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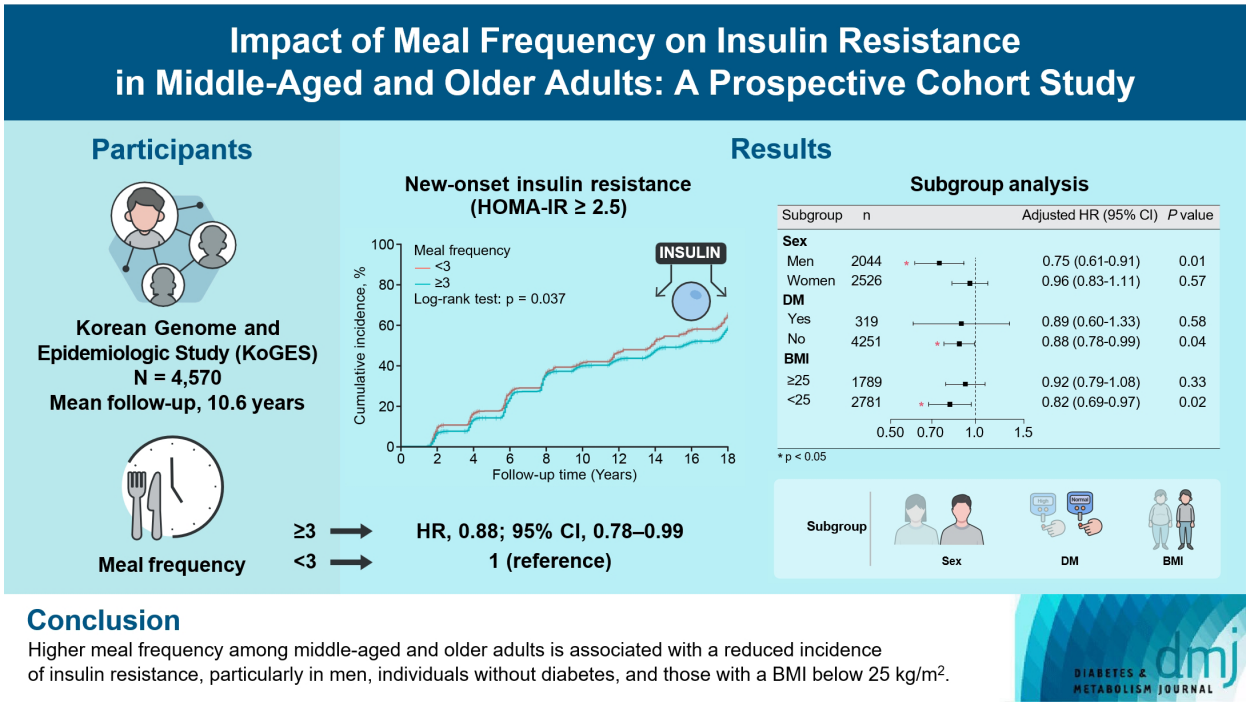
Diabetes Metab J 2025;49:311-320 | *https://doi.org/10.4093/dmj.2024.0407*



Highlights

- **This study explores the link between meal frequency and insulin resistance in adults.**
- **Eating ≥3 meals/day reduces the risk of insulin resistance compared to <3 meals/day.**
- **The effect is significant in men, people without diabetes, and those without obesity.**
- **These results highlight the role of meal frequency in managing insulin resistance.**

How to cite this article:
Ryu HE, Lee JH, Park B, Heo SJ, Kwon YJ. Impact of Meal Frequency on Insulin Resistance in Middle-Aged and Older Adults: A Prospective Cohort Study. Diabetes Metab J 2025;49:311-320. https://doi.org/10.4093/dmj.2024.0407

Original Article
Lifestyle and Behavioral Interventions

Diabetes Metab J 2025;49:311-320
https://doi.org/10.4093/dmj.2024.0407
pISSN 2233-6079 · eISSN 2233-6087

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Impact of Meal Frequency on Insulin Resistance in Middle-Aged and Older Adults: A Prospective Cohort Study

Ha-Eun Ryu[1,2], Jong Hee Lee[1,2], Byoungjin Park[1,2], Seok-Jae Heo[3], Yu-Jin Kwon[1,2]

[1]Department of Family Medicine, Yongin Severance Hospital, Yonsei University College of Medicine, Yongin,
[2]Department of Family Medicine, Yonsei University College of Medicine, Seoul,
[3]Biostatistics Collaboration Unit, Department of Biomedical Systems Informatics, Yonsei University College of Medicine, Seoul, Korea

Background: Insulin resistance (IR) is central to metabolic disorders and significantly influenced by diet. Studies on meal frequency (MF) and metabolic indicators have shown mixed results. This study explores the link between MF and IR in middle-aged and older adults.
Methods: This prospective cohort study included 4,570 adults aged 40 to 69 years from the Korean Genome and Epidemiologic Study. MF were divided into two groups based on whether they consumed three or more, or fewer than three, meals daily. IR was evaluated using the homeostasis model assessment of insulin resistance (HOMA-IR); participants were classified as IR if their HOMA-IR value was ≥2.5. Multiple Cox proportional hazard regression analyses were conducted to examine the association between MF and the incidence of IR.
Results: After adjusting for all variables, individuals in the MF ≥3 group showed a reduced incidence of IR compared to those in the MF <3 group (hazard ratio, 0.880; 95% confidence interval, 0.782 to 0.990). Additionally, subgroup analyses by sex, diabetes mellitus (DM), and body mass index (BMI) showed that this association persisted only in men, individuals without DM, and those with a BMI <25.
Conclusion: Our findings indicate that a higher MF among middle-aged and older adults is associated with a reduced incidence of IR. However, this association was maintained only in men, individuals without DM, and those without obesity.

Keywords: Feeding behavior; Insulin resistance; Metabolic diseases

INTRODUCTION

Insulin resistance (IR) is characterized by a state of reduced responsiveness of target tissues to insulin, which leads to inadequate regulation of postprandial blood glucose levels and results in hyperglycemia and hyperinsulinemia [1]. As a major pathophysiological feature of both type 2 diabetes mellitus (DM) and metabolic syndrome, it is intimately linked with the development of significant chronic conditions such as cardiovascular disease (CVD) [2,3]. IR arises from a complex interplay of genetic factors related to the insulin action cascade and environmental factors such as decreased physical activity and increased energy intake [4]. Given the current lifestyle trends contributing to the increasing prevalence of IR, it is important to identify modifiable factors to mitigate the risk thereof [5].

