

## Research Article

**Cite this article:** Lesani A, Zeraattalab-Motlagh S, Djafarian K, Majdi M, Akbarzade Z, and Shab-Bidar S (2024). Association of chrono-nutrition components with cardiometabolic health in a sample of Iranian adults: a cross-sectional study. *British Journal of Nutrition*, page 1 of 13. doi: [10.1017/S0007114524002745](https://doi.org/10.1017/S0007114524002745)

Received: 23 May 2024

Revised: 16 October 2024

Accepted: 24 October 2024

**Keywords:**

Chrono-nutrition; Meal timing; Meal frequency; Irregularity; Cardiometabolic risk factors

**Abbreviations:**





EO, eating occasions; FDR, false discovery rate; HOMA, homeostatic model assessment; MET, metabolic equivalent; TC, total cholesterol; WC, waist circumference

**Corresponding author:**

Sakineh Shab-Bidar;

Email: [s\\_shabbidar@tums.ac.ir](mailto:s_shabbidar@tums.ac.ir)

# Association of chrono-nutrition components with cardiometabolic health in a sample of Iranian adults: a cross-sectional study

Azadeh Lesani<sup>1</sup> , Sheida Zeraattalab-Motlagh<sup>1</sup> , Kurosh Djafarian<sup>2</sup>,  
Maryam Majdi<sup>1</sup>, Zahra Akbarzade<sup>1</sup>  and Sakineh Shab-Bidar<sup>1,3</sup> 

<sup>1</sup>Department of Community Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences (TUMS), Tehran, Iran; <sup>2</sup>Department of Clinical Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran and <sup>3</sup>Sports Medicine Research Center, Neuroscience Institute, Tehran University of Medical Sciences (TUMS), Tehran, Iran

**Abstract**

Chrono-nutrition is an emerging field that examines how the frequency and timing of meals impact health. Previous research shows inconsistency in the relationship between chrono-nutritional components and cardiometabolic health. We investigated cross-sectional associations between these components and cardiometabolic health in 825 Iranian adults aged 20–59 years. Dietary data, including the number of eating occasions, meal timing and meal irregularity of energy intake, were collected using three 24-h dietary recalls. Anthropometric measurements, blood pressure and laboratory tests (fasting plasma glucose, lipid profile, insulin, uric acid and C-reactive protein) were conducted. Insulin resistance and sensitivity (homeostatic model assessment for insulin resistance, homeostatic model assessment for insulin sensitivity), the TAG-glucose, the lipid accommodation product and BMI were calculated. The demographic and morning-evening questionnaire was completed. General linear regression was used to assess associations between chrono-nutritional components and outcomes. Interactions with age and BMI were examined in all associations. Chrono-nutrition components were not significantly related to cardiometabolic risk factors in the total population. However, a lower number of eating occasions was associated with an increased LDL-cholesterol:HDL-cholesterol ratio ( $\beta$  (95% CI): 0.26 (0.06, 0.48)) among overweight and obese participants. Additionally, less irregularity in breakfast energy intake was associated with a lower total cholesterol:HDL-cholesterol ratio (−0.37 (−0.95, −0.18)) and a lower LDL-cholesterol:HDL-cholesterol ratio (−0.32 (−0.79, −0.13)) among participants with a normal BMI (all  $P < 0.05$ ). The study concluded that more frequent meals and regular energy intake might enhance cardiometabolic health cross-sectionally, highlighting the need for prospective studies to further investigate these associations and the mediating role of BMI.

Chrono-nutrition is an exciting and rapidly growing field in nutritional epidemiology that examines the interplay of meal frequency, timing and regularity. This innovative area underscores how ‘when to eat’ can significantly impact health<sup>(1)</sup>. The timing of food intake could influence various physiological processes and metabolism. Additionally, irregular eating patterns can disrupt the biological clock, causing misalignment in wake/sleep, fasting/feeding and light/dark cycles, potentially leading to metabolic dysregulation<sup>(2,3)</sup>.

Meal timing patterns are known to be factors associated with the development of chronic diseases, for example, atherosclerosis and metabolic abnormalities<sup>(4–6)</sup>. Irregularity in meal timing can disrupt the circadian rhythm, which can cause abnormal metabolic regulation and increased cardiometabolic risks<sup>(7)</sup>. Current evidence also shows that nutrient composition<sup>(8–10)</sup>, frequency, time<sup>(11,12)</sup> and regularity of meals<sup>(11,13)</sup> can affect cardiometabolic risk factors, including insulin resistance, dyslipidaemia and obesity. Eating in circadian misalignment worsens several cardiometabolic factors, particularly glucose tolerance<sup>(14–16)</sup>, and impairs insulin sensitivity and secretion<sup>(17,18)</sup>. A study of Korean adults showed that eating two meals a day increased the risk of metabolic syndrome compared with eating three meals a day<sup>(19)</sup>. Furthermore, studies have shown an increased incidence of obesity among shift workers, revealing the role of circadian rhythms<sup>(20–22)</sup>. Prior research has focused on one dimension of chrono-nutrition. In this study, we will examine all three dimensions of chrono-nutrition.

Despite our ever-growing knowledge of circadian rhythms, we still have little insight into meal timing patterns in the context of mixed meals and their impact on cardiometabolic health. Therefore, this study aimed to identify the relationships between chrono-nutritional components and cardiometabolic health in the Iranian adult population.

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## Methods

### Study design

A cross-sectional study was conducted among apparently healthy men and women) who did not report any previous diagnosis of chronic diseases such as diabetes, CVD and chronic kidney, lung and liver diseases (from Iran who attended the healthcare centres of Tehran (February 2019 to August 2019). A sample size of 546 individuals was calculated using the formula  $n = (z^2 p(1-p))/d^2$ <sup>(23)</sup>, based on the prevalence of obesity (68.5 %) in Tehran<sup>(24)</sup>, an error coefficient of  $d = 0.04$  and an  $\alpha$  level of 0.05. Considering the effect design of 1.3 and the exclusion of participants with under- and overreporting (20 %), the final sample size was estimated to be 850 participants. We recruited using two-stage cluster sampling from five geographic areas of Tehran, selecting participants from twenty-five healthcare centres using a proportion-to-size sampling method. The inclusion criteria required participants to be 20–59 years old, have a BMI between 18.5 and 39.9 kg/m<sup>2</sup> and, crucially, not be diagnosed with any acute diseases. Exclusion criteria included pregnancy, lactation and individuals with under- or overreporting of total energy intake.

### Dietary intake assessment, eating occasion and meal timing

Dietary data were obtained according to three 24-h dietary recalls on non-consecutive days within the week, one weekend and two weekdays. We conducted all recalls by trained dietitians during a private interview. The first 24-h dietary recall was recorded during the first visit to the healthcare centre. The following data were collected via telephone on random days. Eating occasions (EO) were defined as events that provided at least 50 kilocalories, with a separation in time from a preceding or following eating event of at least 15 min<sup>(25)</sup>. Subjects reported the following types of EO in which food was consumed: breakfast, lunch, dinner and snacks. The definition of the main mealtime of food intake was explained in a prior article<sup>(26)</sup>. The fasting window or nightly fasting duration was defined by calculating the hours between the last EO reported in the 24-h dietary recall for the previous day and the first EO obtained from a question regarding the current day. This method allowed us to accurately assess the fasting duration based on participants' responses.

