UNIVERSITY OF CALIFORNIA,
IRVINE

The timing of food intake, body weight, and chronic disease risk

DISSERTATION

submitted in partial satisfaction of the requirements
for the degree of

DOCTOR OF PHILOSOPHY

in Epidemiology

by

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FIELD OF STUDY

Dietary Patterns and Chronic Disease Risk

ABSTRACT OF THE DISSERTATION

The Timing of Food Intake, Body Weight, and Chronic Disease Risk

By

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Doctor of Philosophy in Epidemiology

University of California, Irvine, 2022

Associate Professor Andrew Odegaard, Chair

Several studies have demonstrated an association between timing of eating, circadian rhythms, metabolism, and chronic disease risk. However, a long-term relationship between the timing of eating and disease remains unclear due to the length of time required to study this association, among other reasons. This dissertation intends to explore further the relationship between the time, type 2 diabetes risk, breast cancer risk, and weight loss maintenance over time by using breakfast and after-dinner snacks as proxies of eating timing.

This dissertation consisted of three separate research projects aiming to 1) examine the association between the consumption of breakfast and after-dinner snack patterns and breast cancer risk among post-menopausal; 2) estimate the causal effect of long-term breakfast consumption and night snacking on type 2 diabetes risk via causal inference modeling among young adults; 3) investigate if consuming breakfast and evening snacks have a differential effect on weight loss maintenance among individuals with obesity undergoing a standard weight loss intervention.

The first study conducted a prospective analysis of 70501 post-menopausal women aged 49 to 81 years from the Women's Health Initiative Observational cohort study. In the second study, we emulated a target trial using observational data from 3737 subjects from the Coronary Artery Risk Development in Young Adults (CARDIA) Study. Finally, in the third study, we

emulated a target trial using observational data from 372 subjects in the Innovative Approaches to Diet, Exercise and Activity (IDEA) study.

The analyses showed no association between breakfast meals or after-dinner snack habits and the risk of breast cancer in post-menopausal women. In addition, the estimates from causal inference analysis supported that avoiding post-dinner snacks might be beneficial in reducing the long-term risk of diabetes; however, the role of starting regular breakfast consumption in midlife may have no major impact on the 20-y risk of diabetes. Finally, regular breakfast consumption and minimizing evening snacking may have a modest impact on lessening weight and body fat regain over 18 months after initial weight loss. In conclusion, the frequency of breakfast and after-dinner snacks is associated with metabolic disease risk and body weight maintenance.

INTRODUCTION

Rising healthcare costs and the growing public health burden of chronic diseases require a change of emphasis of a healthcare system from disease treatment to disease prevention. Lifestyle factors, such as diet and physical activity, represent modifiable factors that are practical targets of prevention efforts in populations. In fact, some groups have reported dietary intake as the largest contributing factor to the leading causes of death in the United States.[1] However, dietary intake is multi-faceted, and overall diet quality and energy intake predominate the evidence base, while the effects of the timing of eating on metabolism and risk of chronic diseases are relatively understudied. Thus, "chrono-nutrition" has been gaining interest among scientists, and a small body of studies demonstrates an association between timing of eating, circadian rhythms, metabolism, and chronic disease risk.[2], [3], [4]Indeed, dietary patterns are recognized as having a significant role in the etiology of different cancers and type 2 diabetes.[5]–[9] Several studies suggest that weight loss has a major beneficial effect on reducing the risk of several types of cancer and type 2 diabetes.[10]–[15] Despite the potential for health benefits of weight loss maintenance, a few studies have explicitly tested alternative dietary strategies to sustain weight loss for longer periods of time.[16], [17] Traditional analytical approaches to study the long-term prospective relationship between diet and disease risk have also largely not accounted for changes in dietary exposure and confounding factors during the duration of the study and have not applied causal inference modeling for estimating diet-disease effects. Finally, while randomized controlled trials are the gold standard for causal inference, this study design is largely infeasible for dietary exposures and actual disease outcomes due to the length of time required, among other reasons. To begin addressing these gaps in the evidence base, I developed the following specific objectives for this dissertation research:

Aim 1: Examine the association between the consumption of breakfast and after-dinner snack patterns and breast cancer risk among post-menopausal women in the Women's Health Initiative Observational Study cohort.

Aim 2: Estimate the causal effect of long-term breakfast consumption and night snacking on type 2 diabetes risk via causal inference modeling among young adults in the CARDIA study.

Aim 3: Estimate if consuming breakfast and evening snacks have a differential effect on weight loss maintenance among individuals with obesity undergoing a standard weight loss intervention in the IDEA study.

CHAPTER 1: Meal patterns and post-menopausal breast cancer risk

ABSTRACT

Background: Different aspects of dietary intake have a demonstrable role in post-menopausal breast cancer risk. However, there has been little investigation into how the timing of meals and eating occasions associates with post-menopausal breast cancer risk.

Objective: We examined the association between the consumption frequency of breakfast meals and after-dinner snacks with the risk for post-menopausal breast cancer.

Methods: A prospective analysis of 70501 post-menopausal women aged 49 to 81 years was conducted from the Women's Health Initiative Observational cohort study. Each participant's breakfast and after-dinner snack intake were assessed at the study Year 1 exam. Multivariable Cox proportional hazards regression models examined breakfast and after-dinner snack consumption frequencies and the risk of invasive and in situ breast cancer diagnosed before February 28, 2020. The models were adjusted for age, race, education, income, physical activity, smoking, alcohol intake, diet quality score (HEI 2015), energy intake, diabetes status, and BMI.

Results: During the average 14.7-year follow-up period, 4667 participants were diagnosed with invasive breast cancer, and 1041 participants were diagnosed with in situ breast cancer. Compared to participants who did not eat breakfast, daily breakfast consumption was not associated with invasive breast cancer (HR 1.06 (95%CI: 0.93, 1.22)) nor in situ (HR 1.32 (95%CI: 0.96, 1.83) breast cancer. Compared to participants who reported daily after-dinner snacks, avoidance of after-dinner snacks was not associated with invasive breast cancer (HR 0.97 (95%CI: 0.87, 1.08)) nor in situ (HR 1.09 (95%CI: 0.86, 1.37)) breast cancer.

Conclusions: There was no association between breakfast meals or after-dinner snack habits and with risk of breast cancer in post-menopausal women.

INTRODUCTION/BACKGROUND

Dietary intake has a demonstrable role in post-menopausal breast cancer risk.[18], [5], [19] However, there has been little investigation into how meal patterns, particularly breakfast meals and after-dinner snacks, relate to post-menopausal breast cancer risk.[20] Indeed, there is a strong biologic rationale for the role of the timing of eating occasions as studies suggest that a prolonged overnight fast could be associated with a reduced risk of breast cancer.[21], [22] Further, consumption of breakfast and after-dinner snacks directly affects the length of the night fast, altering the circadian rhythms.[23] Disruptions to circadian rhythms in humans have also been associated with the development of several cancer types, including breast cancer.[24] A study has shown that skipping breakfast impacts circadian clocks independently from the sleep-wake cycle.[25] On the molecular level, disruption of melatonin and cortisol synthesis and associated signaling pathways affects normal breast epithelium and activates breast cancer cell growth.[26],[27] Breakfast consumption is associated with a greater plasma melatonin concentration,[28] and late-night food consumption has been associated with alteration in the synthesis of plasma cortisol.[29]

In short, there is evidence that circadian rhythms have a role in breast cancer etiology; and there is evidence that meal timing, mainly eating occasions that bookend the daily meal pattern, may influence breast cancer risk via hormones associated with circadian rhythms. Thus, the WHI is able to inform the hypothesis that the timing of eating occasions is associated with breast cancer risk.

The objective of this study was to examine the relation between the frequency of consumption of breakfast meals and after-dinner snacks and the risk of breast cancer among post-menopausal women. We hypothesized that a higher frequency of breakfast meals was inversely associated

with breast cancer risk, and a lower frequency of after-dinner snack consumption was inversely associated with breast cancer risk.

METHODS

Women's Health Initiative

The WHI is an ongoing multicenter clinical trial and observational study designed to address major causes of morbidity and mortality in U.S. post-menopausal women.[30] Briefly, 161,808 women aged 50–79 years were recruited between September 1, 1993, and December 31, 1998. Details of the scientific rationale, eligibility requirements, and baseline characteristics of the participants in the WHI have been published elsewhere.[31] [32] The WHI Observational Study included 93,676 women, over 85,000 of whom provided information on their breakfast and evening snack habits. The following participants were excluded from the analysis: 2,221 women who had a history of breast cancer at year 1 or prevalent breast cancer at the year 1 exam where the exposures were assessed, so the focus is on incident cases after year 1. The women who had implausible energy intake (>=5000kcal and <600 kcal) were also excluded. We also excluded 462 women who had no follow-up time after Y1 and 4,051 women who had missing information on the confounders (income 3159 observations, education, 572 observations, smoking status 501 observations).

This yielded a sample of 70,501 women for further analysis. The average follow-up time was 14.67 (95% CI: 14.62, 14.72).

Measurement of exposure and confounders

In the WHI, the information on meal frequency consumption was collected at year 1 of the Observational cohort follow-up. We analyzed the sample of participants who responded to the following questions at the year 1 exam (form 48): "How many times per week do you usually eat breakfast?" and "How many times per week do you usually eat an after-dinner snack?". The following categorical response options were offered to the participants: "Never or less than

once", "1-2 times", "3-4 times", "5-6 times", and "7 or more times". In this analysis, we measured the exposure by the number of breakfasts and after-dinner snacks per week (on average) divided into categories of 0, 1-2, 3-4, 5-6, and 7+ times per week.

By utilizing the observational data, we were looking for associational relative risk, which is subject to structural bias. To minimize the association due to the structural bias, we adjusted for covariates that could serve as potential confounding.[33] Covariates like age, ethnicity, education, income, physical activity, overall diet quality and energy intake, smoking, and alcohol intake were identified as common causes of the exposure (meal frequency) and outcome (breast cancer) using directed acyclic graphs (DAGs) and existing evidence of the underlying confounding effect of the known covariates on the association between exposure and outcome. These noted confounders were included in models in sets to examine their statistical effect on the relative risk measure. The following confounding covariates used in multivariable analyses were measured at year 0, and we assumed that they represented year 1 measures: age at enrollment (<55, 55–59, 60–64, 65–69, 70–74, ≥75 years); ethnicity (American Indian or Alaska Native, Asian or Pacific Islander, black or African American, Hispanic/Latino, non-Hispanic whites, and other); education (high school or less, some college/technical training, college or some post-college, and master's degree or higher); body mass index; physical activity (measured as metabolic equivalent tasks (METs) per week); alcohol intake (non-drinker, past drinker, <1 drink/month, 1 drink/month–<1 drink/week, 1–<7 drinks/week, ≥7 drinks/week); overall diet quality (HEI 2015) and total energy intake.

Follow-up and ascertainment of cases

Annual self-administered questionnaires ascertained initial reports of cancer, and all self-reports of breast cancer were confirmed by a review of medical records, including pathology reports (if a

biopsy or resection was done). Per program coding guidelines, the breast cancer cases were then coded by an experienced Surveillance, Epidemiology, and End Results (SEER) coder.[34] Primary site and histology were coded using the International Classification of Diseases for Oncology, Second Edition (ICD-O-2). The completion rate of annual questionnaires was 93%–96% through 2005—the end of the main study period. As of February 28, 2020, with an average of 14.67 (95% CI: 14.62, 14.72) years of follow-up, 4,667 invasive incident breast cancers and 1,041 in-situ incident breast cancer cases were identified in the selected population.

Statistical analysis

All participants were followed up from Y1 questionnaire until the date of breast cancer diagnosis (invasive or in situ, whichever was diagnosed first), date of death, loss to follow-up, or February 28, 2020, whichever occurred first.

We described the breakfast and after-dinner snack habits by estimating means and standard deviations (SD) for continuous covariates and count and proportion for categorical covariates (Table 1 and Table 2).

Cox proportional hazard models with time since Year 1 exam as the underlying time metric were fitted to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the relationship between breakfast frequency, after-dinner snack frequencies, and the risk of developing breast cancer. Exposure variables were treated as categorical, time-fixed covariates. Five models were fitted for all outcomes with adjustments for several established risk factors for breast cancer. In model 1, adjustment was made for age and race. Model 2 was additionally adjusted for education and income. Model 3 additionally introduced the physical activity, smoking, and alcohol intake. Model 4 was additionally adjusted for diet quality score (HEI 2015) and energy intake.

Furthermore, model 5 also accounted for diabetes status and BMI. All covariates were measured at year 0 (except primary exposure variables, measured at year 1) and treated as time-fixed covariates. The Cox models fulfilled the proportionality assumption (models using Kolmogorov-type supremum test based on a sample of 1,000 simulated residual patterns). Continuous exposure variables (range, 0-4) were used for the trend test calculation. The α level for the analyses is 0.05.

We also present the stratified models 1) by BMI (using the median of 27.11 as a threshold, <27.11 vs. >=27.11), 2) by smoking status (ever smokers vs. never smokers), 3) breakfast by after-dinner snacks (0-2 times/week, 3-7 times/week categories), and 4) after-dinner snacks by breakfast (0-2 times/week, 3-7 times/week categories).

We carried out the following sensitivity analyses to inform the interpretation of the results: 1. excluded all cases within the first two years to account for potential reverse causality, 2. incorporated an inverse probability weight at year 1 to account for potential selection bias into the analysis.[33]

We also performed a posthoc analysis by estimating the association of breakfast and after-dinner snacks with breast cancer recurrence in women with a history of breast cancer at year 0 (but cancer-free at year 1).

All analyses were carried out using SAS 9.4.

RESULTS

The final sample for analyses included 70,501 women with a mean follow-up of 14.67 years (95% CI: 14.62, 14.72), during which a total of 5624 breast cancer cases occurred. Out of all included study participants, 22.96% (n=16,189) ate after dinner never or less than once a week, and 11.81% (n=8,328) consumed after dinner meal 7 or more times a week (Table 2). Only 5.7% (n=4,016) women never eat breakfast or eat it less than once a week, and 68.75% (n=48,469) consumed breakfast 7 or more times a week. (Table 1). Women who did not consume breakfast regularly (never or less than once a week) were predominantly 60-69 years old (44.64%) and were overweight (40.12%). More black than white women skipped breakfast (Table 1). More regular breakfast consumption was associated with higher overall diet quality. On the other hand, more regular after-dinner snack consumption was associated with a slightly lower overall diet quality (Table 2). 27.23% (n=19,196) of women ate after dinner 1-2 times/week. Those who ate after dinner daily had a slightly lower income, had a higher rate of thyroid gland problems, were mainly white, and had a slightly higher proportion of smokers (Table 2). Overall, those who consumed after-dinner snacks 7 or more times a week had, on average, 200 kcal/day greater energy consumption than those who avoided after-dinner snacks. Also, those who avoided after-dinner snacks consumed more alcohol and exercised more than those who ate after-dinner snacks daily (Table 2).

The incidence rate of developing breast cancer in the WHI OS was 5.5 cases per 1,000 person-years among those who consumed breakfast every day and 5.6 cases per 1,000 person-years among those who avoided eating after-dinner snacks from 1997 to February 28, 2020 (Table 3, 4). The HR (95% CI) (model 5) for consuming breakfast daily (7 times/week) compared to avoiding breakfast (<1 time/week) was 1.06 (95%CI: 0.93, 1.22) for invasive breast cancer risk

(Table 3). For in situ breast cancer risk, compared with women who avoided breakfast meals (<1 time/week), those who consumed breakfast 1-2 times/week had an HR of 1.1 (95% CI: 0.73, 1.67), those who consumed breakfast 3-4 times/week had an HR of 1.24 (95% CI: 0.82, 1.88), those who consumed breakfast 5-6 times/week had an HR of 1.21 (95% CI: 0.84, 1.73) and those who consumed breakfast 7 times/week had an HR of 1.32 (95% CI: 0.96, 1.83) (P = .04 for trend). There was no association of breakfast frequency with in situ breast cancer incidence; however, a statistical test for trend suggests an additional residual influence of breakfast consumption (Table 3).

The HR for avoiding after-dinner snacks (<1 time/week) compared to consuming after-dinner snacks daily (7 times/week) was 0.97 (95% CI: 0.87, 1.08) for invasive breast cancer and 1.09 (95% CI: 0.86, 1.37) for in situ breast cancer risk (Table 4).

For in situ breast cancer risk, women with BMI >=27.11, compared with women who avoided breakfast meals (<1 time/week), those who consumed breakfast 1-2 times/week had an HR of 1.81 (95% CI: 0.87, 3.79), those who consumed breakfast 3-4 times/week had an HR of 2.11 (95% CI: 1.01, 4.39), those who consumed breakfast 5-6 times/week had an HR of 2.13 (95% CI: 1.09, 4.17) and those who consumed breakfast 7 times/week had an HR of 2.38 (95% CI: 1.26, 4.48) (P = .006 for trend) (Table 5).

Overall, there was no effect modification by smoking found; however, never smokers who consumed more regular (5-6 times/week) and habitual breakfast (7 or more times/week) had a higher risk of in situ breast cancer diagnosis compared to those never smokers who avoided breakfast (HRs 1.83 (95%CI: 1.01, 3.48) and 2.00 (95%CI: 1.09, 3.65), respectively) (Table 6).

When women who consumed after dinner snacks 0-2 times/week consumed breakfast 0-2

times/week, they had HR 0.78 (95% CI: 0.58, 0.98) of in situ breast cancer diagnosis compared to women who consumed breakfast 3-7 times/week (Table 7).

Excluding breast cancer diagnosis during the first two years of the follow-up did not result in any noticeable change in the estimates (Supplementary Table 1). Using inverse probability weights adjusted for age, race, education, income, physical activity, smoking, alcohol intake, diet quality score (HEI 2015), energy intake, diabetes status, and BMI resulted in a greater magnitude of association between breakfast consumption and in situ breast cancer risk as well as more statistically significant estimates; however, the direction of the association remained the same as in the conventional analysis.

The posthoc analysis that evaluated the association between after-dinner snacks, breakfast and breast cancer recurrence risk among women with a history of breast cancer suggested no association between those meals and disease recurrence risk (Table 8).

DISCUSSION

Previous studies have reported the relation of numerous aspects of dietary intake to breast cancer risk.[35], [36],[37] However, this study is the first to assess the association of breakfast meals and after-dinner snacks with the risk of breast cancer in a large cohort of post-menopausal women. Overall, we observed no association between higher frequency of breakfast intake and risk for invasive and in situ breast cancer compared to no/infrequent breakfast intake. There was no statistical signal of higher breakfast frequency with risk for in situ breast cancer either, but there were monotonic higher point estimates for each higher category of breakfast intake. Lastly, there was no association between the frequency of after-dinner snacks/eating occasions and the risk for breast cancer.

The suggestive association of increased risk of in situ breast cancer linked with regular breakfast consumption could reflect confounding by systematic surveillance behavior of women. Indeed, this study has shown that women who consumed breakfast regularly were also more likely to get a mammogram and a physical breast exam (Table 1). Furthermore, we saw that those who consumed breakfast more regularly had a healthier diet, exercised more, and were less likely to smoke. These factors serve as a proxy for the health consciousness of women who are more likely to take advantage of breast cancer screening.[38], [39] Having undergone a mammogram exam is one of the strongest and most prevalent risk factors associated with diagnosing in situ breast cancers.[40] Regular cancer screening allows diagnosis of an earlier stage of tumor progression (in situ), which increases the chances of preventing invasive breast cancer.[41] Thus, some of the tumors identified at an earlier stage would not progress to an invasive stage in such a scenario, creating an artifactual "harm" of regular breakfast consumption.

Higher BMI is reported to be associated with increased mammographic sensitivity, which could potentially lead to the overestimated relationship between BMI and the risk of developing in situ breast cancer.[42], [43] This might explain a higher magnitude of association estimates between breakfast consumption and in situ breast cancer risk observed among participants with BMI above 27 kg/m^2.

Similar to our findings, a large prospective cohort study in 2018 concluded no association between cancer risk and the number of eating episodes, night-time fasting duration, and time of first eating episode.[44] In a cross-sectional study, Marinac suggested that a longer night-time duration was significantly associated with improved glycemic regulation, particularly noting that each 3-hour increase in night-time fasting duration was associated with roughly a 20% reduced odds of elevated HbA1c.[21] While there is contradicting evidence on the association between HbA1c and risk of breast cancer, we addressed the potential association between prolonged night fast and risk of breast cancer in this study.[45], [46] Night fasting time can be prolonged by avoiding after-dinner snacks, breakfast, or both. Supporting the findings of the abovementioned study, we observed that participants who avoided breakfast and who did not eat after-dinner snacks regularly had a lower in situ breast cancer risk. However, there was no association between skipping after-dinner snacks and invasive breast cancer risk in those participants who did not eat breakfast regularly.

Another study concluded that fasting less than 13 hours per night was associated with an increase in the risk of breast cancer recurrence compared with fasting 13 or more hours per night.[22] In our posthoc analysis, we assessed the risk of breast cancer recurrence among women with a history of breast cancer at year 1. We found that regularly consuming neither after-dinner snacks nor breakfast was associated with an increased risk of breast cancer recurrence compared to

avoiding those meals. A small number of women with a history of breast cancer were included in the analysis, which could result in type II error.

One of the primary strengths of this study was the large sample of post-menopausal women in the WHI Observational Study cohort, which made it feasible to examine incremental differences in breakfast and after-dinner snacks as risk factors for breast cancer as allowed for performing stratified analyses by tumor stage. In addition, a breast cancer diagnosis was confirmed by a medical record review, and all cases were adjudicated. Careful adjustment for confounders like including validated dietary data was also advantageous for this analysis. A prospective design of this study, excluding all prevalent breast cancer cases at baseline, allowed producing the estimates for breast cancer-free subjects. The mean 14.7-year follow-up period provided a considerable latency period for potential disease occurrence.

Due to the study's observational nature, the results should only be generalized to the healthy, post-menopausal women population. Another limitation of this study is the participants' self-reported meal frequency and other confounding variables, which might be subject to measurement error. Single breakfast and after-dinner snack exposure measures may not fully reflect long-term associations with breast cancer risk. Furthermore, it is essential to note that breakfast and after-dinner snack frequency could serve as a proxy for circadian rhythms that are the actual correlates of cancer development and that these also depend on many other lifestyle and environmental factors. Although we attempted to control confounding, residual confounding cannot be ruled out.

In summary, there was no association between breakfast meals or after-dinner snack habits and the risk of breast cancer in post-menopausal women. Nevertheless, the nature of our analysis precludes inferring causality or making clinical recommendations.