Meal frequency (MF) is a dietary factor that has evolved

Corresponding authors: Seok-Jae Heo https://orcid.org/0000-0002-8764-7995
Biostatistics Collaboration Unit, Department of Biomedical Systems Informatics, Yonsei University College of Medicine, 50 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea
E-mail: SJHEO@yuhs.ac

Yu-Jin Kwon https://orcid.org/0000-0002-9021-3856
Clinical Assistant Professor, Department of Family Medicine, Yongin Severance Hospital, Yonsei University College of Medicine, 363 Dongbaekjukjeon-daero, Giheung-gu, Yongin 16995, Korea
E-mail: digda3@yuhs.ac

Received: Jul. 22, 2024; Accepted: Sep. 7, 2024

from the traditional pattern of three meals per day to irregular eating habits characterized by skipped meals in contemporary lifestyles [6]. Previous observational studies have indicated that increased MF is associated with metabolic benefits. A study of Korean adults showed a significantly lower risk of metabolic syndrome among men consuming three meals a day compared to those consuming fewer meals [6]. Similarly, a cross-sectional study conducted among young Australian adults identified a link between higher eating frequency and decreased cardiometabolic risk factors among males [7]. Conversely, with the global increase in obesity, there has been a notable rise in interest regarding weight loss strategies, including intermittent fasting and time-restricted eating, which potentially entail a decrease in MF [8]. Many studies conducted on this topic have demonstrated various metabolic benefits [8-10]. However, it is important to note that these dietary regimens typically place an emphasis on calorie restriction.

While previous research has investigated the relationship between metabolic risk factors and MF, there is a significant lack of prospective cohort studies. Therefore, we aimed to investigate the influence of MF on IR, using the reliable IR marker, the homeostasis model assessment of insulin resistance (HOMA-IR) [11,12], in a large population-based cohort study with a long follow-up time.

METHODS

Data source and study population

Initiated in 2001 by the Korean Center for Disease Control and Prevention, the Korean Genome and Epidemiologic Study (KoGES) embarked on a long-term exploration focusing on two distinct South Korean communities: the rural Ansung cohort and the urban Ansan cohort. Biennially conducted from the baseline in 2001–2002 through the ninth follow-up in 2019–2020, KoGES targeted individuals aged 40 to 69 years. The details of KoGES and the methodology employed therein have been published previously [13]. The selection process of the study population is depicted in Fig. 1. Among the initial 10,030 participants, 4,570 were selected for inclusion after excluding individuals: (1) with a baseline HOMA-IR ≥2.5 (n=1,314); (2) with implausible total energy intake (<600 kcal/day or >5,000 kcal/day) (n=105); (3) with incomplete baseline data (n=4,181); and (4) those who did not follow-up after the baseline survey (n=869). The KoGES study protocol was reviewed and approved by the Institutional Review Board (IRB number: 9-2024-0115) of the Korea Centers for Disease Control and Prevention, with informed consent obtained from all participants. Additionally, this study received approval from the IRB of Yongin Severance Hospital.

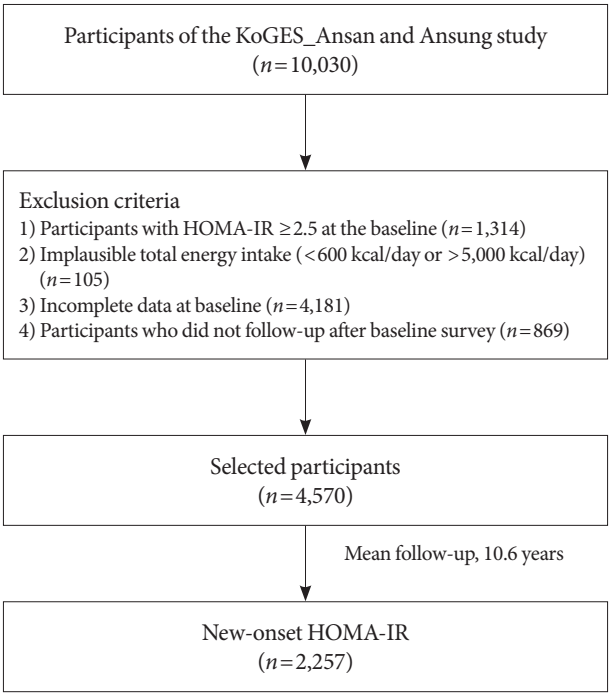


Fig. 1. Flow chart of the study population. KoGES, Korean Genome and Epidemiologic Study; HOMA-IR, homeostasis model assessment of insulin resistance.

Assessment of diet

A semi-quantitative 103-food item food frequency questionnaire (FFQ), which is a validated and commonly used nutritional assessment tool in several prospective cohort studies, was administered by trained dietitians [14]. The Korea National Health and Nutrition Examination Survey data, representing a cross-section of the Korean population, was utilized to determine serving sizes based on the median quantities of various food items [15]. A questionnaire assessed the amount of each food item consumed per serving, with serving sizes classified as small (1/2 serving), medium (1 serving), and large (2 or more servings). Visual aids were provided to enhance participants' understanding of serving sizes for different foods.

The food intake frequency, which assessed how often specific foods were consumed over the past year, was categorized into nine groups: never or less than once in a month, once a month, 2–3 times per month, once or twice a week, 3–4 times

a week, 5–6 times a week, once daily, twice daily, or 3 times daily. Frequency data obtained from the FFQ were converted into daily frequencies for the calculation of daily nutrient intake. Daily energy intake was determined by converting the reported weight based on the frequency of food consumption and portion sizes. MF was assessed through a dietary habits survey in which participants selected from the options of once, twice, three times, or four or more times per day. Participants were divided into two groups based on a previous study's cut-off of three daily meals for MF [6,16]. Additionally, a 24-hour recall method was employed to assess participants' food and nutrient intake over the past day. Participants were asked to recall all foods and beverages consumed during the previous 24 hours, with meal and snack distinctions applied based on participant responses. The total grams of carbohydrates, fat, protein were determined using data from the FFQ. The intake of carbohydrates, protein, and fat was subsequently converted into energy intake in calories (1 g of carbohydrates=4 kcal, 1 g of protein=4 kcal, and 1 g of fat=9 kcal). The proportion of carbohydrates, protein, and fat in the diet was calculated as follows: (calories from carbohydrates, protein, and fat/total calorie intake)×100.