Daily and main meal intake of all food items, derived from three 24-h dietary recalls, were converted into grams per d by using household measures and standard portions<sup>(27)</sup>. The intake of food groups was adjusted for energy intake using the residual method<sup>(28)</sup>. We used Nutritionist IV software (First Databank), modified for Iranian foods, to obtain the values of energy and nutrient intake per d. Based on the predefined dietary energy cut-off values, men and women were excluded if their reported average dietary energy intake levels were below < 800 kcal/d or above > 4000 kcal/d and < 500 kcal/d or above > 3500 kcal/d, respectively<sup>(29)</sup>. We excluded participants who underreported or overreported their total energy intake from the analysis to evaluate the potential impact on the results. Out of the 850 participants, we excluded twenty-five participants – two individuals due to underreporting and the other twenty-three participants due to overreporting their energy intake. Ultimately, 825 participants were included. (online Supplementary Fig. S1)

### Energy intake irregularity at the main meal level

The irregularity score of meal energy intake was calculated. The variance in energy intake per meal was used as a proxy. The

absolute difference of the individual energy intake from the 3-d mean energy intake was divided by the 3-d mean energy intake, multiplied by 100, and then the average over the 3 d. A low score indicated more regular energy intake patterns, while a higher score reflected more irregular energy intake patterns<sup>(30)</sup>.

### Data collection

The data were collected from each participant through a face-to-face interview. Sociodemographic information was gathered using prespecified data extraction forms and included age, sex, smoking status (not smoking, ex-smoking, current smoking), education level (illiterate, under diploma and diploma, educated), occupation status (employed, unemployed, retired), night sleep duration on weekdays/weekend and supplement intake (yes or no).

### Physical activity

Physical activity was measured by the short form of the validated International Physical Activity Questionnaire<sup>(31)</sup>. Participants reported the time spent walking or performing moderate- and/or vigorous-intensity activities within the previous 7 d. The overall physical activity level was measured in the form of metabolic equivalent minutes per week (MET-min/week). MET scores were then categorised into three levels: a point score < 600 MET-min/week indicated low physical activity, a point score 600–3000 MET-min/week indicated moderate physical activity and a point score > 3000 MET-min/week indicated high physical activity<sup>(32)</sup>.

### Morning-evening questionnaire

The morning-evening questionnaire was a nineteen-item scale with several different options developed by Horn and Steberg in which the subject was asked to specify the rhythm and habits of life and the hours of sleep and wakefulness at night<sup>(33)</sup>. The questions had different options and specific scoring methods. The participants were asked about their hours of sleep and wakefulness and their preferences for physical and mental tasks to determine their daily mood. The questionnaire options did not have equal values, and based on the initial analysis of its creators, the possibilities of some questions being given different values than other questions. The score range varied from 16 to 86; higher scores indicated a preference for morningness, while lower scores suggested eveningness, based on the Persian Validation Questionnaire<sup>(34)</sup>.

### Assessment of blood pressure

Blood pressure was measured by a digital barometer (BC 08) after at least 10–15 min of rest and sitting. Blood pressure was measured twice for each person, and the average blood pressure was reported for each person.

### Anthropometric measurements

Weight was measured using a Seca weighing scale (Seca and Co. KG; 22 089 Hamburg; Model: 874 1321009; designed in Germany; made in China) with light clothing (without shoes, coat or raincoat). A wall stadiometer board with a sensitivity of 0.1 cm was used to measure standing height without shoes. BMI was calculated as weight (in kilograms) divided by height (in metres squared). Waist circumference (WC) was measured using a non-stretchable fibreglass measuring tape at the midpoint between the lower

border of the rib cage and the iliac crest, according to the guiding protocol of the WHO<sup>(35)</sup>.

### Laboratory investigations

Participants donated 10 ml of blood from 07.00–10.00 after fasting for 12 h. Blood samples were subsequently collected in acid-washed test tubes without anticoagulants. After being stored at room temperature for 30 min and after clot formation, blood samples were centrifuged at 1500 g for 20 min. The serum samples were stored at  $-80^{\circ}\text{C}$  until future testing. Fasting plasma glucose was assayed by the enzymatic (glucose oxidase) colorimetric method using a commercial kit (Pars Azmun). Serum total cholesterol (TC) and HDL-cholesterol were measured using the cholesterol oxidase phenol aminoantipyrine method, and serum TAG was measured using the glycerol-3 phosphate oxidase phenol aminoantipyrine enzymatic method. Serum LDL-cholesterol was calculated using the Friedewald formula<sup>(36)</sup>. The serum insulin concentration was measured using commercial kits (Insulin AccuBind ELISA, Monobind, Inc.) and enzyme-linked immunosorbent assays (ELISA). Serum uric acid was measured by calorimetry using commercial kits (Bionic, Bionic, Inc.) and biolysis 24. Serum C-reactive protein was measured by a commercial kit (CRPLX, Roche, Inc.) via the immunoturbidimetric method.

### Definition of cardiometabolic outcomes

Hypercholesterolaemia was a vital CVD risk factor among the population. Both increased serum TC and decreased HDL-cholesterol were related to CVD risk. The TC:HDL-cholesterol ratio was an independent lipoprotein predictor of the development of CVD<sup>(37)</sup>. The LDL-cholesterol:HDL-cholesterol ratio was defined as an index of CVD and served as the main target for therapy<sup>(38,39)</sup>.

Serum uric acid was the end product of purine metabolism in the body. Hyperuricaemia was related to an increased future risk of type 2 diabetes<sup>(40)</sup> and appeared to be a consequence of insulin resistance<sup>(41)</sup>.

The lipid accommodation product index, a marker of CVD, was a simple indicator of high lipid accumulation in adults<sup>(42)</sup> and had greater sensitivity and specificity than WC measurements for detecting insulin resistance<sup>(43)</sup>. Based on the values of WC and fasting TAG, the lipid accommodation product score was calculated using the sex difference formula: in men =  $(\text{WC (Cm)} - 65) \times \text{TAG (mmol/l)}$  and in women =  $(\text{WC (Cm)} - 58) \times \text{TAG (mmol/l)}$ .

Homeostatic model assessment (HOMA) was a measure of insulin resistance and  $\beta$ -cell function among diabetic and nondiabetic people<sup>(44)</sup>. The HOMA of beta cell function or insulin sensitivity was thought to be a good measure of beta cell function. High HOMA for insulin resistance and low HOMA for insulin sensitivity values were associated with glucose intolerance and subsequent risk of type 2 diabetes<sup>(45,46)</sup>. HOMA for insulin resistance =  $\text{fasting insulin } (\mu\text{IU/ml}) \times \text{fasting plasma glucose (mg/dl)} / 405$ , and HOMA for insulin sensitivity =  $(20 \times \text{fasting insulin } (\mu\text{IU/ml})) / (\text{fasting plasma glucose (mg/dl)} - 3.5)$ .

The TAG-glucose index is a marker of insulin resistance<sup>(47)</sup> and predicts the development of metabolic disorders and CVD<sup>(48)</sup>. The TAG-glucose index was calculated based on the following formula:  $\text{In (fasting TAG (mg/dl)} \times \text{fasting plasma glucose (mg/dl)}) / 2$ .

### Statistical analysis

The statistical analysis was conducted with SPSS version 26 (IBM). Descriptive statistics were primarily reported as the means (SD)

and/or percentages for the total population and stratified with BMI (BMI < 25 v. BMI  $\geq$  25). The  $\chi^2$  test and one-way ANOVA were used for categorical and continuous variables to show the differences between general characteristics and dietary habits according to chrono-nutrition components, number of EO, meal timing and irregularity of the main meal scores in the overall population. Additionally, one-way ANOVA was employed to compare the number of EO and meal timing between weekends and weekdays.

To address the possibility of false positive results from conducting multiple statistical tests, we controlled for multiple comparisons by applying the false discovery rate (FDR) method, setting the FDR threshold at 5%. This approach ensures that no more than 5% of the statistically significant results are expected to be false positives, maintaining the integrity of the findings<sup>(49)</sup>.