TABLES AND FIGURES

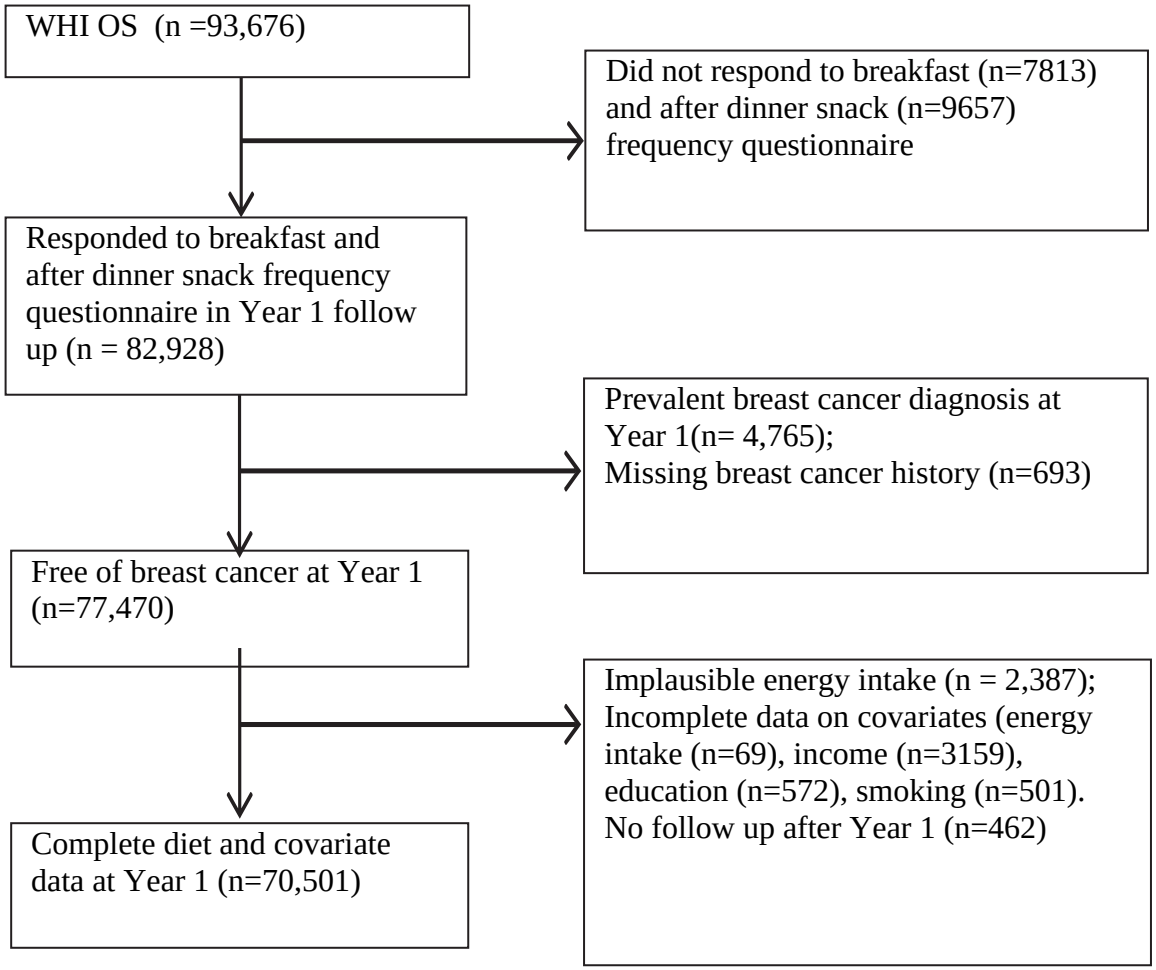


Figure 1. Flowchart of eligibility from the WHI OS (1994-2020).

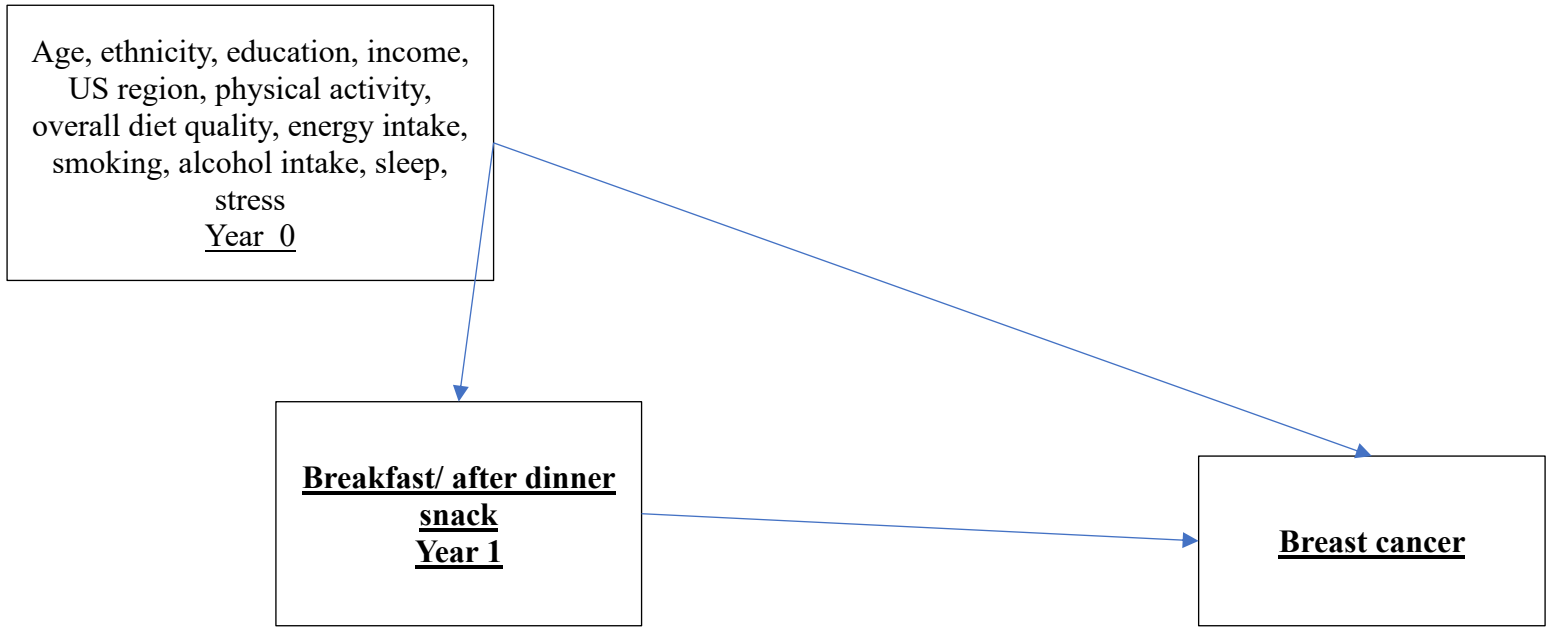


Figure 2. Simplified directed acyclic graph (DAG) for the effect of breakfast and evening snack consumption and breast cancer incidence.

Table 1. Baseline[1] characteristics (N (%) or Mean (SD), if noted) of eligible participants in the WHI OS population (1994-2020) by breakfast frequency

		Eat breakfast, times/wk					
		Overall	Never or less than once	1-2 times	3-4 times	5-6 times	7 or more times
N		70501 (100)	4016 (5.7)	4823 (6.84)	3896 (5.53)	9297 (13.19)	48469 (68.75)
Eat after dinner, times/wk	Never or less than once	16189 (22.96)	1799 (44.8)	1237 (25.65)	709 (18.2)	1688 (18.16)	10756 (22.19)
	1-2 times	19196 (27.23)	945 (23.53)	1869 (38.75)	1116 (28.64)	2637 (28.36)	12629 (26.06)
	3-4 times	16891 (23.96)	612 (15.24)	913 (18.93)	1128 (28.95)	2677 (28.79)	11561 (23.85)
	5-6 times	9897 (14.04)	322 (8.02)	477 (9.89)	557 (14.3)	1651 (17.76)	6890 (14.22)
	7 or more times	8328 (11.81)	338 (8.42)	327 (6.78)	386 (9.91)	644 (6.93)	6633 (13.69)
Age group at screening	<50-59	23011 (32.64)	1390 (34.61)	2073 (42.98)	1752 (44.97)	3865 (41.57)	13931 (28.74)
	60-69	31272 (44.36)	1711 (42.6)	1849 (38.34)	1634 (41.94)	3876 (41.69)	22202 (45.81)
	70-79+	16218 (23)	915 (22.78)	901 (18.68)	510 (13.09)	1556 (16.74)	12336 (25.45)
Family Income	Less than $10,000	2381 (3.38)	305 (7.59)	330 (6.84)	189 (4.85)	360 (3.87)	1197 (2.47)
	$10,000 to $19,999	7274 (10.32)	608 (15.14)	650 (13.48)	475 (12.19)	951 (10.23)	4590 (9.47)
	$20,000 to $34,999	15803 (22.42)	1020 (25.4)	1132 (23.47)	834 (21.41)	1959 (21.07)	10858 (22.4)

	$35,000 to $49,999	14116 (20.02)	731 (18.2)	885 (18.35)	795 (20.41)	1854 (19.94)	9851 (20.32)
	$50,000 to $74,999	14350 (20.35)	651 (16.21)	850 (17.62)	739 (18.97)	1909 (20.53)	10201 (21.05)
	$75,000 to $99,999	6760 (9.59)	258 (6.42)	377 (7.82)	342 (8.78)	946 (10.18)	4837 (9.98)
	$100,000 to $149,999	5026 (7.13)	189 (4.71)	291 (6.03)	255 (6.55)	688 (7.4)	3603 (7.43)
	$150,000 or more	2837 (4.02)	120 (2.99)	147 (3.05)	163 (4.18)	385 (4.14)	2022 (4.17)
	Don't know	1954 (2.77)	134 (3.34)	161 (3.34)	104 (2.67)	245 (2.64)	1310 (2.7)
Body-mass Index (BMI), kg/m^2	Underweight (< 18.5)	814 (1.15)	54 (1.34)	63 (1.31)	50 (1.28)	97 (1.04)	550 (1.13)
	Normal (18.5 - 24.9)	845 (1.2)	59 (1.47)	55 (1.14)	36 (0.92)	65 (0.7)	630 (1.3)
	Overweight (25.0 - 29.9)	28287 (40.12)	1439 (35.83)	1648 (34.17)	1235 (31.7)	3222 (34.66)	20743 (42.8)
	Obesity I (30.0 - 34.9)	23734 (33.66)	1320 (32.87)	1612 (33.42)	1310 (33.62)	3281 (35.29)	16211 (33.45)
	Obesity II (35.0 - 39.9)	10635 (15.08)	678 (16.88)	829 (17.19)	702 (18.02)	1600 (17.21)	6826 (14.08)
	Extreme Obesity III (>= 40)	3884 (5.51)	270 (6.72)	360 (7.46)	347 (8.91)	645 (6.94)	2262 (4.67)
Female relative had breast cancer	No	19779 (28.05)	1052 (26.2)	1330 (27.58)	1029 (26.41)	2566 (27.6)	13802 (28.48)
	Yes	12686 (17.99)	678 (16.88)	803 (16.65)	694 (17.81)	1627 (17.5)	8884 (18.33)
	Missing	38036 (53.95)	2286 (56.92)	2690 (55.77)	2173 (55.78)	5104 (54.9)	25783 (53.19)
Cancer ever, excluding non-melanoma skin cancer	No	65140 (92.4)	3687 (91.81)	4443 (92.12)	3576 (91.79)	8609 (92.6)	44825 (92.48)

	Yes	5263 (7.47)	323 (8.04)	370 (7.67)	317 (8.14)	678 (7.29)	3575 (7.38)
	Missing	98 (0.14)	6 (0.15)	10 (0.21)	3 (0.08)	10 (0.11)	69 (0.14)
Diabetes ever	Yes	66881 (94.87)	3779 (94.1)	4548 (94.3)	3735 (95.87)	8890 (95.62)	45929 (94.76)
	Diabetes ever	3556 (5.04)	232 (5.78)	270 (5.6)	161 (4.13)	398 (4.28)	2495 (5.15)
	Missing	64 (0.09)	5 (0.12)	5 (0.1)	. (.)	9 (0.1)	45 (0.09)
Thyroid gland problem ever	No	52403 (74.33)	3060 (76.2)	3706 (76.84)	3025 (77.64)	7071 (76.06)	35541 (73.33)
	Yes	17723 (25.14)	920 (22.91)	1073 (22.25)	855 (21.95)	2175 (23.39)	12700 (26.2)
	Missing	375 (0.53)	36 (0.9)	44 (0.91)	16 (0.41)	51 (0.55)	228 (0.47)
Eat dinner, times/wk	Never or less than once	2276 (3.23)	1653 (41.16)	227 (4.71)	46 (1.18)	77 (0.83)	273 (0.56)
	1-2 times	2514 (3.57)	477 (11.88)	1608 (33.34)	88 (2.26)	98 (1.05)	243 (0.5)
	3-4 times	2058 (2.92)	224 (5.58)	385 (7.98)	397 (10.19)	406 (4.37)	646 (1.33)
	5-6 times	8314 (11.79)	341 (8.49)	777 (16.11)	1118 (28.7)	3124 (33.6)	2954 (6.09)
	7 or more times	54812 (77.75)	1235 (30.75)	1769 (36.68)	2200 (56.47)	5516 (59.33)	44092 (90.97)
	Missing	527 (0.75)	86 (2.14)	57 (1.18)	47 (1.21)	76 (0.82)	261 (0.54)
Education	Didn't go to school	40 (0.06)	5 (0.12)	3 (0.06)	7 (0.18)	4 (0.04)	21 (0.04)
	Grade school (1-4 years)	158 (0.22)	21 (0.52)	27 (0.56)	9 (0.23)	15 (0.16)	86 (0.18)
	Grade school (5-8 years)	558 (0.79)	95 (2.37)	85 (1.76)	41 (1.05)	58 (0.62)	279 (0.58)
	Some high school (9-11 years)	2002 (2.84)	249 (6.2)	285 (5.91)	154 (3.95)	279 (3)	1035 (2.14)

	High school diploma or GED	11127 (15.78)	848 (21.12)	864 (17.91)	694 (17.81)	1427 (15.35)	7294 (15.05)
	Vocational or training school	6662 (9.45)	445 (11.08)	589 (12.21)	431 (11.06)	914 (9.83)	4283 (8.84)
	Some college or Associate Degree	19009 (26.96)	1130 (28.14)	1407 (29.17)	1166 (29.93)	2708 (29.13)	12598 (25.99)
	College graduate or Baccalaureate Degree	8388 (11.9)	368 (9.16)	477 (9.89)	389 (9.98)	1029 (11.07)	6125 (12.64)
	Some post-graduate or professional	8706 (12.35)	333 (8.29)	438 (9.08)	414 (10.63)	1113 (11.97)	6408 (13.22)
	Master's Degree	11767 (16.69)	449 (11.18)	544 (11.28)	492 (12.63)	1484 (15.96)	8798 (18.15)
	Doctoral Degree (Ph.D,M.D.,J.D.,etc.)	2084 (2.96)	73 (1.82)	104 (2.16)	99 (2.54)	266 (2.86)	1542 (3.18)
Race categories for NIH reporting	American Indian/Alaska Native	193 (0.27)	21 (0.52)	36 (0.75)	23 (0.59)	27 (0.29)	86 (0.18)
	Asian	2020 (2.87)	95 (2.37)	175 (3.63)	109 (2.8)	305 (3.28)	1336 (2.76)
	Native Hawaiian/Other PI	50 (0.07)	3 (0.07)	7 (0.15)	5 (0.13)	9 (0.1)	26 (0.05)
	Black	4229 (6)	528 (13.15)	640 (13.27)	589 (15.12)	868 (9.34)	1604 (3.31)
	White	62186 (88.21)	3206 (79.83)	3729 (77.32)	3022 (77.57)	7764 (83.51)	44465 (91.74)
	More than one race	732 (1.04)	38 (0.95)	64 (1.33)	52 (1.33)	138 (1.48)	440 (0.91)
	Unknown/Not reported	1091 (1.55)	125 (3.11)	172 (3.57)	96 (2.46)	186 (2)	512 (1.06)
HRT use ever	Never used hormones	19384 (27.49)	1333 (33.19)	1509 (31.29)	1147 (29.44)	2555 (27.48)	12840 (26.49)
	Past hormone user	13666 (19.38)	858 (21.36)	980 (20.32)	778 (19.97)	1856 (19.96)	9194 (18.97)
	Current hormone user	36122 (51.24)	1689 (42.06)	2224 (46.11)	1917 (49.2)	4733 (50.91)	25559 (52.73)

	Missing	1329 (1.89)	136 (3.39)	110 (2.28)	54 (1.39)	153 (1.65)	876 (1.81)
Eat lunch, times/wk	Never or less than once	3213 (4.56)	2024 (50.4)	324 (6.72)	114 (2.93)	184 (1.98)	567 (1.17)
	1-2 times	3772 (5.35)	521 (12.97)	1894 (39.27)	314 (8.06)	340 (3.66)	703 (1.45)
	3-4 times	5870 (8.33)	315 (7.84)	679 (14.08)	1017 (26.1)	1413 (15.2)	2446 (5.05)
	5-6 times	14676 (20.82)	410 (10.21)	985 (20.42)	1448 (37.17)	4611 (49.6)	7222 (14.9)
	7 or more times	42150 (59.79)	645 (16.06)	842 (17.46)	927 (23.79)	2602 (27.99)	37134 (76.61)
	Missing	820 (1.16)	101 (2.51)	99 (2.05)	76 (1.95)	147 (1.58)	397 (0.82)
Oral contraceptive use ever	No	41126 (58.33)	2473 (61.58)	2669 (55.34)	2053 (52.7)	5099 (54.85)	28832 (59.49)
	Yes	29375 (41.67)	1543 (38.42)	2154 (44.66)	1843 (47.3)	4198 (45.15)	19637 (40.51)
Number of Term Pregnancies	Never pregnant	7056 (10.01)	379 (9.44)	417 (8.65)	310 (7.96)	884 (9.51)	5066 (10.45)
	Never had term pregnancy	1818 (2.58)	127 (3.16)	141 (2.92)	141 (3.62)	275 (2.96)	1134 (2.34)
	1	6210 (8.81)	405 (10.08)	522 (10.82)	425 (10.91)	866 (9.31)	3992 (8.24)
	2	18563 (26.33)	1038 (25.85)	1253 (25.98)	994 (25.51)	2452 (26.37)	12826 (26.46)
	3	17164 (24.35)	916 (22.81)	1073 (22.25)	884 (22.69)	2234 (24.03)	12057 (24.88)
	4	10196 (14.46)	574 (14.29)	664 (13.77)	567 (14.55)	1333 (14.34)	7058 (14.56)
	5+	9151 (12.98)	556 (13.84)	732 (15.18)	553 (14.19)	1198 (12.89)	6112 (12.61)
	Missing	343 (0.49)	21 (0.52)	21 (0.44)	22 (0.56)	55 (0.59)	224 (0.46)

Smoked at least 100 cigarettes ever	No	35424 (50.25)	1752 (43.63)	2225 (46.13)	1672 (42.92)	4444 (47.8)	25331 (52.26)
	Yes	35077 (49.75)	2264 (56.37)	2598 (53.87)	2224 (57.08)	4853 (52.2)	23138 (47.74)
Mammogram in last 5 years	Yes	66158 (93.84)	3614 (89.99)	4363 (90.46)	3589 (92.12)	8672 (93.28)	45920 (94.74)
	No	3604 (5.11)	348 (8.67)	401 (8.31)	270 (6.93)	521 (5.6)	2064 (4.26)
	Missing	739 (1.05)	54 (1.34)	59 (1.22)	37 (0.95)	104 (1.12)	485 (1)
How many mammograms in last 5 years	1	4181 (5.93)	359 (8.94)	411 (8.52)	353 (9.06)	643 (6.92)	2415 (4.98)
	2	7974 (11.31)	572 (14.24)	657 (13.62)	499 (12.81)	1128 (12.13)	5118 (10.56)
	3	9547 (13.54)	544 (13.55)	676 (14.02)	576 (14.78)	1315 (14.14)	6436 (13.28)
	4	11721 (16.63)	597 (14.87)	752 (15.59)	618 (15.86)	1671 (17.97)	8083 (16.68)
	5 or more	32365 (45.91)	1523 (37.92)	1835 (38.05)	1531 (39.3)	3868 (41.6)	23608 (48.71)
	Missing	4713 (6.69)	421 (10.48)	492 (10.2)	319 (8.19)	672 (7.23)	2809 (5.8)
How many physical breast exams in last 5 years	None	1586 (2.25)	127 (3.16)	167 (3.46)	118 (3.03)	219 (2.36)	955 (1.97)
	1 exam	3704 (5.25)	323 (8.04)	351 (7.28)	307 (7.88)	507 (5.45)	2216 (4.57)
	2 exams	6272 (8.9)	508 (12.65)	538 (11.15)	386 (9.91)	908 (9.77)	3932 (8.11)
	3 exams	7503 (10.64)	485 (12.08)	545 (11.3)	521 (13.37)	1103 (11.86)	4849 (10)
	4 exams	9533 (13.52)	520 (12.95)	651 (13.5)	518 (13.3)	1413 (15.2)	6431 (13.27)

	5 or more exams	40723 (57.76)	1930 (48.06)	2465 (51.11)	1969 (50.54)	4969 (53.45)	29390 (60.64)
	Missing	1180 (1.67)	123 (3.06)	106 (2.2)	77 (1.98)	178 (1.91)	696 (1.44)
Age at screening[a]		63.38 (7.31)	63.15 (7.44)	61.72 (7.53)	60.91 (6.94)	61.76 (7.19)	64.07 (7.21)
Body-mass Index (BMI), kg/m^2 [a]		27.11 (5.77)	27.79 (6.37)	28.12 (6.29)	28.57 (6.64)	27.9 (5.89)	26.68 (5.5)
Dietary Energy (kcal/day)[a]		1585.93 (647.65)	1525.09 (795.28)	1575.72 (841.71)	1604.96 (780.13)	1562.02 (666.25)	1595.05 (593.85)
Total HEI-2015 score[a]		67.27 (10.24)	63.41 (11.13)	63.04 (10.68)	63.07 (10.25)	65.94 (10.11)	68.6 (9.81)
Alcohol servings per week[a]		2.63 (5.25)	2.67 (6.09)	2.61 (6.55)	2.57 (5.26)	2.61 (5.41)	2.63 (4.99)
Total energy expend from recreational phys activity (MET-hours/week)[a]		13.95 (14.33)	12.59 (15)	11.74 (14.37)	11.87 (14.58)	13.17 (14.16)	14.6 (14.23)
Energy expenditure from hard exercise (MET-hours/week)[a]		3.98 (8.54)	3.7 (8.57)	3.53 (8.35)	3.39 (8.08)	3.78 (8.21)	4.13 (8.65)
Energy expend from moderate exercise (MET-hours/week)[a]		3.42 (5.43)	3 (5.53)	2.72 (5.05)	2.75 (4.95)	3.24 (5.27)	3.61 (5.51)
Energy expenditure from mild exercise (MET-hours/week)[a]		1.38 (3.16)	1.16 (2.99)	1.16 (2.86)	1.4 (3.18)	1.4 (3.14)	1.42 (3.2)
Gail 5 year risk[a]		1.81 (1)	1.68 (1)	1.59 (0.97)	1.58 (0.92)	1.68 (0.98)	1.89 (1.01)

[1] Baseline is Year 1 of the WHI OS follow-up
[a] Mean (SD)
Abbreviations: WHI OS, Women's Health Initiative Observational Study; SD, standard deviation, HEI, Healthy Eating Index; BMI, body mass index; MET, metabolic equivalent of task; HRT, hormone replacement therapy.

Table 2. Baseline[1] characteristics (N (%) or Mean (SD), if noted) of eligible participants in the WHI OS population (1994-2020) by after dinner snack frequency.

