)
Henan (R)	0.055 (0.035 , 0.083)	0.255 (0.202 , 0.322)	0.313 (0.241 , 0.398)
Haikou (U)	0.055 (0.035 , 0.074)	0.241 (0.192 , 0.293)	0.296 (0.230 , 0.358)
Liuzhou (U)	0.049 (0.030 , 0.072)	0.238 (0.188 , 0.287)	0.287 (0.222 , 0.357)
Hunan (R)	0.046 (0.028 , 0.068)	0.235 (0.190 , 0.285)	0.282 (0.224 , 0.346)
Sichuan (R)	0.045 (0.028 , 0.066)	0.223 (0.179 , 0.261)	0.268 (0.211 , 0.321)
all Rural	0.054 (0.032 , 0.092)	0.250 (0.195 , 0.339)	0.305 (0.231 , 0.428)
all Urban	0.057 (0.035 , 0.089)	0.263 (0.202 , 0.341)	0.321 (0.244 , 0.423)

Correlation between total OCFA and total dairy intake

Figure 1. Median concentrations (10^{th} - 90^{th}) (% total fatty acids) of 15:0, 17:0, and total odd-chain fatty acid across ten CKB study regions

Correlation between total odd-chain fatty acid and total dairy intake was adjusted for age, sex, study regions, education, smoking, alcohol drinking, family history of cardiovascular diseases and diabetes, physical activity, and other food groups.