Independent variables, including the number of EO, meal timing and irregularity in the energy intake of meals, were divided into two groups based on the median number of EO: less than 6.33 n/d v. more than 6.33 n/d. Meal timing categories were as follows: early-B (early-Breakfast), 05.00–08.00 v. late-B, 08.00–11.00; early-L (early-Lunch), 11.00–13.30 v. late-L 13.30–16.00; and early-D (early-Dinner), 18.00–20.45 v. late-D 20.45–23.00. Irregularity in energy intake was categorised as less irregularity-B  $\leq$  31.77 v. more irregularity-B > 31.77, less irregularity-L  $\leq$  30.19 v. more irregularity-L > 30.19 and less irregularity-D  $\leq$  34.02 v. more irregularity-D > 34.02, respectively. We used logistic regression to investigate the associations between chrono-nutritional components and cardiometabolic risk factors while controlling for confounders, including age, sex, education, energy intake, physical activity, income, supplement intake, menopausal status, smoking status, morning-evening questionnaire score, fasting window, sleep duration and BMI. Additionally, the interaction effect of BMI on all associations was assessed in a sensitivity analysis, where the model was adjusted for all confounders except BMI. Similarly, the interaction effect of age (< 41 years old v.  $\geq$  41 years old) on all associations was assessed in a sensitivity analysis, where the model was adjusted for all confounders except age.

### Results

In this cross-sectional study, 825 participants – 140 males (16.96%) and 685 females (83.03%) – with ages ranging from 20 to 59 years and a mean (SD) age of 42.17 (SD 10.5) years, were analysed. Participants had moderate to low levels of physical activity, with most participants reporting not smoking. The mean (SD) energy intake was 1681.63 (SD 374.12) kcal/d, with three main meals (breakfast, lunch and dinner) comprising roughly equal energy intake. The mean (SD) average number of EO was 6.35 (SD 0.93), with a range of 1–11 n/d, and only 1.17% and 4.51% of the population had  $\leq$  4 and  $\geq$  8 EO, respectively. In addition, the daily irregularity energy score was 22.30 (SD 19.01), ranging from 3.71 to 92.12, and the morning-evening questionnaire score was 58.65 (SD 5.73), ranging from 36 to 78. All the variable data were available for 825 participants. Participants with a BMI  $\geq$  25 exhibited significantly lower physical activity levels, with 64.38% categorised as having low activity, compared with just 33.53% in the BMI < 25 group. Furthermore, non-smokers were notably more prevalent among those with a BMI  $\geq$  25 (96.98%) than in the BMI < 25 group (91.46%). This group was also older on average, at 43.79 years, compared with 38.98 years for the BMI < 25 participants, highlighting a distinct age disparity between the two groups. The general characteristics, eating habits and serum biomarkers of the

**Table 1.** Baseline lifestyle, sociodemographic and dietary characteristics of the total population sample and stratified by BMI (*n* 825) (Mean values and standard deviations; numbers and percentages)

Characteristics	Total population*		BMI < 25		BMI ≥ 25	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Number (%) ( <i>n</i> (%))	825	100	328	39.75	497	60.25
Age (years)						
Mean	42.21		38.98		43.79	
sd	10.62		11.47		9.63	
Sex (women)	685	83.03	269	82.01	416	83.71
Physical activity level (MET.min.week)						
Low ( <i>n</i> (%))	430	52.13	110	33.53	320	64.38
Moderate ( <i>n</i> (%))	315	36.94	187	57.01	128	25.75
High ( <i>n</i> (%))	80	9.69	31	9.46	49	9.86
Education						
Illiterate ( <i>n</i> (%))	56	6.74	19	5.79	37	6.82
Under diploma and diploma ( <i>n</i> (%))	472	57.15	162	49.32	310	62.37
Educated	297	36.05	145	44.22	152	30.58
Smoking status						
Not smoking ( <i>n</i> (%))	782	94.83	300	91.46	482	96.98
Ex-smoking ( <i>n</i> (%))	14	1.71	12	3.66	2	0.40
Smoking ( <i>n</i> (%))	29	3.53	16	4.88	13	2.62
Sleep duration (h.m)						
Mean	6:49		6:47		6:51	
sd	1:09		1:12		1:06	
Supplement intake (Yes) ( <i>n</i> (%))	201	24.33	76	23.17	135	27.16
	Mean	sd	Mean	sd	Mean	sd
Energy intake (kcal/d)						
Daily	1681.63	374.15	1662.85	374.23	1685.98	381.45
Breakfast	418.32	151.54	419.41	148.26	417.67	158.66
Lunch	535.85	179.34	537.43	183.38	534.43	176.99
Dinner	508.17	196.30	507.08	196.64	510.99	196.07
Breakfast (% of TEI)	25.09	7.73	24.93	7.72	27.07	7.74
Lunch (% of TEI)	32.16	8.91	31.95	8.89	32.25	8.94
Dinner (% of TEI)	30.29	9.48	30.40	9.49	30.18	9.46
Eating occasions (EO) ( <i>n</i> /d)	6.35	0.93	6.34	0.95	6.36	0.91
Frequency main meals ( <i>n</i> /d)	2.92	0.16	2.90	0.15	2.95	0.18
Frequency snacks ( <i>n</i> /d)	3.43	0.83	3.40	0.81	3.46	0.85
Breakfast irregularity score	34.16	20.03	34.12	19.71	34.19	20.39
Lunch irregularity score	37.41	13.71	38.18	14.02	36.63	13.48
Dinner irregularity score	36.13	26.14	35.86	23.82	36.61	28.96
Daily irregularity score	22.30	19.01	23.12	18.76	23.12	19.34
Breakfast time (h.m, am)	8.05	0.44	8.07	0.42	8.01	0.46
Lunchtime (h.m, pm)	1.58	0.33	1.54	0.35	2.08	0.31
Dinner time (h.m, pm)	8.42	0.34	8.45	0.33	8.39	0.35
Morning-evening questionnaire (MEQ)	58.65	5.73	58.13	5.70	59.49	5.77

(Continued)

**Table 1.** (Continued)

Characteristics	Total population*		BMI < 25		BMI ≥ 25	
	n	%	n	%	n	%
SBP (mmHg)	118-22	14-36	113-61	14-22	121-54	14-51
DBP (mmHg)	78-35	9-32	76-59	8-62	79-98	9-74
WC (cm)	89-09	11-63	78-80	6-46	92-32	9-87
BMI (kg.m <sup>2</sup> )	27-34	3-01	22-71	1-72	29-07	3-05
LAP index (cm.mmol/l)	49-25	33-93	39-24	29-27	59-17	35-19
FPG (mg.dl)	105-13	19-02	102-83	17-88	105-23	19-97
TAG (mg.dl)	144-53	72-11	135-15	78-39	154-58	65-31
$\frac{LDL-C}{HDL-C}$	2-41	0-80	2-30	0-75	2-47	0-75
$\frac{TC}{HDL-C}$	4-03	1-06	3-83	0-92	4-13	1-14
Uric acid (mg/dl)	4-63	1-30	4-45	1-26	4-72	1-33
Insulin serum (μU/ml)	13-58	12-50	13-09	11-90	14-37	12-70
HOMA-IR	3-66	2-94	3-36	2-91	3-84	3-08
HOMA-IS	2-56	1-98	2-45	1-90	2-74	2-14
CRP (μg/dl)	0-23	0-21	0-19	0-16	0-24	0-23
TyG index (cm.mgdl)	4-82	2-82	4-13	2-38	5-25	3-09

H.m, hour.minute; EO, eating occasions; TEI, total energy intake; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose;  $\frac{LDL-C}{HDL-C}$ ,  $\frac{LDL-cholesterol}{HDL-cholesterol}$ ;  $\frac{TC}{HDL-C}$ ,  $\frac{total\ cholesterol}{HDL-cholesterol}$ ; LAP, lipid accumulation product; HOMA-IR, homeostatic model assessment for insulin resistance; HOMA-IS, homeostatic model assessment for insulin sensitivity; CRP, C-reactive protein; TyG, TAG-glucose.

