

Original Research Article

Mediating Effects of Waist Circumference and Body Mass Index on the Association between Meal Frequency and Mortality

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S.S. (Sangah Shin): Undertook program administration.

All authors critically reviewed and edited subsequent drafts of the manuscript. All authors read and approved the final manuscript.

Data Sharing Statement

Restrictions apply to the availability of these data, which were used under license for this study. Data described in the manuscript, codebook, and analytic code are available from the authors with the permission of National Genome Research Institute, Korea Centers for Disease Control and Prevention. Requests to access the datasets should be directed to National Genome Research Institute, Korea Centers for Disease Control and Prevention; <https://kdca.go.kr/contents.es?mid=a40504060300>

Ethical approve

This KoGES-based study protocol received approval from the Chung-Ang university institutional review board (IRB number: 1041078-202109-HR-278-01).

Abstract

Objective: To examine the potential indirect effect of meal frequency on mortality via obesity indices.

Design: prospective cohort study

Setting: Korean Genome and Epidemiology Study

Participants: This cohort study involved 148,438 South Korean adults aged 40 years and older.

Results: Meal frequency at the baseline survey was assessed using a validated food frequency questionnaire. Outcomes included all-cause mortality, cancer mortality, and cardiovascular disease (CVD) mortality. Cox proportional hazards regression models were employed to examine the relationship between meal frequency and the risk of mortality. Mediation analyses were performed with changes in obesity indices (body mass index and waist circumference (WC)) as mediators. In comparison to the three-times group, the once-per-day and four-times-per-day groups had a higher risk for all-cause mortality. The irregular frequency group had a higher risk for CVD mortality. Both once-per-day and four-times-per-day groups exhibited higher risks for cancer mortality. The effect of meal frequency on all-cause mortality was partially mediated by WC. For specific-cause mortality, similar mediation effects were found.

Conclusions: The data suggests that three meals per day have a lower mortality and longer life expectancy compared to other meal frequencies. Increased waist circumference partially mediates this effect. These findings support the implementation of a strategy that addresses meal frequency and weight reduction together.

Keywords: mediation analysis, mortality, obesity, survival analysis, meal frequency

Introduction

The general public overwhelmingly believes that adhering to three meals a day is a preferable choice for maintaining good health. This belief is deeply rooted in cultural heritage and early epidemiological research^(1, 2). Previous studies have consistently indicated that a reduced meal frequency is linked to an elevated risk of cardiovascular disease (CVD) and associated mortality^(3, 4). A prospective study examined the relationship between eating behaviors such as meal frequency, skipping, and intervals, and all-cause and CVD mortality in 24,011 US adults aged 40+⁽³⁾. The researchers reported that eating one meal per day was associated with increased risks of mortality compared to eating three meals per day⁽³⁾. Another prospective study found that skipping breakfast was associated with a significantly increased risk of CVD mortality in a nationally representative cohort of US adults aged 40-75, with 17-23 years of follow-up⁽⁵⁾. Eating breakfast every day was associated with lower risk of CVD mortality⁽⁵⁾. A systematic review and meta-analysis of prospective cohort studies found that skipping breakfast was associated with a higher risk of all-cause, CVD, and cancer mortality in general adults⁽⁶⁾. A national US cohort study found that skipping breakfast was associated with increased risks of all-cause and cancer-related mortality in adults aged 40 and older⁽⁷⁾. A study conducted in older Japanese adults found that women who snacked one to four times a week had a slightly lower risk of all-cause mortality compared to those who did not snack⁽⁸⁾.

Overweight and obesity (and possibly underweight) were associated with increased mortality. A national cohort study of US adults found an increasing trend in body roundness index (BRI) over nearly 20 years and a U-shaped association between BRI and all-cause mortality⁽⁹⁾. A large population-based cohort study also reported a U-shaped association between BRI and both all-cause mortality and CVD mortality⁽¹⁰⁾. Lower and higher BRI quartiles were associated with higher mortality risks, with the lowest risks observed in the middle BRI quartiles⁽¹⁰⁾. A population-based cohort study in the UK examined the associations between BMI and all-cause mortality, and a range of cause-specific mortality outcomes⁽¹¹⁾. They found BMI had a J-shaped association with overall mortality and most causes of death, with lowest risk at 21-25 kg/m²⁽¹¹⁾. A study of 1.46 million white adults also found a J-shaped relationship between BMI and all-cause mortality, with the lowest risk occurring at a BMI of 20.0 to 24.9 kg/m²⁽¹²⁾. A study of over 10 million participants from four continents found that all-cause mortality was lowest at a BMI of 20.0-25.0 kg/m² and increased significantly both below and above this range⁽¹³⁾. A study examined the association

between waist circumference and all-cause mortality in older adults in Indonesia⁽¹⁴⁾. They found a significant U-shaped relationship between waist circumference and mortality among rich women, and a higher mortality risk among poor men and women with low waist circumference⁽¹⁴⁾. A study in China investigated the causal associations of BMI and waist circumference with mortality in the oldest-old people⁽¹⁵⁾. Higher BMI was associated with decreased mortality risk, while waist circumference was positively associated with mortality. The lowest mortality risk was observed among those with higher BMI and lower waist circumference, suggesting that weight management guidelines should be cautiously designed for this age group⁽¹⁵⁾.