		Eat after dinner, times/wk					
		Overall	Never or less than once	1-2 times	3-4 times	5-6 times	7 or more times
N		70501 (100)	16189 (22.96)	19196 (27.23)	16891 (23.96)	9897 (14.04)	8328 (11.81)
Eat breakfast, times/wk	Never or less than once	4016 (5.7)	1799 (11.11)	945 (4.92)	612 (3.62)	322 (3.25)	338 (4.06)
	1-2 times	4823 (6.84)	1237 (7.64)	1869 (9.74)	913 (5.41)	477 (4.82)	327 (3.93)
	3-4 times	3896 (5.53)	709 (4.38)	1116 (5.81)	1128 (6.68)	557 (5.63)	386 (4.63)
	5-6 times	9297 (13.19)	1688 (10.43)	2637 (13.74)	2677 (15.85)	1651 (16.68)	644 (7.73)
	7 or more times	48469 (68.75)	10756 (66.44)	12629 (65.79)	11561 (68.44)	6890 (69.62)	6633 (79.65)
Age group at screening	<50-59	23011 (32.64)	4647 (28.7)	6433 (33.51)	5649 (33.44)	3496 (35.32)	2786 (33.45)
	60-69	31272 (44.36)	7051 (43.55)	8453 (44.04)	7669 (45.4)	4392 (44.38)	3707 (44.51)
	70-79+	16218 (23)	4491 (27.74)	4310 (22.45)	3573 (21.15)	2009 (20.3)	1835 (22.03)
Family Income	Less than $10,000	2381 (3.38)	625 (3.86)	634 (3.3)	506 (3)	287 (2.9)	329 (3.95)
	$10,000 to $19,999	7274 (10.32)	1621 (10.01)	1870 (9.74)	1786 (10.57)	995 (10.05)	1002 (12.03)
	$20,000 to $34,999	15803 (22.42)	3208 (19.82)	4326 (22.54)	3948 (23.37)	2309 (23.33)	2012 (24.16)

	$35,000 to $49,999	14116 (20.02)	2983 (18.43)	3905 (20.34)	3486 (20.64)	2047 (20.68)	1695 (20.35)
	$50,000 to $74,999	14350 (20.35)	3180 (19.64)	3957 (20.61)	3452 (20.44)	2132 (21.54)	1629 (19.56)
	$75,000 to $99,999	6760 (9.59)	1698 (10.49)	1934 (10.08)	1542 (9.13)	937 (9.47)	649 (7.79)
	$100,000 to $149,999	5026 (7.13)	1402 (8.66)	1347 (7.02)	1142 (6.76)	640 (6.47)	495 (5.94)
	$150,000 or more	2837 (4.02)	906 (5.6)	748 (3.9)	580 (3.43)	326 (3.29)	277 (3.33)
	Don't know	1954 (2.77)	566 (3.5)	475 (2.47)	449 (2.66)	224 (2.26)	240 (2.88)
Body-mass Index (BMI), kg/m2	Underweight (< 18.5)	814 (1.15)	188 (1.16)	211 (1.1)	173 (1.02)	127 (1.28)	115 (1.38)
	Normal (18.5 - 24.9)	845 (1.2)	254 (1.57)	202 (1.05)	167 (0.99)	96 (0.97)	126 (1.51)
	Overweight (25.0 - 29.9)	28287 (40.12)	7581 (46.83)	7674 (39.98)	6268 (37.11)	3683 (37.21)	3081 (37)
	Obesity I (30.0 - 34.9)	23734 (33.66)	5146 (31.79)	6574 (34.25)	5896 (34.91)	3388 (34.23)	2730 (32.78)
	Obesity II (35.0 - 39.9)	10635 (15.08)	1945 (12.01)	2920 (15.21)	2785 (16.49)	1614 (16.31)	1371 (16.46)
	Extreme Obesity III (>= 40)	3884 (5.51)	662 (4.09)	1040 (5.42)	1003 (5.94)	627 (6.34)	552 (6.63)
Female relative had breast cancer	No	19779 (28.05)	4348 (26.86)	5323 (27.73)	4819 (28.53)	2870 (29)	2419 (29.05)
	Yes	12686 (17.99)	2958 (18.27)	3424 (17.84)	2974 (17.61)	1825 (18.44)	1505 (18.07)
	Missing	38036 (53.95)	8883 (54.87)	10449 (54.43)	9098 (53.86)	5202 (52.56)	4404 (52.88)
Cancer ever, excluding non-melanoma skin cancer	No	65140 (92.4)	14929 (92.22)	17740 (92.42)	15634 (92.56)	9156 (92.51)	7681 (92.23)

	Yes	5263 (7.47)	1240 (7.66)	1426 (7.43)	1234 (7.31)	728 (7.36)	635 (7.62)
	Missing	98 (0.14)	20 (0.12)	30 (0.16)	23 (0.14)	13 (0.13)	12 (0.14)
Diabetes ever	Yes	66881 (94.87)	15557 (96.1)	18304 (95.35)	16006 (94.76)	9352 (94.49)	7662 (92)
	Diabetes ever	3556 (5.04)	620 (3.83)	870 (4.53)	871 (5.16)	537 (5.43)	658 (7.9)
	Missing	64 (0.09)	12 (0.07)	22 (0.11)	14 (0.08)	8 (0.08)	8 (0.1)
Thyroid gland problem ever	No	52403 (74.33)	12198 (75.35)	14404 (75.04)	12570 (74.42)	7268 (73.44)	5963 (71.6)
	Yes	17723 (25.14)	3911 (24.16)	4685 (24.41)	4243 (25.12)	2568 (25.95)	2316 (27.81)
	Missing	375 (0.53)	80 (0.49)	107 (0.56)	78 (0.46)	61 (0.62)	49 (0.59)
Eat dinner, times/wk	Never or less than once	2276 (3.23)	1391 (8.59)	467 (2.43)	213 (1.26)	106 (1.07)	99 (1.19)
	1-2 times	2514 (3.57)	824 (5.09)	1233 (6.42)	274 (1.62)	108 (1.09)	75 (0.9)
	3-4 times	2058 (2.92)	484 (2.99)	612 (3.19)	531 (3.14)	288 (2.91)	143 (1.72)
	5-6 times	8314 (11.79)	1608 (9.93)	2671 (13.91)	2259 (13.37)	1289 (13.02)	487 (5.85)
	7 or more times	54812 (77.75)	11798 (72.88)	14052 (73.2)	13485 (79.84)	8020 (81.03)	7457 (89.54)
	Missing	527 (0.75)	84 (0.52)	161 (0.84)	129 (0.76)	86 (0.87)	67 (0.8)
Education	Didn't go to school	40 (0.06)	17 (0.11)	10 (0.05)	8 (0.05)	3 (0.03)	2 (0.02)
	Grade school (1-4 years)	158 (0.22)	75 (0.46)	35 (0.18)	22 (0.13)	9 (0.09)	17 (0.2)
	Grade school (5-8 years)	558 (0.79)	228 (1.41)	134 (0.7)	87 (0.52)	52 (0.53)	57 (0.68)
	Some high school (9-11 years)	2002 (2.84)	480 (2.96)	522 (2.72)	458 (2.71)	261 (2.64)	281 (3.37)

	High school diploma or GED	11127 (15.78)	2160 (13.34)	2996 (15.61)	2834 (16.78)	1645 (16.62)	1492 (17.92)
	Vocational or training school	6662 (9.45)	1478 (9.13)	1800 (9.38)	1659 (9.82)	920 (9.3)	805 (9.67)
	Some college or Associate Degree	19009 (26.96)	4182 (25.83)	5269 (27.45)	4710 (27.88)	2599 (26.26)	2249 (27.01)
	College graduate or Baccalaureate Degree	8388 (11.9)	2152 (13.29)	2343 (12.21)	1866 (11.05)	1164 (11.76)	863 (10.36)
	Some post-graduate or professional	8706 (12.35)	2191 (13.53)	2334 (12.16)	2020 (11.96)	1193 (12.05)	968 (11.62)
	Master's Degree	11767 (16.69)	2669 (16.49)	3179 (16.56)	2768 (16.39)	1784 (18.03)	1367 (16.41)
	Doctoral Degree (Ph.D,M.D.,J.D.,etc.)	2084 (2.96)	557 (3.44)	574 (2.99)	459 (2.72)	267 (2.7)	227 (2.73)
Race categories for NIH reporting	American Indian/Alaska Native	193 (0.27)	55 (0.34)	57 (0.3)	44 (0.26)	16 (0.16)	21 (0.25)
	Asian	2020 (2.87)	509 (3.14)	557 (2.9)	516 (3.05)	248 (2.51)	190 (2.28)
	Native Hawaiian/Other PI	50 (0.07)	15 (0.09)	17 (0.09)	12 (0.07)	3 (0.03)	3 (0.04)
	Black	4229 (6)	919 (5.68)	1342 (6.99)	1066 (6.31)	536 (5.42)	366 (4.39)
	White	62186 (88.21)	14187 (87.63)	16706 (87.03)	14847 (87.9)	8893 (89.86)	7553 (90.69)
	More than one race	732 (1.04)	149 (0.92)	210 (1.09)	193 (1.14)	97 (0.98)	83 (1)
	Unknown/Not reported	1091 (1.55)	355 (2.19)	307 (1.6)	213 (1.26)	104 (1.05)	112 (1.34)
HRT use ever	Never used hormones	19384 (27.49)	4538 (28.03)	5291 (27.56)	4589 (27.17)	2615 (26.42)	2351 (28.23)
	Past hormone user	13666 (19.38)	3107 (19.19)	3583 (18.67)	3370 (19.95)	1903 (19.23)	1703 (20.45)
	Current hormone user	36122 (51.24)	8172 (50.48)	9968 (51.93)	8663 (51.29)	5214 (52.68)	4105 (49.29)

	Missing	1329 (1.89)	372 (2.3)	354 (1.84)	269 (1.59)	165 (1.67)	169 (2.03)
Eat lunch, times/wk	Never or less than once	3213 (4.56)	1683 (10.4)	675 (3.52)	425 (2.52)	205 (2.07)	225 (2.7)
	1-2 times	3772 (5.35)	1029 (6.36)	1595 (8.31)	626 (3.71)	292 (2.95)	230 (2.76)
	3-4 times	5870 (8.33)	1203 (7.43)	1701 (8.86)	1615 (9.56)	819 (8.28)	532 (6.39)
	5-6 times	14676 (20.82)	2759 (17.04)	4331 (22.56)	4124 (24.42)	2403 (24.28)	1059 (12.72)
	7 or more times	42150 (59.79)	9352 (57.77)	10658 (55.52)	9904 (58.63)	6056 (61.19)	6180 (74.21)
	Missing	820 (1.16)	163 (1.01)	236 (1.23)	197 (1.17)	122 (1.23)	102 (1.22)
Oral contraceptive use ever	No	41126 (58.33)	9770 (60.35)	11069 (57.66)	9688 (57.36)	5597 (56.55)	5002 (60.06)
	Yes	29375 (41.67)	6419 (39.65)	8127 (42.34)	7203 (42.64)	4300 (43.45)	3326 (39.94)
Number of Term Pregnancies	Never pregnant	7056 (10.01)	1748 (10.8)	1839 (9.58)	1604 (9.5)	1002 (10.12)	863 (10.36)
	Never had term pregnancy	1818 (2.58)	486 (3)	508 (2.65)	390 (2.31)	232 (2.34)	202 (2.43)
	1	6210 (8.81)	1468 (9.07)	1709 (8.9)	1440 (8.53)	878 (8.87)	715 (8.59)
	2	18563 (26.33)	4198 (25.93)	5007 (26.08)	4527 (26.8)	2616 (26.43)	2215 (26.6)
	3	17164 (24.35)	3834 (23.68)	4683 (24.4)	4183 (24.76)	2416 (24.41)	2048 (24.59)
	4	10196 (14.46)	2353 (14.53)	2842 (14.81)	2412 (14.28)	1424 (14.39)	1165 (13.99)
	5+	9151 (12.98)	2024 (12.5)	2521 (13.13)	2258 (13.37)	1273 (12.86)	1075 (12.91)
	Missing	343 (0.49)	78 (0.48)	87 (0.45)	77 (0.46)	56 (0.57)	45 (0.54)

Smoked at least 100 cigarettes ever	No	35424 (50.25)	8204 (50.68)	10013 (52.16)	8605 (50.94)	4805 (48.55)	3797 (45.59)
	Yes	35077 (49.75)	7985 (49.32)	9183 (47.84)	8286 (49.06)	5092 (51.45)	4531 (54.41)
Mammogram in last 5 years	Yes	66158 (93.84)	15067 (93.07)	18063 (94.1)	15878 (94)	9343 (94.4)	7807 (93.74)
	No	3604 (5.11)	935 (5.78)	928 (4.83)	851 (5.04)	458 (4.63)	432 (5.19)
	Missing	739 (1.05)	187 (1.16)	205 (1.07)	162 (0.96)	96 (0.97)	89 (1.07)
How many mammograms in last 5 years	1	4181 (5.93)	1026 (6.34)	1096 (5.71)	978 (5.79)	563 (5.69)	518 (6.22)
	2	7974 (11.31)	1782 (11.01)	2313 (12.05)	1893 (11.21)	1080 (10.91)	906 (10.88)
	3	9547 (13.54)	2158 (13.33)	2707 (14.1)	2282 (13.51)	1298 (13.12)	1102 (13.23)
	4	11721 (16.63)	2493 (15.4)	3249 (16.93)	2953 (17.48)	1709 (17.27)	1317 (15.81)
	5 or more	32365 (45.91)	7520 (46.45)	8600 (44.8)	7684 (45.49)	4643 (46.91)	3918 (47.05)
	Missing	4713 (6.69)	1210 (7.47)	1231 (6.41)	1101 (6.52)	604 (6.1)	567 (6.81)
How many physical breast exams in last 5 years	None	1586 (2.25)	399 (2.46)	399 (2.08)	355 (2.1)	221 (2.23)	212 (2.55)
	1 exam	3704 (5.25)	883 (5.45)	967 (5.04)	846 (5.01)	511 (5.16)	497 (5.97)
	2 exams	6272 (8.9)	1424 (8.8)	1766 (9.2)	1487 (8.8)	862 (8.71)	733 (8.8)
	3 exams	7503 (10.64)	1709 (10.56)	2135 (11.12)	1856 (10.99)	1017 (10.28)	786 (9.44)
	4 exams	9533 (13.52)	2055 (12.69)	2664 (13.88)	2402 (14.22)	1334 (13.48)	1078 (12.94)

	5 or more exams	40723 (57.76)	9375 (57.91)	10948 (57.03)	9678 (57.3)	5820 (58.81)	4902 (58.86)
	Missing	1180 (1.67)	344 (2.12)	317 (1.65)	267 (1.58)	132 (1.33)	120 (1.44)
Age at screening[a]		63.38 (7.31)	64.32 (7.42)	63.22 (7.32)	63.12 (7.21)	62.78 (7.19)	63.18 (7.26)
Body-mass Index (BMI), kg/m^2 [a]		27.11 (5.77)	26.24 (5.52)	27.12 (5.67)	27.46 (5.7)	27.52 (5.91)	27.59 (6.19)
Dietary Energy (kcal/day)[a]		1585.93 (647.65)	1500.15 (625.73)	1537.91 (614.84)	1597.85 (631.63)	1674.27 (680.17)	1734.23 (713.07)
Total HEI-2015 score[a]		67.27 (10.24)	68.65 (10)	67.37 (10.11)	66.89 (10.13)	66.36 (10.39)	66.17 (10.69)
Alcohol servings per week[a]		2.63 (5.25)	3.9 (6.69)	2.61 (5.15)	2.19 (4.52)	1.98 (4.22)	1.82 (4.24)
Total energy expend from recreational phys activity (MET-hours/week)[a]		13.95 (14.33)	15.71 (15.43)	13.91 (14.24)	13.18 (13.6)	12.97 (13.57)	13.37 (14.31)
Energy expenditure from hard exercise (MET-hours/week)[a]		3.98 (8.54)	4.64 (9.36)	3.95 (8.42)	3.63 (8.02)	3.69 (8.13)	3.8 (8.59)
Energy expend from moderate exercise (MET-hours/week)[a]		3.42 (5.43)	3.65 (5.77)	3.4 (5.34)	3.3 (5.24)	3.22 (5.18)	3.46 (5.59)
Energy expenditure from mild exercise (MET-hours/week)[a]		1.38 (3.16)	1.5 (3.4)	1.43 (3.18)	1.34 (3.04)	1.3 (3.07)	1.24 (2.97)
Gail 5 year risk[a]		1.81 (1)	1.85 (1.02)	1.79 (1)	1.8 (1.02)	1.8 (0.98)	1.81 (1)

[1] Baseline is Year 1 of the WHI OS follow-up
[a] Mean (SD)
Abbreviations: WHI OS, Women's Health Initiative Observational Study; SD, standard deviation, HEI, Healthy Eating Index; BMI, body mass index; MET, metabolic equivalent of task; HRT, Hormone replacement therapy.

Table 3. Relative risk[b] of Breast Cancer (all, invasive, in situ) by breakfast frequency, Women's Health Initiative Observational Study, 1994–2020

Model[a]	Breakfast frequency	Person-time[c]	All breast			Invasive			In situ		
			N cases	HR (95% CI)	P for trend[e]	N cases	HR (95% CI)	P for trend[e]	N cases	HR (95% CI)	P for trend[e]
Model 1	Never or less than once	54461.41	266	Reference	0.006	227	Reference	0.06	40	Reference	0.007
	1-2 times	65846.48	324	1.01 (0.86, 1.19)		272	1 (0.83, 1.19)		57	1.16 (0.77, 1.74)	
	3-4 times	55154.12	282	1.05 (0.89, 1.24)		236	1.03 (0.86, 1.24)		53	1.27 (0.84, 1.92)	
	5-6 times	134407.8	738	1.12 (0.98, 1.29)		617	1.11 (0.95, 1.29)		129	1.28 (0.9, 1.82)	
	7 or more times	724348.4	4014[d]	1.13 (1, 1.28)		3315	1.09 (0.96, 1.25)		762	1.43 (1.04, 1.97)	
Model 2	Never or less than once			Reference	0.07		Reference	0.28		Reference	0.02
	1-2 times			1 (0.85, 1.18)			0.99 (0.83, 1.18)			1.15 (0.77, 1.72)	
	3-4 times			1.03 (0.87, 1.22)			1.02 (0.85, 1.23)			1.25 (0.83, 1.89)	
	5-6 times			1.09 (0.95, 1.26)			1.08 (0.93, 1.26)			1.24 (0.87, 1.76)	
	7 or more times			1.09 (0.96, 1.23)			1.05 (0.92, 1.21)			1.37 (0.99, 1.88)	
Model 3	Never or less than once			Reference	0.03		Reference	0.18		Reference	0.01
	1-2 times			1 (0.85, 1.17)			0.99 (0.83, 1.18)			1.12 (0.75, 1.69)	

	3-4 times			1.02 (0.86, 1.21)			1.01 (0.84, 1.21)			1.24 (0.82, 1.89)	
	5-6 times			1.1 (0.95, 1.26)			1.08 (0.92, 1.26)			1.26 (0.88, 1.81)	
	7 or more times			1.1 (0.97, 1.24)			1.06 (0.93, 1.22)			1.4 (1.01, 1.93)	
Model 4	Never or less than once			Reference	0.07		Reference	0.25		Reference	0.04
	1-2 times			0.99 (0.84, 1.17)			0.98 (0.82, 1.18)			1.12 (0.74, 1.69)	
	3-4 times			1.02 (0.86, 1.2)			1 (0.83, 1.21)			1.24 (0.82, 1.88)	
	5-6 times			1.09 (0.95, 1.25)			1.07 (0.92, 1.25)			1.23 (0.86, 1.77)	
	7 or more times			1.08 (0.95, 1.23)			1.05 (0.92, 1.21)			1.34 (0.97, 1.85)	
Model 5	Never or less than once			Reference	0.05		Reference	0.16		Reference	0.04
	1-2 times			1 (0.84, 1.17)			0.99 (0.83, 1.19)			1.1 (0.73, 1.67)	
	3-4 times			1.01 (0.85, 1.19)			0.99 (0.82, 1.19)			1.24 (0.82, 1.88)	
	5-6 times			1.09 (0.94, 1.25)			1.07 (0.92, 1.26)			1.21 (0.84, 1.73)	
	7 or more times			1.09 (0.96, 1.24)			1.06 (0.93, 1.22)			1.32 (0.96, 1.83)	

[a] Model 1 is adjusted for age and race; model 2 is adjusted for age, race, education, and income; model 3 is adjusted for age, race, education, income, physical activity, smoking, and alcohol intake; model 4 is adjusted for age, race, education, income, physical activity, smoking, alcohol intake, diet quality score (HEI 2015), energy intake; model 5 is adjusted for age, race, education, income, physical activity, smoking, alcohol intake, diet quality score (HEI 2015), energy intake, diabetes status, BMI.
[b] Calculated using Cox proportional hazards models and presented as hazard ratios and 95% confidence intervals.
[c] Person-years

[d] Incidence rate of developing breast cancer (all) in the WHI OS was 5.5 cases per 1,000 person-years among those who consumed breakfast from 1997 to February 28, 2020.
[e] The α level for the analyses is 0.05. The trend test calculation (Wald statistics) uses continuous exposure variables (range, 0-4).