\*Values are mean (sd) otherwise it is indicated.

study participants were presented in [Table 1](#), both for the total population and stratified by BMI.

The difference between the number of EO and meal timing based on weekend and weekday data was presented in online Supplementary Table S1, with no significant differences observed.

[Table 2](#) indicates the differences in general characteristics and dietary habits based on the number of EO: those with less EO ( $\leq 6.33$ ) compared with those with more EO ( $> 6.33$ ). The group with more EO tended to have greater morningness ( $P < 0.001$ ) after adjusting for sex and age. Additionally, they consumed more total energy ( $P = 0.002$ ), particularly at breakfast ( $P = 0.02$ ) and dinner ( $P = 0.03$ ), than the group with fewer EO. Individuals with more EO had a shorter fasting window ( $P < 0.001$ ) and shorter sleep duration ( $P < 0.001$ ) but exhibited more regular breakfast consumption ( $P = 0.002$ ) along with earlier breakfast ( $P < 0.001$ ) and dinner ( $P = 0.01$ ) intake habits.

The differences between lifestyle and eating behaviour according to the time of the main meal are indicated in [Table 3](#). Earlier-B participants (before 08.00) were more likely to be more morningness ( $P < 0.001$ ) and a greater number of EO ( $P < 0.001$ ) but a shorter fasting window ( $P < 0.001$ ) and shorter sleep duration ( $P < 0.001$ ) than later B participants (after 08.00). In addition, earlier lunch ( $P = 0.009$ ) and dinner ( $P = 0.01$ ) were also observed in this group. According to the lunchtime analysis, the individuals in the earlier-L group (before 13.30) had a lower BMI than those in the later-L group (after 13.30),  $P = 0.03$ . The time of breakfast ( $P < 0.001$ ) and dinner intake ( $P = 0.002$ ) for earlier-L participants were earlier than those for later-L participants. Later-D participants (before 20.45) had a shorter fasting window ( $P = 0.03$ ), a lower frequency of intake ( $P = 0.01$ ) and later breakfast ( $P = 0.007$ ) and lunch ( $P < 0.001$ ) consumption in comparison to earlier-D participants (after 20.45).

[Table 4](#) illustrates differences between the two groups based on the irregularity energy score of the main meal, labelled 'less irregular' and 'more irregular'. The less irregular-B group,  $\leq 31.77$ , consumed more energy at breakfast ( $P = 0.009$ ) but had lower irregular energy scores at lunch and dinner than did the more irregular-B group ( $> 31.77$ ),  $P < 0.001$  and  $P < 0.001$ . Furthermore, less irregular-L participants,  $\leq 30.19$ , had lower energy intake during lunch and dinner and less irregular-B scores than did more irregular-L participants,  $> 30.19$  ( $P < 0.001$ ), in all associations. The more irregular-D group,  $> 34.02$ , consumed more daily and lunch energy but less breakfast energy than did the other group,  $P < 0.001$ ,  $P < 0.001$  and  $P = 0.002$ , respectively. Additionally, the more irregular-D group had greater irregularity scores at breakfast and lunch than did the other groups,  $P < 0.001$  for both. However, they slept less and had a shorter fasting duration in comparison to less irregular-D participants ( $P = 0.003$  and  $P = 0.02$ , respectively).

Chrono-nutrition components showed no significant associations with cardiometabolic risk factors across the entire population. Also, there was no interaction by age observed in any of the associations. Due to a significant interaction by BMI, the data were stratified based on BMI categories (online Supplementary Tables S2, S3 and S4).

In the BMI-stratified analysis, having fewer number of EO was associated with a higher LDL-cholesterol:HDL-cholesterol ratio ( $\beta$  (95 % CI), 0.26 (0.06, 0.48),  $P_{FDR} = 0.04$ ) among overweight and obese individuals. However, no significant association was found between the number of EO and other cardiometabolic risk factors, as shown in [Table 5](#).

In [Table 6](#), meal timing was not associated with cardiometabolic risk when stratified by BMI.

Only, for participants with a normal BMI, less irregularity of breakfast energy intake was associated with lower TC/HDL-

**Table 2.** The difference between general characteristics and dietary habits according to the number of eating occasions (EO) in Iranian adults (*n* 825) (Mean values and standard deviations; numbers and percentages)

Variables	Number of Eating Occasion (EO) ( <i>n</i> / <i>d</i> )				<i>P</i>
	Less EO ( $\leq 6$ -33)		More EO ( $> 6$ -33)		
	<i>(n</i> 465)		<i>(n</i> 360)		
	Mean	SD	Mean	SD	
Sex, women	385		318		0.32
<i>n</i>	82.79		88.33		
%					
Age (years)	41.92	10.37	42.47	10.39	0.45
Morning-evening questionnaire score (MEQ)*	57.44	7.30	59.27	5.75	<b>&lt; 0.001</b>
BMI*	26.94	4.01	27.30	4.41	0.29
Total daily energy intake (kcal/d)*	1639.71	379.10	1721.68	375.60	<b>0.002</b>
Breakfast energy intake (kcal/d)*	405.72	159.12	433.28	148.46	<b>0.01</b>
Lunch energy intake (kcal/d)*	540.96	182.19	530.71	171.87	0.42
Dinner energy intake (kcal/d)*	489.92	204.02	529.01	181.65	<b>0.03</b>
Supplement intake (yes/no)					
Yes					
<i>n</i>	100		101		0.93
%	21.50		28.05		
Breakfast time (h.m, am)*	8.09	0.47	7.54	0.41	<b>&lt; 0.001</b>
Lunchtime (h.m, pm)*	1.54	0.35	1.52	0.31	0.62
Dinner time (h.m, pm)*	8.49	0.38	8.40	0.30	<b>0.01</b>
Fasting window (h.m)*	9.56	1.19	9.06	1.09	<b>&lt; 0.001</b>
Sleep duration (h.m)*	8.53	1.23	8.36	1.41	<b>&lt; 0.001</b>
Breakfast irregularity score*	36.02	20.04	31.79	18.89	<b>0.002</b>
Lunch irregularity score*	37.66	13.01	38.21	14.51	0.13
Dinner irregularity score*	35.94	23.88	34.20	22.05	0.29

EO, eating occasions; h.m, hour.minute; MEQ, morning-evening questionnaire.

Values are mean (sd); otherwise, it is indicated.

Calculated by  $\chi^2$  and one-way ANOVA for qualitative and quantitative variables, respectively.

Significant *P* value (*P* < 0.05) is presented in bold.

\*Adjusted for sex and age.

cholesterol (−0.37 (−0.95, −0.18),  $P_{FDR} = 0.01$ ) and LDL-cholesterol:HDL-cholesterol ratio (−0.32 (−0.79, −0.13),  $P_{FDR} = 0.01$ ). (Table 7)

## Discussion

Chrono-nutrition components were not significantly associated with cardiometabolic risk factors in the overall population. However, when stratified by BMI, a lower number of EO was linked to a higher LDL-cholesterol:HDL-cholesterol ratio among overweight and obese individuals. Additionally, more consistent breakfast energy intake was associated with improved lipid profiles, specifically lower TC/HDL-cholesterol and LDL-cholesterol:HDL-cholesterol ratios, in participants with a normal BMI.

In our study, the negative association between the LDL-cholesterol:HDL-cholesterol ratio and the number of EO aligns with findings by Tapolska *et al.*, who reported that participants consuming four or more meals daily had lower TAG levels and

higher HDL-cholesterol levels compared with those who consumed three or fewer meals<sup>(50)</sup>. Consistent with our findings, other studies also demonstrated that a greater number of EO was associated with lower cholesterol concentrations<sup>(51,52)</sup>. Increased meal frequency (nibbling) might also decrease the insulin concentration<sup>(53,54)</sup>. However, Arciero *et al.* did not observe a significant association between the frequency of eating and cholesterol concentration<sup>(55)</sup>. Additionally, similar to our non-significant associations, in previous research, the number of EO was not significantly associated with TAG<sup>(52)</sup> or blood pressure<sup>(56)</sup>.