A cross-sectional analysis conducted in the United States indicated that a meal frequency exceeding four times a day was associated with a reduced risk of obesity compared to a frequency of less than three times⁽¹⁶⁾. A prospective cohort study in Spain also reported a negative correlation between meal frequency and standardized BMI and waist-to-height ratio based on a follow-up of 1400 children⁽¹⁷⁾. However, there have also been studies that yielded results inconsistent with the aforementioned findings^(18, 19). As part of strategies aimed at reducing energy intake (including diet, medication, and weight loss surgery) and increasing energy output (through exercise and non-exercise means), meal timing and frequency have been considered to exert a significant impact on weight control and weight loss⁽²⁰⁾. In a study by Murakami et al., cross-sectional data analysis revealed a positive association between eating frequency and increasing BMI and WC among British adults aged 19-64 years⁽¹⁸⁾.

The relationship between meal frequency, obesity, and mortality remains unclear. In previous studies, when evaluating the impact of skipping breakfast and meal timing on mortality, obesity was often treated as confounding factors, suggesting that their impact on mortality may be independent^(5, 21). And a global study in 195 countries conducted in 2017 demonstrated that 4.7 million deaths and 147.7 million disability-adjusted life years of noncommunicable diseases were significantly related to high BMI⁽²²⁾.

Within this paradigm, reducing both obesity and controlling meal frequency can be considered independent goals for the primary prevention of mortality. However, recent evidence suggesting a correlation between these two risk factors^(23, 24) raises the possibility that obesity mediates the impact of meal frequency on mortality. The conceptual distinction between confounding and mediating is of crucial clinical significance, not only for understanding disease mechanisms but also for designing disease prevention interventions. If a mediating effect exists, the combined intervention of meal frequency and obesity

management hold more promise than their individual application. To the best of our knowledge, no previous study has specifically focused on the mediating role of obesity index in the relationship between meal frequency and mortality. The objective of this study is to examine the potential indirect effect of meal frequency on all-cause and specific-cause mortality via obesity using a mediation analysis approach. Our hypothesis posits that obesity indices partially mediate the effect of meal frequency on mortality.

Materials and Methods

Population Selection

We curated and organized baseline data from adult participants aged ≥ 40 years, drawn from the Korean Genome and Epidemiology Study (KoGES), including the Ansan-Ansung Study (KoGES_Ansan-Ansung) (2001–2002), the Health Examinees Study (KoGES_HEXA) (2004–2013), and the KoGES Cardiovascular Disease Association Study (KoGES_CAVAS) (2005–2011). HEXA involves volunteers aged ≥ 40 from nationwide medical institutions. Ansan-Ansung focuses on residents from an industrialized community and a rural area near Seoul. CAVAS aims to investigate CVD risk factors in rural counties, recruiting community-dwellers aged ≥ 40 from 11 rural counties during 2005–2011, with a male-to-female ratio close to 1:2. Follow-up examinations for Ansan-Ansung were conducted every two years, while the first phase of HEXA's follow-up began in 2007. CAVAS initiated its first follow-up in 2007 and second in 2010. KoGES is a comprehensive, longitudinal, and prospective cohort study, with detailed information available in a prior publication ⁽²⁵⁾.

Among the 211,569 participants in the baseline survey (2001–2013), we focused on 148,438 participants, excluding 63,131 individuals due to the absence of the following data: (1) age and lifestyle factors ($n = 2659$); (2) laboratory test results ($n = 2661$); (3) dietary information and implausible total calorie intake (< 500 or > 6000 kcal/day; $n = 7537$); (4) those not linked to the mortality database ($n = 50,274$). A detailed flowchart of the participant selection process is provided in eFigure 1.

Dietary Assessment

The population underwent questioning by trained interviewers using a semi-quantitative food frequency questionnaire (FFQ) comprising 106 food items, developed by the KoGES group. Eating frequency was determined by responses to questions such as "How many times a day do you eat?" and "Which meal do you usually skip?" Based on their answers,

participants' dietary habits were categorized as "once per day," "twice per day," "three times per day," "four times per day," and "irregular." To assess total energy intake and macronutrient intake, KoGES FFQ data were linked to the Korean Standard Food Components Data. The validity of the FFQ was evaluated against a nonconsecutive 12-day 24-hour diet record^(25, 26).

Ascertainment of Mortality

Participants' deaths were reported to the study personnel by Statistics Korea (KOSTAT), the national statistics organization, through death codes following the International Classification of Diseases, Tenth Revision (ICD 10)⁽²⁷⁾. In cases where death codes were unavailable, information about the cause of death was obtained by contacting family members via telephone during attempts to reach participants for their follow-up interview. Causes of death were grouped as cancer (C00-D48), and cardiovascular disease (I00-I99).

Mediation Analysis

In the current study, changes in BMI and WC between the baseline and the last follow-up survey before death or censorship were chosen as mediators. BMI was computed as the weight in kilograms divided by the square of the height in meters. WC was measured by trained KoGES staff⁽²⁵⁾.