Covariates

Trained medical personnel conducted all health examination procedures. Participants were instructed to wear lightweight clothing and remove their shoes prior to height, weight, and waist circumference (WC) measurements, which were recorded to the nearest 0.1 cm or 0.1 kg. Body mass index (BMI) was calculated by dividing weight in kilograms by height in meters squared. WC was measured three times at the narrowest point between the lowest rib and the uppermost border of the iliac crest, and the average was used. Blood pressure was measured using a Baumanometer mercury sphygmomanometer (W.A. Baum Co., Copiague, NY, USA) following standardized protocols, with participants resting for 5 minutes in a seated position before measurements. Blood pressure was defined as the average of the last two of three measurements. Blood tests were conducted after an 8-hour fast. Total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), C-reactive protein (CRP), fasting plasma glucose (FPG), and insulin levels were determined using a Chemistry Analyzer (Hitachi 7600, Hitachi, Tokyo, Japan until August 2002; and ADVIA 1650, Siemens, Tarrytown, NY, USA from September 2002). Low-density lipoprotein cholesterol (LDL-C) level was calculated using the Friedewald equation [17]. A 75-g oral glucose tolerance test (OGTT) was performed with fasting, and post-load glucose was measured at 1 and 2 hours. The 2-hour post-load glucose level was used to interpret OGTT results.

Smoking habits (every day, some days, former, and never smoker), alcohol intake, and physical activity were self-reported via questionnaire. Total alcohol intake in grams per day was calculated by summing the alcohol consumption of each type of drink. The metabolic equivalent of task (MET) per day was computed for each participant, accounting for the types and intensity of physical activity. DM was defined as FPG ≥126 mg/dL, a plasma glucose level of ≥200 mg/dL at 2 hours after a 75-g OGTT, glycosylated hemoglobin (HbA1c) ≥6.5%, diagnosis by a physician, or current use of oral anti-diabetic medication or insulin therapy. Hypertension was defined as systolic blood pressure (SBP) of ≥140 mm Hg, diastolic blood pressure (DBP) of ≥90 mm Hg, diagnosis by a physician, or use of antihypertensive medication. Dyslipidemia was defined as TC ≥240 mg/dL, TG ≥200 mg/dL, HDL-C <40 mg/dL, LDL-C ≥160 mg/dL, diagnosis by a physician, or use of dyslipidemia medication.

Definition of IR

For assessing IR, HOMA-IR was computed using the following equation: [fasting plasma insulin (μIU/mL)×FPG (mg/dL)/405] [11]. Participants were identified as IR if their HOMA-IR value was ≥2.5, as indicated by previous studies [11,12,18,19].

Statistical analysis

Continuous variables were presented as mean±standard deviation, while categorical variables were expressed as number (percentage). Differences in continuous variables between two for were assessed using independent *t*-tests or one-way analysis of variance (ANOVA). The chi-squared test was employed for categorical variables.

To compare the cumulative incidence rate of new-onset IR between the two groups, Kaplan-Meier curves and the log-rank test were utilized. Multiple Cox proportional hazard regression analyses were conducted to determine the hazard ratio (HR) and 95% confidence interval (CI) for IR incidence. Model 2 adjusted for age, sex, BMI, WC; Model 3 additionally adjusted for physical activity, smoking, and alcohol consumption; Model 4 further adjusted for hypertension, DM, dyslipidemia, and total energy intake. Finally, subgroup analyses based on sex, DM, and BMI were conducted. We used a linear mixed

model was used to identify MF group difference of changes in clinical variables. The Satterthwaite's method was used to calculated *P* values for time, MF group, and interaction effect.

All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and R software version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria). A significance level of $P<0.05$ was set to determine statistically significant associations or differences.

Availability of data and materials

The dataset used in this study was obtained after the review and evaluation of the research plan by the Korea Centers for Disease Control and Prevention (https://www.kdca.go.kr/contents.es?mid=a40504020100).

RESULTS

Baseline characteristics of the study population

Baseline characteristics of the study population are shown in Table 1. Participants within the MF ≥3 group exhibited significantly higher mean values in age, WC, SBP, DBP, serum TG levels, physical activity (METs), and total energy intake. Additionally, they had a higher proportion of men, daily and former smokers, hypertension, and dyslipidemia were present in the MF ≥3 group than in the MF <3 group. Conversely, individuals with MF <3 demonstrated significantly higher mean values in BMI, serum TC, HDL-C, LDL-C levels, and a higher proportion of women, never and someday smokers. There were no significant between-group differences in the mean values of CRP, FPG level, insulin, OGTT 2-hour, HbA1c, HOMA-IR, alcohol consumption, and snack frequency, or in the proportion of individuals with DM. Regarding meal composition, the MF ≥3 group had a significantly higher proportion of carbohydrate intake and significantly lower proportions of fat and protein intake compared to the MF <3 group (Supplementary Table 1).

Longitudinal association between MF and HOMA-IR

In total, 2,257 of 4,570 individuals, with a median follow-up period of 9.75 years, developed IR during the observation period. Table 2 illustrates the incidence of IR over the follow-up period, with 2,257 new cases arising over 48,442.0 person-years, a biennial incidence rate ranging from 3.2 to 14.8.

Fig. 2 depicts Kaplan-Meier curves alongside the log-rank test, illustrating the cumulative incidence rate of IR based on MF. The cumulative incidence rate of IR was significantly higher in individuals with MF <3 compared to those with MF ≥3 during the follow-up (log-rank test, $P=0.037$).

Table 3 presents the results of the Cox proportional regression analysis for incident IR relative to MF groups. The HRs and 95% CIs for IR incidence in the MF ≥3 group were 0.868 (95% CI, 0.775 to 0.972) compared to those in the MF <3 group. After adjusting for confounding variables, including age, sex, BMI, WC, smoking and drinking status, physical activity, hypertension, DM, dyslipidemia, and total energy intake, the adjusted HRs for IR incidence in the MF ≥3 group were 0.880 (95% CI, 0.782 to 0.990) compared to those in the MF <3 group.

We conducted a linear mixed model analysis to assess changes over time BMI, WC, SBP, DBP, glucose, insulin, TG, and HDL-C—components of metabolic syndrome—based on MF (Supplementary Fig. 1). Significant group*time interactions were observed for BMI ($P=0.007$), WC ($P<0.001$), DBP ($P<0.001$), glucose ($P=0.015$), and TG ($P=0.003$). Both BMI and glucose levels consistently remained lower in the MF ≥3 group compared to the MF <3 group. Additionally, increases in BMI, WC, and glucose were smaller over time, while reductions in DBP and TG were more pronounced in the MF ≥3 group compared to the MF <3 group. These findings suggest that individuals in the MF ≥3 group tend to experience more favorable metabolic outcomes compared to those in the MF <3 group.

