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Energy intake at different times of the day: Its association with elevated total and LDL cholesterol levels

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Abstract *Background and aims:* This study examined the association between macronutrient intake at different times of the day and blood lipid levels.
Methods and results: The study was based on the Nutrition and Health Survey in Taiwan, a cross-sectional study of non-institutionalized and non-pregnant healthy adults (≥19-years-old). A one-day (24 h) dietary recall assessed participants' food intake. Fasting plasma triglycerides, total cholesterol, and high-density lipoprotein (HDL) cholesterol were determined. Low-density lipoprotein (LDL) cholesterol was estimated based on the Friedewald formula. According to the data of eligible subjects (n = 1283), the time of energy intake was categorized into three meal times 0500–0929 (morning), 1130–1329 (noon), and 1730–2029 (evening), along with three snack times 0930–1129 (mid-morning), 1330–1729 (afternoon), and 2030–0459 (night). Energy and macronutrient intake were calculated for the 6 time periods, based on 24 h recall data. An adjusted regression model showed that by transferring 100 kcal intake at night to the morning or noon, LDL cholesterol would be lower by 1.46 (95% CI: 2.42–0.50) and 1.27 mg/dL (95% CI: 2.24–0.30), respectively. Transferring 100 kcal of fat intake at night to earlier periods was associated with a lower LDL cholesterol level, especially transferring to noontime (significantly lower by 5.21 mg/dL, 95% CI: [7.42–2.99]) and evening (significantly lower by 3.19 mg/dL, 95% CI: [6.29–0.08]).
Conclusions: Total cholesterol and LDL cholesterol had the same pattern of association with the timing of energy intake. The study showed that elevated total and LDL cholesterol were positively associated with nighttime energy and fat intake.

Introduction

The timing of eating and nutrient intake and its effect on cardiovascular health has drawn attention in nutrition research [1]. Meal frequency, timing of feeding, and regularity of meal times are associated with obesity, blood pressure, metabolic syndrome, and cardiovascular risks [2–7]. Elevated blood LDL cholesterol, as an important risk factor for cardiovascular disease [8], has been associated with temporal patterns of eating as well. Shifting the time of snack consumption (about 192 kcal) from 10 a.m. to 11 p.m. for thirteen days increased LDL cholesterol by 7 mg/dL in young Japanese women [5]. Another study showed that shifting the three daily meals by 5 h later to 1300, 1800, and 2300 for two weeks would increase total and

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LDL cholesterol and triglyceride levels in young Japanese men [9]. These experimental studies suggest a relationship between late-night eating and risk of dyslipidemia, in terms of elevated LDL cholesterol.

Human blood lipid levels have diurnal variations [10–12]. Lipid metabolism involves multiple organs and tissues, which has been shown to be regulated by circadian rhythm genes [13]. Observational studies showed that, for example, the postprandial response of very low-density lipoprotein (VLDL) cholesterol was more drastic at night than in the morning [14]. The misalignment between the circadian rhythm of lipid metabolism and meal time could lead to aberrations in lipid profiles, as shown in the above-mentioned small-scale trials [5,9]. It is unknown whether the association between energy intake at a later time of day and the risk of dyslipidemia could be reproduced in free-living population. This study aimed to examine the association of time of energy and macronutrient intake with blood lipid levels, based on a representative survey in Taiwan.

Methods

Population

The Nutrition and Health Survey in Taiwan (NAHSIT) is a representative survey of the population. The survey was conducted from 2005 to 2008, and recruited non-institutionalized and non-pregnant residents. The target population was Taiwan citizens, aged ≥19 years. The sampling frame was based on the residence registry. In addition, this survey utilized a multistage, clustered, and stratified complex sampling scheme, with a probability proportional to size for representative estimates; this was done through a feasible survey method, and the response rate for a household interview was 65%. That is, 4665 adults participated in the survey and completed the dietary recall. Please see Ref. [15] for details of the survey design: this secondary data analysis was based on open-domain anonymous data and approved by the National Yang-Ming University Internal Review Board (YM104136E-1).

The present study used adult data (age ≥ 19 years), excluding those with a diagnosis of diabetes, heart disease, or stroke (n = 946), who reported having an energy intake ranging from 1200 kcal to 4000 kcal in a 24 h dietary recall (n = 1423), who did not complete their physical exams and blood draws (n = 944), and who had missing information on covariates (n = 65). The final sample size for analysis was 1283. The range of plausible energy intake level was set according to estimated total energy expenditure (TEE). TEE was estimated using sex, age, height, and weight with a parameter of a person's physical activity level [16]. Since subjects' physical activity on the day of the dietary interview was unknown, we estimated TEE in which subjects were least active (physical activity level, PAL = 1) and for those who were most active (PAL = 1.54 for men and 1.45 for women) [16]. The range of TEE for the least active was 1227–2748 kcal, while for the most active it was 1861–3899 kcal. Combining the ranges and rounding cutoffs to 100, we excluded data with a total energy intake <1200 kcal and data >4000 kcal as extreme values.