Table 4 Relative risk[b] of Breast Cancer (all, invasive, in situ) by after dinner snack frequency, Women's Health Initiative Observational Study, 1994–2020

Model[a]	After dinner snack frequency	Person-time[c]	All breast			Invasive			In situ		
			N cases	HR (95% CI)	P for trend[e]	N cases	HR (95% CI)	P for trend[e]	N cases	HR (95% CI)	P for trend[e]
Model 1	Never or less than once	233625.5	1300[d]	1.02 (0.93, 1.12)	0.35	1074	0.99 (0.9, 1.1)	0.44	251	1.17 (0.94, 1.46)	0.55
	1-2 times	283001.8	1562	1.01 (0.93, 1.11)		1310	1 (0.91, 1.11)		272	1.03 (0.83, 1.29)	
	3-4 times	248847.9	1313	0.97 (0.88, 1.07)		1087	0.95 (0.86, 1.05)		239	1.03 (0.82, 1.29)	
	5-6 times	148240.9	793	0.98 (0.89, 1.09)		640	0.94 (0.84, 1.05)		167	1.2 (0.95, 1.53)	
	7 or more times	120502.1	656	Reference		556	Reference		112	Reference	
Model 2	Never or less than once			1 (0.91, 1.1)	0.62		0.97 (0.88, 1.08)	0.64		1.13 (0.91, 1.42)	0.76
	1-2 times			1 (0.92, 1.1)			1 (0.9, 1.1)			1.02 (0.82, 1.27)	
	3-4 times			0.96 (0.88, 1.06)			0.94 (0.85, 1.05)			1.02 (0.82, 1.28)	
	5-6 times			0.98 (0.88, 1.08)			0.93 (0.83, 1.04)			1.19 (0.94, 1.51)	
	7 or more times			Reference			Reference			Reference	
Model 3	Never or less than once			0.98 (0.89, 1.08)	0.99		0.95 (0.86, 1.06)	0.99		1.11 (0.89, 1.39)	0.93
	1-2 times			1 (0.91, 1.09)			0.99 (0.89, 1.09)			1.01 (0.81, 1.26)	
	3-4 times			0.96 (0.87, 1.06)			0.94 (0.85, 1.04)			1.02 (0.81, 1.28)	

	5-6 times			0.97 (0.88, 1.08)			0.93 (0.83, 1.04)			1.18 (0.93, 1.5)	
	7 or more times			Reference			Reference			Reference	
Model 4	Never or less than once			0.98 (0.89, 1.08)	0.87		0.96 (0.87, 1.07)	0.87		1.1 (0.87, 1.38)	0.95
	1-2 times			1 (0.91, 1.1)			0.99 (0.9, 1.1)			1 (0.8, 1.25)	
	3-4 times			0.96 (0.88, 1.06)			0.94 (0.85, 1.05)			1.02 (0.81, 1.27)	
	5-6 times			0.97 (0.88, 1.08)			0.93 (0.83, 1.04)			1.18 (0.93, 1.5)	
	7 or more times			Reference			Reference			Reference	
Model 5	Never or less than once			0.99 (0.9, 1.09)	0.85		0.97 (0.87, 1.08)	0.84		1.09 (0.86, 1.37)	0.99
	1-2 times			1 (0.91, 1.1)			0.99 (0.9, 1.1)			1 (0.8, 1.25)	
	3-4 times			0.96 (0.87, 1.06)			0.94 (0.85, 1.04)			1.01 (0.8, 1.26)	
	5-6 times			0.98 (0.88, 1.08)			0.94 (0.83, 1.05)			1.18 (0.92, 1.5)	
	7 or more times			Reference			Reference			Reference	

[a] Model 1 is adjusted for age and race; model 2 is adjusted for age, race, education, and income; model 3 is adjusted for age, race, education, income, physical activity, smoking, and alcohol intake; model 4 is adjusted for age, race, education, income, physical activity, smoking, alcohol intake, diet quality score (HEI 2015), energy intake; model 5 is adjusted for age, race, education, income, physical activity, smoking, alcohol intake, diet quality score (HEI 2015), energy intake, diabetes status, BMI.

[b] Calculated using Cox proportional hazards models and presented as hazard ratios and 95% confidence intervals.

[c] Person-years

[d] Incidence rate of developing breast cancer in the WHI OS was 5.6 cases per 1,000 person-years among those who avoided eating after dinner from 1997 to February 28, 2020.

[e] The α level for the analyses is 0.05. The trend test calculation (Wald statistics) uses continuous exposure variables (range, 0-4).

Table 5 Stratified analysis of the association between meal frequencies and risk of breast cancer by BMI, Women's Health Initiative Observational Study, 1994–2020.

			All breast		Invasive		In situ	
BMI[a]	**meal**	Frequency	HR (95%CI)[b]	P for trend[e]	HR (95%CI)[b]	P for trend[e]	HR (95%CI)[b]	P for trend[e]
Below median	After dinner snack	Never or less than once	1.02 (0.9, 1.16)	0.21	1 (0.87, 1.15)	0.26	1.17 (0.87, 1.57)	0.30
		1-2 times	1.01 (0.89, 1.14)		1 (0.87, 1.14)		1.03 (0.77, 1.38)	
		3-4 times	0.95 (0.83, 1.08)		0.92 (0.8, 1.06)		1.04 (0.77, 1.4)	
		5-6 times	0.93 (0.81, 1.08)		0.9 (0.77, 1.06)		1.05 (0.76, 1.46)	
		7 or more times	Reference		Reference		Reference	
	Breakfast	Never or less than once	Reference	0.72	Reference	0.78	Reference	0.76
		1-2 times	0.94 (0.75, 1.17)		0.97 (0.76, 1.24)		0.86 (0.51, 1.43)	
		3-4 times	0.93 (0.73, 1.18)		0.95 (0.73, 1.24)		0.94 (0.56, 1.59)	
		5-6 times	1.04 (0.86, 1.26)		1.09 (0.88, 1.34)		0.89 (0.58, 1.38)	
		7 or more times	0.99 (0.84, 1.17)		1.01 (0.84, 1.22)		0.96 (0.66, 1.41)	
Above Median	After dinner snack	Never or less than once	0.91 (0.79, 1.04)	0.18	0.9 (0.76, 1.06)	0.28	0.92 (0.63, 1.34)	0.15
		1-2 times	1 (0.88, 1.14)		0.98 (0.84, 1.14)		0.96 (0.68, 1.36)	
		3-4 times	0.97 (0.85, 1.1)		0.96 (0.82, 1.12)		0.96 (0.68, 1.36)	
		5-6 times	1 (0.87, 1.15)		0.97 (0.82, 1.15)		1.34 (0.93, 1.91)	

		7 or more times	Reference		Reference		Reference	
	Breakfast	Never or less than once	Reference	0.008	Reference	0.07	Reference	0.006
		1-2 times	1.08 (0.84, 1.38)		1.02 (0.78, 1.32)		1.81 (0.87, 3.79)	
		3-4 times	1.11 (0.87, 1.43)		1.04 (0.8, 1.36)		2.11 (1.01, 4.39)	
		5-6 times	1.15 (0.93, 1.43)		1.07 (0.85, 1.35)		2.13 (1.09, 4.17)	
		7 or more times	1.26 (1.05, 1.5)		1.14 (0.93, 1.4)		2.38 (1.26, 4.48)	

[a] Median BMI is 27.11 kg/m^2

[b] Calculated using Cox proportional hazards models and presented as hazard ratios and 95% confidence intervals. The models are adjusted for age, race, education, income, physical activity, smoking, alcohol intake, diet quality score (HEI 2015), energy intake, and diabetes status.

[c] The α level for the analyses is 0.05. The trend test calculation (Wald statistics) uses continuous exposure variables (range, 0-4).

Table 6 Stratified analysis of the association between meal frequencies and risk of breast cancer by smoking status, Women's Health Initiative Observational Study, 1994–2020.

			All breast		Invasive		In situ	
Smoking Ever	**Meal**	Frequency	HR (95%CI)[a]	P for trend[b]	HR (95%CI)[a]	P for trend[b]	HR (95%CI)[a]	P for trend[b]
No	After dinner snack	Never or less than once	1.02 (0.89, 1.18)	0.87	0.99 (0.85, 1.16)	0.97	1.22 (0.87, 1.71)	0.52
		1-2 times	1 (0.87, 1.15)		0.98 (0.85, 1.14)		1.08 (0.77, 1.5)	
		3-4 times	1.01 (0.88, 1.16)		0.99 (0.85, 1.15)		1.11 (0.79, 1.56)	
		5-6 times	1.02 (0.87, 1.19)		0.97 (0.82, 1.15)		1.21 (0.84, 1.74)	
		7 or more times	Reference		Reference		Reference	

	Breakfast	Never or less than once	Reference	0.06	Reference	0.3347	Reference	0.002
		1-2 times	0.97 (0.75, 1.26)		0.96 (0.74, 1.26)		1.19 (0.56, 2.52)	
		3-4 times	1.02 (0.78, 1.33)		1 (0.76, 1.33)		1.69 (0.81, 3.54)	
		5-6 times	1.04 (0.84, 1.3)		1 (0.79, 1.26)		1.83 (1.01, 3.48)	
		7 or more times	1.11 (0.91, 1.35)		1.06 (0.86, 1.3)		2 (1.09, 3.65)	
Yes	After dinner snack	Never or less than once	0.97 (0.85, 1.11)	0.80	0.96 (0.83, 1.1)	0.7015	1 (0.73, 1.36)	0.57
		1-2 times	1.02 (0.9, 1.15)		1.01 (0.88, 1.16)		0.95 (0.7, 1.29)	
		3-4 times	0.92 (0.81, 1.05)		0.9 (0.78, 1.04)		0.93 (0.68, 1.27)	
		5-6 times	0.95 (0.83, 1.1)		0.91 (0.78, 1.07)		1.15 (0.84, 1.6)	
		7 or more times	Reference		Reference		Reference	
	Breakfast	Never or less than once	Reference	0.22	Reference	0.21	Reference	0.99
		1-2 times	1.03 (0.83, 1.28)		1.04 (0.82, 1.32)		1.11 (0.68, 1.82)	
		3-4 times	1 (0.8, 1.25)		1.04 (0.81, 1.32)		1.06 (0.64, 1.76)	
		5-6 times	1.14 (0.94, 1.37)		1.18 (0.96, 1.45)		0.95 (0.61, 1.49)	
		7 or more times	1.09 (0.92, 1.29)		1.11 (0.92, 1.33)		1.04 (0.7, 1.54)	

[a] Calculated using Cox proportional hazards models and presented as hazard ratios and 95% confidence intervals. The models are adjusted for age, race, education, income, physical activity, alcohol intake, diet quality score (HEI 2015), energy intake, diabetes status, and BMI.

[b] The α level for the analyses is 0.05. The trend test calculation (Wald statistics) uses continuous exposure variables (range, 0-4).

Table 7. Stratified analysis of the association between meal frequencies and risk of breast cancer by after-dinner snack and breakfast frequencies, Women's Health Initiative Observational Study, 1994–2020.

			All breast		Invasive		In situ	
Strata	**Meal**	Frequency	HR (95%CI)[a]	P for trend[b]	HR (95%CI)[a]	P for trend[b]	HR (95%CI)[a]	P for trend[b]
After-dinner snack 0-2 times/wk	Breakfast	0-2 times/wk	0.91 (0.82, 0.99)	0.14	0.95 (0.84, 1.07)	0.37	0.78 (0.58, 0.98)	0.08
After-dinner snack 3-7 times/wk	Breakfast	0-2 times/wk	0.93 (0.8, 1.07)	0.29	0.92 (0.78, 1.08)	0.20	0.92 (0.65, 1.28)	0.21
Breakfast 0-2 times/wk	After-dinner snack	0-2 times/wk	0.97 (0.82, 1.15)	0.86	0.79 (0.53, 1.19)	0.82	0.79 (0.53, 1.19)	0.35
Breakfast 3-7 times/wk	After-dinner snack	0-2 times/wk	1.05 (1, 1.11)	0.26	1.06 (0.93, 1.21)	0.25	1.06 (0.93, 1.21)	0.27

[a] Calculated using Cox proportional hazards models and presented as hazard ratios and 95% confidence intervals. The models are adjusted for age, race, education, income, physical activity, smoking, alcohol intake, diet quality score (HEI 2015), energy intake, diabetes status, and BMI. Breakfast or after-dinner snacks 3-7 times/week are reference groups.

[b] The α level for the analyses is 0.05. The trend test calculation (Wald statistics) uses continuous exposure variables.

Table 8. Stratified analysis of the association between meal frequencies and risk of recurrence[a] of breast cancer by after-dinner snack and breakfast frequencies, Women's Health Initiative Observational Study, 1994–2020.

			All breast			Invasive			In situ		
Strata	**Meal**	Frequency (times/week)	N[1]	HR (95%CI)[b]	P for trend[c]	N[1]	HR (95%CI)[b]	P for trend[c]	N[1]	HR (95%CI)[b]	P for trend[c]
	Breakfast	0-2	35	Reference	0.99	29	Reference	0.87	6	Reference	0.60

After-dinner snack 0-2 times/wk		3-7	176	1 (0.68, 1.48)		138	0.97 (0.63, 1.48)		42	1.27 (0.52, 3.1)	
After-dinner snack 3-7 times/wk	Breakfast	0-2	25	Reference	0.48	22	Reference	0.31	4	Reference	0.09
		3-7	203	0.86 (0.56, 1.32)		159	0.78 (0.49, 1.25)		53	1.22 (0.43, 3.46)	
Breakfast 0-2 times/wk	Snack[2]	0-2	35	Reference	0.37	29	Reference	0.27	6	Reference	0.91
		3-7	25	1.28 (0.74, 2.2)		22	1.39 (0.77, 2.5)		4	1.08 (0.28, 4.17)	
Breakfast 3-7 times/wk	Snack2	0-2	176	Reference	0.78	138	Reference	0.86	42	Reference	0.02
		3-7	203	1.03 (0.83, 1.27)		159	1.02 (0.81, 1.3)		53	1.13 (0.74, 1.74)	

[a] Total of 4060 women who satisfied all inclusion criteria had a history of breast cancer at baseline. They developed 439 recurring breast cancers (248 invasive and 105 in situ) between 1994–2020.

[b] Calculated using Cox proportional hazards models and presented as hazard ratios and 95% confidence intervals. The models are adjusted for age, race, education, income, physical activity, smoking, alcohol intake, diet quality score (HEI 2015), energy intake, diabetes status, and BMI.

[c] The α level for the analyses is 0.05. The trend test calculation (Wald statistics) uses continuous exposure variables.

[1] Number of cases.

[2] After-dinner snacks.

Supplementary Table 1 Relative risk[a] of breast cancer (all, invasive, in situ) by after-dinner snacks and breakfast meal frequency, Women's Health Initiative Observational Study, 1994–2020, excluding all cases diagnosed during the first two years of the follow-up.

		All breast	Invasive	In situ
Meal	Frequency (per week)	HR (95%CI)[a]	HR (95%CI)[a]	HR (95%CI)[a]
After dinner snack	Never or less than once	1 (0.9, 1.11)	0.98 (0.87, 1.1)	1.07 (0.84, 1.37)
	1-2 times	0.95 (0.86, 1.05)	0.93 (0.84, 1.04)	0.97 (0.76, 1.23)
	3-4 times	1.04 (0.94, 1.15)	1.02 (0.91, 1.14)	1.08 (0.84, 1.37)
	5-6 times	1.03 (0.92, 1.15)	0.97 (0.86, 1.1)	1.27 (0.98, 1.64)
	7 or more times	Reference	Reference	Reference
Breakfast	Never or less than once	Reference	Reference	Reference
	1-2 times	0.98 (0.87, 1.1)	0.97 (0.8, 1.18)	1.21 (0.78, 1.88)
	3-4 times	0.93 (0.84, 1.04)	1.02 (0.84, 1.24)	1.27 (0.81, 1.98)
	5-6 times	1.02 (0.91, 1.14)	1.05 (0.89, 1.24)	1.31 (0.89, 1.92)
	7 or more times	0.97 (0.86, 1.1)	0.94 (0.81, 1.09)	1.26 (0.88, 1.78)

[a] Calculated using Cox proportional hazards models and presented as hazard ratios and 95% confidence intervals. The models are adjusted for age, race, education, income, physical activity, smoking, alcohol intake, diet quality score (HEI 2015), energy intake, diabetes status, and BMI.

Supplementary Table 2 Weighted relative risk[a] of breast cancer (all, invasive, in situ) by after-dinner snack and breakfast meal frequency, Women's Health Initiative Observational Study, 1994–2020.

		All breast	Invasive	In situ
Meal	Frequency (per week)	HR (95%CI)[a]	HR (95%CI)[a]	HR (95%CI)[a]
After dinner snack	Never or less than once	0.97 (0.91, 1.04)	0.95 (0.88, 1.02)	1.09 (0.93, 1.27)
	1-2 times	0.94 (0.88, 1.01)	0.93 (0.86, 1)	0.98 (0.84, 1.14)
	3-4 times	1.04 (0.98, 1.12)	1.02 (0.95, 1.1)	1.09 (0.93, 1.28)
	5-6 times	1.02 (0.94, 1.1)	0.96 (0.89, 1.05)	1.25 (1.06, 1.48)
	7 or more times	Reference	Reference	Reference
Breakfast	Never or less than once	Reference	Reference	Reference
	1-2 times	1.02 (0.84, 1.24)	0.96 (0.78, 1.19)	1.6 (0.96, 2.66)
	3-4 times	1.07 (0.87, 1.31)	1.03 (0.83, 1.28)	1.63 (0.96, 2.76)
	5-6 times	1.13 (0.95, 1.35)	1.07 (0.89, 1.29)	1.71 (1.07, 2.73)
	7 or more times	1.02 (0.88, 1.19)	0.95 (0.81, 1.12)	1.64 (1.07, 2.51)

[a] Calculated using Cox proportional hazards models and presented as hazard ratios and 95% confidence intervals. Estimated weighted HRs were derived using inverse probability weights adjusted for age, race, education, income, physical activity, smoking, alcohol intake, diet quality score (HEI 2015), energy intake, diabetes status, and BMI.

CHAPTER 2: Estimating the effect of hypothetical interventions of breakfast and post-dinner snack frequency on risk for type 2 diabetes: An emulated target trial with data from the Coronary Artery Risk Development in Young Adults (CARDIA) Study

ABSTRACT

Background: Previous observational studies have reported that habitual breakfast meal intake and nighttime (post-dinner) eating occasions predict future risk of type 2 diabetes. However, there are no long-term randomized trials testing interventions in these domains or alternative analytic approaches that inform the evidence base for the topic.

Objective: We estimated the effect of hypothetical interventions of different frequencies of long-term breakfast consumption and post-dinner snacking on type 2 diabetes risk via a target trial framework.

Methods: We emulated a target trial using observational data from 3737 subjects from the Coronary Artery Risk Development in Young Adults (CARDIA) Study. We applied the parametric g-formula to estimate the 20-y diabetes risk under several hypothetical intervention strategies (breakfast consumption 0-1, 2-4, and 5-7 times/week and post-dinner snack consumption 0-1, 2-4, and 5-7 times/week).

Results: During the 20-y follow-up, there were 501 incident cases of diabetes diagnosed. The estimated 20-y diabetes risks under a 0-1 times/week post-dinner snack strategy versus no intervention were 12.11% (95% CI: 9.94%, 15.72%) compared with 13.94% (95% CI: 11.27%, 16.36%) respectively (risk difference -1.82% (95% CI: -2.12%, -0.03%). The corresponding risk ratio was 0.87 (95% CI: 0.84, 1.01). Similarly, the estimated 20-y diabetes risks under a 5-7 times/week breakfast strategy was 13.53% (95% CI: 11.05%, 16.4%) (risk difference, -0.4% (95% CI: -0.52%, 0.32%) and risk ratio, 0.97 (95% CI: 0.96, 1.03) compared with no intervention).

Conclusions: The estimates from this analysis support that avoiding post-dinner snacks might be beneficial in reducing the long-term risk of diabetes; however, the role of starting regular breakfast consumption in midlife may have no major impact on the 20-y risk of diabetes.

INTRODUCTION/BACKGROUND

To move the field of nutritional epidemiology forward and provide more robust statistical estimates of the potential benefits of dietary interventions on the risk of the most common chronic diseases of the era, we need to consider alternative approaches toward analysis other than traditional predictive analyses. Previous research from several observational studies, including CARDIA, suggested that skipping breakfast was associated with an increased risk of a spectrum of metabolic conditions, including type 2 diabetes.[47],[48], [49] A few studies investigated the association between evening or night snacking and the incidence of type 2 diabetes, showing that late-night eating was associated with an increased risk of metabolic disease.[50],[51],[52] This association is hypothesized to be partially mediated by interrupted sleep patterns, which have an effect on glucose metabolism, obesity, and risk of diabetes. However, the associations in these studies may reflect prevalent exposure bias and residual confounding by other factors on the risk of diabetes.[53], [54], [55] Also, most of the noted existing studies considered only a single measurement of the breakfast/post-dinner snacking factors at baseline and do not account for changes in dietary habits and other associated factors over time, and do not estimate how changes in these aspects of dietary intake affect the risk of diabetes. Some studies analyzed repeated dietary measurements, but none have employed analytic methods that analyze observational data as if it were from a randomized trial (and thus attempt to estimate a causal effect of a hypothetical intervention), nor employed statistical methods accounting for potential time-dependent confounding. When there are time-varying exposures (changing dietary factors over time), incorporating time-varying confounders (e.g., overall diet quality, income, BMI) with traditional standard statistical methods used to adjust for confounding may not provide a valid estimate of risk.[56]

This study aims to apply modern causal inference modeling methods to CARDIA data and estimate the effect of long-term breakfast consumption and post-dinner snacking on type 2 diabetes risk via hypothetical interventions. We hypothesize that the hypothetical interventions of habitual breakfast consumption and avoiding post-dinner snack consumption will decrease the risk of developing type 2 diabetes over 20 years of follow-up in the CARDIA study. Analyzing longitudinal data in this manner will allow us to estimate the effectiveness of different dietary interventions related to breakfast eating and post-dinner snacking on diabetes risk since long-term randomized trial data is not available.

METHODS

First, we outline a hypothetical randomized trial design to test the above-noted question of interest, and then we proceed to describe the methods we used to emulate this randomized trial using the available observational data.

Target trial specification

Table 9 summarizes the key components of the target trial. Briefly, the trial would enroll healthy young adults. They would be randomly assigned to a dietary strategy intended to test how the frequency of different timing of day eating occasions impacts the risk of diabetes. The primary outcome would be a diagnosis of type 2 diabetes. Each eligible participant would be followed from treatment assignment until the loss to follow-up or administrative end of follow-up (20 years after assignment), whichever happens first.[16]

Dietary strategies. Participants would be randomly assigned to one of the following dietary strategies for 20 years to test the hypothesis: 1. Regular early morning eating(breakfast 5-7 times/wk), 2. Irregular to rare early morning eating(breakfast 2-4 times/wk), 3. Avoidance to rare morning eating (breakfast 0-1 time/wk), 4. Avoidance to rare post-dinner evening eating (post-dinner snacks 0-1 time/wk), 5. More frequent to habitual post-dinner evening eating (post-dinner snacks 2-4 times/wk), 6. Regular post-dinner evening eating (post-dinner snack 5-7 times/wk). Individuals assigned to a dietary strategy would be expected to maintain their dietary intake within the range prespecified by the corresponding intervention.[57] For example, an individual assigned to "breakfast 2-4 times/wk" would have to consume breakfast 2-4 servings per week, which may be operationalized as follows: at the beginning of each week, the participant would be asked how many days breakfast they would eat per week if they were now reassigned to "no intervention."[58] If the answer is between 2 and 4, the participant would be instructed to make

no dietary changes. If the answer is more than 4, the individual would be instructed to eat exactly 4 breakfasts per week: that is, to reach the maximum threshold of servings compatible with the intervention.[57], [58], [59]

Causal contrasts and statistical analysis. The target trial's primary(intent-to-treat) effect would be estimated by comparing 20-year diabetes risk since the randomization to each breakfast and post-dinner snack strategy(with adjustment for loss to follow-up, if necessary). However, the information provided by the intent-to-treat effect would be limited if, as expected, many individuals deviated from their dietary assignments during the 20-year follow-up. In this setting, a contrast of diabetes risks that would have been observed if all individuals had adhered to their assigned dietary strategy(i.e., per-protocol effect) may be more relevant for informing potential effects of the dietary approaches.[60] These risks can be estimated in the target trial using the parametric g-formula with the assumptions of no unmeasured confounding and selection bias(incomplete follow-up expanded to include questionnaire nonresponses and incomplete responses to dietary questions), no measurement error, and no model misspecification.[56], [60], [61], [62]

The parametric g-formula has been described elsewhere.[59] Briefly, the method is a generalized form of standardization in which the standardized risk of the outcome is calculated as a weighted average of the outcome risks conditional on the time-varying confounders, with the distribution of the time-varying confounders used as weights.[57] Threshold starts by estimating the distribution of the time-varying confounders and the outcome using linear or logistic regression models with previous dietary and covariate histories as covariates. For each dietary strategy, the conditional probabilities of the outcome given past covariates are then calculated under dietary values compatible with the intervention. Under the above assumptions, the probability of the

outcome that would have been observed if everyone in the population had adhered to the dietary strategy is the standardized(to confounder history) risk. The weighted average required for the standardization is approximated via a Monte Carlo simulation. Nonparametric bootstrapping with 1000 samples can be used to construct percentile-based 95% CIs of the estimated risks at the time points of interest.