We did not find any associations between meal timing and cardiometabolic health in contrast to Garaulet *et al.* who reported that early lunch eaters (before 15.00) experienced more weight loss and lower insulin resistance during weight loss treatment than late lunch eaters (after 15.00) among 420 obese Spanish adults despite the similarities in appetite hormones, energy expenditure and intake of macronutrients. Late eating patterns also decrease insulin sensitivity<sup>(57)</sup>, change metabolism<sup>(58)</sup> and result in weight gain and

**Table 3.** The difference between general characteristics and dietary habits according to main meal timing in Iranian adults (*n* 825) (Mean values and standard deviations; numbers and percentages)

Variables	Breakfast time (h.m)					Lunchtime (h.m)					Dinner time (h.m)				
	Earlier-B (Before 08.00)		Later-B (After 08.00)		<i>P</i>	Earlier-L (Before 13.30)		Later-L (After 13.30)		<i>P</i>	Earlier-D (Before 20.45)		Later-D (After 20.45)		<i>P</i>
	<i>(n</i> 422)		<i>(n</i> 402)			<i>(n</i> 414)		<i>(n</i> 411)			<i>(n</i> 411)		<i>(n</i> 414)		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Sex, women															
<i>n</i>	359		344		0.14	351		352		0.11	364		339		0.17
%	85.07		85.57			84.78		85.46			88.56		81.88		
Age (years)	42.33	10.61	41.99	10.46	0.46	42.29	10.56	42.04	10.56	0.72	42.45	10.58	41.87	10.50	0.42
Morning-evening questionnaire score (MEQ)*	59.05	6.38	57.38	7.05	<b>&lt; 0.001</b>	58.48	6.78	58.03	6.65	0.32	58.63	6.55	57.01	6.95	0.09
BMI*	26.68	4.50	27.26	4.02	0.09	26.81	4.44	27.42	4.19	<b>0.03</b>	26.92	4.16	27.32	4.49	0.17
Total daily energy intake (kcal/d)*	1643.08	305.96	1709.24	430.89	0.82	1655.58	356.37	1695.71	398.47	0.12	1690.59	361.00	1661.1	397.52	0.26
Breakfast energy intake (kcal/d)*	423.28	146.98	412.85	163.33	0.35	413.19	150.36	422.52	159.30	0.38	424.92	142.54	410.83	166.70	0.18
Lunch energy intake (kcal/d)*	532.27	175.54	540.51	180.02	0.49	527.36	176.88	544.63	178.15	0.15	540.13	168.18	532.21	186.99	0.51
Dinner energy intake (kcal/d)*	507.43	194.10	508.27	196.88	0.95	509.27	191.31	504.27	196.98	0.66	509.20	200.31	506.27	190.59	0.83
	<i>n</i>	%	<i>n</i>	%		<i>n</i>	%	<i>n</i>	%		<i>n</i>	%	<i>n</i>	%	
Supplement intake (yes/no)											94	22.87	107	25.87	0.21
Yes	101	23.93	100	24.87	0.51	99	23.91	102	24.81	0.85					
	Mean	SD	Mean	SD		Mean	SD	Mean	SD		Mean	SD	Mean	SD	
Number EO ( <i>n</i> /d)	6.48	0.84	6.16	0.88	<b>&lt; 0.001</b>	6.32	0.90	6.33	0.87	0.86	6.42	0.89	6.25	0.87	<b>0.01</b>
Breakfast time (h.m, am)*	–		–		–	7.56	0.42	8.09	0.47	<b>&lt; 0.001</b>	7.58	0.47	8.07	0.45	<b>0.007</b>
Lunchtime (h.m, pm)*	1.50	0.33	1.56	0.34	<b>0.009</b>	–		–		–	1.46	0.32	1.57	0.34	<b>&lt; 0.001</b>
Dinner time (h.m, pm)*	8.42	0.32	8.48	0.37	<b>0.01</b>	8.41	0.35	8.49	0.34	<b>0.002</b>	–		–		–
Fasting window (h.m)*	9.06	1.13	10.01	1.14	<b>&lt; 0.001</b>	9.27	1.17	9.37	1.18	0.07	9.38	1.16	9.26	1.17	<b>0.03</b>
Sleep duration (h.m)*	8.12	1.24	9.03	1.39	<b>&lt; 0.001</b>	8.30	1.26	8.42	1.41	0.05	8.41	1.26	8.31	1.14	0.12
Breakfast irregularity score*	33.49	19.15	41.85	13.51	0.32	33.43	19.26	34.71	20.26	0.74	32.47	19.52	35.85	20.14	<b>0.01</b>
Lunch irregularity score*	37.13	13.51	37.87	13.92	0.46	37.91	13.51	37.71	13.69	0.06	36.61	13.96	37.37	13.72	<b>0.04</b>
Dinner irregularity score*	34.45	22.59	36.00	23.96	0.35	34.47	23.11	35.47	23.14	0.37	34.47	22.96	35.87	23.14	0.42

B, breakfast; L, lunch; D, dinner; h.m, hour:minute; MEQ, morning-evening questionnaire; EO, eating occasions.

Values are mean (sd); otherwise, it is indicated.

Calculated by  $\chi^2$  and one-way ANOVA for qualitative and quantitative variables, respectively.

Significant *P* value (*P* < 0.05) is presented in bold.

\*Adjusted for sex and age.

**Table 4.** The difference between general characteristics and dietary habits according to main meal irregularity energy intake score in Iranian adults (*n* 825) (Mean values and standard deviations; numbers and percentages)

Variables	Breakfast irregularity score (range: 0-6-133.4, median: 31.77)					Lunch irregularity score (range: 1-5-102.4, median: 30.19)					Dinner irregularity score (range: 1-4-133.5, median: 34.02)				
	Less irregular- B ≤ 31.77		More irregular- B > 31.77			Less irregular- L ≤ 30.19		More irregular- L > 30.19			Less irregular- D ≤ 34.02		More irregular- D > 34.02		
	<i>(n</i> 412)		<i>(n</i> 413)			<i>(n</i> 410)		<i>(n</i> 415)			<i>(n</i> 411)		<i>(n</i> 414)		
	Mean	SD	Mean	SD	<i>P</i>	Mean	SD	Mean	SD	<i>P</i>	Mean	SD	Mean	SD	<i>P</i>
Sex, women															
<i>n</i>	356		347		0.71	341		362		0.06	346		357		0.31
%	86.40		90.55			83.17		87.22			84.18		86.23		
Age (years)	41.31	10.43	42.01	10.69	0.92	42.46	10.58	41.86	10.49	0.41	41.77	10.48	42.56	10.56	0.27
Morning-evening questionnaire score (MEQ)*	57.44	7.30	59.27	5.75	0.09	58.50	6.91	58.00	6.60	0.27	58.51	6.64	58.01	6.87	0.29
BMI*	26.92	4.25	27.31	4.39	0.30	26.79	4.50	27.43	4.02	0.10	26.92	4.37	27.02	4.29	0.51
Total daily energy intake (kcal/d)*	1691.07	318.10	1639.16	421.00	0.18	1643.08	438.89	1709.35	305.26	<b>0.02</b>	1623.08	406.70	1729.35	342.43	<b>&lt; 0.001</b>
Breakfast energy intake (kcal/d)*	437.73	125.88	393.23	177.40	<b>0.009</b>	420.28	128.22	415.16	177.89	0.59	434.09	150.76	402.88	159.66	<b>0.002</b>
Lunch energy intake (kcal/d)*	526.96	164.12	546.71	181.13	0.37	488.99	179.74	581.51	162.49	<b>&lt; 0.001</b>	514.15	181.99	558.63	178.15	<b>&lt; 0.001</b>
Dinner energy intake (kcal/d)*	505.92	204.16	510.01	186.13	0.78	484.70	171.62	530.96	124.16	<b>&lt; 0.001</b>	508.19	154.63	507.83	229.12	0.92
Supplement intake															
Yes															
<i>n</i>	100		101		0.91	93		108		0.51	97		104		0.57
%	24.27		24.45			22.68		26.02			23.60		25.12		
Number of EO ( <i>n</i> /d)	6.36	0.86	6.28	0.92	0.18	6.37	0.83	6.28	0.94	0.14	6.39	0.84	6.26	0.91	0.03
Breakfast time (h.m, am)*	8.09	0.47	7.54	0.41	0.91	8.01	0.44	8.04	0.45	0.28	8.03	0.45	8.03	0.45	0.96
Lunchtime (h.m, pm)*	1.54	0.35	1.52	0.31	0.51	1.52	0.31	1.53	0.36	0.62	1.52	0.33	1.53	0.34	0.70
Dinner time (h.m, pm)*	8.43	0.30	8.48	0.38	0.06	8.44	0.33	8.46	0.36	0.41	8.45	0.37	8.46	0.35	0.67
Fasting window (h.m)*	9.30	1.23	9.35	1.16	0.22	9.29	1.15	9.35	1.21	0.31	9.26	1.12	9.38	1.24	<b>0.02</b>
Sleep duration (h.m)*	8.41	1.30	8.31	1.38	0.32	8.42	1.34	8.33	1.35	0.09	8.46	1.38	8.26	1.29	<b>0.003</b>
Breakfast irregularity score*	-		-		-	28.23	17.95	40.06	20.01	<b>&lt; 0.001</b>	29.84	18.57	38.44	20.25	<b>&lt; 0.001</b>
Lunch irregularity score*	32.26	7.01	34.27	16.56	<b>&lt; 0.001</b>	-		-		-	32.26	8.53	42.71	15.76	<b>&lt; 0.001</b>
Dinner irregularity score*	29.96	20.68	40.20	24.32	<b>&lt; 0.001</b>	26.68	20.01	43.70	22.91	<b>0.01</b>	-		-		-