Independent variables

A one-day (24 h) dietary recall [17] was used to assess participants' food intake of the previous day. Food items as well as the consumed portion size were estimated based on food models of similar shape, household measures, bottle and can pictures, and extract models, and data in the dietary recall were converted to calories from carbohydrates, proteins, and fats based on the food composition tables [18] including the Taiwan Food Nutrient Database and associated software (FNDB971205), the USDA National Nutrient Database, and the Food Composition Database of Sugiyama University.

In addition to food and nutrients, the dietary recall recorded eating times, with these occasions grouped into six time-intervals. According to the distribution of eating times in the population, most occurred in three periods: 0500–0929 (morning), 1130–1329 (noon), and 1730–2029 (evening). These three time-intervals tended to be the usual meal times for this population. The other off-meal periods of time between major meal hours were: 0930–1129 (mid-morning), 1330–1729 (afternoon), and 2030–0459 (night). Total calories and carbohydrates, proteins and fat intake, were calculated for six time periods for every subject.

Outcomes of interest

After the interview, a physical examination was scheduled for 1–3 weeks later. Subjects were asked to fast overnight for 8 h or longer. Blood drawn in the morning was centrifuged on site to isolate plasma. Plasma specimens were stored at a temperature of −70 °C on the day of collection. Fasting plasma triglycerides, total cholesterol, and high-density lipoprotein (HDL) cholesterol were tested using the Hitachi Model 747 Automatic Analyzer (Bellport, NY, USA). Low-density lipoprotein (LDL) cholesterol (LDL-C) was determined based on the Friedewald formula [19].

Covariates

Potential confounders include sex, age, postmenopausal status, and employment status, which were associated with temporal eating patterns in this population [20]. Body mass index (BMI) was calculated on measured height (m) and weight (kg) on calibrated scales with the physical examination. Leisure physical activity level was measured based on subjects' self-report on selected leisure activities over the past year, including sports (e.g., table tennis, volleyball, golf, tennis, and soccer), dancing, and gymnastics, Chinese traditional activities (e.g., Qigong and Tai Chi), walking, running, biking, hiking, swimming, and house chores. The average metabolic equivalent (MET) scores were multiplied with recalled frequency and duration of

activity, so that the MET-hour value indicated overall activity level [21]. Moreover, the season and weekend/weekday of the dietary recall, plus weeks between the interview and physical exam, were considered.

Statistical analysis

Blood lipid levels were first compared by energy intake level of the six time periods of the day and potential confounders. Multiple linear regression models with different specifications for the calorie and macronutrient intake of six time periods of the day were fitted for different interpretation of the associations. Univariate models estimated the association between energy intake of a particular time period and outcomes. Additive models estimated the difference in outcome as associated with 100 kcal energy intake of six time periods of the day, while total energy intake was not adjusted for in the model. Substitution models estimated the difference in the outcome as associated with 100 kcal energy intake of five time periods, except for energy intake at nighttime (2030–0459 h), while total energy intake was controlled. Regression coefficients of substitution models demonstrated the difference in outcome variables associated with substituting 100 kcal energy intake at night with 100 kcal energy intake during earlier periods. Substitution models were applied to examine the difference in lipid levels associated with replacing macronutrient intake at night with the intake at earlier time periods of the day. All models were adjusted for age, sex, menopausal status, employment status, physical activity level, BMI, number of weeks between dietary recall and physical examination, and seasonality and weekday/weekend. A sex-stratified analysis was done to assess related differences. Sampling weight and design effect were examined by SAS-callable SUDAAN 11 (Research Triangle Park, NC, USA).

Results

Univariate analysis shows that blood lipid levels are associated with factors that could affect time of eating: age, sex, employment status, weekday/weekend, and season. In terms of energy intake at different times of the day, only HDL cholesterol was significantly higher in people who ate less at noon time than those who ate more. Except for common meal time periods, about half or more of participants did not have food or beverages in off-meal times. The blood lipid levels did not differ between those who had and did not have energy intake during these times (Table 1).