Subgroup analysis

Fig. 3 shows the results of the subgroup analyses by sex, DM, and BMI, adjusting for the same confounding variables as in model 4 of Table 3. The adjusted HRs and 95% CIs for the incidence of IR in the MF ≥3 group versus the MF <3 group were 0.747 (95% CI, 0.611 to 0.914) in the male subgroup, 0.879 (95% CI, 0.777 to 0.995) in the subgroup without DM, and 0.815 (95% CI, 0.686 to 0.969) in the BMI <25 subgroup. No significant associations were observed between MF and HOMA-IR in the women, those with DM, and those with a BMI ≥25.

DISCUSSION

The results of our study show a significant association between the consumption of fewer than three meals per day and an increased incidence of IR, defined as HOMA-IR ≥2.5. This observation suggests that a lower MF may contribute to the de-

Table 1. Baseline characteristics of the study population based on the meal frequency

Variable	Total	Meal frequency ≥3	Meal frequency <3	*P* value
Number	4,570	3,896	674	
Age, yr	50.73±8.48	51.14±8.58	48.39±7.48	<0.001
Gender				<0.001
Men	2,044 (44.7)	1,852 (47.5)	192 (28.5)	
Women	2,526 (55.3)	2,044 (52.5)	482 (71.5)	
Body mass index, kg/m^2	24.34±2.93	24.27±2.88	24.72±3.18	<0.001
Waist circumference, cm	80.91±8.43	81.17±8.37	79.40±8.63	<0.001
SBP, mm Hg	118.37±17.60	118.89±17.53	115.33±17.73	<0.001
DBP, mm Hg	78.66±11.30	78.93±11.24	77.04±11.51	<0.001
Total cholesterol, mg/dL	190.59±34.19	189.93±34.12	194.40±34.35	0.002
Triglyceride, mg/dL	151.27±95.39	152.66±95.46	143.26±94.60	0.018
HDL-C, mg/dL	45.13±10.16	44.94±10.16	46.19±10.08	0.003
LDL-C, mg/dL	115.21±32.27	114.46±32.30	119.56±31.74	<0.001
CRP, mg/L	0.21±0.42	0.21±0.44	0.20±0.32	0.322
FPG, mg/dL	83.41±11.89	83.29±11.08	84.10±15.75	0.199
Insulin, μIU/mL	6.58±2.66	6.59±2.65	6.53±2.71	0.638
OGTT 2hr, mg/dL	120.17±40.84	119.98±40.20	121.27±44.38	0.480
HbA1c, %	5.59±0.51	5.60±0.50	5.56±0.57	0.155
HOMA-IR	1.35±0.55	1.35±0.55	1.34±0.57	0.800
Smoking status				<0.001
Never smoker	2,873 (62.9)	2,402 (61.7)	471 (69.9)	
Former smoker	686 (15.0)	621 (15.9)	65 (9.6)	
Someday smoker	114 (2.5)	94 (2.4)	20 (3.0)	
Everyday smoker	897 (19.6)	779 (20.0)	118 (17.5)	
Alcohol drinking, g/day	8.61±20.35	8.76±20.42	7.70±19.93	0.206
METs, hr/day	22.14±13.78	22.76±14.11	18.61±11.05	<0.001
DM	319 (7.0)	273 (7.0)	46 (6.8)	0.929
Hypertension	1,196 (26.2)	1,048 (26.9)	148 (22.0)	0.008
Dyslipidemia	2,078 (45.5)	1,812 (46.5)	266 (39.5)	<0.001
Snack frequency	1.20±0.95	1.20±0.95	1.20±0.96	0.862
Energy, kcal	1,967.36±597.04	2,005.64±592.36	1,746.11±575.98	<0.001
Carbohydrate, g	342.88±100.72	351.32±99.12	294.14±96.04	<0.001
Carbohydrate, %	70.25±6.55	70.66±6.37	67.85±7.03	<0.001
Fat, g	34.09±18.27	34.08±18.33	34.20±17.90	0.869
Fat, %	15.10±5.06	14.74±4.90	17.15±5.48	<0.001
Protein, g	67.75±25.39	68.59±25.48	62.88±24.26	<0.001
Protein, %	13.66±2.22	13.55±2.18	14.33±2.35	<0.001

Values are presented as mean±standard deviation or number (%). *P* values were calculated using the independent *t*-test or chi-squared test. Carbohydrate (%)=carbohydrate (g)×4 kcal/total energy intake (kcal)×100; Fat (%)=fat (g)×9 kcal/total energy intake (kcal)×100; Protein (%)=protein (g)×4 kcal/total energy intake (kcal)×100.

SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; CRP, C-reactive protein; FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; HbA1c, glycosylated hemoglobin; HOMA-IR, homeostasis model assessment of insulin resistance; MET, metabolic equivalent of task; DM, diabetes mellitus.

Table 2. Incidence of insulin resistance during the follow-up period

Year range	Follow-up, yr	Total numbers	No. of incident cases	Incident HOMA-IR ≥2.5 rate per 2 years
2001–2002	Baseline	4,570		
2003–2004	2	4,259	349	8.2
2005–2006	4	4,033	285	7.1
2007–2008	6	3,403	504	14.8
2009–2010	8	3,383	410	12.1
2011–2012	10	3,214	112	3.5
2013–2014	12	3,077	136	4.4
2015–2016	14	3,204	199	6.2
2017–2018	16	3,147	101	3.2
2019–2020	18	3,021	161	5.3

HOMA-IR, homeostasis model assessment of insulin resistance.

Table 3. Multiple Cox proportional hazard regression analysis for HOMA-IR incidence according to meal frequency

Variable	Hazard ratio with 95% confidence interval		*P* value
	Meal frequency <3	Meal frequency ≥3	
Model 1	1 (reference)	0.868 (0.775–0.972)	0.014
Model 2	1 (reference)	0.879 (0.783–0.987)	0.029
Model 3	1 (reference)	0.900 (0.801–1.011)	0.076
Model 4	1 (reference)	0.880 (0.782–0.990)	0.033

Model 1: unadjusted; Model 2: adjusted for age, sex, body mass index (BMI), and waist circumference (WC); Model 3: adjusted for age, sex, BMI, WC, smoking, drinking, and exercise; Model 4: adjusted for age, sex, BMI, WC, smoking, drinking, exercise, hypertension, diabetes mellitus, dyslipidemia, and total energy intake. Significance was set at $P<0.05$.
HOMA-IR, homeostasis model assessment of insulin resistance.

velopment of IR, even after adjusting for total calorie intake. However, subgroup analyses stratified by sex, DM status, and obesity revealed that this association was only significant in men, individuals without DM, and those with a BMI <25.