To identify potential subgroups of participants for whom the intervention strategies may be more or less beneficial, subgroup analyses can be conducted in the study population defined at pre-baseline according to sex(males versus females), race(white vs. black), and pre-baseline BMI(<25 kg/m^2 vs. ≥ 25 kg/m^2).

Target trial emulation

We emulated the above target trial using data from the Coronary Artery Risk Development in Young Adults(CARDIA) study, a prospective cohort study initiated in 1984 to investigate lifestyle and other factors influencing coronary heart disease risk evolution in young adulthood.[63]

Observational data. A random sample of 5116 black and white women and men aged 18–30 years were recruited and examined in four urban areas: Birmingham, Alabama; Chicago, Illinois; Minneapolis, Minnesota; and Oakland, California. The frequency of breakfast, lunch, dinner, morning, afternoon, and post-dinner snacks(days/week) was assessed at years 7, 10, and 20 using an interviewer-administered CARDIA diet history questionnaire.[64] Diabetes status was assessed at examination years 0, 7, 10, 15, 20, 25, and 30 via the assessment of serum glucose levels.[63] Participants completed self-administered verified questionnaires to collect information on sociodemographic, psychosocial, and medical backgrounds at baseline and follow-up examinations.[65]

Eligibility criteria. We identified individuals in the above cohort who met all eligibility criteria to emulate the above target trial using CARDIA observational data (Figure 1). We applied all eligibility criteria to participants in the CARDIA study and also excluded subjects who did not have information on breakfast and post-dinner snack frequency, assessment of diabetes, had implausible energy intake(<600 kcal/day or >6,000 kcal/day for women and <800 kcal/day or >8,000 kcal/day for men) at year 7.

Modifications to the target trial protocol. Eligible individuals were followed from their baseline assessments until incomplete follow-up(lack of outcome measures or incomplete responses to dietary questions) or 20 years after baseline, whichever happened first. To utilize the most available data points, we defined baseline as year 10 follow-up. However, the available observational data impose significant assumptions for the emulation of the target trial protocol.[16]

Dietary strategies. First, dietary strategies described above cannot be directly emulated because dietary observational data lacked the timing of eating occasion measures. Therefore, we assumed that breakfast meal consumption frequency accurately reflects early morning eating frequency and post-dinner snack frequency reflects late evening eating frequency. For the analyses, we have defined dietary strategies as 0-1, 2-4, and 5-7 times/week for breakfast and a post-dinner snack. Eligible individuals were analyzed according to the following dietary strategies: 1. Regular early morning eating(breakfast 5-7 times/wk), 2. Irregular to rare early morning eating(breakfast 2-4 times/wk), 3. Avoidance to rare morning eating(breakfast 0-1 time/wk), 4. Avoidance to rare post-dinner evening eating (post-dinner snacks 0-1 time/wk), 5. More frequent to habitual post-dinner evening eating (post-dinner snacks 2-4 times/wk), 6. Regular post-dinner evening eating (post-dinner snack 5-7 times/wk).

Second, the dietary strategies described in the target trial cannot be directly emulated because dietary data were collected at years 7, 10, and 20 rather than yearly. Individuals were not asked about their intended breakfast and post-dinner snack consumption in the absence of an intervention. Therefore, we assumed that each breakfast and post-dinner snack frequency questionnaire accurately reflects 1) the average meal frequency during the gap periods between the assessments; and 2) the intended diet under no intervention that the individuals would have reported at the start of every follow-up period.

Third, we attempted to emulate the randomized assignment to the dietary strategies by adjusting for potential pre-baseline confounders: age at pre-baseline, sex, race, education, income, physical activity, smoking status, alcohol intake, diet quality, total energy intake, breakfast/post-dinner snack consumption. We anticipate that the available observational data will allow us to characterize diet for approximately 20 years and to adjust for known confounding; nevertheless, we realize that dietary not remain constant for 20 years.

Primary outcome.

An incidence of diabetes was defined as the use of diabetes medication(all years including 2 and 5), a fasting blood glucose concentration of ≥7 mmol/L(126 mg/dL), 2-hour post-challenge glucose ≥11.1 mmol/L(200 mg/dL), and/or an HbA1c ≥48 mmol/mol(6.5%).[65] The 2-hour glucose test was done at Years 10, 20, and 25, while HbA1c was done at Years 20 and 25. CARDIA did not differentiate between type 1 and type 2 diabetes mellitus; however, most incident cases identified during follow-up likely were type 2 diabetes, given the age of the cohort and known distributions of types 1 and 2 diabetes.[65]

Statistical analysis

We attempted to reproduce the risk that would have been obtained in a(hypothetical) target trial in which individuals had been randomly assigned and adhered to the above dietary strategies over 20 years. We then compared those risk estimates with the risk estimated under no dietary intervention. We applied the parametric g-formula using the above pre-baseline covariates and the following time-varying variables at years 10, 15, 20, 25, and 30: income, physical activity, smoking status, diet quality, total energy intake, breakfast/post-dinner snack consumption. If a time-varying covariate was not assessed in certain years, we carried forward the value from the last available measurement. If our emulation procedures had been successful, the risk estimates would have a straightforward interpretation because the target trial is well defined. However, our estimates are only valid under strong assumptions—no unmeasured confounding, no measurement error, and no model misspecification.

Sensitivity analysis. We also assessed the robustness of our estimates to various analytical decisions. Specifically, we 1) defined different cutoff points for exposure categories (0, 1-5, and 6-7 times/week for breakfast and post-dinner snacks, and 2) used only age, sex, race, and

education at pre-baseline as only pre-baseline confounders, 3) assessed dinner consumption and before bed eating as negative exposure control. We also evaluated the sensitivity of the estimates to model misspecification by using different functional forms for covariates(replaced identity function with the cubic function of a-priori diet quality and income); and by changing the order of time-varying covariates.

All analyses were conducted using SAS 9.4 software(SAS Institute, Inc., Cary, North Carolina) and the GFORMULA macro, which is publicly available at http://www.hsph.harvard.edu/causal/software.

RESULTS

Pre-baseline characteristics of participants

Out of 5115 screened participants of the IDEA study, 3737 were eligible for this analysis (Figure 1). Tables 10 and Table 11 show the pre-baseline characteristics of the participants by the frequency of breakfast and evening consumption at the pre-baseline. Of 3,737 eligible individuals, 44.6% were men. The mean age was 32 years, and 52% of the participants had a college education. During the 20-y follow-up, there were 501 incident cases of diabetes diagnosed. The observed 20-y diabetes risk was 15.51%. 863 individuals adhered to 5-7 time/week breakfast and 552 individuals adhered to 0-1 time/week post-dinner snack strategies throughout the entire follow-up period.

The 20-year risk of diabetes: emulated trial results

Table 12 shows the estimated 20-y risk of diabetes under breakfast and post-dinner snack strategies of 0-1, 2-4, and 5-7 times/week. The estimated 20-y risk of diabetes under no intervention was 13.94% (95% CI: 11.27%, 16.36%), comparable to the observed 15.51% risk. When comparing post-dinner snack intervention with no intervention, those who consumed post-dinner snack 0-1 times/week had 1.82% (95% CI: -2.12%, -0.03%) lower 20-year risk of diabetes. The estimated 20-y risk difference was -0.4% (95% CI: -0.52%, 0.32%) among those who consumed breakfast 5-7 times/week. The corresponding risk ratios were 0.87 (95% CI: 0.84, 1.01) among those who consumed post-dinner snacks 0-1 time/week and 0.97 (95% CI: 0.96, 1.03) among those who consumed breakfast 5-7 times/week. The average proportion of participants who would need to change their breakfast or post-dinner snack consumption to adhere to the proposed dietary strategies(had they adhered through the previous period) ranged between 50% and 90% for all treatment strategies(Table 12).

We also estimated the 10-y and 15-y risk of diabetes under those interventions(Table 13 and Table 14).

The estimated risks of diabetes and risk ratios were similar in subgroups defined by race for post-dinner snack and breakfast strategies(Table 15). Although the estimated 20-year risks of diabetes were overall higher among black, the estimated risk ratios (compared to no intervention) were similar among black and white participants for all interventions. The estimated risks were larger among participants with pre-baseline BMI≥25 than those with BMI < 25. For the dietary strategy of consuming post-dinner snack 0-1 times/week the estimated 20-y risk ratio (compared to no intervention) was 0.79 (95% CI: 0.65, 0.98) for participants with pre-baseline BMI <25, compared with 0.91 (95% CI: 0.88, 1.08) for participants with BMI ≥ 25. The risk ratios were similar among all BMI categories for breakfast meal strategies.

Sensitivity analyses

The risk estimates did not substantially change under any sensitivity analyses (Supplementary Table 3). The estimated risk ratio of diabetes under dinner and lunch as negative exposure control and the risk ratio of those to no intervention was close to null.

DISCUSSION

This manuscript describes the findings of the analysis of observational data that estimated the causal effects of hypothetical meal timing-related dietary interventions on the risk of type 2 diabetes in US young adults. The results suggest that limiting or avoiding post-dinner snacks may have a slight benefit for mitigating the risk of type 2 diabetes for over 20 years in young adults. Notably, this effect is applied to the participants with a BMI below 25 at the beginning of the study. On the other hand, the results suggest that habitual consumption of a morning meal (breakfast) has no protective effect against the 20-y risk of type 2 diabetes. Also, in shorter terms (10 and 15 years), neither avoidance of post-dinner snacks nor habitual consumption of breakfast meals have an effect on the risk of type 2 diabetes

The validity of our effect estimates cannot be directly confirmed because no randomized trials have assessed the effects of breakfast meals and post-dinner snack eating on the risk of diabetes. However, the potential impact of the timing of food intake on the risk of diabetes is informed by an understanding of glucose metabolism. A randomized crossover trial concluded that meal timing affected glucose tolerance, suggesting that late eating promoted significantly higher glucose levels than early eating.[66] Indeed, the timing of food intake is associated with improved 24-hour glucose levels, which suggests that consumption of food during the circadian day, independent of more traditional risk factors such as the amount or content of food intake, plays an important role in determining the risk of type 2 diabetes.[67], [68] Another trial suggests that skipping breakfast has a long-term influence on glucose regulation that persists throughout the day in individuals with type 2 diabetes.[69] However, other salient studies demonstrated no meaningful, beneficial effect of time-restricted eating on fasting glucose levels fasting insulin, HOMA-IR, and HbA1C.[4], [70], [71] As Cienfuegos suggested, fasting glucose is not likely to change when baseline values are in

the healthy range, which was the case for most of the participants of those trials.[72], [73] In this study, we excluded the subjects with prevalent diabetes diagnoses at baseline. Further investigation needs to be done to address how various frequencies of breakfast and post-dinner snack consumption affect the variability in glucose metabolism among participants with prediabetes and diabetes specifically.

Several studies have found that early time-restricted eating improves glycemic and insulin responses; however, none of those studies investigated the long-term effect of early eating.[67], [74] In supplemental analysis, we demonstrated that consuming regular breakfast might have a slightly beneficial effect on the prevention of diabetes (Table 6). However, this protective effect seems to disappear over the 20-y follow-up.

Besides the timing and frequency of breakfast consumption, meal size and composition play an essential role in glycemic control.[75] In this hypothetical trial, we did adjust for overall diet quality and total energy intake to emulate randomization; however, we did not assess how the effect of diet quality of individual meals on the risk of type 2 diabetes.

Given the current research interest in the effect of the chronotypes on energy and glucose metabolism in meal timing, it is reasonable to wonder how different chronotypes would interact with the treatment strategies assigned in this hypothetical trial. While the observational data used in this analysis did not allow us to assess the effect of the chronotype on the association between meal frequencies and type 2 diabetes, a recent meta-analysis compared evening and morning subjects by pooling the results of 8 cross-sectional studies.[76] It showed significantly higher fasting blood glucose concentrations in evening subjects than in morning subjects(mean difference: 7.82 (95% CI: 3.18, 12.45).[76] They have also reported a strong association between evening type and the risk of diabetes(odds ratio: 1.30 (95% CI: 1.20, 1.41). Chronotype directly

affects the frequency of breakfast meals and post-dinner snacking. Thus, further investigation needs to address the effect of the chronotype as a confounder in the association between meal frequencies and the risk of type 2 diabetes.

A previous CARDIA study suggested that daily breakfast consumption decreases the risk of type 2 diabetes (hazard ratio 0.81 (95% CI: 0.63, 1.05); these estimates cannot be interpreted in a straightforward manner even if we assume no unmeasured confounding, no measurement error, and no model misspecification. Here the target trial approach eliminates the above limitations. First, the target trial specification clarifies the question of interest as a randomized trial would include minimum and maximum breakfast and snack frequencies and the starting points and durations of the sustained dietary interventions and follow-up periods. Second, unlike traditional outcome regression, the g-formula appropriately adjusts for time-varying confounders affected by past exposure. Such time-varying confounders are often present when, for example, a newly appeared confounder(predictive of the outcome) influences future dietary patterns. Also, the confounder itself can be affected by past dietary patterns. For example, changes in diet quality, energy intake, and physical activity(which are predictive of the risk of diabetes) influence future consumption of breakfast and post-dinner snacks. Also, they can be affected by past breakfast and post-dinner snack habits.

Nevertheless, like any observational study, the target trial approach does not exclude the possibility of unmeasured confounding, measurement error, and model misspecification. Particularly, we cannot rule out the possibility of unmeasured confounding, despite adjustments for many potential confounders. An estimated null effect of dinner and lunch consumption frequency on the risk of diabetes(negative exposure control) is reassuring but not proof of lack of confounding. Although we cannot rule out bias due to model misspecification, our estimates under no dietary intervention

were close to observed ones, which suggested no gross model misspecification under the no intervention condition.[77] In addition, we relied on self-reported frequency of meals to measure dietary intake, and therefore some degree of measurement error in the diet was expected.[64] Finally, the results may not apply to populations with different dietary practices(because the effects are estimated compared to the usual diet) or race distributions(because we found differences among cohorts that might be explained by race).

In summary, we estimated that adhering to habitual breakfast consumption has almost no impact on the 20-y risk of diabetes while avoiding post-dinner snacks could slightly reduce the risk of type 2 diabetes in some populations. In the face of the lack of long-term randomized trials investigating the timing of eating occasions on the risk of type 2 diabetes, our explicit emulation of a target trial helped define and compare dietary strategies used to inform potential recommendations for diabetes prevention. Although our approach did not rule out the potential for influential unmeasured confounding and measurement errors, we could not access an alternative to rich longitudinal data from observational cohorts for estimating the effects of long-term diet.

TABLES AND FIGURE

Table 9. Emulation of a target trial of dietary interventions using observational data from the CARDIA study.

Component	Target trial specifications	Target trial emulation
Aim	To estimate the effect of the timing of eating occasions that likely influence circadian metabolic and energy intake considerations, specifically breakfast and post-dinner snack intake, on 20-year-risk of type 2 diabetes in healthy young US individuals.	Same. Due to the lack of timing of eating occasions measures in the observational data, we assumed that regular breakfast consumption stands for regular early morning eating and rare post-dinner snack consumption stands for rare post-dinner eating.
Eligibility criteria	Age 18 to 30 years. Exclusion criteria: prevalent diabetes at baseline.	Same. We also required complete questions on breakfast and post-dinner snack frequency, data composition, weight data, and plausible energy intake (<600 kcal/day or >6,000 kcal/day for women and <800 kcal/day or >8,000 kcal/day for men) at pre-baseline. Pre-baseline is defined as the Year 7 (1992-93) follow-up.
Treatment strategies	Each individual would be assigned to one of the following early morning and post-dinner eating strategies: • Regular early morning eating (breakfast 5-7 times/wk), • Irregular to rare early morning eating (breakfast 2-4 times/wk), • Avoidance to rare morning eating (breakfast 0-1 time/wk), • Avoidance to rare post-dinner evening eating (post-dinner snacks 0-1 times/wk), • More frequent to habitual post-dinner evening eating (post-dinner snacks 2-4 times/wk), • Regular post-dinner evening eating (post-dinner snack 5-7 times/wk), Participants assigned to a dietary strategy are expected to maintain their breakfast and post-dinner snack frequency within the range prespecified by the corresponding	Same. We assumed that breakfast consumption frequency accurately reflects early morning eating frequency and post-dinner snack frequency reflects late evening eating frequency.

	intervention.	
Treatment assignment	Participants are randomly assigned to a strategy at baseline and aware of their assigned strategy.	We attempted to emulate randomized assignment by adjusting for pre-baseline covariates: age, sex, ethnicity, income, breakfast frequency, post-dinner snack frequency, education, physical activity, smoking, alcohol consumption, diet quality, and total energy intake.
Follow-up	From assignment until withdrawal/loss to follow-up or administrative end of follow-up (20 years after assignment), whichever happens first.	Same. Incomplete follow-up is defined as non-participation in the outcome measure or nonresponses to the dietary frequency questionnaire. The complete follow-up period is 20 years.
Outcome	20-y risk of type 2 diabetes.	Same.
Causal contrast of interest	The intention-to-treat effect, i.e., the effect of being assigned to a regular early morning eating frequency vs. rare early morning eating frequency at baseline. The per-protocol effect, i.e., the effect that would have been observed if all subjects adhered to their assigned strategy over the 30-years follow-up.	Observational analog of the per-protocol effect.
Statistical analysis	Intention-to-treat analysis. Per-protocol analysis: apply g-formula to compare 20-month estimates between groups receiving each treatment strategy and no treatment group with adjustment for pre-baseline and time-varying covariates associated with adherence to strategies and loss to follow-up.	Same as per-protocol analysis.

Abbreviation: CARDIA, Coronary Artery Risk Development in Young Adults.

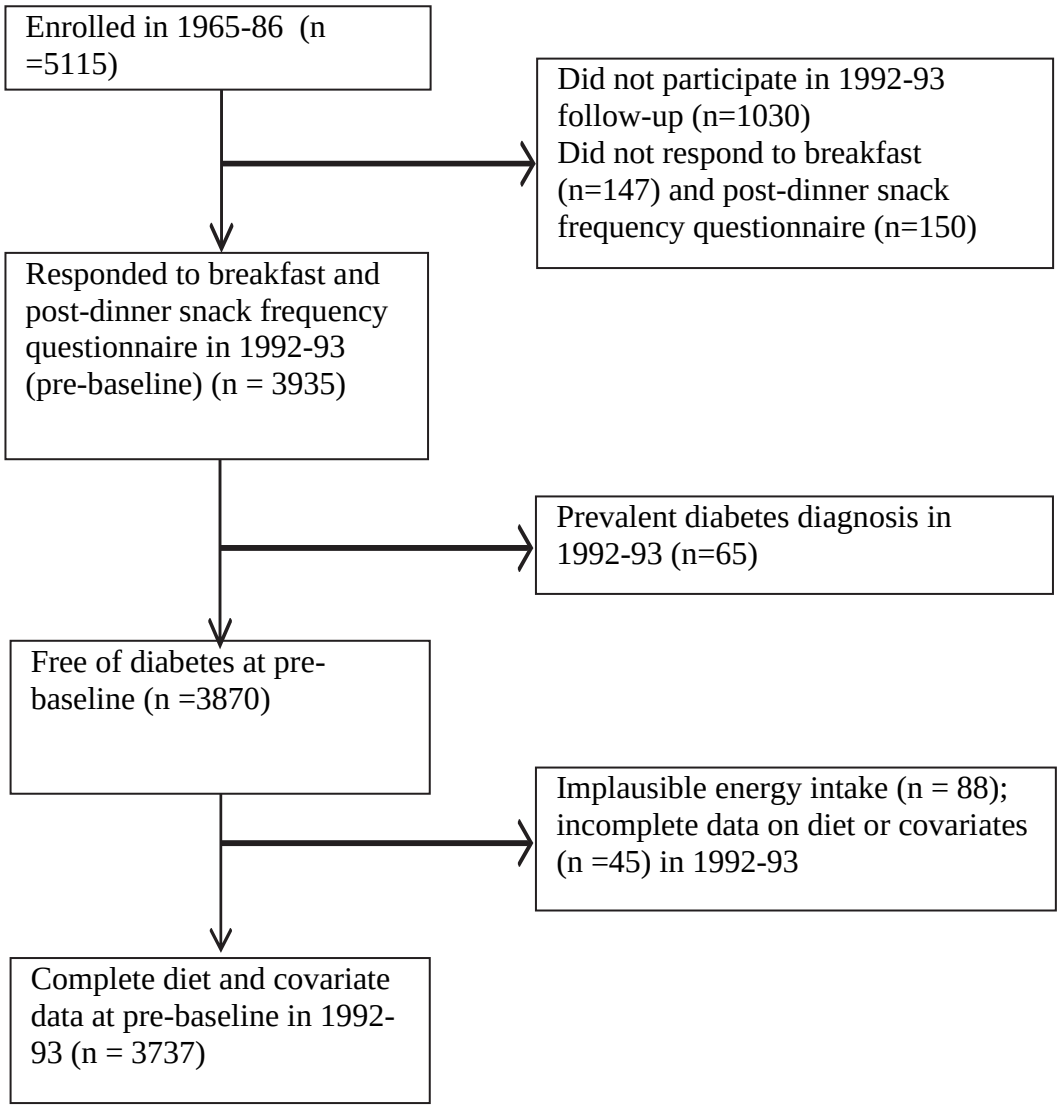


Figure 3. Flowchart of eligible individuals for the emulation of a target trial of dietary interventions in the CARDIA study, 1992–2016.

Table 10 Pre-baseline[1] characteristics (N (%)) of eligible participants in the CARDIA study by breakfast frequency.