The average and confidence interval of energy intake was 385 (95% CI: 353–416), 123 (106–140), 522 (483–561), 171 (141–200), 557 (516–597), and 169 (139–200) kcal, respectively for morning, mid-morning, noon, afternoon, evening, and nighttime periods among those who reported food and beverage intake in those periods (Fig. 1). Macronutrient composition (±S.E.) was 59.4 ± 0.8%:14.7 ± 0.3%:25.9 ± 0.8% (carbohydrate:protein:fat) for morning meal times, 66.0 ± 1.4%:13.0 ± 0.7%:21.0 ± 1.2% for morning snack times, and 48.7 ± 0.9%:18.5 ± 0.3%:32.8 ± 0.8% for lunch times, 66.6 ± 1.6%:10.8 ± 0.6%:22.6 ± 1.3% for afternoon snack time, 46.7 ± 0.8%:20.1 ± 0.5%:33.2 ± 0.7% for dinner times, and 65.5 ± 1.2%:12.3 ± 0.7%:22.2 ± 1.0% for evening snack times. Foods consumed during snack times contained higher carbohydrates than that consumed at meal times. Protein and fat composition were higher at dinner and lunch compared with morning meals.

As shown in Table 2, after adjusting for potential confounders, the additive models suggested that consuming 100 kcal more at night was associated with a higher LDL cholesterol level by 0.94 mg/dL (95% CI: 0.27, 1.61). This 100 kcal at night also contributed to 100 kcal for total energy intake. For isocaloric comparisons, the substitution model suggested that displacement of 100 kcal in the morning and at noon to the nighttime period, LDL cholesterol would be higher by 1.46 (95% CI: 2.42, 0.50) and 1.27 mg/dL (95% CI: 2.24, 0.30), respectively. The total cholesterol level was found to have a similar association pattern with the time of energy intake. Fasting triglycerides and HDL cholesterol levels were not associated with the time of energy intake, however. After outcome variables were taken by log transformation to minimize skewedness, regression models showed similar results (Supplementary Table 1). Table 3 demonstrates that the association between timing of intake and the lipid profile may differ by sex. Only in women, a lower total cholesterol level was associated with the replacement of energy intake at night with energy intake at an earlier time. In women and men, a lower LDL cholesterol level was associated with the replacement of energy intake at night with intake of earlier time.

Further exploration on timing of macronutrient intake showed that fat intake was associated with cholesterol and LDL cholesterol levels (Fig. 2). An additional 100 kcal of fat intake at night was associated with a higher value of LDL cholesterol by 2.98 mg/dL (95% CI: 0.89, 5.07). When total energy intake for the day was fixed, transferring 100 kcal fat intake at night to the earlier time period was associated with a decrement in LDL cholesterol, especially transferring intake to the noon time (significantly lower by 5.21 mg/dL, 95% CI: [−7.42, −2.99]) and to the evening time (significantly lower by 3.19 mg/dL, 95% CI: [−6.29, −0.08]).

Discussion

Based on a population-representative nutrition survey in Taiwan, adults who consumed more energy at night would have higher levels of total and LDL cholesterol. Although a greater weight loss was associated with an earlier main meal [22,23], the present study showed that timing of fat intake might be associated with elevated total and LDL cholesterol, even though BMI was controlled. The association of certain daytime hours with lipid parameters may reflect the adverse impact of misalignment between intrinsic circadian rhythm and timing of nutrient intake.

Table 1 Lipid profile by participants' basic characteristics.