In mediation analysis, the total effect of exposure on the outcome is decomposed into a direct effect and an indirect effect via the mediator (Figure 1)⁽²⁸⁾. The statistical framework for the mediation analysis has been summarized previously and is briefly described below. Mediation analysis is generally based on three regression equations:

$$\text{Equation 1: mediator} = a * \text{exposure}$$

$$\text{Equation 2: outcome} = c * \text{exposure}$$

$$\text{Equation 3: outcome} = d * \text{exposure} + b * \text{mediator}$$

Here, the total effect = $d + (a * b)$, the direct effect = d , and the indirect effect = $a * b$. In Equation 2, c is the total effect of exposure on outcome, and in Equation 3, d is the direct effect, which is the effect of exposure on outcome controlling for mediator. The indirect effect of exposure on outcome via mediator is $a*b$ or $c-d$, which are algebraically equivalent.

For each outcome (all-cause or specific-cause mortality), two linear regression models were fitted: the first fitted meal frequency and other covariates on obesity indices, and the second fitted meal frequency, obesity indices, and other covariates on mortality.

Based on the two regression models, the total effect of meal frequency on the outcome was decomposed into a direct effect and an indirect effect via obesity indices (BMI or WC).

Assessment of Covariates

Sociodemographic data, as well as data on alcohol consumption, smoking status, physical activity, and medical conditions, were obtained via questionnaires, created for KoGES, and which were applied by interviewers trained in the use of the standardized manual. This data was collected at baseline and in each follow-up survey. The covariates of interest in our study encompassed age, sex (categorized as male and female), smoking status (stratified into never smokers, past smokers, and current smokers), drinking status (divided into three levels), physical activity level (categorized into two levels), educational level (stratified into three levels), total energy intake, the percentage of energy derived from carbohydrates and proteins, and self-reported sleeping duration. Baseline exercise was classified as follows: exercise more than 30 min at least two times a week (yes or no). Alcohol consumption status was ascertained by asking participants whether they had ever consumed alcoholic beverages in their lifetime, whether there was a time in their life when they regularly consumed alcohol, and whether they drank alcohol in the past 30 days. Self-reported smoking status (never, former, or current smoker) was also collected. Height, body weight, and waist circumference of participants were measured through standard methods. Sleeping duration was also adjusted in analytical models by self-reported answers.

Statistical Analysis

All statistical analyses were done using SAS software (version 9.4, SAS Institute, Cary, NC, USA). Demographic, lifestyle, clinical, and sleep characteristics of study participants were expressed as the means (SDs) for continuous variables or numbers (percentages) for categorical variables according to eating frequency categories. A general linearized model was used for testing the differences of continuous variables among analytical groups, and the χ^2 test was used for testing the differences of categorical variables among analytical groups.

The main analysis utilized the Cox proportional hazards regression method to generate adjusted hazard ratios (HRs) and 95% confidence intervals (CIs). The proportionality assumption of the Cox model was assessed before its use, and no violation of the assumption was observed (Schofield Test for Proportional Hazards Assumption). Hazard ratios for eating frequency were calculated, with "three times per day" defined as the reference group. results

are presented as crude (model 1) and adjusted HRs with 95% CIs. Model 2 was adjusted for age and sex. Model 3 incorporated adjustments for age, sex, educational level, drinking status, smoking status, physical activity level, total energy intake, BMI, and self-reported sleeping duration. Furthermore, Model 4 included adjustments for all the aforementioned variables along with the percentage of energy derived from carbohydrates and proteins. A two-tailed p -value less than 0.05 was considered statistically significant. Additionally, survival analysis was conducted to generate Kaplan-Meier curves at each survey time point or death-reported time point ⁽²⁹⁾. The analysis is based on the hazard at each time point, and participants who were censored were dropped out from the at-risk group.

Results

Baseline General Characteristics of Selected Participants

The average follow-up period was about 11 years. The baseline median age was 53.6 years and differed substantially among the eating frequency groups, with the highest age being in the habitual three times per day (mean 54.2 years). The irregular frequency group had higher numbers of current smokers and alcohol drinkers compared to the three times group (Table 1). Education level differed substantially among the frequency groups, with a lower frequency of college or above graduates in the irregular frequency group. The baseline mean BMI was 24.2 kg/m² among the irregular frequency group and differed significantly compared to the three times per day. But waist circumference values varied substantially among the analytical groups and the three times group showed the highest mean value (81.6 ± 8.7 cm).

Association Between Daily Meal Frequency and All-Cause and Specific Mortality

eTable 1 presents all-cause and specific-cause mortality according to self-reported daily meal frequency among KoGES participants. After a follow-up of 11 years involving 148,548 participants, 6,754 death cases were recorded, including 1,243 associated with cardiovascular disease and 2,858 with cancer.