Characteristics	Breakfast frequency, times/week				
	Overall (n=3737)	0-1 (n=767)	2-3 (n=856)	4-5 (n=634)	6-7 (n=1480)
Age at Year 7, years [a]	32 (3.6)	31.8 (3.8)	31.9 (3.7)	32 (3.6)	32.3 (3.5)
Male	1668 (44.63)	352 (45.89)	407 (47.55)	300 (47.32)	609 (41.15)
White	1744 (46.67)	427 (55.67)	554 (64.72)	330 (52.05)	433 (29.26)
Education					
Elementary school	10 (0.27)	2 (0.26)	5 (0.58)	. (.)	3 (0.2)
High school	1015 (27.16)	254 (33.12)	286 (33.41)	178 (28.08)	297 (20.07)
College	2012 (53.84)	411 (53.59)	463 (54.09)	341 (53.79)	797 (53.85)
Graduate school	700 (18.73)	100 (13.04)	102 (11.92)	115 (18.14)	383 (25.88)
Annual household income					
$15,999 or less	690 (18.46)	159 (20.73)	197 (23.01)	120 (18.93)	214 (14.46)
$16,000-$34,999	1120 (29.97)	267 (34.81)	253 (29.56)	203 (32.02)	397 (26.82)
$35,000-$49,999	735 (19.67)	134 (17.47)	172 (20.09)	128 (20.19)	301 (20.34)
$50,000-$74,999	650 (17.39)	118 (15.38)	135 (15.77)	110 (17.35)	287 (19.39)
$75,000 or greater	489 (13.09)	76 (9.91)	88 (10.28)	67 (10.57)	258 (17.43)
Don't know	32 (0.86)	5 (0.65)	7 (0.82)	5 (0.79)	15 (1.01)
No response	21 (0.56)	8 (1.04)	4 (0.47)	1 (0.16)	8 (0.54)
Smoking status					
1	607 (16.24)	103 (13.43)	124 (14.49)	90 (14.2)	290 (19.59)
2	976 (26.12)	297 (38.72)	276 (32.24)	166 (26.18)	237 (16.01)
0	2154 (57.64)	367 (47.85)	456 (53.27)	378 (59.62)	953 (64.39)
Physical activity [b]					
Physically inactive	234 (6.26)	60 (7.82)	57 (6.66)	36 (5.68)	81 (5.48)
Inactive-Moderately active	654 (17.5)	156 (20.34)	145 (16.94)	107 (16.88)	246 (16.62)
Moderately active	1743 (46.64)	369 (48.11)	445 (51.99)	293 (46.21)	636 (42.97)

Moderately active-Very active	688 (18.41)	116 (15.12)	127 (14.84)	119 (18.77)	326 (22.03)
Very active	418 (11.19)	66 (8.6)	82 (9.58)	79 (12.46)	191 (12.91)
Post-dinner snack, time/week					
0-1	1296 (34.68)	287 (37.42)	303 (35.4)	216 (34.07)	490 (33.11)
2-3	1069 (28.61)	223 (29.07)	258 (30.14)	191 (30.13)	397 (26.82)
4-5	718 (19.21)	118 (15.38)	145 (16.94)	137 (21.61)	318 (21.49)
6-7	654 (17.5)	139 (18.12)	150 (17.52)	90 (14.2)	275 (18.58)
Body Mass Index, kg/m^2 [a]	26.7 (6)	27.7 (6.4)	28 (6.4)	26.8 (6)	25.2 (5.2)
Alcohol, g/day [a]	10.1 (19.4)	12.6 (25)	10.9 (17.8)	9.6 (15.3)	8.6 (18.3)
Total energy intake, kcal[a]	2770.3 (1227.1)	2735.2 (1304.5)	2801.6 (1234.2)	2809.3 (1249)	2753.7 (1171.2)
A-priori diet quality score[a]	66.9 (12.3)	64.1 (11.3)	64.3 (11.8)	66 (11.6)	70.2 (12.4)

[a] Mean (SD)
[b] Physical activity in the past year
[1] Pre-baseline is year 7 follow-up of the CARDIA study (1992-93)
Abbreviations: CARDIA, Coronary Artery Risk Development in Young Adults

Table 11 Pre-baseline[1] characteristics (N (%)) of eligible participants in the CARDIA study by post-dinner snack frequency.

Characteristics	Post-dinner snack frequency, times/week				
	Overall (n=3737)	0-1 (n=1296)	2-3 (n=1069)	4-5 (n=718)	6-7 (n=654)
Age at Year 7, years [a]	32 (3.6)	32 (3.6)	32 (3.5)	32.1 (3.7)	32.1 (3.6)
Male	1668 (44.63)	530 (40.9)	473 (44.25)	345 (48.05)	320 (48.93)
White	1744 (46.67)	605 (46.68)	501 (46.87)	301 (41.92)	337 (51.53)
Education					
Elementary school	10 (0.27)	3 (0.23)	2 (0.19)	1 (0.14)	4 (0.61)
High school	1015 (27.16)	345 (26.62)	296 (27.69)	175 (24.37)	199 (30.43)
College	2012 (53.84)	691 (53.32)	578 (54.07)	399 (55.57)	344 (52.6)
Graduate school	700 (18.73)	257 (19.83)	193 (18.05)	143 (19.92)	107 (16.36)
Annual household income					
$15,999 or less	690 (18.46)	218 (16.82)	182 (17.03)	133 (18.52)	157 (24.01)
$16,000-$34,999	1120 (29.97)	379 (29.24)	332 (31.06)	217 (30.22)	192 (29.36)
$35,000-$49,999	735 (19.67)	250 (19.29)	205 (19.18)	151 (21.03)	129 (19.72)
$50,000-$74,999	650 (17.39)	240 (18.52)	201 (18.8)	121 (16.85)	88 (13.46)
$75,000 or greater	489 (13.09)	193 (14.89)	135 (12.63)	85 (11.84)	76 (11.62)
Don't know	32 (0.86)	9 (0.69)	6 (0.56)	7 (0.97)	10 (1.53)
No response	21 (0.56)	7 (0.54)	8 (0.74)	4 (0.56)	2 (0.31)
Smoking status					
1	607 (16.24)	218 (16.82)	158 (14.78)	123 (17.13)	108 (16.51)
2	976 (26.12)	344 (26.54)	277 (25.91)	169 (23.54)	186 (28.44)
0	2154 (57.64)	734 (56.64)	634 (59.31)	426 (59.33)	360 (55.05)
Physical activity [b]					
Physically inactive	234 (6.26)	83 (6.4)	59 (5.52)	38 (5.29)	54 (8.26)
Inactive-Moderately active	654 (17.5)	214 (16.51)	198 (18.52)	121 (16.85)	121 (18.5)

Moderately active	1743 (46.64)	625 (48.23)	491 (45.93)	348 (48.47)	279 (42.66)
Moderately active-Very active	688 (18.41)	225 (17.36)	216 (20.21)	129 (17.97)	118 (18.04)
Very active	418 (11.19)	149 (11.5)	105 (9.82)	82 (11.42)	82 (12.54)
Breakfast, time/week					
0-1	767 (20.52)	287 (22.15)	223 (20.86)	118 (16.43)	139 (21.25)
2-3	856 (22.91)	303 (23.38)	258 (24.13)	145 (20.19)	150 (22.94)
4-5	634 (16.97)	216 (16.67)	191 (17.87)	137 (19.08)	90 (13.76)
6-7	1480 (39.6)	490 (37.81)	397 (37.14)	318 (44.29)	275 (42.05)
Body Mass Index, kg/m^2 [a]	26.7 (6)	26.5 (5.7)	26.7 (5.7)	26.7 (6.5)	26.9 (6.6)
Alcohol, g/day [a]	10.1 (19.4)	11 (20.1)	10 (21.2)	9.4 (16.4)	9.2 (17.7)
Total energy intake, kcal[a]	2770.3 (1227.1)	2538.9 (1155.2)	2645.7 (1128.4)	2945.6 (1239.4)	3240.2 (1346.2)
A-priori diet quality score[a]	66.9 (12.3)	67.6 (12.4)	67 (12)	67.2 (12.2)	64.8 (12.3)

[a] Mean (SD)
[b] Physical activity in the past year
[1] Pre-baseline is year 7 follow-up of the CARDIA study (1992-93)
Abbreviations: CARDIA, Coronary Artery Risk Development in Young Adults

Table 12 Estimated 20-y risks of diabetes under dietary strategies in the Coronary Artery Risk Development in Young Adults Study (1995–2016).

	20-y risk[b] (95% CI), %	Risk ratio (95% CI)	Risk difference (95% CI), %	% needed to change diet[a]
Natural course	13.94 (11.27, 16.36)	1 (Reference)	0 (Reference)	0
Breakfast 0-1 times/week	13.7 (10.9, 16.04)	0.98 (0.97, 1.03)	-0.23 (-0.38, 0.39)	90.18
Breakfast 2-4 times/week	13.52 (11.05, 16.6)	0.97 (0.96, 1.03)	-0.42 (-0.48, 0.39)	67.65
Breakfast 5-7 times/week	13.53 (11.05, 16.4)	0.97 (0.96, 1.03)	-0.4 (-0.52, 0.32)	69.5
Post-dinner snack 0-1 times/week	12.11 (9.94, 15.72)	0.87 (0.84, 1.01)	-1.82 (-2.12, -0.03)	49.9
Post-dinner snack 2-4 times/week	13.71 (11.02, 16.07)	0.98 (0.96, 1.03)	-0.23 (-0.51, 0.46)	68
Post-dinner snack 5-7 times/week	15.08 (12.12, 18.17)	1.08 (0.98, 1.2)	1.15 (-0.28, 2.63)	63.6

[a] Average proportion of the participants would need to change their diet in each follow-up period to keep adhering to the dietary strategy.
[b] Observed risk was 15.51%.
Estimates are based on the parametric g-formula with pre-baseline covariates: pre-baseline age, race, sex, income, education, smoking status, alcohol intake, a-priori diet quality, total energy intake, physical activity, and time-varying covariates: income, smoking status, a-priori diet quality, total energy intake, alcohol intake, physical activity, post-dinner snack/breakfast consumption.

Table 13 Estimated 15-y risks of diabetes under dietary strategies in the Coronary Artery Risk Development in Young Adults Study (1995–2011)

	15-y risk[b] (95% CI), %	Risk ratio (95% CI)	Risk difference (95% CI), %	% needed to change diet[a]
Natural course	10.69 (8.77, 12.72)	1 (Reference)	0 (Reference)	0
Breakfast 0-1 times/week	10.41 (8.74, 12.45)	0.97 (0.96, 1.04)	-0.28 (-0.39, 0.44)	89.68
Breakfast 2-4 times/week	10.29 (8.69, 12.2)	0.96 (0.95, 1.04)	-0.4 (-0.42, 0.47)	66.15
Breakfast 5-7 times/week	10.25 (8.52, 12.41)	0.96 (0.96, 1.04)	-0.44 (-0.36, 0.41)	67.7
Post-dinner snack 0-1 times/week	9.33 (7.58, 11.84)	0.87 (0.83, 1.01)	-1.36 (-1.81, 0.05)	50.73
Post-dinner snack 2-4 times/week	10.3 (8.57, 12.58)	0.96 (0.95, 1.04)	-0.4 (-0.53, 0.37)	65.9
Post-dinner snack 5-7 times/week	11.17 (9.05, 13.92)	1.04 (0.99, 1.22)	0.48 (-0.11, 2.08)	64.67

[a] Average proportion of the participants would need to change their diet in each follow-up period to keep adhering to the dietary strategy.
[b] Observed risk was 11.86%.
Estimates are based on the parametric g-formula with pre-baseline covariates: pre-baseline age, race, sex, income, education, smoking status, alcohol intake, a-priori diet quality, total energy intake, physical activity, and time-varying covariates: income, smoking status, a-priori diet quality, total energy intake, alcohol intake,physical activity, post-dinner snack/breakfast consumption.

Table 14 Estimated 10-y risks of diabetes under dietary strategies in the Coronary Artery Risk Development in Young Adults Study (1995–2006).

	10-y risk[b] (95% CI), %	Risk ratio (95% CI)	Risk difference (95% CI), %	% needed to change diet[a]
Natural course	7.55 (5.92, 8.77)	1 (Reference)	0 (Reference)	0
Breakfast 0-1 times/week	7.31 (5.8, 8.74)	0.97 (0.95, 1.05)	-0.24 (-0.31, 0.43)	89.4
Breakfast 2-4 times/week	7.4 (5.94, 8.74)	0.98 (0.96, 1.06)	-0.15 (-0.28, 0.4)	65.85
Breakfast 5-7 times/week	7.08 (5.94, 8.85)	0.94 (0.96, 1.05)	-0.48 (-0.29, 0.33)	68.2
Post-dinner snack 0-1 times/week	6.75 (5.4, 8.26)	0.89 (0.83, 1.01)	-0.81 (-1.33, 0.04)	63.3
Post-dinner snack 2-4 times/week	7.29 (5.8, 8.68)	0.97 (0.94, 1.04)	-0.26 (-0.38, 0.31)	62.95
Post-dinner snack 5-7 times/week	8.1 (6.29, 9.53)	1.07 (0.96, 1.18)	0.55 (-0.32, 1.31)	68.85

[a] Average proportion of the participants would need to change their diet in each follow-up period to keep adhering to the dietary strategy.
[b] Observed risk was 6.9%.
Estimates are based on the parametric g-formula with pre-baseline covariates: pre-baseline age, race, sex, income, education, smoking status, alcohol intake, a-priori diet quality, total energy intake, physical activity, and time-varying covariates: income, smoking status, a-priori diet quality, total energy intake, alcohol intake,physical activity, post-dinner snack/breakfast consumption.

Table 15 Estimated risk of 20-y risk of diabetes under hypothetical interventions versus no intervention in subgroup analyses.

	Dietary strategies	20-y risk (95% CI), %	Risk ratio (95% CI), %
Black	Natural course	18.12 (14.14, 18.76)	1 (Reference)
	Breakfast 0-1 times/week	17.9 (14.45, 18.89)	0.99 (0.98, 1.11)
	Breakfast 2-4 times/week	17.86 (14.19, 19.16)	0.99 (0.96, 1.05)
	Breakfast 5-7 times/week	18.56 (14.06, 18.72)	1.02 (0.97, 1.08)
	Post-dinner snack 0-1 times/week	18.19 (13.34, 18.88)	1 (0.92, 1.01)
	Post-dinner snack 2-4 times/week	18.35 (13.97, 18.76)	1.01 (0.97, 1.08)
	Post-dinner snack 5-7 times/week	18.84 (14.86, 20.04)	1.04 (0.96, 1.15)
White	Natural course	9.11 (6.46, 10.43)	1 (Reference)
	Breakfast 0-1 times/week	8.74 (6.31, 10.78)	0.96 (0.91, 1.05)
	Breakfast 2-4 times/week	8.78 (6.57, 10.98)	0.96 (0.93, 1.1)
	Breakfast 5-7 times/week	8.35 (6.74, 11.07)	0.92 (0.91, 1.06)
	Post-dinner snack 0-1 times/week	7.18 (4.31, 8.95)	0.79 (0.67, 0.93)
	Post-dinner snack 2-4 times/week	8.85 (6.74, 10.56)	0.97 (0.96, 1.11)
	Post-dinner snack 5-7 times/week	10.96 (7.2, 13.34)	1.2 (0.97, 1.5)
Male	Natural course	12.34 (9.75, 13.54)	1 (Reference)
	Breakfast 0-1 times/week	12.14 (9.81, 14.18)	0.98 (0.96, 1.08)
	Breakfast 2-4 times/week	11.99 (9.84, 14.95)	0.98 (0.97, 1.11)
	Breakfast 5-7 times/week	12.57 (10.14, 14.3)	1.02 (0.99, 1.1)
	Post-dinner snack 0-1 times/week	11.09 (8.47, 13.68)	0.9 (0.81, 1.03)
	Post-dinner snack 2-4 times/week	12.41 (10.15, 14.63)	1.01 (0.96, 1.08)
	Post-dinner snack 5-7 times/week	13.14 (11.43, 17.36)	1.07 (0.99, 1.3)
Female	Natural course	14.29 (11.47, 17.29)	1 (Reference)
	Breakfast 0-1 times/week	13.46 (12.03, 17.41)	0.94 (0.9, 1.09)
	Breakfast 2-4 times/week	13.29 (11.96, 17.64)	0.94 (0.93, 1.07)

	Breakfast 5-7 times/week	13.83 (11.97, 16.74)	0.97 (0.95, 1.07)
	Post-dinner snack 0-1 times/week	12.32 (10.93, 15.78)	0.89 (0.86, 1.04)
	Post-dinner snack 2-4 times/week	13.71 (12.06, 17.7)	0.97 (0.96, 1.05)
	Post-dinner snack 5-7 times/week	14.74 (13.07, 18.41)	1.03 (0.98, 1.18)
BMI<25	Natural course	9.38 (5.94, 9.82)	1 (Reference)
	Breakfast 0-1 times/week	8.62 (6.1, 10.3)	0.95 (0.92, 1.06)
	Breakfast 2-4 times/week	9.11 (6.41, 10.45)	0.97 (0.95, 1.08)
	Breakfast 5-7 times/week	9.4 (6.08, 10.55)	1 (0.92, 1.08)
	Post-dinner snack 0-1 times/week	7.37 (4.68, 8.95)	0.79 (0.65, 0.98)
	Post-dinner snack 2-4 times/week	8.65 (5.88, 10.78)	0.92 (0.85, 1.11)
	Post-dinner snack 5-7 times/week	10.3 (7.39, 12.56)	1.1 (1.01, 1.33)
BMI>=25	Natural course	20.24 (13.46, 20.73)	1 (Reference)
	Breakfast 0-1 times/week	19.05 (14.17, 21.7)	0.94 (0.93, 1.05)
	Breakfast 2-4 times/week	19.43 (13.89, 21.33)	0.96 (0.94, 1.08)
	Breakfast 5-7 times/week	18.86 (14.03, 20.58)	0.95 (0.93, 1.04)
	Post-dinner snack 0-1 times/week	18.5 (13.46, 21.03)	0.91 (0.88, 1.07)
	Post-dinner snack 2-4 times/week	20.04 (13.47, 21.28)	0.99 (0.98, 1.05)
	Post-dinner snack 5-7 times/week	20.67 (14.93, 22.49)	1.02 (1.01, 1.15)

Estimates are based on the parametric g-formula with pre-baseline covariates: pre-baseline age, race, sex, income, education, smoking status, alcohol intake, a-priori diet quality, total energy intake, physical activity, and time-varying covariates: income, smoking status, a-priori diet quality, total energy intake, alcohol intake, physical activity, post-dinner snack/breakfast consumption.

Supplementary Table 3. Estimated 20-y risk of diabetes under hypothetical dietary intervention strategies in the Coronary Artery Risk Development in Young Adults Study (1995–2016).

	Intervention	20-y risk (95% CI), %	Risk ratio (95% CI), %
Primary analyses	Natural course	13.94 (11.27, 16.36)	1 (Reference)
	Breakfast 0-1 times/week	13.7 (10.9, 16.04)	0.98 (0.97, 1.03)
	Breakfast 2-4 times/week	13.52 (11.05, 16.6)	0.97 (0.96, 1.03)
	Breakfast 5-7 times/week	13.53 (11.05, 16.4)	0.97 (0.96, 1.03)
	Post-dinner snack 0-1 times/week	12.11 (9.94, 15.72)	0.87 (0.84, 1.01)
	Post-dinner snack 2-4 times/week	13.71 (11.02, 16.07)	0.98 (0.96, 1.03)
	Post-dinner snack 5-7 times/week	15.08 (12.12, 18.17)	1.08 (0.98, 1.2)
Different threshold cutoff points	Natural course	13.08 (10.24, 17.4)	1 (Reference)
	Breakfast 0 times/week	12.55 (10.69, 16.14)	0.96 (0.93, 1.07)
	Breakfast 1-5 times/week	12.83 (10.4, 16.99)	0.98 (0.95, 1.09)
	Breakfast 6-7 times/week	13.08 (11.06, 16.89)	1 (0.94, 1.08)
	Post-dinner snack 0 times/week	11.71 (9.52, 15.76)	0.89 (0.81, 1.02)
	Post-dinner snack 1-5 times/week	13.04 (10.34, 16.94)	1 (0.95, 1.08)
	Post-dinner snack 6-7 times/week	14.18 (11.8, 18.47)	1.08 (0.94, 1.27)
Only age, race, sex, and education as baseline covariates	Natural course	12.49 (9.73, 19.65)	1 (Reference)
	Breakfast 0-1 times/week	12.17 (9.96, 19.12)	0.97 (0.93, 1.07)
	Breakfast 2-4 times/week	12.12 (10.04, 19.77)	0.97 (0.93, 1.09)
	Breakfast 5-7 times/week	12.69 (9.87, 19.2)	1.02 (0.95, 1.11)
	Post-dinner snack 0-1 times/week	11.69 (8.5, 18.46)	0.94 (0.83, 1.01)
	Post-dinner snack 2-4 times/week	12.25 (10.1, 20.62)	0.98 (0.94, 1.05)

	Post-dinner snack 5-7 times/week	13.71 (12.29, 21.89)	1.1 (1.05, 1.26)
Different order of covariates	Natural course	13.56 (11.17, 15.9)	1 (Reference)
	Breakfast 0-1 times/week	13.46 (11.16, 16.28)	0.99 (0.96, 1.03)
	Breakfast 2-4 times/week	13.12 (11.18, 16)	0.97 (0.96, 1.03)
	Breakfast 5-7 times/week	13.51 (11.16, 16.13)	1 (0.96, 1.03)
	Post-dinner snack 0-1 times/week	12.81 (10.27, 15.81)	0.94 (0.86, 1.02)
	Post-dinner snack 2-4 times/week	13.7 (11.16, 15.96)	1.01 (0.96, 1.02)
	Post-dinner snack 5-7 times/week	14.47 (11.96, 17.45)	1.07 (0.98, 1.17)
Different functional form of covariates	Natural course	11.41 (8.32, 15.3)	1 (Reference)
	Breakfast 0-1 times/week	11.37 (8.27, 15.2)	1 (0.94, 1.1)
	Breakfast 2-4 times/week	11.14 (7.89, 15.6)	0.98 (0.93, 1.08)
	Breakfast 5-7 times/week	11.16 (8.77, 15.03)	0.98 (0.92, 1.11)
	Post-dinner snack 0-1 times/week	10.08 (7.82, 14.86)	0.88 (0.85, 1.12)
	Post-dinner snack 2-4 times/week	11.38 (8.44, 14.95)	1 (0.94, 1.08)
	Post-dinner snack 5-7 times/week	11.78 (9.26, 16.63)	1.03 (0.98, 1.21)
Use of dinner and lunch as a negative exposure control	Natural course	14.05 (10.93, 19.32)	1 (Reference)
	Lunch 0-1 times/week	13.27 (7.7, 18.23)	0.94 (0.7, 1.15)
	Lunch 2-4 times/week	13.46 (10.06, 19.26)	0.96 (0.92, 1.07)
	Lunch 5-7 times/week	14.11 (11.13, 19.93)	1 (0.95, 1.09)
	Dinner 0-1 times/week	14.02 (10.97, 19.49)	1 (0.96, 1.05)
	Dinner 2-4 times/week	13.58 (10.7, 18.97)	0.97 (0.95, 1.06)
	Dinner 2-4 times/week	13.61 (10.56, 20.08)	0.97 (0.95, 1.06)
Estimates are based on the parametric g-formula with pre-baseline covariates: pre-baseline age, race, sex, income, education, smoking status, alcohol intake, a-priori diet quality, total			

energy intake, physical activity, and time-varying covariates: income, smoking status, a-priori diet quality, total energy intake, alcohol intake, physical activity, post-dinner snack/breakfast consumption.

CHAPTER 3: Estimating the effect of hypothetical interventions on the timing of dietary intake and weight loss maintenance: Data from the Innovative Approaches to Diet, Exercise and Activity (IDEA) study

ABSTRACT

Background: A fundamental challenge for obesity care is weight maintenance and minimizing weight regain following initial weight loss. The timing of eating occasions, specifically breakfast and evening snack consumption, is hypothesized to influence the mitigation of weight regain after weight loss.