B, breakfast; L, lunch; D, dinner; h.m, hour.minute; MEQ, morning-evening questionnaire; EO, eating occasions.

Values are mean (sd); otherwise, it is indicated.

Calculated by  $\chi^2$  and one-way ANOVA or qualitative and quantitative variables, respectively.

Significant *P* value (*P* < 0.05) is presented in bold.

\*Adjusted for sex and age.



**Table 5.** Associations between the number of eating occasions (EO) and cardiometabolic risk factors stratified by BMI\*\*, BMI < 25 v. BMI ≥ 25, in 825 Iranian adults (Beta and 95% confidence interval)

Outcomes	BMI category	Number of eating occasions (EO) (n/d)				P <sub>FDR</sub> *
		(Range, 1–11; Median, 6–33)				
		Less EO ≤ 6–33 (n 465)		More EO > 6–33 (n 360)		
Beta	95% CI	Beta	95% CI			
SBP	BMI < 25 (n 328)	-3.21	-7.12, 0.39	References	0.11	
	BMI ≥ 25 (n 497)	0.88	-1.73, 3.41	References	0.55	
DBP	BMI < 25 (n 328)	-6.96	-12.98, 0.65	References	0.23	
	BMI ≥ 25 (n 497)	1.43	-0.31, 3.21	References	0.15	
LAP index	BMI < 25 (n 328)	-13.01	-27.32, 0.28	References	0.12	
	BMI ≥ 25 (n 497)	-1.71	-3.29, 0.23	References	0.15	
$\frac{TC}{HDL-C}$	BMI < 25 (n 328)	0.08	-0.45, 0.32	References	0.54	
	BMI ≥ 25 (n 497)	0.26	0.06, 0.48	References	<b>0.04</b>	
$\frac{LDL-C}{HDL-C}$	BMI < 25 (n 328)	0.23	0.005, 0.45	References	0.13	
	BMI ≥ 25 (n 497)	0.18	0.04, 0.37	References	0.09	
Uric acid	BMI < 25 (n 328)	-0.03	-0.64, 0.03	References	0.16	
	BMI ≥ 25 (n 497)	-0.02	-0.25, 0.21	References	0.91	
HOMA-IR	BMI < 25 (n 328)	-0.83	-1.61, 0.08	References	0.16	
	BMI ≥ 25 (n 497)	-0.16	-0.73, 0.41	References	0.73	
HOMA-IS	BMI < 25 (n 328)	0.44	-0.19, 0.86	References	0.87	
	BMI ≥ 25 (n 497)	0.003	-0.43, 0.44	References	0.90	
CRP (µg/dl)	BMI < 25 (n 328)	0.04	-0.03, 0.09	References	0.16	
	BMI ≥ 25 (n 497)	0.03	-0.06, 0.01	References	0.27	
TyG index	BMI < 25 (n 328)	-0.23	-0.54, 0.01	References	0.12	
	BMI ≥ 25 (n 497)	-0.03	-0.05, -0.08	References	0.09	

B, breakfast; L, lunch; D, dinner; SBP, systolic blood pressure; DBP, diastolic blood pressure; LAP, lipid accumulation product;  $\frac{TC}{HDL-C}$ ,  $\frac{\text{total cholesterol}}{\text{HDL-cholesterol}}$ ;  $\frac{LDL-C}{HDL-C}$ ,  $\frac{\text{LDL-cholesterol}}{\text{HDL-cholesterol}}$ ; HOMA-IR, homeostatic model assessment for insulin resistance; HOMA-IS, homeostatic model assessment for insulin sensitivity; CRP, C-reactive protein; TyG index, TAG-glucose index.

General linear regression was used, and the model was adjusted for age, sex, education, energy intake, physical activity, sleep duration, supplement intake, menopausal status, smoking, fasting window and MEQ; values are Beta (95% confidence interval) of outcomes.

\*P(FDR) refers to P values obtained in linear regression models. Multiple testing adjustments were performed using the false discovery rate of 5%.

\*\*The cut-off of 25 was used to categorise BMI into two main groups: BMI < 25 as normal weight and BMI ≥ 25 as overweight/obese.

Significant P value (P < 0.05) is presented in bold.

obesity. Moreover, compared with a delayed eating schedule from 12.00 to 23.00, a daytime eating schedule from 8.00 to 19.00 for 8 weeks (the intake of three main meals and two snacks by similar macronutrient contributions) promoted weight loss and improvements in energy metabolism and insulin<sup>(59)</sup>.

Another finding of this study was that greater irregularity in energy intake at breakfast was associated with elevated TC/HDL-cholesterol and LDL-cholesterol:HDL-cholesterol ratio, suggesting a potential increase in cardiometabolic risk. Plot *et al.* reported that higher irregular energy intake at breakfast and lunch led to a greater risk of metabolic syndrome and a greater BMI<sup>(30)</sup>. Moreover, eating meals regularly was inversely associated with metabolic syndrome, insulin resistance<sup>(13)</sup> and lipid profiles<sup>(60)</sup>, which was similar to our findings. However, irregularity in energy intake at breakfast and between meals was related to increased metabolic syndrome risk factors among British adults<sup>(30)</sup>.