The association between daily meal frequency and all-cause and specific-cause mortality is detailed in Table 2. In the crude model, compared to the three-times group, the irregular frequency group and the twice group exhibited lower risks for all-cause mortality (irregular: HR 0.664, 95% CI 0.531–0.830; twice: HR 0.616, 95% CI 0.568–0.668). However, after adjusting for covariates, these associations lost significance. In comparison to the three-times group, the once-per-day group and the four-times-per-day group had a higher risk for all-

cause mortality (once: adjusted HR 1.938, 95% CI 1.324–2.835; four times: adjusted HR 1.640, 95% CI 1.175–2.288).

The association between specific-cause mortality and meal frequency was further assessed. The results showed that, compared to the three-times group, the irregular frequency group had a higher risk for CVD-mortality (adjusted HR 1.831, 95% CI 1.126–2.978). Two analytical groups exhibited higher risks for cancer-mortality (once: adjusted HR 2.256, 95% CI 1.352–3.765; four times: adjusted HR 1.922, 95% CI 1.222–3.022) compared to the three-times group.

Kaplan–Meier Survival Analysis for All-Cause and Specific-Cause Mortality

According to the Kaplan–Meier analysis (Figure 2), the risk for all-cause and specific-cause mortality varied significantly among all five meal frequency groups (all log-rank test p values < 0.05). Figure 2 presents the Kaplan–Meier analysis of the proportion of patients who remained free of all-cause or specific-cause mortality during the total follow-up period (for as long as 18 years after the baseline survey) according to self-reported daily meal frequency groups. The one-time-per-day group presented the poorest survival rate for all-cause and specific-cause mortality.

Obesity Indices as Mediators of The Impact on The Association between All-Cause and Specific-Cause Mortality and Meal Frequency

The results of the mediation analysis are shown in eFigure 2 and Figure 3. Meal frequency showed a positive association with BMI level (beta = 0.10020, $p < 0.05$), but BMI is not a mediator on the influence between meal frequency and all-cause and specific-cause mortality (all Sobel test p -values > 0.05).

We observed another obesity index, WC, mediated indirect effect on all-cause and specific-cause mortality. For all-cause mortality, meal frequency had a positive association with WC and WC was also positively associated with all-cause mortality. When meal frequency and WC were simultaneously included in the model, both meal frequency and WC were positively associated with all-cause mortality (all p -values < 0.05). These results suggested that the effect of meal frequency on all-cause mortality was partially mediated by WC (the proportion of mediation was 84.8% estimated by the Sobel test). For specific-cause mortality, similar mediation effects were found. The proportion of total effect on CVD mortality and cancer mortality mediated by WC was 77.2% and 84.7%, respectively (all p values < 0.05).

Discussion

The main findings are that meal frequency had both a direct effect and obesity indices-mediated indirect effect on mortality, and the indirect effect via WC was observed in all-cause and specific-cause mortality, but no indirect effect via BMI was found. The current data reveals that three meals per day had a lower mortality and longer life expectancy than other meal frequencies, with increased WC partially mediating the effect.

The study revealed the three-times frequency had a lower CVD-mortality compared to an irregular frequency pattern, after adjusting for various socioeconomic, lifestyle, and dietary covariates. This aligns with previous research, where irregular eating patterns were found to be less favorable for cardiovascular health ⁽⁴⁾. Cahill et al. found that, when compared to the three meals per day, 1-2 times per day or more than 3 times per day had a deleterious effect on coronary heart disease ⁽³⁰⁾. The author believed that this association was potentially due to the mechanism between meal frequency and obesity ⁽³⁰⁾. Other studies have also indicated that meal frequency and its impact on obesity could be a potential mechanism contributing to cardiovascular outcomes. A review paper found that decreasing meal frequency among obese participants was beneficial for weight loss ⁽³¹⁾. A cross-sectional study of 2685 participants showed that eating more than three meals per day was associated with overweight or obesity, regardless of age (younger or older) ⁽³²⁾. The NutritionDay study reported that eating less food than regular meals was associated with an increased risk for mortality among hospital patients, a result which may be due to malnutrition ⁽³³⁾. The current study, focusing on normal-weight middle-aged and older participants (aged 40 years or more), revealed a strong association between meal frequency and obesity, particularly WC. This association could be attributed to a disrupted body clock and an imbalance in energy intake, leading to metabolic disorders and an increased risk of overweight or obesity.

The current study also suggested that, when compared to the three-meal per day, a meal frequency that was less or more than three-meals per day were both associated with increased cancer mortality. Previous studies demonstrated that meal frequency seemed to be associated with cancer, especially cancers of the digestive tract (colorectal cancer, colon cancer, gastric cancer risk) ⁽³⁴⁾. Researchers considered meal frequency to be closely related to energy restriction, which plays an important role in suppressing cancer formation by enhancing apoptosis and inhibiting angiogenesis ⁽³⁵⁾.