Methods: We emulated a target trial using observational data from 372 subjects in the Innovative Approaches to Diet, Exercise and Activity (IDEA) study. In the IDEA study, subjects participated in the standard in-person behavioral weight control program during the initial 6 months of treatment, followed by either continuation of the standard behavioral weight control program or an enhanced weight control program with the addition of the BodyMedia Fit System. We followed the subjects for 18 months after the initial behavioral weight loss program and estimated body weight and composition change under several hypothetical interventions (breakfast consumption 0-4 times/week vs. 5-7 times/week and evening snack consumption 0-2 times/week vs. 3-7 times/week). The estimates were adjusted for pre-baseline and time-varying confounders and censoring using inverse probability weights with marginal structural models.

Results: On average, participants lost 10 % (8.41 kg) of weight during the initial 6 months and regained 34% (2.94 kg) of initial weight loss by 18 months. If all participants consumed a breakfast meal 5-7 times/week, on average, they would have regained 2.34 kg of body fat (95% confidence interval (CI): 1.51, 3.13) over 18 months which is 0.57 kg (95% CI: -0.82, -0.33) lower than if all participants consumed breakfast 0-4 times/week. If all participants consumed an evening snack 0-2 times/week, on average, they would have regained 2.29 kg of body fat (95%

CI: 0.95, 4.12) over 18 months which is 0.59 kg (95% CI: -0.78, -0.39) lower than if all consumed an evening snack 3-7 times/week.

Conclusions: We estimated that regular breakfast consumption and minimizing evening snacking might have a modest impact on lessening weight and body fat regain over 18 months after initial weight loss.

INTRODUCTION/BACKGROUND

The primary challenge in obesity-related care and prevention is long-term body weight maintenance -particularly after weight loss.[78],[79] Body weight maintenance has multiple determinants, including a growing body of evidence that informs the hypothesis that in addition to diet quality and energy intake, the timing of eating occasions may influence metabolic and weight-related health outcomes due to the influence on circadian rhythms.[80], [81] Eating occasions that bookend the daily meal pattern draw particular interest, given the potential interactions with metabolism and circadian patterns.[23], [82] Although these observations have led to weight loss interventions aiming to leverage the hypothesized basic biological phenomena, the optimal meal timing strategy for weight management remains poorly defined.[83], [84]

In particular, the role of the timing of eating occasions on weight maintenance after initial weight loss remains largely unaddressed. To begin informing this question, we estimated the causal effects of hypothetical randomized dietary interventions using a cohort of existing data (i.e., a target trial). Specifically, we estimated the effects of habitual sustained breakfast meal intake v. avoidance/irregular breakfast meal intake; and avoidance or rare consumption of evening (post-dinner) snacks v. irregular to habitual post-dinner snacks on 18-month weight-loss maintenance in a population that had lost significant weight after 6 months of a standard weight loss program. We estimated absolute and relative change in weight and body composition variables and applied modeling assumptions that appropriately account for time-varying confounding.[56] Based upon basic biological, clinical, and observational epidemiologic research, we hypothesized that habitual, sustained breakfast consumption and avoidance or rare consumption of after-dinner snacks would be more favorable dietary approaches for mitigating weight regain after initial weight loss.

METHODS

First, we outline a hypothetical randomized trial design to test the above-noted question of interest, and then we proceed to describe the methods we used to emulate this randomized trial using the available observational data.

Target trial specification

Table 16 summarizes the key components of the target trial. Briefly, the trial would enroll young adults with overweight and obesity into a standard 6-month behavioral weight loss intervention. After 6 months, usually the nadir of weight loss, they would be randomly assigned to a dietary strategy intended to inform whether the timing of eating occasions impacts weight loss maintenance. The primary outcomes would be body weight, body fat, and lean mass change. Each eligible participant would be followed from assignment until withdrawal/loss to follow-up or administrative end of follow-up (18 months after assignment), whichever happens first.

Dietary strategies. Participants would be randomly assigned after 6-months of the weight loss intervention to one of the following dietary strategies for 18 months to test the hypotheses related to mitigating weight gain: 1. Regular breakfast meals (breakfast 5-7 times/wk), 2. Irregular to rare breakfast (breakfast 0-4 times/wk), 3. Avoidance to rare post-dinner evening eating (night snacks 0-2 times/wk), 4. More irregular to habitual post-dinner evening eating (night snacks 3-7 times/wk).

Causal contrasts and statistical analysis. The target trial's primary (intent-to-treat) effect would be estimated by comparing the body weight and composition change since the randomization to each breakfast and evening snack strategy (with adjustment for loss to follow-up, if necessary). However, the information provided by the intent-to-treat effect would be limited if, as expected, many individuals deviated from their dietary assignments during the 18-months follow-up. In

this setting, a contrast of the body weight and fat change that would have been observed if all individuals had adhered to their assigned dietary strategy (i.e., per-protocol effect) may be more relevant for informing potential effects of the dietary approaches.[85] These estimates can be generated in the target trial using marginal structural models (MSMs) with inverse-probability weights (IPW). If our emulation procedures had been successful, the estimates would have a straightforward interpretation because the target trial is well defined. The robustness of the estimates and causal inference is achieved by minimizing unmeasured confounding (selection of confounders through a thorough review of existing studies), selection bias (incomplete follow-up expanded to include questionnaire nonresponses and incomplete responses to dietary questions), measurement error (quality control of the assessments and data in the IDEA study), model misspecification (using DAGs to select potential confounders) and maximizing consistency (indicated range of dietary exposure like frequency of breakfast and evening snack consumption and the starting points and durations of the dietary interventions and follow-up periods).[56], [61], [85]

The MSMs with IPWs have been described elsewhere.[86], [87] Briefly, MSMs are an alternative to the g-estimation of structural nested models. The standardized estimate of the outcome is calculated as a weighted average of the outcome estimates conditional on the time-varying confounders, with the distribution of the time-varying confounders used as weights. Unlike standard statistical methods, weighting can appropriately adjust for confounding and selection bias due to time-varying covariates affected by prior exposure.

The method starts by estimating the denominator and numerator of stabilized weights using pooled logistic models for the probability of exposure initiation at each follow-up occasion.[88] Final weights may be truncated to achieve more precise estimates and improve the trade-off

between variance and residual confounding by measured covariates.[89] For each dietary strategy, the conditional probabilities of the outcome given past covariates are then calculated under dietary values compatible with the intervention. Under the above assumptions, the mean estimate of the outcome that would have been observed if everyone in the population had adhered to the dietary strategy is the standardized (to confounder history) estimate. Nonparametric bootstrapping with 100 samples can be used to construct percentile-based 95% CIs of the estimates and mean difference from estimates under two arms of every intervention. To identify potential subgroups of participants for whom the dietary strategies may be more beneficial, analyses can be conducted separately in subsets of the study population defined at baseline according to pre-baseline breakfast consumption (regular versus irregular to rare) or evening snack consumption (irregular to habitual versus avoidance to rare).

Target trial emulation

We emulated the above target trial using data from the Innovative Approaches to Diet, Exercise and Activity study, a randomized clinical trial that was one of the studies within the Early Adult Reduction of Weight through Lifestyle intervention (EARLY) Trials consortium.

Observational data. The participants with BMI of 25.0 to <40.0 kg/m^2 were enrolled between October 2010 and October 2012 at the University of Pittsburgh using direct mail, mass media advertisements, or referral from clinical research registries. Males and females aged 18–35 years at enrollment reported detailed clinical and lifestyle information at enrollment and every 6 months, including diet, cigarette smoking, alcohol consumption, sleep practices, physical activity, and socio-demographic factors. The protocol of the study is mentioned elsewhere.[90]

Eligibility criteria. To emulate the above target trial using these observational data (see the last column of Causal contrasts and statistical analysis. The target trial's primary(intent-to-treat)

effect would be estimated by comparing 20-year diabetes risk since the randomization to each breakfast and post-dinner snack strategy(with adjustment for loss to follow-up, if necessary). However, the information provided by the intent-to-treat effect would be limited if, as expected, many individuals deviated from their dietary assignments during the 20-year follow-up. In this setting, a contrast of diabetes risks that would have been observed if all individuals had adhered to their assigned dietary strategy(i.e., per-protocol effect) may be more relevant for informing potential effects of the dietary approaches.[60] These risks can be estimated in the target trial using the parametric g-formula with the assumptions of no unmeasured confounding and selection bias(incomplete follow-up expanded to include questionnaire nonresponses and incomplete responses to dietary questions), no measurement error, and no model misspecification.[56], [60], [61], [62]

The parametric g-formula has been described elsewhere.[59] Briefly, the method is a generalized form of standardization in which the standardized risk of the outcome is calculated as a weighted average of the outcome risks conditional on the time-varying confounders, with the distribution of the time-varying confounders used as weights.[57] Threshold starts by estimating the distribution of the time-varying confounders and the outcome using linear or logistic regression models with previous dietary and covariate histories as covariates. For each dietary strategy, the conditional probabilities of the outcome given past covariates are then calculated under dietary values compatible with the intervention. Under the above assumptions, the probability of the outcome that would have been observed if everyone in the population had adhered to the dietary strategy is the standardized(to confounder history) risk. The weighted average required for the standardization is approximated via a Monte Carlo simulation. Nonparametric bootstrapping

with 1000 samples can be used to construct percentile-based 95% CIs of the estimated risks at the time points of interest.

To identify potential subgroups of participants for whom the intervention strategies may be more or less beneficial, subgroup analyses can be conducted in the study population defined at pre-baseline according to sex(males versus females), race(white vs. black), and pre-baseline BMI(<25 kg/m2 vs. ≥25 kg/m2).

), we identified individuals in the above cohort who met all eligibility criteria. We applied all eligibility criteria to participants in the IDEA study and also excluded subjects who did not have information on breakfast and evening snack frequency, body composition, and weight measures, had implausible energy intake (<600 kcal/day or >6,000 kcal/day for women and <800 kcal/day or >8,000 kcal/day for men) at 0 and 6 months.

Modifications to the target trial protocol. Eligible individuals were followed from their baseline assessments until censoring (lack of outcome measures or incomplete responses to dietary questions) or 18-months after baseline, whichever happened first. To allow for adjustments of pre-baseline covariates, we used data from the 0-month time point or original study baseline.

Dietary strategies. Dietary strategies described above cannot be directly emulated because dietary observational data lacked the time stamp of eating occasion measures. Therefore, we assumed that breakfast consumption accurately reflects morning eating frequency and evening (after-dinner) snack frequency reflects late evening eating frequency. For the analyses, we have defined dietary strategies as 0-4 (irregular to rare) and 5-7 (regular) times/week for breakfast and 0-2 (avoidance to rare) and 3-7 (frequent to habitual) times/week for an evening snack. Eligible individuals were analyzed according to the following dietary strategies: 1. Regular breakfast meals (breakfast 5-7 times/wk), 2. Irregular to rare breakfast (breakfast 0-4 times/wk), 3.

Avoidance to rare post-dinner evening eating (night snacks 0-2 times/wk), 4. More irregular to habitual post-dinner evening eating (night snacks 3-7 times/wk).

Treatment assignment. We attempted to emulate the randomization info the specified treatment groups at the 6-month point (baseline for this analysis) by adjusting for pre-baseline (time 0), time-invariant, and other "pre-intervention" confounders (age, sex, ethnicity, income, breakfast frequency, evening snack frequency, education, physical activity, smoking, alcohol consumption, sleep duration, BMI, diet quality, total energy intake, depression, initial weight loss between 0-6 months) via IPWs.

Primary outcome. The primary outcomes are changes in body weight and body composition (fat mass and lean mass) 18-month after baseline. The IDEA study measured body composition using a GE Lunar iDXA dual-energy x-ray absorptiometer (GE Healthcare, Madison, WI, USA) every 6 months of the follow-up. A calibrated digital scale that measures weight to 0.1 kg was used to assess body weight. The average of the 3 measures was used for study-wide analyses at each follow-up visit. Absolute changes in body weight and body composition are calculated as (measured value at 24 months – values of the same measure at 6 months), where a negative change means a reduction in body weight or body composition. Relative changes in body weight and body composition are calculated as (100x(value at 24 months – value of the same measure at 6 months)/ value of the same measure at 6 months), where a negative change means a reduction in body weight or body composition.[91]

Statistical analysis

Emulated target trial. We implemented parametric MSMs to estimate the causal effect of each dietary strategy on body fat and weight maintenance between 6 and 24 months.[87], [92]To emulate the random strategy assignment at baseline and adherence to the treatment for 18

months, we adjusted for all baseline confounding factors required to maximize the exchangeability (comparability) of the groups defined by initiation of the treatment strategies.[93] The probability of treatment strategy was estimated at 6 (baseline), 12, and 18 months of the follow-up. Subjects who had a missing measure of the outcome or nonresponse to the breakfast or evening snack frequency questionnaire were censored at the time of nonresponse or 18 months follow-up. The model for the denominator of the weight included baseline covariates measured at pre-baseline (month 0): age, sex, race, smoking, education, BMI, vigorous and moderate physical activity, breakfast frequency, evening snack frequency, energy intake, diet quality, alcohol intake, sleep duration, depression; and the following time-varying covariates measured at all previous time-points and at the times of treatment: vigorous and moderate physical activity, body mass/body fat change since pre-baseline, breakfast frequency, evening snack frequency, energy intake, diet quality, alcohol intake, sleep duration, depression. DAG used to select the potential confounders is illustrated in Supplemental figure 2. IPTW created from the weights of treated subjects allows generating the estimates that represent not only the outcomes of treated subjects but also other similar individuals who did not receive treatment. Stabilized inverse probability of censoring weights (IPCW) were calculated using a similar approach to account for non-informative censoring, and the distribution of the combined treatment and censoring weights were examined.[86] This modeling approach attempts to create a pseudo-population in which the following assumptions hold: exchangeability (no unmeasured confounding); consistency (unambiguously defined exposure); positivity (nonzero probability of each possible exposure value at each possible confounder value); and correct model specification of the marginal structural model and weights.[86] This approach allows one to estimate a causal effect (assuming the above assumptions hold) in the overall population.

Last observation carried forward (LOCF) was used to impute income and smoking status, if not measured in a particular interval.[89] Other covariates were imputed using the Monte Carlo multiple imputation method, assuming that data are missing at random and the models used to perform the imputation were correctly specified.[94] The percentage of missing data is shown in Supplementary Table 11. Due to the extensive range of the IPTW, weights were truncated at 5th and 95th. This decision was made to improve the trade-off between variance and residual confounding by measured covariates, understanding the bias-variance trade-off associated with weight truncation.[86] Because the estimated weight distribution may serve as an indicator of the "positivity assumption," we examined the distribution of weights. The mean of the weights was 1.00.

Nonparametric bootstrapping with 100 samples was used to construct percentile-based 95% CIs of the estimated mean differences between the estimated outcomes of treatments (breakfast 0-4 vs. 5-7 times/week, evening snack 0-2 vs. 3-7 times/week).

Sensitivity analysis. We assessed whether initiation of treatment strategies in some participants had a different effect on body weight and composition maintenance compared to no treatment in the same participants. We also performed an intent-to-treat analysis adjusting for adherence for all subjects, including those who did not adhere to the treatment assigned at baseline. We also assessed the robustness of our estimates to various analytical decisions. Specifically, we 1) evaluated whether observed associations could have been driven by a small number of persons with extreme weights by applying various truncation rules to the treatment and censoring weights, 2) defined different cutoff points for exposure categories, 3) additionally adjusted for smoking as a time-varying confounder, 4) assessed dinner consumption and before bed eating as

primary exposure, 5) used only age, sex, race, education, and BMI at baseline as baseline confounders.

All analyses were conducted using SAS 9.4 (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Baseline characteristics of participants

Out of 647 screened participants of the IDEA study, 372 were eligible for this analysis (Figure 4). Of 372 eligible individuals, 71% were female (Table 17, Table 18). The mean age was 30 years, the mean BMI was 31, mean body fat was 41%, mean body weight was 91 kg, 24% had >=150 minutes/week of moderate-intensity physical activity, and 64% had >=75 minutes/week of vigorous-intensity physical activity. 69% of participants consumed breakfast 5-7 times/week (n=245), and 41% of participants consumed evening snacks 0-2 times/week (n=151), most of which were white, had baccalaureate degrees, and were non-smokers. The crude mean weight loss % during the first 6 months of the weight loss intervention was 10.2% in the eligible population.

Body fat and body weight maintenance: emulated trial results

Table 19 and Figure 5 show the estimated change in body weight, fat and lean mass from month 6 to month 24 under strategies of consuming breakfast 0-4, vs 5-7. Compared with the 3.56 kg (95% confidence interval (CI): 0.67, 5.63) increase in body weight under 0-4 times/week breakfast frequency, body weight increase was 2.97 kg, or 0.59 kg (95% CI: -0.86, -0.32) lower if all participants had followed the strategy of 5-7 breakfasts per week. These estimates should be interpreted as if all participants adhered to the assigned treatment strategies at 6, 12, and 18 months of the follow-up. Similar trends were observed in body fat maintenance. The proportion of subjects who followed the hypothetical intervention strategies in the source observational dataset is shown in Supplementary Table 4. The treatment and censoring weights distribution are shown in Supplementary Figure 1 and Supplemental Figure 2.

Table 19 also shows the estimated change in body weight and composition under strategies of consuming evening snacks 0-2 and 3-7 times/week. Compared with the 3.7 kg (95% CI: 2.3, 4.9) increase in body weight under 3-7 times/week intervention, body weight increase was 2.87 kg, or 0.83 kg (95% CI: -1.06, -0.59) lower in the strategy of 0-2 evening snacks per week. Similarly, these estimates should be interpreted as per-protocol in the context that all participants adhered to the assigned treatment strategies at 6, 12, and 18 months of the follow-up. Similar trends were observed in body fat maintenance. Lean body mass increased by 0.22 kg (95% CI: -0.29, -0.16) during the follow-up among those who avoided consuming evening snacks regularly.

The estimates from the analysis emulating an intent-to-treat analysis adjusted for adherence should be interpreted in the context that all participants were assigned to treatment at baseline (month 6), but some were non-adherent at 12 or 18 months of the follow-up, which was adjusted for in the analysis. The results of the analysis emulating an intent-to-treat analysis are similar direction with the estimates obtained from emulating a per-protocol analysis.

Supplementary Table 5 presents this analysis using relative measures of body weight (%) and body fat (%) change as the outcome of interest. The results are consistent with the absolute body weight and composition changes.

Table 20 and Figure 6 show the sensitivity analysis results of restricted populations. The estimates suggest that the participants who consumed breakfast 0-4 times/week at pre-baseline (time 0), were to follow breakfast 5-7 times/week strategy during the 18 months intervention, would regain 2.21 kg, or 1.23kg (95% CI: -1.78, -0.67) less body weight than if they continued consuming 0-4 breakfasts per week, where we estimated they would gain 3.44 kg (95% CI: 1.57, 5.64) of body weight. Due to the small sample size informing the models and a limited number

of participants to intervene on, the estimates for evening snack interventions among those who habitually consumed evening snacks at pre-baseline are not presented in this analysis.

Supplementary Table 6 presents this analysis using relative measures of body weight (%) and body fat (%) change as the outcome of interest. The results are consistent with the absolute body weight and composition changes.

Supplementary Table 7, Supplementary Table 8, Supplementary Table 9, and Supplementary Table 10 present sensitivity analyses using extreme threshold cutoff points for breakfast consumption strategies (0-6 times/wk and 7 times/wk). The estimates did not materially change under any of the sensitivity analyses. Due to the relatively small sample size and a limited number of participants to intervene on (evening snack 0 times/week strategies), some estimates have inflated precision and thus are not presented in this analysis (Supplementary Table 4).

DISCUSSION

This manuscript describes an analysis of observational data that estimated the causal effects of hypothetical meal timing-related dietary interventions on weight maintenance after a weight loss intervention in young adults. The results suggest that limiting or avoiding evening eating occasions post-dinner meals (evening snack) and habitual consumption of a morning meal (breakfast) may have modest benefits for mitigating weight and body fat regain over 18 months in young adults after clinically significant weight loss. The estimated effect was of greater magnitude (i.e., less weight regain) if all participants who ate breakfast 0-4 times pre-weightloss, increased their breakfast meal intake to 5-7 times as part of a hypothetical intervention.

The validity of our effect estimates cannot be directly benchmarked because no randomized trials have assessed the effect of implementing early or avoiding late daytime eating on weight-loss maintenance. However, the potential impact of the timing of food intake on weight and body fat

is informed by an understanding of metabolism and circadian rhythms. Indeed, the timing of food intake relative to melatonin onset is associated with the percentage of body fat and body mass index, which suggests that consumption of food during the circadian evening and/or night, independent of more traditional risk factors such as amount or content of food intake and activity level, plays an important role in body composition.[95], [96] Further evidence supports diet-circadian rhythm influences body weight, appetite, and glucose and lipid metabolism.[96], [97], [98], [99]A fundamental question we aimed to inform is what the potential impact of leveraging this knowledge has on weight and body composition dynamics in individuals who had lost weight over 6 months.

Other salient research also informs this topic. A recent randomized controlled trial aimed to evaluate the effect of late versus early evening meal consumption on weight loss in women and found that eating an earlier evening meal resulted in favorable changes in weight loss during a 12-week weight loss program.[99]

Time-restricted eating is a dietary strategy that focuses on consolidating all calorie intake in a restricted time period of the day (usually 6-11 hours) and avoiding eating outside of this period. The short-term TREAT trial has demonstrated that time-restricted eating was associated with a modest decrease (1.17%) in weight, but the estimates suggest that longer trials are needed to detect a long-term effect of meal timing on weight regain it may take years for differences to emerge across strategies.[71] If we stopped our emulated trial at 12-weeks post-intervention initiation, the estimated weight difference would also be close to null (see Supplemental Figure 1 and Supplemental Figure 2). In addition, because our study population was younger with a slightly lower range of baseline BMI than the TREAT trial, the dynamic of weight change is expected to be different from that in participants from that trial. The ongoing Rhythm trial aims to evaluate

whether restricting the timing of energy intake to a short-defined period during wakefulness can be used to improve fuel utilization patterns and enhance circadian rhythms in metabolic tissues to optimize health, but results have not yet been reported.[100] Breakfast is commonly defined as any caloric intake after an overnight fast or fasting period of ≥8 h in duration.[101] An RCT that analyzed the effectiveness of the recommendation for eating breakfast on weight loss in adults trying to lose weight in a free-living setting concluded there was no discernable effect of the recommendation for breakfast consumption on weight loss.[102] Other recent trials suggested that late evening meals result in less favorable changes in weight during weight loss programs.[99], [103], [104] These prior studies are related but are fundamentally different from our question and analysis, as we were focused on weight maintenance/mitigation of weight regain.