		n	Triglycerides (mg/dL)		Total Cholesterol (mg/dL)		LDL-Cholesterol (mg/dL)		HDL-Cholesterol (mg/dL)	
			mean	se	mean	se	mean	se	mean	se
Sex	Men	713	140.1	(8.0)	187.7	(2.6)	120.2	(2.6)	49.5	(0.4)
	Women, premenopausal	363	87.3	(3.0)	182.0	(2.5)	111.3	(1.8)	61.3	(1.3)
	Women, postmenopausal	207	112.3 ***	(6.0)	207.4 ***	(2.5)	133.3 ***	(2.0)	59.9 ***	(1.5)
Weight	Normal/under	655	95.7	(5.4)	180.7	(2.0)	112.1	(1.9)	58.2	(0.9)
	Over	359	146.8	(7.9)	197.7	(2.8)	127.7	(2.7)	50.5	(1.0)
	Obese	269	159.1 ***	(11.7)	197.2 ***	(2.8)	126.6 ***	(2.7)	48.2 ***	(1.1)
Age	19–44	526	113.5	(6.1)	180.0	(2.4)	111.4	(2.2)	55.1	(0.8)
	45–64	479	130.6	(7.4)	202.4	(2.2)	132.3	(2.1)	53.5	(0.8)
	65+	278	120.3	(4.0)	196.8 ***	(3.1)	124.5 ***	(2.5)	55.1	(1.1)
Employment status	Full-time	583	124.8	(7.4)	185.9	(2.4)	116.4	(2.1)	54.1	(0.7)
	Part-time	50	112.5	(17.8)	191.8	(5.6)	122.4	(5.9)	53.2	(2.4)
	Self-employed	69	140.2	(27.0)	190.2	(9.1)	122.8	(8.2)	49.0	(1.7)
	Unemployed	77	125.4	(13.2)	191.5	(7.1)	125.0	(6.8)	51.0	(2.6)
	Students	50	80.2	(6.3)	170.4	(5.8)	102.5	(4.7)	60.3	(3.0)
	Retired	251	118.1	(5.0)	200.3	(3.6)	129.1	(3.3)	56.3	(1.7)
	Housekeeping	187	103.9	(4.8)	195.2	(3.6)	125.5	(3.0)	57.6	(1.3)
	Other	16	105.3 ***	(18.5)	167.9 ***	(13.0)	102.6 ***	(12.3)	50.0 ***	(4.8)
By the situation of the interview										
Length between interview and physical examination										
	1wk	237	124.2	(8.5)	186.4	(4.3)	116.7	(4.7)	52.1	(1.0)
	2wk	894	119.2	(6.1)	188.6	(2.0)	119.2	(1.8)	55.1	(0.7)
	3wk	152	89.2 *	(8.6)	169.5 ***	(3.4)	105.5 **	(3.0)	54.3	(1.9)
Day of the dietary interview										
	Weekday	983	123.4	(4.4)	188.9	(2.3)	118.9	(2.2)	54.4	(0.8)
	Weekend	300	105.9 *	(9.0)	184.1	(2.8)	116.8	(2.1)	55.5	(0.9)
Season of the dietary interview										
	Jan–Mar	297	115.4	(9.7)	195.3	(3.1)	125.9	(2.3)	55.9	(0.9)
	Apr–Jun	381	110.8	(5.0)	184.0	(2.8)	118.0	(1.8)	53.6	(1.4)
	Jul–Sep	305	131.3	(8.6)	188.6	(2.1)	115.4	(1.6)	54.1	(1.0)
	Oct–Dec	300	120.4	(10.3)	181.9 *	(3.3)	112.6 **	(4.1)	55.3	(0.4)
By energy intake level at the six time interval of the day										
Morning	Lower (<381 kcal)	641	113.5	(6.1)	187.8	(2.0)	118.9	(1.8)	55.2	(0.8)
	Higher (≥381 kcal)	642	125.4	(7.2)	187.4	(2.5)	117.8	(2.7)	54.1	(0.8)
Late morning	Lower (0 kcal)	878	119.5	(5.7)	186.9	(2.3)	118.2	(1.9)	53.9	(0.7)
	Higher (>0 kcal)	405	117.8	(5.4)	189.1	(2.5)	118.8	(2.5)	56.1	(0.8)
Noon	Lower (<497 kcal)	641	121.2	(6.2)	188.6	(1.8)	117.6	(1.6)	56.1	(0.9)
	Higher (≥497 kcal)	642	116.6	(6.1)	186.7	(2.7)	119.2	(2.2)	53.2	(0.8)
Afternoon	Lower (<11 kcal)	641	113.1	(4.9)	186.9	(2.6)	118.4	(2.1)	55.2	(0.9)
	Higher (≥11 kcal)	642	124.2	(6.9)	188.4	(2.3)	118.4	(2.0)	54.2	(0.8)
Evening	Lower (<509 kcal)	641	121.4	(6.0)	189.3	(2.1)	119.0	(1.8)	55.2	(0.6)
	Higher (≥509 kcal)	642	116.6	(5.4)	186.1	(2.6)	117.8	(2.2)	54.1	(0.8)
Night	Lower (0 kcal)	744	121.0	(7.2)	188.6	(2.4)	118.4	(2.4)	55.2	(0.8)
	Higher (>0 kcal)	539	116.8	(6.8)	186.7	(2.3)	118.3	(1.7)	54.1	(0.6)

P values for ANOVA: *p < .05, **p < .01, ***p < .001.

As the present study suggests, higher total cholesterol and LDL cholesterol levels were associated with energy and fat intake in the late evening and night. It is known that fat intake affects hepatic metabolism of lipoproteins and de novo cholesterol synthesis [24,25]. Cholesterol metabolic processes, including intestinal cholesterol uptake, cholesterol synthesis, and cholesterol utilization by certain tissues, vary with time of the day. The circadian intestinal uptake of cholesterol in humans is still unknown, but an animal model suggests that cholesterol absorption increases at night [26]. As for the cholesterol synthetic rate in humans, studies show that it rises in the evening and night [27,28], which might be a result of peak activity of HMG-CoA reductase at midnight, the rate-