To our knowledge, this study is the first to investigate the potential mediation effect of obesity indices on the association between meal frequency and mortality among Korean

middle-aged and older adults. Previous studies have confined themselves to examining obesity as an effect confounder. For example, Chen et al. adjusted four weight statuses (underweight, normal weight, overweight, and obese) in the analysis of the correlation between meal frequency and mortality⁽³⁶⁾. A BMI-stratified analysis reported that, when eating irregularly, Japanese participants with a BMI of 23.0 to 24.9 kg/m² had a higher risk for CVD mortality (adjusted HR 1.17, 95% CI 1.20–2.43)⁽³⁷⁾. In a Lancet commentary by Berrigan et al., a J-shaped association between BMI and mortality was highlighted, suggesting that BMI within various overweight or obesity categories does not consistently correlate with increased mortality⁽³⁸⁾. In our current study, we observed a positive association between meal frequency and BMI increment. Nevertheless, we did not find a significant association between BMI and mortality. It's worth noting that the mean BMI value for our study was around 24 kg/m², considered as a cut-off value of the J-shaped curve, which may contribute to a nuanced relationship with mortality—either positive or negative.

Although we did not find the BMI mediation effect, our study did improve our understanding of the role of WC, as a potential mediator in the pathway, with this greater understanding being supported by consistent results from the mediation analysis. Overall, the indirect effect via WC explained 84.8% of meal frequency-all-cause mortality. Within the context of potential mediation by waist circumference, the "direct" association can be described as the segment of the relationship that operates through mechanisms unrelated to being overweight and obesity. Conversely, the "indirect" association pertains to the segment mediated by mechanisms linked to central obesity, specifically waist circumference. The WC-mediated indirect effect involves a two-stage process: first, meal frequency increases WC, and second, WC elevates mortality. For the initial stage, we noted a robust correlation between meal frequency and WC, with a 0.9 cm increase in WC associated with meal frequency (linear regression coefficient of 0.99). This association remained significant across all mortality phenotypes which was consistent with previous meta-analyses⁽³⁹⁾. A previous cross-sectional study revealed an inverse association between meal frequency and waist circumference among Korean adults⁽⁴⁰⁾. The underlying mechanisms remain uncertain but may include meal frequency being associated with energy intake (eucaloric vs. isocaloric), causing hunger or satiety responses⁽⁴¹⁾.

Our results, along with previous observational and experimental studies, provide evidence for the second step: WC increases mortality. Our analysis showed that 0.1% all-cause mortality increased risk was associated with a one cm increase in WC (linear regression

coefficient 0.001). A pooled analysis of 11 cohort studies found that higher WC was positively associated with higher mortality among 650,386 white adults⁽⁴²⁾. Another survival analysis also found the positive linear association between WC and all-cause mortality among 23,263,878 Korean adults⁽⁴³⁾. A systematic review and meta-analysis quantified the association of various indices of central obesity with all-cause mortality risk in the general population⁽⁴⁴⁾. The study included 72 prospective cohort studies with 2,528,297 participants⁽⁴⁴⁾. Indices such as waist circumference, waist-to-hip ratio, waist-to-height ratio, etc., were positively associated with higher mortality risk, while larger hip and thigh circumference were associated with lower risk⁽⁴⁴⁾. The potential mechanisms may be the effect of visceral adipose tissue on cardiometabolic diseases associated mediator's secretion⁽⁴⁵⁾. Another potential biological mechanism that appears to underline the detrimental role of central obesity, is adipose tissue inflammation. Adipose tissue inflammation is initiated and sustained over time by dysfunctional adipocytes that secrete inflammatory adipokines and by infiltration of bone marrow-derived immune cells that signal via production of cytokines and chemokines. This process is characterized by an increased secretion of pro-inflammatory cytokines by adipocytes and the infiltration of immune cells (including macrophages and T-cells) into the adipose tissue⁽⁴⁶⁾. Besides, WC is also associated with inflammation and insulin resistance both which are associated with aging and mortality⁽⁴⁷⁻⁴⁹⁾.

The current study has some limitations. First, due to limitations in the survival data, we did not stratify the cancer type. Second, daily energy distribution and breakfast skipping were also related to metabolic disorder and mortality, which was not adjusted in the current study⁽⁵⁰⁾. Additionally, micronutrients play a crucial role in mortality and obesity, yet due to the characteristics of the data, we were unable to assess their impact on the outcome or as mediators. Therefore, the current findings should be interpreted with caution. The current findings should therefore be interpreted with caution.

This survival study offers valuable insights, particularly regarding the mediation effect of weight change (WC) in the meal frequency-mortality relationship. Understanding this interaction is crucial for reducing mortality risk and adds to current knowledge on mortality's etiology. While meal frequency and weight reduction are both recommended as non-pharmaceutical strategies to prevent mortality and chronic diseases, their combined effect has received limited attention. Moreover, there is a lack of research evidence supporting this co-intervention approach. This study provides evidence in favor of integrating meal frequency with weight reduction. However, current evidence on the effectiveness of this combined

strategy remains scarce. Future studies with larger clinical cohorts are needed to further explore the interaction between meal frequency, obesity, and mortality.

Conclusion

The findings suggest that the consumption of three meals per day is associated with a lower all-cause and specific-cause mortality among KoGES participants. Furthermore, waist circumference was identified as a partial mediator of this effect. The results of this study offer supporting evidence for implementing a strategy that addresses the beneficial effect on life expectancy from both meal frequency and weight reduction simultaneously. Further research is needed across various age groups to facilitate the development of dietary pattern guidelines.