Several mechanisms linking the frequency of meals, meal timing, regularity and health status were known. A previous study showed that a greater number of EO decreased cholesterol due to

decreased insulin secretion and promoted appetite control<sup>(61)</sup>. This reduction was associated with cholesterol synthesis, as insulin activated the key enzyme in biosynthesis, hydroxy methyl glutaryl-CoA reductase<sup>(51)</sup>. An increase in blood glucose and consequent insulin resulted in increased endogenous cholesterol synthesis<sup>(52)</sup>. Regular intake can result in more stable plasma levels of intestinal satiety hormones, such as glucagon-like peptide-1, cholecystokinin and peptide YY<sup>(57)</sup>. Additionally, delayed meal timing may result in decreased melatonin and cortisol concentrations, which play key roles in energy homeostasis by affecting the peripheral circadian rhythm in humans<sup>(62)</sup>. In addition, several factors, such as age and sex, are known to be linked to skipping meals or irregularity in meals<sup>(63,64)</sup>. Young adults skipped their meals more often, men were more likely to skip their breakfast and women were more likely to skip their lunch and dinner. Additionally, behavioural factors such as smoking status, alcoholic drinks and physiological and biomedical factors are related to irregular meal intake<sup>(63)</sup>. However, we did not observe any age-related interactions in our associations.

**Table 6.** Associations between meal timing and cardiometabolic risk factors stratified by BMI\*\*, BMI < 25 v. BMI ≥ 25, in 825 Iranian adults (Beta and 95 % confidence interval)

Outcomes	BMI category	Breakfast time (median = 08.00 (h.m))				Lunchtime (median = 13.30)				Dinner time (median = 20.45)			
		Earlier-B		Later-B (After 08.00) (n 402)	P <sub>FDR</sub> *	Earlier-L		Later-L (After 13.30) (n 411)	P <sub>FDR</sub> *	Earlier-D		Later-D (After 20.45) (n 414)	P <sub>FDR</sub> *
		(Before 08.00) (n 422)				(Before 13.30) (n 414)				(Before 20.45) (n 411)			
		Beta	95 % CI	Beta	95 % CI	Beta	95 % CI	Beta	95 % CI				
SBP	BMI < 25 (n 328)	-0.30	-3.57, 3.08	References	0.85	-1.23	-4.47, 1.99	References	0.67	-0.03	-2.31, 2.23	References	0.86
	BMI ≥ 25 (n 497)	-1.03	-3.59, 1.57	References	0.66	-1.42	-4.51, 1.12	References	0.68	-0.81	-2.44, -1.31	References	0.90
DBP	BMI < 25 (n 328)	1.70	-0.46, 3.71	References	0.80	-1.53	-3.63, 0.55	References	0.75	1.21	-0.51, 3.34	References	0.90
	BMI ≥ 25 (n 497)	-0.94	-2.19, 0.17	References	0.73	-1.04	-2.07, 0.87	References	0.66	-0.76	-2.91, 1.01	References	0.82
LAP index	BMI < 25 (n 328)	-0.21	-2.43, 2.13	References	0.92	0.01	-2.19, 2.123	References	0.87	-0.48	-2.85, 1.88	References	0.84
	BMI ≥ 25 (n 497)	0.04	-5.32, 4.82	References	0.89	-0.79	-7.13, 5.01	References	0.79	-1.63	-5.34, 0.89	References	0.98
$\frac{TC}{HDL-C}$	BMI < 25 (n 328)	0.03	-0.19, 0.26	References	0.93	-0.09	-0.31, 0.13	References	0.70	-0.11	-0.33, 0.11	References	0.83
	BMI ≥ 25 (n 497)	0.03	-0.16, 0.22	References	0.89	0.14	-0.05, 0.33	References	0.93	0.09	-0.09, 0.19	References	0.91
$\frac{LDL-C}{HDL-C}$	BMI < 25 (n 328)	-0.04	-0.23, 0.14	References	0.91	-0.04	-0.22, 0.15	References	0.78	-0.10	-0.23, 0.08	References	0.98
	BMI ≥ 25 (n 497)	0.05	-0.09, 0.15	References	0.73	0.16	0.01, 0.33	References	0.40	0.06	-0.08, 0.21	References	0.91
Uric acid	BMI < 25 (n 328)	-0.006	-0.32, 0.31	References	0.91	-0.13	-0.43, 0.17	References	0.75	-0.33	-0.64, 0.02	References	0.40
	BMI ≥ 25 (n 497)	-0.15	-0.38, 0.02	References	0.63	-0.18	-0.48, 0.02	References	0.93	0.04	-0.21, 0.22	References	0.86
HOMA-IR	BMI < 25 (n 328)	0.52	-0.05, 1.14	References	0.59	-0.29	-1.38, 0.83	References	0.40	-0.15	-0.98, 69	References	0.80
	BMI ≥ 25 (n 497)	-0.69	-1.28, -0.11	References	0.18	-0.24	-3.02, -2.25	References	0.31	-0.14	-0.76, 0.12	References	0.82
HOMA-IS	BMI < 25 (n 328)	0.31	-0.20	References	0.66	0.09	-0.22, 0.40	References	0.75	0.11	-0.31, 0.54	References	0.84
	BMI ≥ 25 (n 497)	0.45	0.04, 0.98	References	0.23	0.18	-0.07, 0.45	References	0.64	-0.007	-0.04, 0.02	References	0.81
CRP (µg.dl)	BMI < 25 (n 328)	-0.02	-0.06, 0.02	References	0.66	-0.02	-0.06, 0.02	References	0.78	-0.11	-0.05, 0.03	References	0.98
	BMI ≥ 25 (n 497)	0.1	-0.2, -0.05	References	0.66	0.01	-0.02, 0.04	References	0.74	-0.02	-0.04, 0.02	References	0.82
TyG index	BMI < 25 (n 328)	-0.03	-0.01, 0.05	References	0.69	0.04	-0.02, 0.03	References	0.83	0.006	-0.03, 0.03	References	0.81
	BMI ≥ 25 (n 497)	-0.01	-0.03, 0.01	References	0.71	-0.009	-0.01, 0.62	References	0.67	-0.01	-0.03, 0.009	References	0.99

B, breakfast; L, lunch; D, dinner; SBP, systolic blood pressure; DBP, diastolic blood pressure; LAP, lipid accumulation product;  $\frac{TC}{HDL-C}$ ,  $\frac{\text{total cholesterol}}{\text{HDL-cholesterol}}$ ;  $\frac{LDL-C}{HDL-C}$ ,  $\frac{\text{LDL-cholesterol}}{\text{HDL-cholesterol}}$ ; HOMA-IR, homeostatic model assessment for insulin resistance; HOMA-IS, homeostatic model assessment for insulin sensitivity; CRP, C-reactive protein; TyG index, TAG-glucose index. General linear regression was used, and the model was adjusted for age, sex, education, energy intake, physical activity, sleep duration, supplement intake, menopausal status, smoking, fasting window and MEQ; values are Beta (95 % confidence interval) of outcomes.

\*P(FDR) refers to P values obtained in linear regression models. Multiple testing adjustments were performed using the false discovery rate of 5 %.

\*\*The cut-off of 25 was used to categorise BMI into two main groups: BMI < 25 as normal weight and BMI ≥ 25 as overweight/obese.

Significant P value (P < 0.05) is presented in bold.