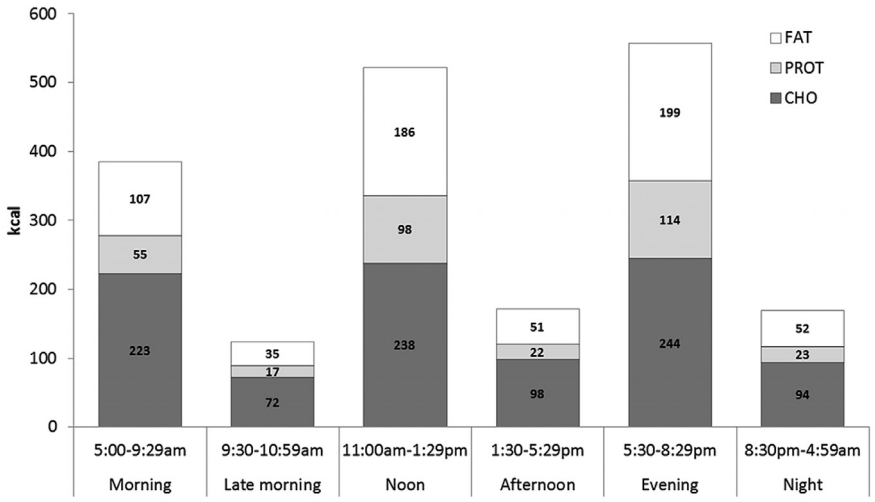

Figure 1 Energy intake and percentage from three macronutrients by time of the day: NAHSIT 2005–2008. PROT, protein; CHO, carbohydrates. For the average compositions of macronutrient intakes, please refer to the text.

limiting enzyme of cholesterol biosynthesis. As for excretion, the human bile acid synthetic rate is lower at night than the day [27]. These temporal patterns of cholesterol-related metabolism indicate that healthy people's cholesterol metabolic systems tend to produce cholesterol at night, which builds up total cholesterol levels. When the exogenous input via food intake is shifted to a later time, the food, especially fats, provides precursors for the machinery when it is most efficient and elevates the cholesterol pool level.

Table 2 The difference in blood lipid levels (mg/dL) associated with +100 kcal energy intake by time of the day: Multiple linear regression analysis.

	Univariate models			Additive model			Substitution model		
	beta	95%CI	p	beta	95%CI	p	beta	95%CI	p
TG									
Morning, 5:00–9:29 a.m.	+0.75	(−1.78, +3.28)	0.554	+0.03	(−2.46, +2.52)	0.981	+1.46	(−1.56, +4.48)	0.335
Late morning, 9:30–10:59 a.m.	−1.75	(−4.24, +0.74)	0.163	−2.18	(−4.69, +0.32)	0.086	−0.75	(−3.67, +2.17)	0.605
Noon, 11:00 a.m.–1:29 p.m.	−1.77	(−3.60, +0.06)	0.057	−1.45	(−3.67, +0.77)	0.194	−0.02	(−3.62, +3.59)	0.992
Afternoon, 1:30–5:29 p.m.	+3.38	(−3.65, +10.41)	0.337	+2.88	(−4.60, +10.37)	0.441	+4.31	(−5.03, +13.66)	0.357
Evening, 5:30–8:29 p.m.	+0.11	(−1.41, +1.63)	0.883	+0.05	(−1.41, +1.52)	0.941	+1.48	(−1.07, +4.04)	0.248
Night, 8:30 p.m.–4:59 a.m.	−1.25	(−3.56, +1.05)	0.279	−1.43	(−3.85, +0.99)	0.239			
Cholesterol									
Morning, 5:00–9:29 a.m.	−0.47	(−1.09, +0.16)	0.138	−0.45	(−1.17, +0.26)	0.208	−1.14	(−2.15, −0.13)	0.028
Late morning, 9:30–10:59 a.m.	+0.30	(−0.51, +1.11)	0.455	−0.07	(−0.98, +0.85)	0.886	−0.75	(−1.92, +0.42)	0.202
Noon, 11:00 a.m.–1:29 p.m.	−0.63	(−1.30, +0.05)	0.068	−0.60	(−1.44, +0.24)	0.158	−1.28	(−2.53, −0.04)	0.044
Afternoon, 1:30–5:29 p.m.	+0.53	(−0.55, +1.62)	0.328	+0.25	(−0.96, +1.46)	0.682	−0.44	(−1.96, +1.08)	0.563
Evening, 5:30–8:29 p.m.	−0.05	(−0.88, +0.78)	0.900	+0.02	(−0.77, +0.81)	0.961	−0.67	(−1.86, +0.53)	0.266
Night, 8:30 p.m.–4:59 a.m.	+0.80	(−0.03, +1.63)	0.059	+0.69	(−0.04, +1.41)	0.062			
LDL									
Morning, 5:00–9:29 a.m.	−0.55	(−1.20, +0.10)	0.093	−0.52	(−1.20, +0.17)	0.134	−1.46	(−2.42, −0.50)	0.004
Late morning, 9:30–10:59 a.m.	+0.18	(−0.67, +1.03)	0.670	−0.13	(−1.11, +0.86)	0.795	−1.07	(−2.35, +0.21)	0.099
Noon, 11:00 a.m.–1:29 p.m.	−0.26	(−0.81, +0.29)	0.340	−0.33	(−1.04, +0.38)	0.350	−1.27	(−2.24, −0.30)	0.012
Afternoon, 1:30–5:29 p.m.	+0.07	(−1.26, +1.40)	0.916	−0.14	(−1.49, +1.21)	0.833	−1.08	(−2.58, +0.42)	0.152
Evening, 5:30–8:29 p.m.	−0.22	(−0.94, +0.51)	0.550	−0.11	(−0.76, +0.54)	0.732	−1.05	(−2.12, +0.01)	0.052
Night, 8:30 p.m.–4:59 a.m.	+1.08	(+0.30, +1.87)	0.008	+0.94	(+0.27, +1.61)	0.007			
HDL									
Morning, 5:00–9:29 a.m.	+0.02	(−0.26, +0.30)	0.907	+0.11	(−0.20, +0.42)	0.476	+0.04	(−0.24, +0.32)	0.781
Late morning, 9:30–10:59 a.m.	+0.36	(−0.15, +0.87)	0.164	+0.38	(−0.15, +0.92)	0.156	+0.31	(−0.32, +0.94)	0.324
Noon, 11:00 a.m.–1:29 p.m.	−0.11	(−0.38, +0.16)	0.407	−0.08	(−0.35, +0.19)	0.568	−0.15	(−0.57, +0.27)	0.478
Afternoon, 1:30–5:29 p.m.	−0.13	(−0.56, +0.30)	0.547	−0.14	(−0.61, +0.32)	0.540	−0.21	(−0.78, +0.35)	0.446
Evening, 5:30–8:29 p.m.	+0.14	(−0.18, +0.46)	0.396	+0.13	(−0.19, +0.44)	0.414	+0.06	(−0.30, +0.42)	0.751
Night, 8:30 pm–4:59 a.m.	+0.00	(−0.24, +0.25)	0.987	+0.07	(−0.19, +0.34)	0.590			