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Table 1. Baseline general characteristics of selected study population in current survival analysis

	Meal frequency, times per day					<i>P</i> value
	Once	Twice	Three times	Four times	Irregular	
N=148,438	563	23,578	121,105	700	2,492	
Person-years	6001.0	261760.3	1406240.0	8341.7	28398.1	
Sex						
Male	117 (20.8)	5835 (24.6)	46460 (38.4)	389 (55.6)	635 (25.5)	<.0001
Female	446 (79.2)	17743 (75.3)	74645 (61.6)	311 (44.4)	1857 (74.5)	<.0001
Age, years	51.5 ± 8.4	51.1 ± 7.9	54.2 ± 8.7	52.3 ± 8.6	51.6 ± 7.9	<.0001
BMI, kg/m ²	23.8 ± 3.2	23.9 ± 3.1	24 ± 2.9	23.7 ± 3.1	24.2 ± 3.3	<.0001
Waist circumference, cm	79.4 ± 9.7	79.9 ± 8.9	81.6 ± 8.7	81.5 ± 9.1	80.9 ± 9.3	<.0001
Total energy intake, kcal/day	1401.9 ± 574.4	1520.2 ± 483.7	1774.9 ± 487.4	2009.6 ± 624.7	1572.8 ± 544.0	<.0001
E% of carbohydrate	67.4 ± 9.3	69.8 ± 7.7	73.5 ± 7.1	72.1 ± 7.3	70.9 ± 8.3	<.0001
E% of protein	14.5 ± 3.2	14.1 ± 2.7	13.3 ± 2.4	13.4 ± 2.4	13.7 ± 2.7	<.0001
E% of fat	18.2 ± 6.9	16.1 ± 5.6	13.2 ± 5.1	14.5 ± 5.4	15.4 ± 6.1	<.0001
Educational level						<.0001
Under middle school	162 (28.8)	6469 (27.4)	46056 (38.0)	287 (41.0)	908 (36.4)	
High school	245 (43.5)	10598 (45.0)	45524 (37.6)	281 (40.1)	1085 (43.5)	
College or above	152 (27.0)	6333 (26.9)	28525 (23.6)	125 (17.9)	463 (18.6)	
Drinking status						<.0001
Non-drinker	259 (46.0)	11530 (48.9)	61355 (50.7)	259 (37.0)	1183 (47.5)	

Past-drinker	25 (4.4)	720 (3.1)	5159 (4.3)	46 (6.6)	102 (4.1)	
Current-drinker	277 (49.2)	11290 (47.9)	54300 (44.8)	391 (55.9)	1201 (48.2)	
Smoking status						<.0001
Non-smoker	445 (79.0)	17917 (76.0)	86249 (71.2)	374 (53.4)	1847 (74.1)	
Past-smoker	42 (7.5)	2208 (9.4)	19165 (15.8)	117 (16.7)	229 (9.2)	
Current-smoker	73 (13.0)	3394 (14.4)	15296 (12.6)	206 (29.4)	404 (16.2)	
Physical active level						<.0001
Low level	6 (1.1)	459 (2.0)	2359 (2.0)	7 (1.0)	0 (0.0)	
Moderate level	351 (62.3)	15310 (64.9)	75264 (62.2)	499 (71.3)	1824 (73.2)	
High level	194 (34.5)	7308 (31.0)	40644 (33.6)	184 (26.3)	619 (24.8)	
SBP, mmHg	121.1 ± 15.3	120.9 ± 15.2	122.9 ± 15.5	122.7 ± 15.5	122.0 ± 15.8	<.0001
DBP, mmHg	75.7 ± 10.0	75.6 ± 10.1	76.6 ± 10.2	77.3 ± 10.6	76.5 ± 10.3	<.0001
Sleeping time, hours	6.7 ± 1.5	6.7 ± 1.3	6.8 ± 1.2	6.8 ± 1.4	6.8 ± 1.4	<.0001

Values are presented as means ± SDs or n (%). *P* values were calculated using generalized linear model for continuous variables and chi-square test for categorical variables. Missing values are not displayed in this table. DBP refers to diastolic blood pressure, and SBP refers to systolic blood pressure.

Table 2. Adjusted hazard ratios for all-cause and specific-cause mortality according to daily meal frequency among KoGES participants.

	Meal frequency, times per day				
	Once	Twice	Three times	Four times	Irregular
N=148,438	563	23,578	121,105	700	2,492
Person-years, mean/sum	10.66/6001.00	11.10/261760.30	11.61/1406239.80	11.92/8341.70	11.40/28398.10
All-cause mortality					
model 1	1.157 (0.793, 1.688)	0.616 (0.568, 0.668)	ref	1.238 (0.923, 1.660)	0.664 (0.531, 0.830)
model 2	1.157 (0.793, 1.688)	0.616 (0.568, 0.668)	ref	1.238 (0.923, 1.660)	0.664 (0.531, 0.830)
model 3	1.925 (1.317, 2.813)	1.081 (0.988, 1.184)	ref	1.639 (1.174, 2.286)	1.014 (0.783, 1.312)
model 4	1.938 (1.324, 2.835)	1.084 (0.988, 1.189)	ref	1.640 (1.175, 2.288)	1.017 (0.785, 1.317)
CVD-mortality					
model 1	0.942 (0.353, 2.515)	0.598 (0.493, 0.725)	ref	0.593 (0.222, 1.583)	0.926 (0.595, 1.442)
model 2	1.522 (0.570, 4.063)	1.168 (0.961, 1.420)	ref	0.713 (0.267, 1.905)	1.630 (1.046, 2.539)
model 3	1.694 (0.632, 4.537)	1.087 (0.869, 1.361)	ref	1.213 (0.454, 3.246)	1.798 (1.107, 2.919)