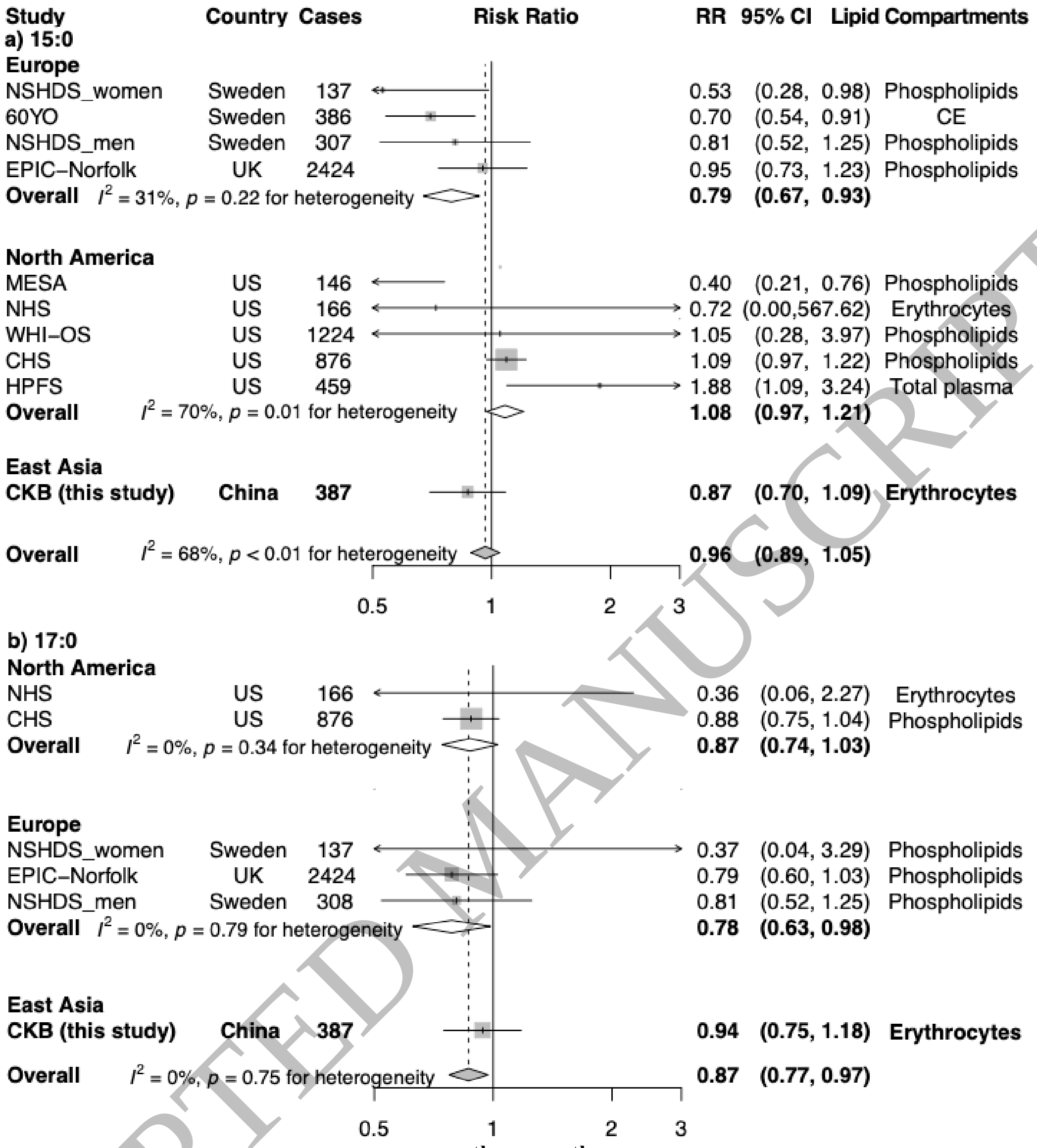

Figure 2. Associations of 15:0 and 17:0 per 10th to 90th percentiles with incident risk of IHD in the updated meta-analysis of CKB and other prospective studies

Study-specific estimates for risk ratios (RRs) and 95% CIs per 10th to 90th percentiles were showed, grouped by continents, and were pooled into risk estimates for overall risks. The dots indicated individual studies and the diamonds represented summary risk estimates from the pooled meta-analysis. The size of grey-shaded square reflected study weights and the results were sorted by the order of each study's effect size.

Abbreviations: CE=cholesteryl ester; CHS=Cardiovascular Health Study; CKB=China Kadoorie Biobank Study; EPIC-Norfolk=European Prospective Investigation Norfolk; HPFS=Health Professionals' Follow-up Study; MESA=Multi-Ethnic Study of Atherosclerosis; NHS=Nurses' Health Study; NSHDS=Northern Sweden Health and Disease Study; WHI-OS=Women's Health Initiative Observational Study; 60YO=the Stockholm Cohort of 60-year-olds.