P value was based on *t*-test of the hypothesis: regression coefficient = 0. All the models were adjusted for age, sex, menopausal status, employment status, leisure physical activity, body mass index, number of weeks between dietary recall and physical examination, seasonality and weekday/weekend of the dietary recall.

Table 3 Stratified analysis by sex: The difference in total and LDL cholesterol levels (mg/dL) associated with +100 kcal energy intake by time of the day.

	Men			Women		
	Beta	95%CI	p	Beta	95%CI	p
Total Cholesterol						
Additive model						
Morning, 5:00–9:29 a.m.	+0.27	(−0.51, +1.06)	0.4990	−1.35	(−2.29, −0.40)	0.0078
Late morning, 9:30–10:59 a.m.	+0.71	(−0.46, +1.89)	0.2392	−0.77	(−2.06, +0.51)	0.2432
Noon, 11:00 a.m.–1:29 p.m.	−0.35	(−1.20, +0.50)	0.4260	−1.15	(−2.26, −0.04)	0.0496
Afternoon, 1:30–5:29 p.m.	+0.08	(−1.23, +1.39)	0.9049	−0.34	(−1.98, +1.30)	0.6897
Evening, 5:30–8:29 p.m.	−0.36	(−1.19, +0.47)	0.3951	+0.36	(−0.83, +1.55)	0.5539
Night, 8:30 pm–4:59 a.m.	+0.42	(−0.37, +1.21)	0.3064	+0.88	(−0.31, +2.07)	0.1564
Substitution model						
Morning, 5:00–9:29 a.m.	−0.15	(−1.23, +0.93)	0.7924	−2.23	(−3.61, −0.84)	0.0030
Late morning, 9:30–10:59 a.m.	+0.29	(−1.15, +1.74)	0.6915	−1.65	(−3.46, +0.15)	0.0803
Noon, 11:00 a.m.–1:29 p.m.	−0.77	(−1.81, +0.27)	0.1532	−2.03	(−3.66, −0.40)	0.0192
Afternoon, 1:30–5:29 p.m.	−0.34	(−1.52, +0.84)	0.5762	−1.22	(−3.69, +1.25)	0.3405
Evening, 5:30–8:29 p.m.	−0.78	(−1.98, +0.41)	0.2054	−0.52	(−2.42, +1.38)	0.5971
LDL-C						
Additive model						
Morning, 5:00–9:29 a.m.	+0.31	(−0.57, +1.20)	0.4914	−1.31	(−2.04, −0.57)	0.0012
Late morning, 9:30–10:59 a.m.	+0.62	(−0.53, +1.78)	0.2974	−0.89	(−2.11, +0.33)	0.1616
Noon, 11:00am–1:29 p.m.	+0.04	(−0.85, +0.93)	0.9291	−0.92	(−1.87, +0.03)	0.0641
Afternoon, 1:30–5:29 p.m.	−0.53	(−2.27, +1.21)	0.5561	+0.06	(−1.19, +1.31)	0.9229
Evening, 5:30–8:29 p.m.	−0.41	(−1.14, +0.32)	0.2747	+0.23	(−0.75, +1.20)	0.6524
Night, 8:30pm–4:59 a.m.	+1.02	(+0.27, +1.77)	0.0106	+0.72	(−0.29, +1.74)	0.1698
Substitution model						
Morning, 5:00–9:29 a.m.	−0.71	(−1.95, +0.53)	0.2668	−2.03	(−3.24, −0.82)	0.0021
Late morning, 9:30–10:59 a.m.	−0.40	(−1.80, +1.00)	0.5763	−1.61	(−3.38, +0.16)	0.0824
Noon, 11:00 a.m.–1:29 pm	−0.98	(−1.84, −0.13)	0.0294	−1.65	(−3.11, −0.18)	0.0329
Afternoon, 1:30–5:29 p.m.	−1.55	(−3.25, +0.15)	0.0807	−0.66	(−2.71, +1.38)	0.5303
Evening, 5:30–8:29 p.m.	−1.44	(−2.50, −0.37)	0.0117	−0.50	(−2.07, +1.08)	0.5402