Insulin and IR

The development of IR is most closely associated with dietary habits [5,20]. The ingestion of glucose and amino acids during a meal stimulates the secretion of insulin from the β-cells of the pancreatic islets of Langerhans. This hormone is intricately involved in maintaining glucose homeostasis. In individuals with normal metabolic function, blood glucose levels are tightly regulated through the control of glucose production by the liver and kidneys, as well as glucose uptake by peripheral tissues such as skeletal muscle, adipose tissue, and the liver. In addition, insulin is involved in lipid metabolism as it both promotes lipid synthesis in the liver and adipocytes and inhibits lipolysis, the breakdown of TG into fatty acids [21]. Chronic inflammation is a precursor to serious health conditions, including cancer, Alzheimer's disease, and CVD [22,23], and some lipids act as messengers in inflammation. Therefore, efforts to break this vicious cycle through dietary strategy are of paramount importance for mitigating the progression of IR and its associated complications.

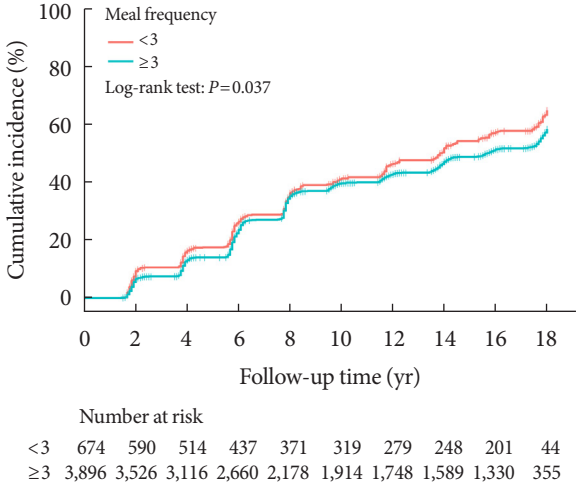


Fig. 2. Kaplan-Meier curve showing the difference in cumulative incidence of insulin resistance risk between the two meal frequency groups.

Association between MF and IR

MF, which was the main focus of this study, has been proposed as a manageable aspect of dietary behavior that can influence metabolic health management, as it is considered an influencing factor in weight management and various health indicators in the blood [24]. More specifically, high MF is generally thought to be beneficial for maintaining metabolic health [25-27]. In a study involving overweight Hispanic youth, it was confirmed that higher eating frequency, defined as consuming three or more meals per day, was associated with decreased BMI, reduced WC, lower fasting insulin levels, improved HOMA-IR values, and lower TG levels [26]. Additionally, in their study, Holmback et al. [27] reported that higher daily eating frequency was associated with a reduced likelihood of both

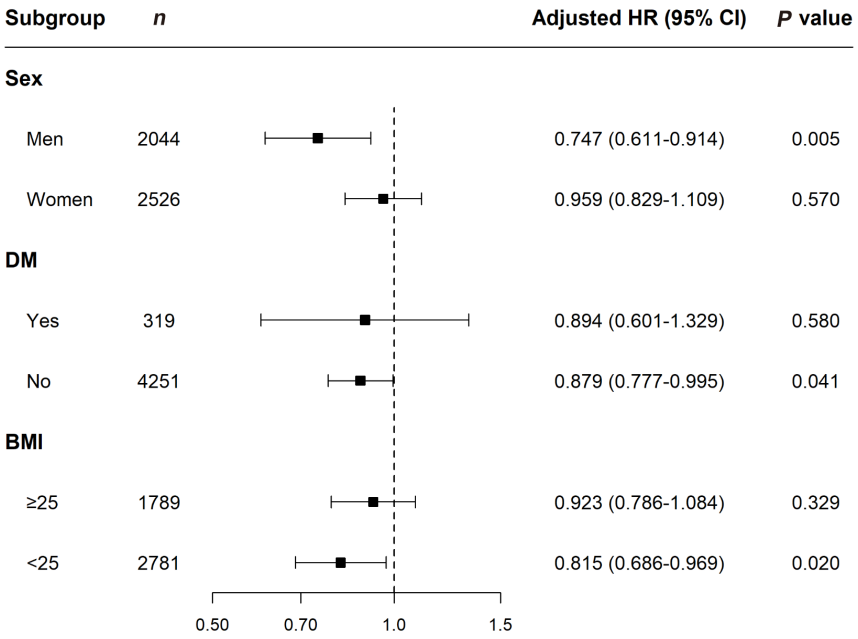


Fig. 3. Forest plot of subgroup analysis stratified by sex, diabetes mellitus (DM), and body mass index (BMI). HR, hazard ratio; CI, confidence interval.

general and central obesity among middle-aged men. This association persisted after adjusting for relevant confounders such as total energy intake, lifestyle factors, and dietary habits.

These results, which are consistent with our study findings, suggest potential benefits for appetite regulation. A previous study involving healthy males showed that individuals who consumed a single large meal per day consumed more energy during later meals compared to those who consumed smaller, evenly spaced meals [28]. This finding indicates that increasing MF improved satiety control, leading to reduced energy intake during subsequent *ad libitum* meals. Better appetite control may therefore promote the adoption of 'good eating habits.' Several prior studies have suggested that consuming a larger proportion of calories in the morning and eating regularly are beneficial [29-31]. Owing to data constraints, our study did not examine meal timing and regularity because of data constraints. However, it is plausible that individuals who eat more frequently exhibit better appetite control, avoid late-night eating, and maintain regular eating patterns [32]. Conversely, individuals who consume fewer meals per day may be more prone to irregular meal timing and overeating during meal times because of prolonged fasting periods between meals, resulting in postprandial glucose spikes [33]. This increased blood glucose variability may, in turn, cause metabolic detriments [34]. Additionally, postprandial thermogenesis, which comprises 5% to 15% of overall daily energy expenditure and involves an acute rise in resting metabolic rate after eating, has been shown to increase with higher MF [35]. Therefore, dividing the same total caloric intake into smaller, more frequent meals, rather than consuming it all in one large meal, improves glucose utilization [35].

In contrast, some studies have shown no association between MF and metabolic impact, or lower MF resulting in better metabolic outcomes [36,37]. These contradictory results are likely because of the complexity and diversity inherent in dietary research. Studies vary in their definitions of MF, such as whether snack consumption is included, as well as in their study populations. In addition, different studies use various metabolic markers for evaluation, such as BMI, lipid profiles, and insulin levels.