model 4	1.760 (0.655, 4.728)	1.117 (0.887, 1.405)	ref	1.211 (0.453, 3.238)	1.831 (1.126, 2.978)
Cancer-mortality					
model 1	1.500 (0.903, 2.492)	0.695 (0.618, 0.782)	ref	1.472 (0.967, 2.240)	0.510 (0.344, 0.756)
model 2	2.231 (1.343, 3.707)	1.144 (1.015, 1.290)	ref	1.586 (1.042, 2.414)	0.788 (0.531, 1.169)
model 3	2.273 (1.365, 3.783)	1.114 (0.980, 1.266)	ref	1.919 (1.220, 3.017)	0.677 (0.430, 1.065)
model 4	2.256 (1.352, 3.765)	1.106 (0.970, 1.261)	ref	1.922 (1.222, 3.022)	0.675 (0.429, 1.062)

Values were presented as hazard ratios and 95% confidence intervals.

model 1: crude model

model 2: model 1 + age, sex

model 3: model 2 + educational level, drinking status, smoking status, physical activity level, total energy intake, BMI, self-reported sleeping duration

model 4: model 3 + E% from macronutrient

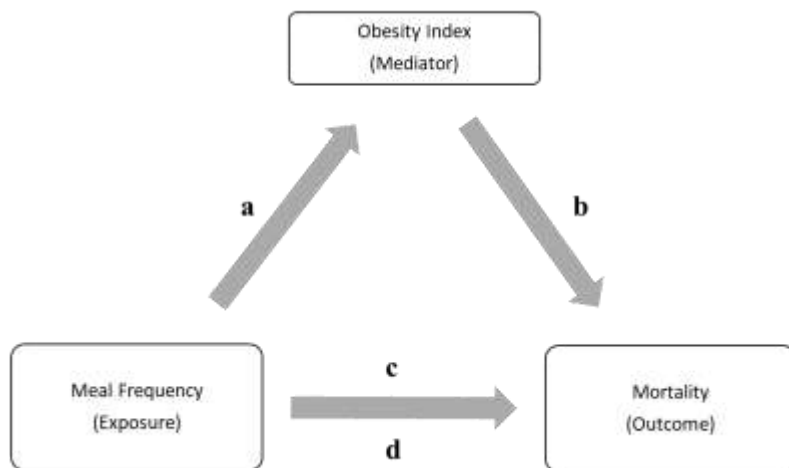


Figure 1. A single mediator model

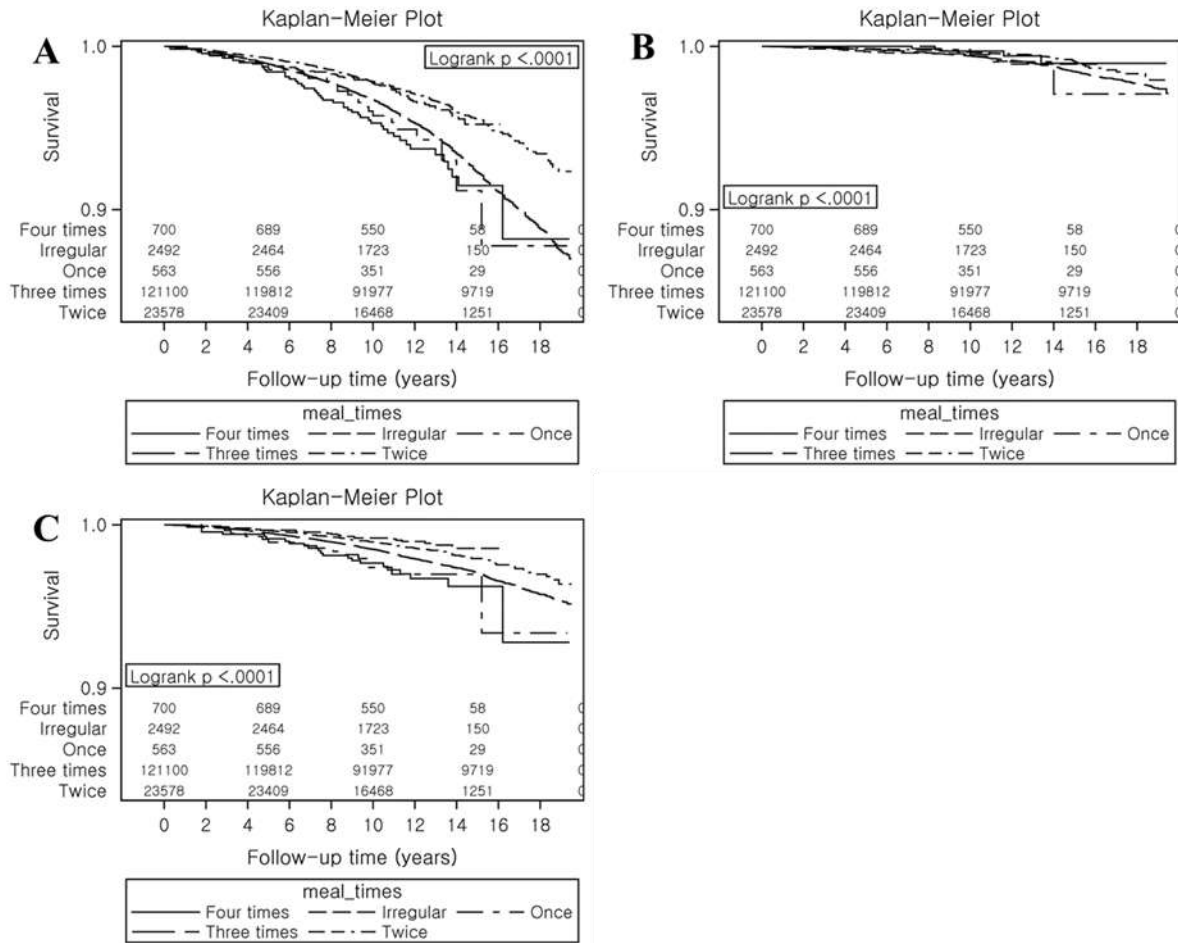


Figure 2. Kaplan-Meier analysis of the proportion of participants who remained free of all-cause mortality or specific-cause mortality.

A) all-cause mortality B) CVD mortality C) cancer mortality

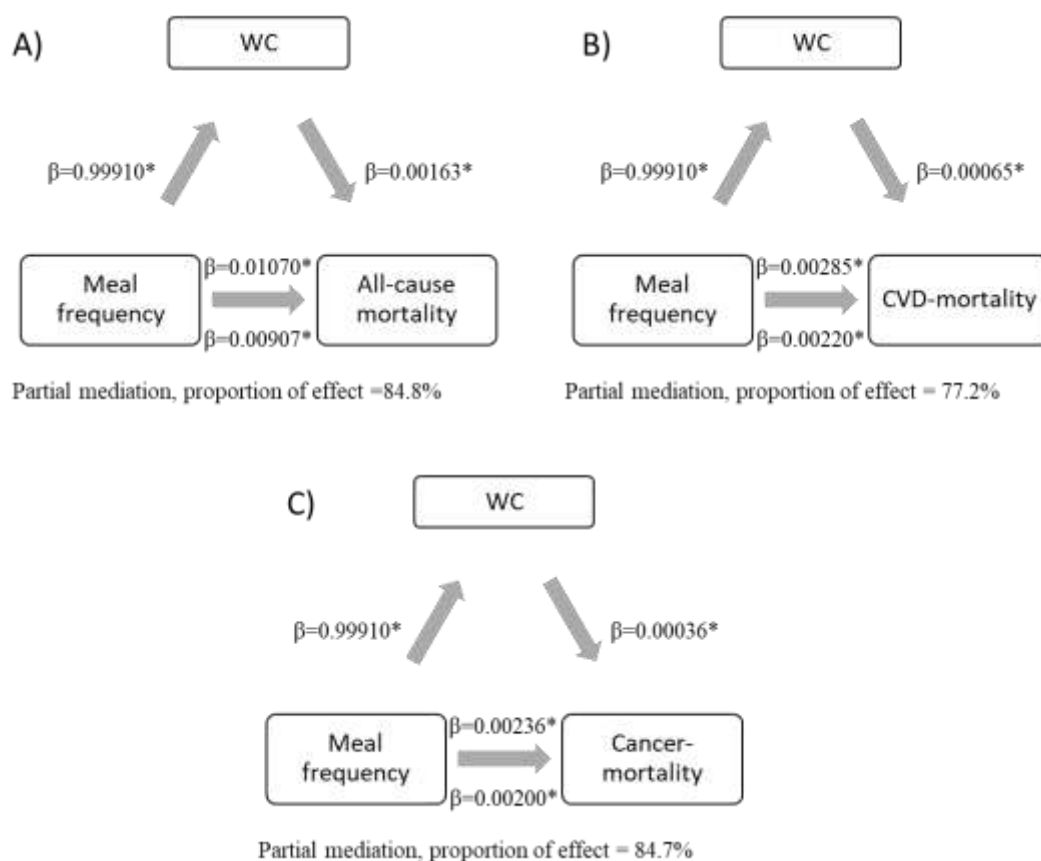


Figure 3. WC mediation models of the association between meal frequency and all-cause and specific-cause mortality.

* p -values < 0.05. WC, waist circumference. A) all-cause mortality B) CVD mortality C) cancer mortality.