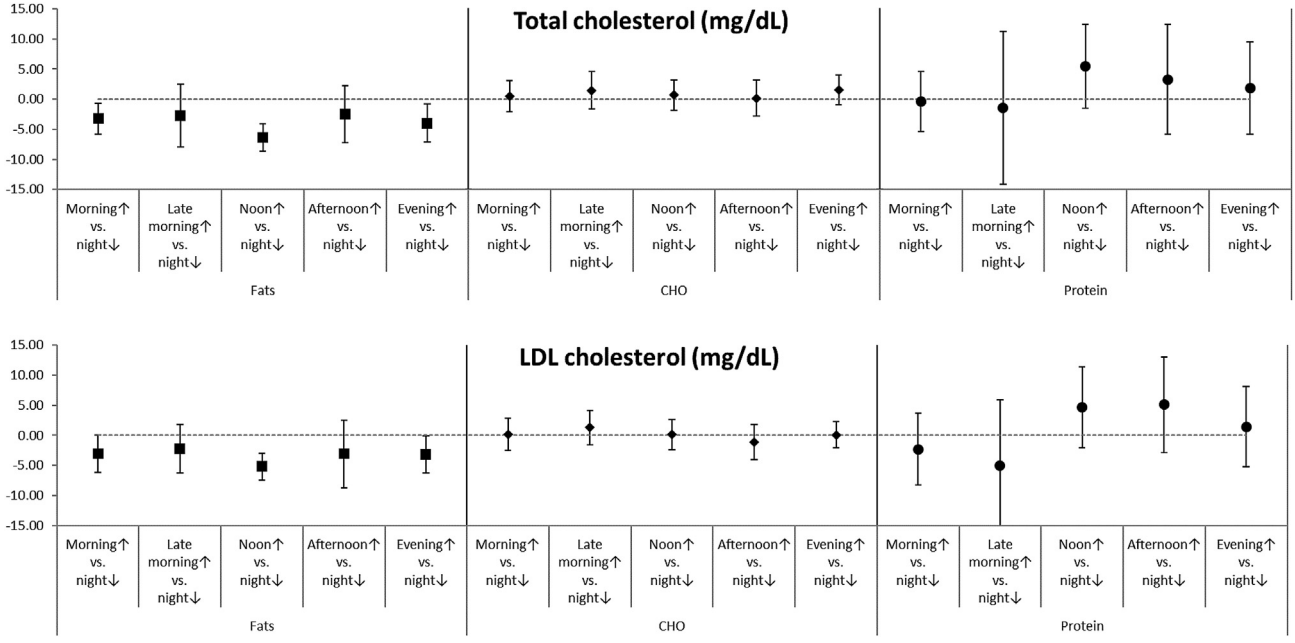

Figure 2 Total and LDL cholesterol levels associated with the substitution of 100 kcal of macronutrient intake from night time to other time of the day. Based on linear regression models adjusted for age, sex, menopausal status, employment status, leisure physical activity, body mass index, number of weeks between dietary recall and physical examination, seasonality and weekday/weekend of the dietary recall, and carbohydrate and fat intake of the six time periods. Symbols: Square for fats, diamond for carbohydrates, close circle for protein.