Moreover, dietary habits encompass multiple factors, including meal timing and regularity, as well as differences in diet quality that cannot be explained by caloric intake alone. In a study among Koreans examining the relationship between eating frequency and obesity indicators across different diet quality groups, a significant inverse correlation was observed between eating frequency and body fat percentage, WC, and BMI in the high diet quality group, whereas no such association ex-

isted in the low diet quality group [38].

Furthermore, the subgroup analysis in our study indicates that certain individual factors may influence the relationship between MF and metabolic outcomes. Firstly, our study found significant associations only in males, consistent with previous studies [7,39]. Although the exact reasons for this gender difference remain unclear, one possible explanation could be the varying patterns of fat distribution between men and women. Men tend to accumulate excess fat as visceral fat in the central abdominal area, whereas women are more likely to store fat as subcutaneous fat in the gluteofemoral region [40]. Visceral fat in the central region is metabolically more detrimental than fat stored in peripheral areas. If individuals with lower MF are more prone to fat storage, this could explain why reduced MF is linked to cardiometabolic risk factors specifically in men.

Additionally, no significant association was observed in individuals with existing metabolic risks, such as those with DM or obesity. A prior study of patients with type 2 DM indicated that consuming two larger, rather than six smaller, meals per day is more beneficial [37]. Another randomized controlled trial involving overweight/obese women showed that although eating frequency did not affect weight loss, groups with higher eating frequency exhibited better metabolic outcomes in body composition analyses [41]. While these studies share some similarities with our findings, the results of the previous study on DM patients, which suggested that lower MF is metabolically beneficial, somewhat contradict our findings. This discrepancy suggests that individuals with pre-existing metabolic conditions may have altered metabolic responses to MF. A BMI of 25 or higher is classified as obesity and is associated with adverse changes in adipose tissue. These changes include the activation of inflammatory processes, a reduction in lipid metabolism, and the deposition of fat in inappropriate areas [42]. Such metabolic disturbances may alter the body's usual response to energy intake, potentially leading to unexpected outcomes. Consequently, it is implied that dietary guidelines should be customized for different population groups based on their specific metabolic profiles.

Limitations

This study has several limitations. Firstly, because of the limitations of the collected data, we could not account for dietary patterns such as meal timing and regularity. Secondly, dietary intake was only assessed once at the beginning of the study, which may introduce measurement bias during follow-up and limits our ability to consider factors like meal nutritional composition that could affect IR. Thirdly, despite adjusting for many potential risk factors, we cannot exclude the possibility of unknown confounders. Fourthly, the use of retrospective self-reported questionnaires for collecting lifestyle data, including diet, may have introduced recall bias. Lastly, the participants were all of a single ethnic origin thus limiting the generalizability of the results.

Despite these limitations, the significance of this study lies in its longitudinal examination of the impact of MF on insulin sensitivity, a key factor in metabolic health, and in providing insights into the need for personalized dietary patterns. In an era where metabolic diseases are increasingly prevalent, the importance of dietary habits is more emphasized, underscoring the need for further research based on tailored medical approaches.

In conclusion, among middle-aged and older adults, a higher MF was associated with better insulin sensitivity. However, this difference was significant only in men, individuals without DM, and those with a BMI <25. These results emphasize the importance of dietary behavior in preventing and managing metabolic disorders, suggesting that addressing MF in dietary interventions may improve insulin sensitivity and reduce the risk of related complications. In the future, randomized trials are needed to clarify the causal relationship between these factors and to determine the most effective meal patterns for promoting metabolic health.

SUPPLEMENTARY MATERIALS

Supplementary materials related to this article can be found online at https://doi.org/10.4093/dmj.2024.0407.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

Conception or design: all authors.
Acquisition, analysis, or interpretation of data: all authors.
Drafting the work or revising: all authors.
Final approval of the manuscript: all authors.

ORCID

Ha-Eun Ryu *https://orcid.org/0000-0002-7211-9882*
Seok-Jae Heo *https://orcid.org/0000-0002-8764-7995*
Yu-Jin Kwon *https://orcid.org/0000-0002-9021-3856*

FUNDING

This research was supported by the Ministry of Small and Medium Enterprises and Startups and the Korea Technology and Promotion Agency for SMEs (TIPA) through the Regional Specialized Industry Development Plus Program (Grant Number: S3370378).

ACKNOWLEDGMENTS

MID (Medical Illustration & Design), as a member of the Medical Research Support Services of Yonsei University College of Medicine, providing excellent support with medical illustration.