**Table 7.** Associations between meal irregularity energy intake and cardiometabolic risk factors stratified by BMI\*\*, BMI < 25 v. BMI ≥ 25, in 825 Iranian adults (Beta and 95 % confidence interval)

Outcomes		Breakfast irregularity score (range, 0-6-133-4, median, 31-77)				Lunch irregularity score (range, 1-5-102-4, median, 30-19)				Dinner irregularity score (range, 1-4-133-5, median 34-02)			
		Less irregular-B		More irregular-B	P <sub>FDR</sub> *	Less irregular-L		More irregular-L	P <sub>FDR</sub> *	Less irregular-D		More irregular-D	P <sub>FDR</sub> *
		≤31-77	(n 412)			≤30-19	(n 410)			≤34-02	(n 411)		
		Beta	95 % CI	(n 413)	Beta	95 % CI	(n 415)	Beta	95 % CI	(n 414)			
SBP	BMI < 25 (n 328)	-0.92	-4.53, 2.15	References	0.78	1.29	-2.26, 4.39	References	0.88	-1.20	-4.5, 2.16	References	0.86
	BMI ≥ 25 (n 497)	0.76	-1.79, 3.32	References	0.71	0.075	-1.91, 3.21	References	0.88	0.75	-1.87, 1.90	References	0.79
DBP	BMI < 25 (n 328)	0.54	1.62, 2.66	References	0.66	0.32	-1.87, 2.51	References	0.87	0.46	-1.65, 2.51	References	0.78
	BMI ≥ 25 (n 497)	-0.82	-1.76, 1.21	References	0.64	-0.25	-2.34, 1.51	References	0.93	-0.67	-2.76, 1.05	References	0.98
LAP index	BMI < 25 (n 328)	-0.56	-2.93, 1.76	References	0.53	-12.87	-28.34, 1.89	References	0.61	-0.72	-1.59, 0.98	References	0.79
	BMI ≥ 25 (n 497)	-0.68	-2.59, 2.56	References	0.67	-14.30	-29.61, 2.96	References	0.40	-2.18	-8.17, 4.11	References	0.99
$\frac{TC}{HDL-C}$	BMI < 25 (n 328)	-0.37	-0.95, -0.18	References	<b>0.01</b>	0.13	-0.08, 35	References	0.88	-0.17	-0.39, 0.04	References	0.98
	BMI ≥ 25 (n 497)	0.03	-0.16, 0.22	References	0.67	0.05	-0.19, 0.21	References	0.93	-0.003	-0.20, 0.19	References	0.81
LDL - CHDL - C	BMI < 25 (n 328)	-0.32	-0.79, -0.13	References	<b>0.01</b>	0.11	-0.06, 0.65	References	0.96	-0.13	-0.31, 0.04	References	0.97
	BMI ≥ 25 (n 497)	0.01	-0.13, 0.15	References	0.43	-0.13	-0.22, 0.18	References	0.82	0.05	-0.09, 0.19	References	0.72
Uric acid	BMI < 25 (n 328)	0.12	-0.18, 0.44	References	0.82	0.02	-0.28, 0.34	References	0.83	-0.09	-0.40, 0.21	References	0.79
	BMI ≥ 25 (n 497)	-0.06	-0.28, 0.11	References	0.63	-0.06	-0.26, 0.15	References	0.85	-0.05	-0.27, 0.65	References	0.79
HOMA-IR	BMI < 25 (n 328)	0.41	-0.41, 1.23	References	0.83	-0.29	-0.68, 0.05	References	0.88	-0.05	-0.87, 0.77	References	0.76
	BMI ≥ 25 (n 497)	0.12	-0.42, 0.68	References	0.65	-0.35	-0.89, 0.62	References	0.99	-0.09	-0.65, 0.63	References	0.94
HOMA-IS	BMI < 25 (n 328)	0.39	-0.08, 0.88	References	0.47	0.04	-0.47, 0.49	References	0.87	-0.26	-0.76, 0.22	References	0.97
	BMI ≥ 25 (n 497)	0.22	-0.17, 0.63	References	0.87	0.10	-0.06, 0.21	References	0.85	0.27	-0.12, 0.68	References	0.90
CRP (µg/dl)	BMI < 25 (n 328)	0.16	-0.28, 0.61	References	0.77	-0.01	-0.04, 0.04	References	0.96	-0.01	-0.05, 0.03	References	0.89
	BMI ≥ 25 (n 497)	-0.002	-0.004, -0.03	References	0.75	-0.02	-0.06, 0.01	References	0.98	-0.03	-0.08, 0.02	References	0.99
TyG index	BMI < 25 (n 328)	-0.005	-0.03, 0.02	References	0.66	-0.009	-0.04, -0.02	References	0.95	-0.37	-0.95, 0.21	References	0.84
	BMI ≥ 25 (n 497)	-0.03	-0.16, 0.15	References	0.78	-0.39	-1.21, -0.34	References	0.48	-0.15	-0.96, 0.38	References	0.89

B, breakfast; L, lunch; D, dinner; SBP, systolic blood pressure; DBP, diastolic blood pressure; LAP, lipid accumulation product;  $\frac{TC}{HDL-C}$ ,  $\frac{\text{total cholesterol}}{\text{HDL-cholesterol}}$ ;  $\frac{LDL-C}{HDL-C}$ ,  $\frac{\text{LDL-cholesterol}}{\text{HDL-cholesterol}}$ ; HOMA-IR, homeostatic model assessment for insulin resistance; HOMA-IS, homeostatic model assessment for insulin sensitivity; CRP, C-reactive protein; TyG index, TAG-glucose index.

General linear regression was used, and the model was adjusted for age, sex, education, energy intake, physical activity, sleep duration, supplement intake, menopausal status, smoking, fasting window and MEQ; values are Beta (95 % confidence interval) of outcomes.

\*P(FDR) refers to P values obtained in linear regression models. Multiple testing adjustments were performed using the false discovery rate of 5 %.

\*\*The cut-off of 25 was used to categorise BMI into two main groups: BMI < 25 as normal weight and BMI ≥ 25 as overweight/obese.

Meal frequency, meal timing and meal skipping are interrelated factors that influence energy distribution throughout the day. Both the content and timing of meals may be crucial for health. These findings highlight the importance of chrono-nutrition in cardiometabolic health and provide valuable insights into the lifestyle and eating behaviour differences. Future research should aim to establish causal links, investigate long-term impacts and delve deeper into the mechanisms at play.

### Limitations

This was a cross-sectional study, and it was impossible to derive causal relationships from the data. Therefore, this study could only provide associations between chrono-nutritional components and cardiometabolic health<sup>(65)</sup>. Additionally, the study relied on self-reported data for the assessment of chrono-nutrition components, such as the frequency of meals and snacks, meal timing and regularity. This method might be subject to recall and social desirability biases, which could lead to inaccurate measurements and potentially weaken the observed associations<sup>(66)</sup>. Moreover, the three dietary reports included only one weekend and two weekdays, limiting the capture of differences between weekdays and weekends. No formal interaction with sex could be assessed, although some differences were observed between men and women. A limitation was the inability to assess sex-specific analysis.

To the best of our knowledge, this is the first study to explore the associations between all chrono-nutrition components and cardiometabolic health in Iranian adults. Furthermore, chronotype, which influences the timing of food intake and eating patterns, was assessed and controlled as a confounder in all associations.

### Conclusion

Our findings provided evidence that a lower number of EO and more irregular energy intake scores at breakfast might be associated with worse cardiometabolic health. More regular intake of more meals seems to improve cardiometabolic health, highlighting the importance of chrono-nutrition in managing cardiometabolic health. However, prospective studies must confirm these associations and clarify their long-term effects.

**Supplementary material.** For supplementary material/s referred to in this article, please visit <https://doi.org/10.1017/S0007114524002745>.

**Acknowledgement.** We thank all those who participated in this study.

The current manuscript was supported by a grant from the Tehran University of Medical Sciences (grant no. 45553).

A. L., Z. A. and S. S-B. contributed to the conception/design of the research; A. L. and S. S-B. contributed to the acquisition, analysis or interpretation of the data; A. L., S. Z. and M. M. drafted the manuscript; S. S-B. and K. Dj. critically revised the manuscript; and S. S-B. agreed to be fully accountable for ensuring the integrity and accuracy of the work. All the authors have read and approved the final manuscript.

The authors report no conflicts of interest.

The sample was collected by coordinating with the healthcare centres of Tehran. This study was conducted according to the guidelines of the Declaration of Helsinki, and all procedures were ethically approved by the Ethics Committee of Tehran University of Medical Sciences (ethics no. IR.TUMS.VCR.REC.1399.295). Participants were fully informed of the study's purpose, and all provided written informed consent before participation. The researcher and illiterate participants had a simple language conversation to give them information, and informed consent was then stamped or fingerprinted as a form of agreement.

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