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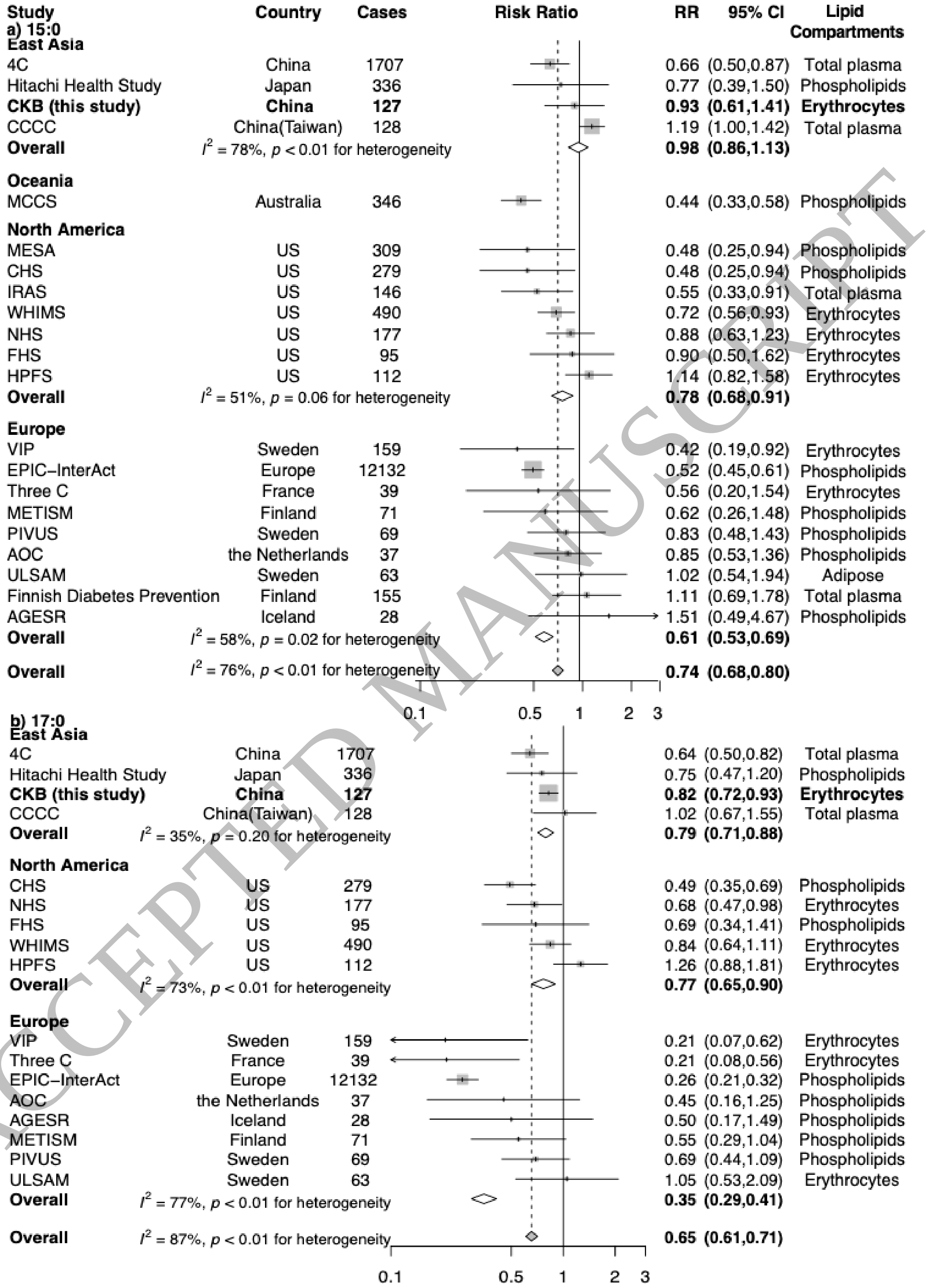

Figure 3. Associations of 15:0 and 17:0 per 10th to 90th percentiles with incident risk of diabetes in the updated meta-analysis of CKB and other prospective studies

Study-specific estimates for risk ratios (RRs) and 95% CIs per 10th to 90th percentiles were showed,

grouped by continents, and were pooled into risk estimates for overall risks. The dots indicated individual studies and the diamonds represented summary risk estimates from the pooled meta-analysis. The size of grey-shaded square reflected study weight and the results were sorted by the order of each study's effect size.
Abbreviations: AGESR=Age, Genes, Environment Susceptibility Study (Reykjavik); AOC=Alpha Omega Cohort; CCCC=Chin-Shan Community Cardiovascular Cohort Study; CHS=Cardiovascular Health Study; CKB=China Kadoorie Biobank Study; EPIC-InterAct=European Prospective Investigation InterAct; FHS=Framingham Heart Study; HPFS=Health Professionals' Follow-up Study; IRAS=Insulin Resistance Atherosclerosis Study; MCCS=Melbourne Collaborative Cohort Study; MESA=Multi-Ethnic Study of Atherosclerosis; METSIM=Metabolic Syndrome in Men Study; NHS=Nurses' Health Study; PIVUS=Prospective Investigation of the Vasculature in Uppsala Seniors; Three C=Three City Study; ULSAM=Uppsala Longitudinal Study of Adult Men; VIP=Vasterbotten Intervention Program; WHIMS=Women's Health Initiative Memory Study; 4C=China Cardiometabolic Disease and Cancer Cohort.