REFERENCES

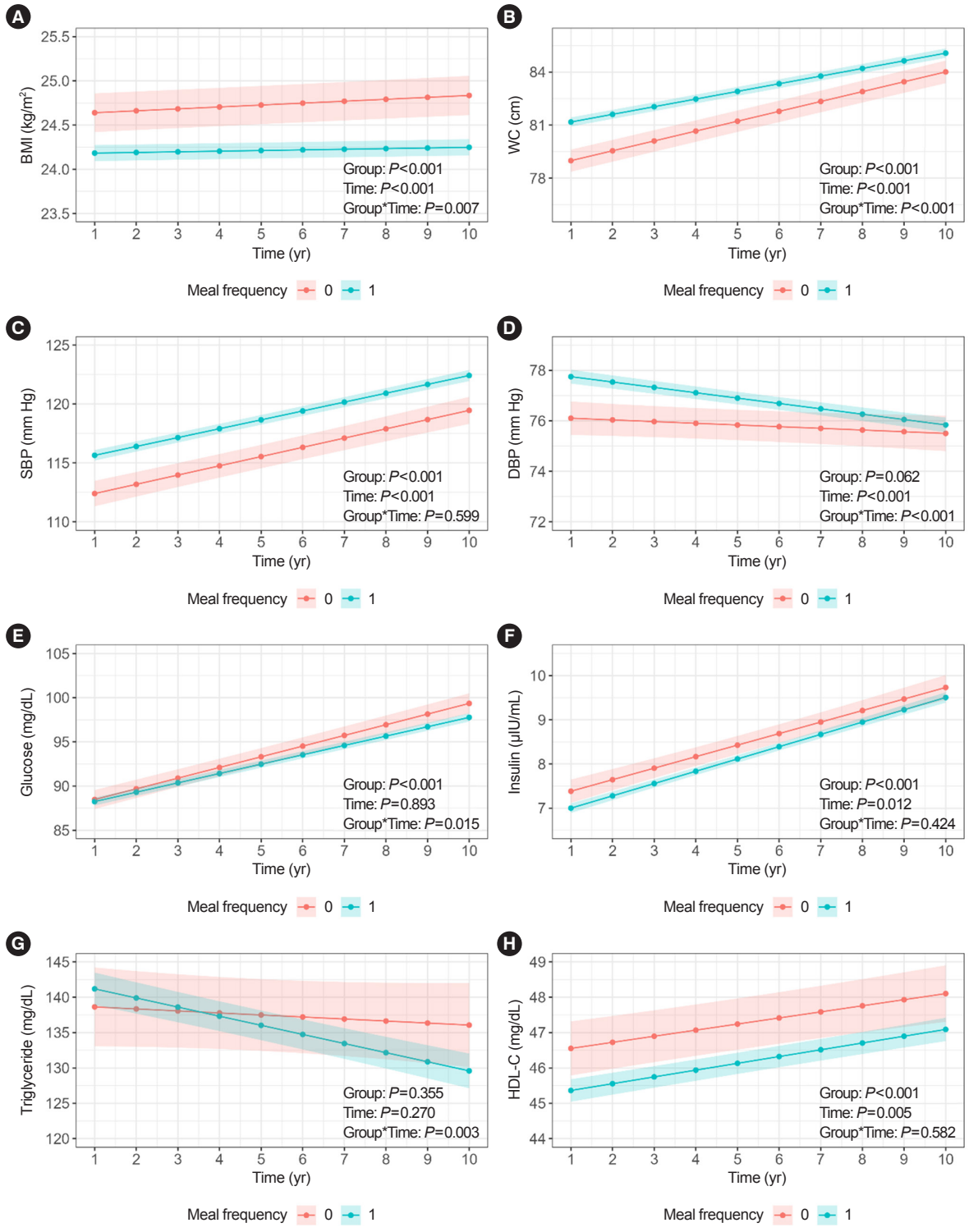
1. Gutch M, Kumar S, Razi SM, Gupta KK, Gupta A. Assessment of insulin sensitivity/resistance. Indian J Endocrinol Metab 2015;19:160-4.
2. Sampath Kumar A, Maiya AG, Shastry BA, Vaishali K, Ravishankar N, Hazari A, et al. Exercise and insulin resistance in type 2 diabetes mellitus: a systematic review and meta-analysis. Ann Phys Rehabil Med 2019;62:98-103.
3. Hill MA, Yang Y, Zhang L, Sun Z, Jia G, Parrish AR, et al. Insulin resistance, cardiovascular stiffening and cardiovascular disease. Metabolism 2021;119:154766.
4. Lebovitz HE. Insulin resistance: definition and consequences. Exp Clin Endocrinol Diabetes 2001;109 Suppl 2:S135-48.
5. Park SI, Suh J, Lee HS, Song K, Choi Y, Oh JS, et al. Ten-year trends of metabolic syndrome prevalence and nutrient intake among Korean children and adolescents: a population-based study. Yonsei Med J 2021;62:344-51.
6. Jung CH, Lee JS, Ahn HJ, Choi JS, Noh MY, Lee JJ, et al. Association of meal frequency with metabolic syndrome in Korean adults: from the Korea National Health and Nutrition Examination Survey (KNHANES). Diabetol Metab Syndr 2017;9:77.
7. Smith KJ, Blizzard L, McNaughton SA, Gall SL, Dwyer T, Venn AJ. Daily eating frequency and cardiometabolic risk factors in young Australian adults: cross-sectional analyses. Br J Nutr 2012;108:1086-94.
8. Fanti M, Mishra A, Longo VD, Brandhorst S. Time-restricted eating, intermittent fasting, and fasting-mimicking diets in weight loss. Curr Obes Rep 2021;10:70-80.
9. Seimon RV, Roekenes JA, Zibellini J, Zhu B, Gibson AA, Hills AP, et al. Do intermittent diets provide physiological benefits over continuous diets for weight loss?: a systematic review of clinical trials. Mol Cell Endocrinol 2015;418 Pt 2:153-72.
10. Varady KA, Hellerstein MK. Alternate-day fasting and chronic disease prevention: a review of human and animal trials. Am J Clin Nutr 2007;86:7-13.
11. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412-9.
12. Tsai SF, Yang CT, Liu WJ, Lee CL. Development and validation of an insulin resistance model for a population without diabetes mellitus and its clinical implication: a prospective cohort study. EClinicalMedicine 2023;58:101934.
13. Kim Y, Han BG; KoGES group. Cohort profile: the Korean Genome and Epidemiology Study (KoGES) Consortium. Int J Epidemiol 2017;46:e20.
14. Ahn Y, Kwon E, Shim JE, Park MK, Joo Y, Kimm K, et al. Validation and reproducibility of food frequency questionnaire for Korean genome epidemiologic study. Eur J Clin Nutr 2007;61:1435-41.
15. Ahn Y, Lee JE, Paik HY, Lee HK, Jo I. Development of a semiquantitative food frequency questionnaire based on dietary data from the Korea National Health and Nutrition Examination Survey. Nutr Sci 2003;6:173-84.
16. Park H, Shin D, Lee KW. Association of main meal frequency and skipping with metabolic syndrome in Korean adults: a cross-sectional study. Nutr J 2023;22:24.
17. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 1972;18:499-502.
18. Yamada C, Mitsuhashi T, Hiratsuka N, Inabe F, Araida N, Takahashi E. Optimal reference interval for homeostasis model assessment of insulin resistance in a Japanese population. J Diabetes Investig 2011;2:373-6.
19. Yun KJ, Han K, Kim MK, Park YM, Baek KH, Song KH, et al. Insulin resistance distribution and cut-off value in Koreans from the 2008-2010 Korean National Health and Nutrition Ex-