With respect to lipoproteins, LDL cholesterol was associated with timing of fat intake in the present study. However, although circadian variations of the LDL level are known [10–12], the circadian patterns of LDL synthesis and disappearance were less clear. Studies show that human lipoprotein lipase activity was lower in the evening

(11:30 p.m.) than in the morning (11:30 a.m.), which implies a lower rate of transforming VLDL to LDL at these times [29]. However, the plasma level of proprotein convertase subtilisin/kexin type 9 (PCSK9) is low in the afternoon until 9 p.m., and rises and peaks at 4 a.m. This circulating protease is responsible for LDL receptor protein degradation [30,31]. The higher level of circulating PCSK9 could result in a lower LDL receptor in peripheral tissues and a higher circulating LDL level at night.

Evidence based on animal models may provide some physiological accounts of the temporal patterns of lipoprotein metabolism. In rats, lipoprotein lipase activity is higher at 7 p.m. than in the morning [32], and VLDL would be more likely to transform to LDL in the evening. Microsomal triglyceride-transfer protein (MTP), which involves in apo-B lipoproteins synthesis in liver and in intestine, has higher activity from afternoon to night in rat and mouse studies, which suggests a higher hepatic production of VLDL of these animals in the afternoon and evening hours [26,33]. As for the disappearance of LDL, a study of rats found that plasma LDL levels started to rise at the onset of darkness, when LDL-receptor expression started to decline [34]. Evidence based on mice and rats, however, must be carefully compared to humans, as the former animals are nocturnal while humans are diurnal.

Few studies have used observational population representative data to examine the association between timing of eating and lipid profiles. A Czech survey applied a meal questionnaire to assess participants' usual meal patterns and their association with cardiovascular risk factors, including total cholesterol; skipping breakfast and skipping afternoon snack were associated with about 69% and 65% greater odds of high cholesterol level, respectively. However, the Czech study did not find total cholesterol level varying by dietary patterns that were characterized by meal frequency, time of the first and the last meal of a day, intervals between meals, and meal skipping. In addition, the information for other blood lipid parameters were not available [6]. A cohort study in the UK based on a five-day diet record showed that a greater proportion of protein at breakfast was associated with a lower risk of low HDL-C, while a greater proportion of carbohydrates at breakfast was associated with a risk of elevated triglycerides [7].

Several limitations in the study need to be considered before we draw conclusions. First, although the cross-sectional study design provided evidence on association, the temporality between timing of eating and blood lipid levels was not clear. That is, the observed association could result from that blood lipid levels affect people's time of food and macronutrient intakes. This is especially possible for people who knew their medical conditions and attempted to modify their diets and lifestyle. However, we tried the best to prevent this issue in our analysis. We excluded data of participants who had known themselves ever being diagnosed with or under treatment for metabolic disorders and major cardiovascular diseases. This could minimize the influence of possible reverse causation. Second, the dietary information was based on a one-day dietary recall. The daily variation of diets would increase the random error in measuring the independent variables of interest of the study and hence underestimate the association with an increase type 2 errors. That is, the estimated degree of association would be more conservative than the true association, although we were unable to adjust the effect size attenuation due to the lack of information on the variations of energy intake during particular time intervals of the day. Third, confounders like physical activity on the same day of dietary recall, sleep quality, and shift work status, were not measured. Activity on the particular day of dietary recall may not influence lipid levels several weeks later. Since usual leisure physical activity has been controlled in the analysis, we expect smaller confounding effects on the same day as dietary recall. Nevertheless, the potential influence of shift work and sleep patterns will need more study to tackle.

Despite the limitations, the major strength of the present study is the population-representative sample. The information on the time of eating, collected with a 24 h dietary recall, allowed us to find the most common time of eating within the population, and to assess energy intake during these hours for meals/snacks. The present study was the first to examine the timing of intake during the day and its association with lipid profiles in an Asian population. In addition, the potential impact of the timing of energy intake on the cholesterol was especially pertinent in women. Further research regarding associated gender differences is warranted.

In conclusion, based on a representative sample of adults in Taiwan, we found that elevated levels of total and LDL cholesterol were associated with energy intake at night. Lower LDL cholesterol was associated with substituting calories and fat intake in the late evening, along with intake at earlier times of the day. The finding is coherent for molecular mechanisms and previous randomized controlled trials. Meanwhile, timing of fat intake, rather than timing of carbohydrate and protein intake, was associated with total and LDL cholesterol levels.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2019.01.003.

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Declaration of interest

The authors report no conflicts of interest.

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