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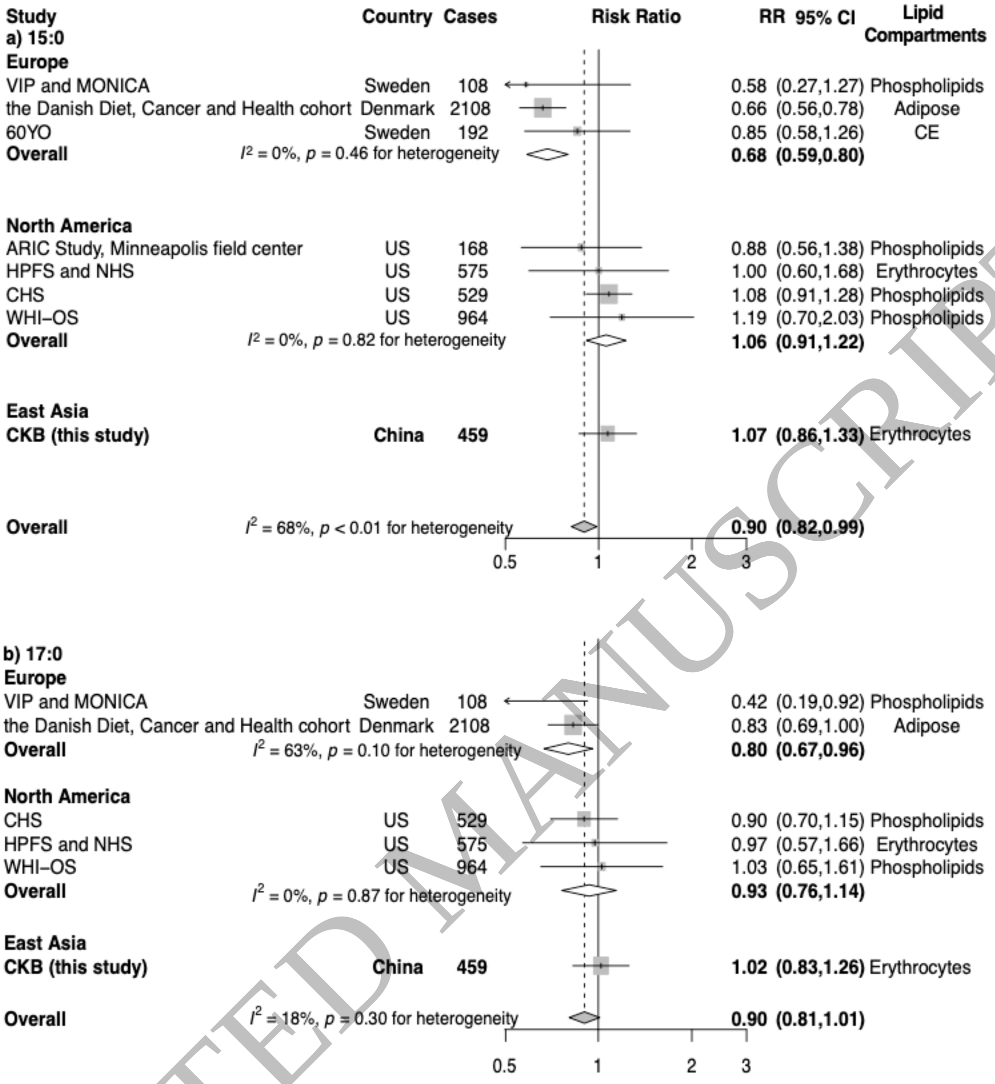

Figure 4. Associations of 15:0 and 17:0 per 10th to 90th percentiles with incident risk of stroke in the updated meta-analysis of CKB and other prospective studies

Study-specific estimates for risk ratios (RRs) and 95% CIs per 10th to 90th percentiles were showed, grouped by continents, and were pooled into risk estimates for overall risks. The dots indicated individual studies and the diamonds represented summary risk estimates from the pooled meta-analysis. The size of grey-shaded square reflected study weights and the results were sorted by the order of each study's effect size.

Abbreviations: ARIC=Minneapolis field center of Atherosclerosis Risk in Communities Study; CE=cholesteryl ester; CHS=Cardiovascular Health Study; CKB=China Kadoorie Biobank Study; HPFS=Health Professionals' Follow-up Study; MONICA=Monitoring of Trends and Determinants in Cardiovascular Disease Study; NHS=Nurses' Health Study; VIP=Vasterbotten Intervention Program; WHI-OS=Women's Health Initiative Observational Study; 60YO=Stockholm Cohort of 60-year-olds.

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