amination Survey. PLoS One 2016;11:e0154593.
20. Ushula TW, Mamun A, Darssan D, Wang WY, Williams GM, Whiting SJ, et al. Dietary patterns and the risks of metabolic syndrome and insulin resistance among young adults: evidence from a longitudinal study. Clin Nutr 2022;41:1523-31.
21. Roberts CK, Hevener AL, Barnard RJ. Metabolic syndrome and insulin resistance: underlying causes and modification by exercise training. Compr Physiol 2013;3:1-58.
22. Tsugane S, Inoue M. Insulin resistance and cancer: epidemiological evidence. Cancer Sci 2010;101:1073-9.
23. Kang S, Lee YH, Lee JE. Metabolism-centric overview of the pathogenesis of Alzheimer's disease. Yonsei Med J 2017;58:479-88.
24. St-Onge MP, Ard J, Baskin ML, Chiuve SE, Johnson HM, Kris-Etherton P, et al. Meal timing and frequency: implications for cardiovascular disease prevention: a scientific statement from the American Heart Association. Circulation 2017;135:e96-121.
25. Jenkins DJ, Wolever TM, Vuksan V, Brighenti F, Cunnane SC, Rao AV, et al. Nibbling versus gorging: metabolic advantages of increased meal frequency. N Engl J Med 1989;321:929-34.
26. House BT, Shearrer GE, Miller SJ, Pasch KE, Goran MI, Davis JN. Increased eating frequency linked to decreased obesity and improved metabolic outcomes. Int J Obes (Lond) 2015;39:136-41.
27. Holmback I, Ericson U, Gullberg B, Wirfalt E. A high eating frequency is associated with an overall healthy lifestyle in middle-aged men and women and reduced likelihood of general and central obesity in men. Br J Nutr 2010;104:1065-73.
28. Speechly DP, Buffenstein R. Greater appetite control associated with an increased frequency of eating in lean males. Appetite 1999;33:285-97.
29. Lombardo M, Bellia A, Padua E, Annino G, Guglielmi V, D'Adamo M, et al. Morning meal more efficient for fat loss in a 3-month lifestyle intervention. J Am Coll Nutr 2014;33:198-205.
30. Paoli A, Tinsley G, Bianco A, Moro T. The influence of meal frequency and timing on health in humans: the role of fasting. Nutrients 2019;11:719.
31. Farshchi HR, Taylor MA, Macdonald IA. Beneficial metabolic effects of regular meal frequency on dietary thermogenesis, insulin sensitivity, and fasting lipid profiles in healthy obese women. Am J Clin Nutr 2005;81:16-24.
32. Mendez-Hernandez P, Dosamantes-Carrasco LD, Siani C, Pierlot R, Martinez-Gomez M, Rivera-Paredez B, et al. Mealtime habits and risk of developing the metabolic syndrome or insulin resistance among Mexican adults. Br J Nutr 2016;116:1824-33.
33. Bertelsen J, Christiansen C, Thomsen C, Poulsen PL, Vestergaard S, Steinov A, et al. Effect of meal frequency on blood glucose, insulin, and free fatty acids in NIDDM subjects. Diabetes Care 1993;16:4-7.
34. Hanssen NM, Kraakman MJ, Flynn MC, Nagareddy PR, Schalkwijk CG, Murphy AJ. Postprandial glucose spikes, an important contributor to cardiovascular disease in diabetes? Front Cardiovasc Med 2020;7:570553.
35. LeBlanc J, Mercier I, Nadeau A. Components of postprandial thermogenesis in relation to meal frequency in humans. Can J Physiol Pharmacol 1993;71:879-83.
36. Kahleova H, Lloren JI, Mashchak A, Hill M, Fraser GE. Meal frequency and timing are associated with changes in body mass index in Adventist Health Study 2. J Nutr 2017;147:1722-8.
37. Kahleova H, Belinova L, Malinska H, Oliyarnyk O, Trnovska J, Skop V, et al. Eating two larger meals a day (breakfast and lunch) is more effective than six smaller meals in a reduced-energy regimen for patients with type 2 diabetes: a randomised crossover study. Diabetologia 2014;57:1552-60.
38. Kim S, Yang JH, Park GH. Eating frequency is inversely associated with BMI, waist circumference and the proportion of body fat in Korean adults when diet quality is high, but not when it is low: analysis of the Fourth Korea National Health and Nutrition Examination Survey (KNHANES IV). Br J Nutr 2018;119:918-27.
39. Canuto R, da Silva Garcez A, Kac G, de Lira PI, Olinto MT. Eating frequency and weight and body composition: a systematic review of observational studies. Public Health Nutr 2017;20:2079-95.
40. Gavin KM, Bessesen DH. Sex differences in adipose tissue function. Endocrinol Metab Clin North Am 2020;49:215-28.
41. Otuken Koroglu Y, Ozturk M. Meal frequency does not affect weight loss in overweight/obese women but affects the body composition: a randomized controlled trial. J Am Nutr Assoc 2024;43:489-97.
42. Sam S, Mazzone T. Adipose tissue changes in obesity and the impact on metabolic function. Transl Res 2014;164:284-92.

Supplementary Table 1. Baseline nutritional composition characteristics of the study population based on the meal frequency

Variable	Total	Meal frequency ≥3	Meal frequency <3	*P* value
Ca, mg	497.58±247.32	498.04±246.90	494.94±249.94	0.766
P, mg	1,045.59±361.96	1,059.10±362.15	967.52±351.08	<0.001
Fe, mg	11.14±4.58	11.29±4.59	10.28±4.39	<0.001
K, mg	2,591.98±1,068.26	2,615.31±1,071.67	2,457.15±1,038.92	<0.001
Vitamin A, retinol equivalent	548.65±365.36	552.88±369.64	524.20±338.79	0.046
Na, mg	3,177.89±1,487.85	3,250.11±1,507.97	2,760.41±1,289.76	<0.001
Vitamin B1, mg	1.27±0.52	1.29±0.52	1.15±0.49	<0.001
Vitamin B2, mg	1.04±0.44	1.05±0.44	1.01±0.43	0.062
Niacin, mg	15.97±6.07	16.14±6.08	14.97±5.92	<0.001
Vitamin C, mg	129.83±89.97	130.81±89.72	124.18±91.24	0.081
Zinc, μg	8.94±4.15	9.09±4.26	8.08±3.35	<0.001
Vitamin B6, mg	1.83±0.69	1.85±0.69	1.68±0.66	<0.001
Folate, μg	251.87±115.48	255.35±116.14	231.74±109.55	<0.001
Retinol, μg	74.40±60.20	73.39±60.96	80.28±55.28	0.003
Carotene, μg	2,783.56±2,152.55	2,813.24±2,171.59	2,611.99±2,032.05	0.019
Ash, mg	21.04±13.34	21.62±13.74	17.66±10.07	<0.001
Fiber, g	7.05±3.09	7.19±3.09	6.20±2.95	<0.001
Vitamin E, mg	9.67±4.66	9.72±4.69	9.41±4.51	0.109
Cholesterol, mg	186.39±129.10	185.77±131.26	189.96±115.85	0.396

Values are presented as mean±standard deviation.



Supplementary Fig. 1. Longitudinal changes in (A) body mass index (BMI), (B) waist circumference (WC), (C) systolic blood pressure (SBP), (D) diastolic blood pressure (DBP), (E) glucose, (F) insulin, (G) triglycerides, and (H) high-density lipoprotein cholesterol (HDL-C) according to the meal frequency group using the linear mixed model. The blue line labeled 'meal frequency (MF) = 1' represents the MF ≥3 group, while the red line labeled 'MF = 0' represents the MF <3 group.