In observational research, a large European cohort study that followed up participants for 10 years suggested that daily breakfast consumption had no association with weight maintenance during the follow-up period.[105], [106] Similar findings were made in the National Weight Control Registry (NWCR) cohort study in the US.[106] A prospective investigation of the association between breakfast consumption and long-term weight gain in a US adult male population observed that men who frequently consumed breakfast had less weight gain compared to those who skipped breakfast.[107] Related, night eating habits were associated with dyslipidemia and hypertriglyceridemia among 17,534 workers and their spouses in Japan.[51] Other studies that inform this topic have demonstrated that breakfast skipping has been shown to impair fasting lipids and postprandial insulin sensitivity and might lead to weight gain in the presence of higher energy intake.[108] This could be mediated by circadian interruptions and increased fat accumulation due to decreased fat oxidation at night.[109]–[111] A cross-sectional study of 872 middle-to-older aged adults suggested that higher dietary consumption after waking

up and lower consumption close to bedtime associate with lower BMI, but the relationship differs by chronotype, suggesting the importance of considering the timing of food intake relative to sleep timing when studying the associations of meal timing with obesity and metabolic health.[112]

Given the state of evidence on this topic, this study's research and analytic design provide a better framework for explicit discussion of methodologic considerations and alternative explanations for findings.[93] First, specifying the target trial clarifies the question of interest as a trial would do, including the indicated range of dietary exposure like frequency of breakfast and evening snack consumption and the starting points and durations of the dietary interventions and follow-up periods. This framework aims to reduce the risk of bias and improve data interpretation.[93] Second, unlike traditional outcome regression, the MSMs with IPW appropriately adjust for time-varying confounders affected by previous exposure.[88] In weight loss research, time-varying confounders are present when weight loss progress affects future dietary habits of participants, and weight loss itself can be affected by past dietary habits, for example, the timing of eating. We analyzed our study by applying MSMs to high-quality (observational) data, allowing us to estimate weight and body composition change under long-term strategies accounting for time-varying confounding factors. Lastly, we performed several analyses to address the potential effectiveness of newly assigned treatment to unexposed individuals and negative exposure control as a tool for detecting bias in observational studies.[113]

Nevertheless, our approach does not eliminate the potential for unmeasured confounding, measurement error, and model misspecification. Like in any observational study, we cannot rule out the possibility of unmeasured confounding, despite adjustments for many potential

confounders. An estimated null effect of lunch frequency on weight maintenance (which was not expected to be influenced by lunch frequency) is reassuring but not proof of lack of confounding. In addition, we relied on self-report of breakfast and evening snacks, and therefore some degree of measurement error in the diet was expected. Due to the logistics difficulties, a questionnaire is common to assess the adherence to timing for food intake strategies. Thus per-protocol effect estimation is also susceptible to measurement error in randomized trials.[114] Finally, the results may not be generalizable to populations with different dietary habits (because the effects are estimated in comparison with regular dietary practices) or age distributions (because the ability to maintain lost weight differs in different age cohorts), or other distribution of other confounders.[57]

In summary, we estimated that dietary strategies of regular breakfast consumption and avoiding evening snacking modestly reduce weight regain over 18 months after initial weight loss among young adults with overweight and obesity defined by BMI. Further, initiating habitual sustained breakfast consumption might be more beneficial for weight-loss maintenance over 18 months in people who did not habitually consume a breakfast meal before weight loss. The analytic approach and results in this research helped define and compare dietary strategies that could be used to inform randomized interventions and potential recommendations for weight maintenance programs in the face of the lack of long-term randomized trials investigating the timing of eating occasions on weight maintenance.

TABLES AND FIGURES

Table 16. Specification and emulation of a target trial of meal timing interventions among young adults with BMI of 25.0 to <40.0 kg/m2 using observational data from the Innovative Approaches to Diet, Exercise and Activity Study

Component	Target trial specifications	Target trial emulation
Aim	To estimate the effect of the timing of eating occasions that likely influence circadian metabolic and energy intake considerations, specifically breakfast and evening snack intake, on body weight, body fat, and lean mass maintenance for 18 months after initial weight loss among young overweight and obese US adults.	Same. Due to the lack of timing of eating occasions measures in the observational data, we assumed that regular breakfast consumption stands for regular early morning eating and rare evening (after-dinner) snack consumption stands for rare post-dinner eating.
Eligibility criteria	Age 18-35 y, pre-baseline BMI of 25.0-40.0 kg/m^2. Exclusion criteria: had past or planned weight loss surgery, current participation in another weight loss intervention study.	Same. We also required complete questions on breakfast and evening snack frequency, data composition and weight data, and plausible energy intake (<600 kcal/day or >6,000 kcal/day for women and <800 kcal/day or >8,000 kcal/day for men) at pre-baseline and baseline. Baseline is defined as the 6-month follow-up to allow for adjustment for pre-baseline confounding (0-month follow-up)
Treatment strategies	Each individual would be assigned to one of the following strategies: • Regular early morning eating (breakfast 5-7 times/wk), • Irregular to rare early morning eating (breakfast 0-4 times/wk), • Avoidance to rare post-dinner evening eating (night snacks 0-2 times/wk), • More frequent to habitual post-dinner evening eating (night snacks 3-7 times/wk). Participants assigned to a dietary	Same. We assumed that breakfast consumption frequency accurately reflects early morning eating frequency and evening (after-dinner) snack frequency reflects late evening eating frequency.

	strategy are expected to maintain their dietary intake within the range prespecified by the corresponding intervention.	
Treatment assignment	Participants are randomly assigned to a strategy at baseline and aware of their assigned strategy.	We attempted to emulate randomized assignment by adjusting for pre-baseline and baseline covariates: age, sex, ethnicity, income, breakfast frequency, evening snack frequency, education, physical activity, smoking, alcohol consumption, sleep duration, BMI, diet quality, total energy intake, depression, initial weight loss between 0-6 months.
Follow-up	From assignment until withdrawal/loss to follow-up or administrative end of follow-up (18 months after assignment), whichever happens first.	Same. Incomplete follow-up is defined as non-participation in the outcome measure or nonresponses to the dietary frequency questionnaire. The complete follow-up period is 18 months.
Outcome	Change in body weight, body fat, and lean mass composition 3 years after baseline.	Same for 18-months of follow-up.
Causal contrast of interest	Intention-to-treat effect, i.e., the effect of being assigned to a regular early morning eating frequency vs. rare early morning eating frequency at baseline.	Observational analog of the per-protocol and intent-to-treat analysis adjusted for adherence.
	Per-protocol effect, i.e., the effect that would have been observed if all subjects adhered to their assigned strategy over the 18-months follow-up.	
Statistical analysis	Apply MSMs to compare 18-month estimates between groups receiving each treatment strategy and no treatment group with adjustment for pre- and post-baseline covariates factors associated with adherence to strategies and loss to follow-up.	Same.

Abbreviation: MSM, marginal structural model

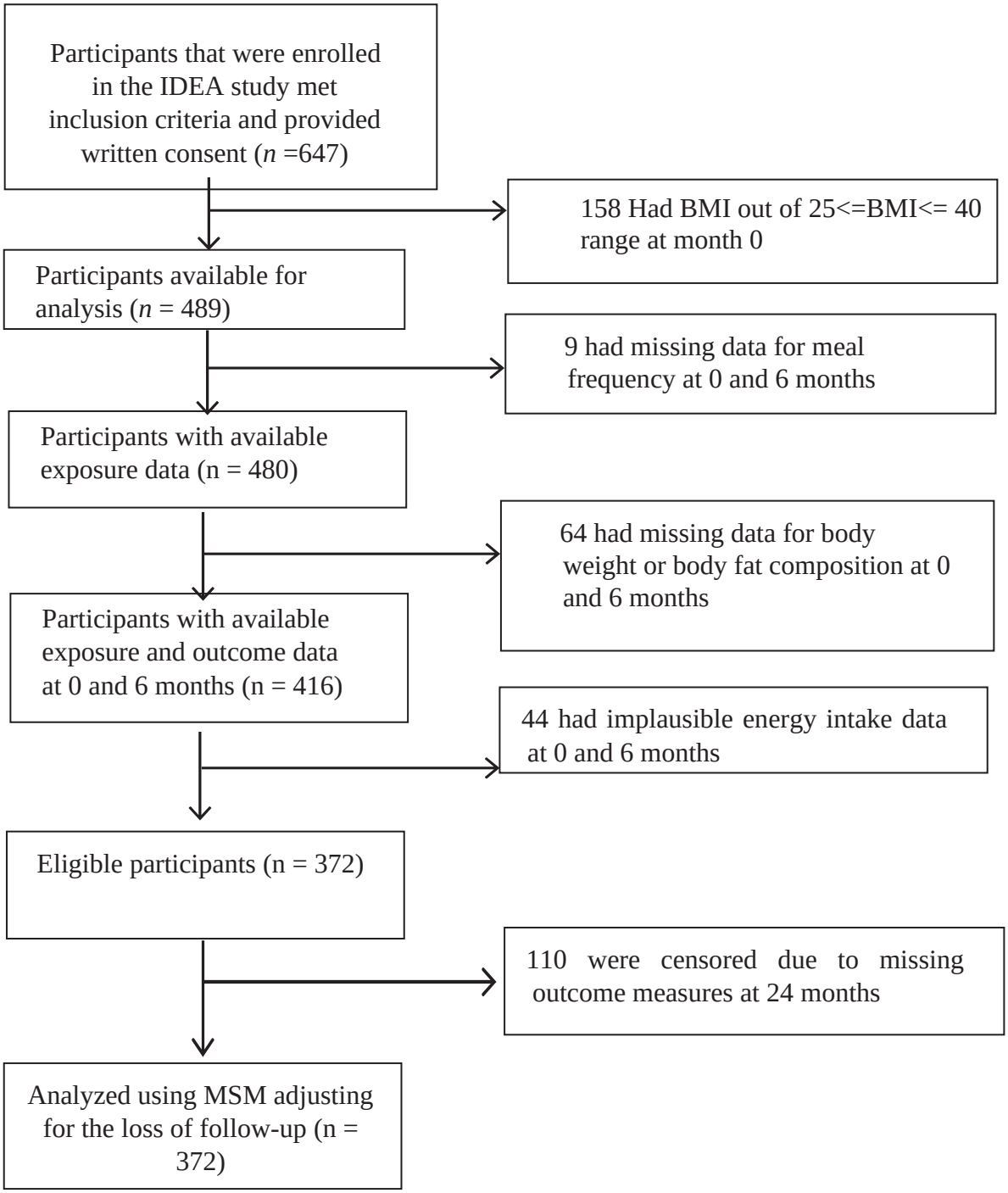


Figure 4. Selection of participants to study meal frequency and body weight and composition among Young Adults with BMI of 25.0 to <40.0 kg/m2 using data from the Innovative Approaches to Diet, Exercise and Activity (IDEA) study. MSM, marginal structural models.

Table 17. Pre-Baseline[a] Characteristics of 372 Eligible Participants by Breakfast Consumption Frequency, the IDEA Study

	Breakfast frequency, times/week			
	Overall (n=372)	0 to 2 (n=67)	3 to 4 (n=60)	5 to 7 (n=245)
	N (%)			
Sex, female	264 (70.97)	45 (67.16)	45 (75)	174 (71.02)
Race				
White	305 (81.99)	49 (73.13)	39 (65)	217 (88.57)
Black	57 (15.32)	17 (25.37)	18 (30)	22 (8.98)
Asian	10 (2.69)	1 (1.49)	3 (5)	6 (2.45)
Education				
HS, GED, or Some college	84 (22.58)	21 (31.34)	23 (38.33)	40 (16.33)
College or Baccalaureate	156 (41.94)	26 (38.81)	21 (35)	109 (44.49)
Graduate Degree	132 (35.48)	20 (29.85)	16 (26.67)	96 (39.18)
Annual household income				
Less than $5,000	146 (39.25)	26 (38.81)	31 (51.67)	89 (36.33)
$5,000 through $11,999	161 (43.28)	31 (46.27)	19 (31.67)	111 (45.31)
$12,000 through $15,999	65 (17.47)	10 (14.93)	10 (16.67)	45 (18.37)
Current smoker	30 (8.06)	9 (13.43)	9 (15)	12 (4.9)
Moderate PA[f], min/week				
<150 min/week	284 (76.34)	51 (76.12)	39 (65)	194 (79.18)
>=150 min/week	88 (23.66)	16 (23.88)	21 (35)	51 (20.82)
Vigorous PA[f], min/week				
<75 min/week	131 (35.22)	31 (46.27)	19 (31.67)	81 (33.06)
>=75 min/week	241 (64.78)	36 (53.73)	41 (68.33)	164 (66.94)
Regular dieting[b]	163 (43.82)	21 (31.34)	27 (45)	115 (46.94)
Depression[c], days/week				
<1	288 (77.42)	51 (76.12)	50 (83.33)	187 (76.33)
1-2	64 (17.2)	10 (14.93)	8 (13.33)	46 (18.78)
3-4	17 (4.57)	5 (7.46)	2 (3.33)	10 (4.08)
5-7	3 (0.81)	1 (1.49)	. (.)	2 (0.82)
Dinner[d], time/week				
0 to 2	5 (1.34)	1 (1.49)	2 (3.33)	2 (0.82)
3 to 4	7 (1.88)	3 (4.48)	2 (3.33)	2 (0.82)
5 to 7	360 (96.77)	63 (94.03)	56 (93.33)	241 (98.37)
Evening snack[d], time/week				
0 to 2	151 (40.59)	25 (37.31)	26 (43.33)	100 (40.82)
3 to 4	94 (25.27)	20 (29.85)	13 (21.67)	61 (24.9)
5 to 7	127 (34.14)	22 (32.84)	21 (35)	84 (34.29)

Eating within an hour of bedtime[d], time/week				
0 to 2	227 (61.02)	34 (50.75)	34 (56.67)	159 (64.9)
3 to 4	78 (20.97)	21 (31.34)	8 (13.33)	49 (20)
5 to 7	67 (18.01)	12 (17.91)	18 (30)	37 (15.1)
	Mean (SD)			
Age, years	30.1 (3.8)	30 (3.9)	30.1 (3.9)	30.2 (3.8)
Body Mass Index, kg/m^2	31.7 (4)	31.7 (3.8)	32.8 (4.5)	31.4 (3.9)
Body weight, kg	91.4 (15.6)	90.6 (14.4)	95.4 (18.1)	90.7 (15.2)
Body fat, %	40.8 (6.3)	41.7 (5.8)	41.6 (5.9)	40.4 (6.4)
Body weight change[h], %	-9.2 (6.6)	-7.8 (6.6)	-7.4 (6.4)	-10 (6.6)
Alcohol[e], days/month	6.5 (5)	6.6 (5)	6.4 (5.1)	6.5 (5)
Sleep on weekdays[g], hrs/day	7.7 (2.1)	8.2 (2.4)	7.6 (1.9)	7.6 (2)
Total energy intake, calories/day	1900.5 (866.7)	1950.6 (935.5)	1928.4 (1130.6)	1879.9 (771.4)
Diet quality, HEI out of 100	64.6 (11.1)	60.1 (9.2)	61.4 (12)	66.5 (10.8)

[a] Pre-baseline refers to the assessment of the characteristics at 0 months of the IDEA study
[b] The participants who responded positively to the following statement: "Since my weight goes up and down, I have gone on reducing diets more than once," referring to the experience prior to the weight loss intervention
[c] The participants who responded positively to the following statement: "I felt depressed," referring to the experience one week prior to the pre-baseline (month 0) assessment
[d] Referring to the meal consumption frequency in a typical week prior to the pre-baseline (month 0) assessment
[e] The participants responded to the following question: “During the past 30 days, how many days did you have at least one drink of any alcoholic beverage?” referring to the experience prior to the pre-baseline (month 0) assessment
[f] “Vigorous-intensity activities” are activities that require hard physical effort and cause large increases in breathing or heart rate; “moderate-intensity activities” are activities that require moderate physical effort and cause small increases in breathing or heart rate.
[g] Referring to the period between which the participants usually went to bed in the evening (turn out the lights in order to go to sleep) and the time they usually got out of bed in the morning in the past month prior to the pre-baseline (month 0) assessment
[h] Weight change during the first 6 months of the conventional weight loss intervention. Relative body weight (%) change is calculated as (100x(absolute body weight (kg) at 6 months - absolute body weight (kg) at 0 months)/ absolute body weight (kg) at 0 months). A negative estimate means a decrease in body weight during the follow-up period.
Abbreviations: HS High School, GED General Education Diploma, PA physical activity

Table 18. Pre-Baseline Characteristics of 372 Eligible Participants by Evening Snack Consumption Frequency, the IDEA Study

	Evening snack frequency, times/week			
	Overall (n=372)	0 to 2 (n=151)	3 to 4 (n=94)	5 to 7 (n=127)
	N (%)			
Sex, female	264 (70.97)	111 (73.51)	55 (58.51)	98 (77.17)
Race				
Asian	10 (2.69)	6 (3.97)	3 (3.19)	1 (0.79)
Black	57 (15.32)	21 (13.91)	9 (9.57)	27 (21.26)
White	305 (81.99)	124 (82.12)	82 (87.23)	99 (77.95)
Education				
College or Baccalaureate	156 (41.94)	72 (47.68)	41 (43.62)	43 (33.86)
HS, GED, or Some college	84 (22.58)	31 (20.53)	17 (18.09)	36 (28.35)
Graduate Degree	132 (35.48)	48 (31.79)	36 (38.3)	48 (37.8)
Annual household income				
$12,000 through $15,999	65 (17.47)	20 (13.25)	22 (23.4)	23 (18.11)
$5,000 through $11,999	161 (43.28)	61 (40.4)	44 (46.81)	56 (44.09)
Less than $5,000	146 (39.25)	70 (46.36)	28 (29.79)	48 (37.8)
Current smoker	30 (8.06)	8 (5.3)	8 (8.51)	14 (11.02)
Moderate PA[f], min/week				
<150 min/week	284 (76.34)	110 (72.85)	76 (80.85)	98 (77.17)
>=150 min/week	88 (23.66)	41 (27.15)	18 (19.15)	29 (22.83)
Vigorous PA[f], min/week				
<75 min/week	131 (35.22)	32 (21.19)	40 (42.55)	59 (46.46)
>=75 min/week	241 (64.78)	119 (78.81)	54 (57.45)	68 (53.54)
Regular dieting[b]	163 (43.82)	56 (37.09)	43 (45.74)	64 (50.39)
Depression[c], time/week				
<1	3 (0.81)	2 (1.32)	. (.)	1 (0.79)
1-2	17 (4.57)	6 (3.97)	5 (5.32)	6 (4.72)
3-4	288 (77.42)	120 (79.47)	72 (76.6)	96 (75.59)
5-7	64 (17.2)	23 (15.23)	17 (18.09)	24 (18.9)
Dinner[d], time/week				
0 to 2	5 (1.34)	3 (1.99)	. (.)	2 (1.57)
3 to 4	7 (1.88)	3 (1.99)	1 (1.06)	3 (2.36)
5 to 7	360 (96.77)	145 (96.03)	93 (98.94)	122 (96.06)
Breakfast[d], time/week				
0 to 2	67 (18.01)	25 (16.56)	20 (21.28)	22 (17.32)
3 to 4	60 (16.13)	26 (17.22)	13 (13.83)	21 (16.54)
5 to 7	245 (65.86)	100 (66.23)	61 (64.89)	84 (66.14)
Eating within an hour of bedtime[d], time/week				

0 to 2	227 (61.02)	126 (83.44)	64 (68.09)	37 (29.13)
3 to 4	78 (20.97)	19 (12.58)	24 (25.53)	35 (27.56)
5 to 7	67 (18.01)	6 (3.97)	6 (6.38)	55 (43.31)
	Mean (SD)			
Age, years	30.1 (3.8)	30 (3.7)	30 (4)	30.3 (3.9)
Body Mass Index, kg/m2	31.7 (4)	31.4 (3.9)	31.9 (4.2)	31.7 (4.1)
Body weight, kg	91.4 (15.6)	90.3 (14.8)	92.9 (15.5)	91.6 (16.6)
Body fat, %	40.8 (6.3)	41 (6.1)	39.8 (6.3)	41.4 (6.4)
Body weight change[h], %	-9.2 (6.6)	-10.1 (6.8)	-10.2 (6.1)	-7.4 (6.4)
Alcohol[e], days/month	6.5 (5)	6.6 (4.9)	6.8 (4.6)	6.1 (5.4)
Sleep on weekdays[g], hrs/day	7.7 (2.1)	7.8 (2)	7.7 (2.3)	7.8 (1.9)
Total energy intake, calories/day	1900.5 (866.7)	1731.1 (708.6)	1839.2 (790.5)	2147.2 (1026.8)
Diet quality, HEI out of 100	64.6 (11.1)	65.2 (10.8)	63.4 (10.4)	64.7 (11.9)

[a] Pre-baseline refers to the assessment of the characteristics at 0 months of the IDEA study
[b] The participants who responded positively to the following statement: "Since my weight goes up and down, I have gone on reducing diets more than once," referring to the experience prior to the weight loss intervention
[c] The participants who responded positively to the following statement: "I felt depressed," referring to the experience one week prior to the pre-baseline (month 0) assessment
[d] Referring to the meal consumption frequency in a typical week prior to the pre-baseline (month 0) assessment
[e] The participants responded to the following question: “During the past 30 days, how many days did you have at least one drink of any alcoholic beverage?” referring to the experience prior to the pre-baseline (month 0) assessment
[f] “Vigorous-intensity activities” are activities that require hard physical effort and cause large increases in breathing or heart rate; “moderate-intensity activities” are activities that require moderate physical effort and cause small increases in breathing or heart rate.
[g] Referring to the period between which the participants usually went to bed in the evening (turn out the lights in order to go to sleep) and the time they usually got out of bed in the morning in the past month prior to the pre-baseline (month 0) assessment
[h] Weight change during the first 6 months of the conventional weight loss intervention. Relative body weight (%) change is calculated as (100x(absolute body weight (kg) at 6 months - absolute body weight (kg) at 0 months)/ absolute body weight (kg) at 0 months). A negative estimate means a decrease in body weight during the follow-up period.
Abbreviations: HS High School, GED General Education Diploma, PA physical activity

Table 19. Estimates[g] of the effect of dietary strategies on the maintenance of total body weight (kg), body fat mass (kg) and body lean mass (kg) relative body fat (%) among all eligible participants of the IDEA study during the 18-month follow-up after initial weight loss. Per protocol and intent-to-treat analysis.

Treatment strategy [a, b]	Total body weight (kg)[c]		Body fat mass (kg)[d]		Body lean mass (kg) [e]	
	Mean change, 95% CI	Mean difference, 95% CI	Mean change, 95% CI	Mean difference, 95% CI	Mean change, 95% CI	Mean difference, 95% CI
Breakfast [h]	Per-protocol analysis					
0 to 4 times/wk	3.56 (0.67, 5.63)	Reference	2.94 (0.44, 4.84)	Reference	0.62 (0.15, 1.06)	Reference
5 to 7 times/wk	2.95 (2.01, 3.96)	-0.59 (-0.86, -0.32)	2.34 (1.51, 3.13)	-0.57 (-0.82, -0.33)	0.61 (0.4, 0.91)	-0.01 (-0.06, 0.05)
Evening snack [h]	Per-protocol analysis					
0 to 2 times/wk	2.86 (0.99, 5.25)	-0.83 (-1.06, -0.59)	2.29 (0.95, 4.12)	-0.59 (-0.78, -0.39)	0.58 (0.12, 1.22)	-0.22 (-0.29, -0.16)
3 to 7 times/wk	3.7 (2.29, 4.9)	Reference	2.89 (1.44, 3.87)	Reference	0.8 (0.47, 1.09)	Reference
Breakfast [h]	Intent-to-treat analysis adjusted for adherence					
0 to 4 times/wk	4.1 (1.67, 6.48)	Reference	3.38 (1.43, 5.38)	Reference	0.72 (-0.18, 1.71)	0.37 (0.34, 0.39)
5 to 7 times/wk	3.01 (0.98, 4.13)	-1.39 (-1.45, -1.33)	2.45 (0.95, 3.96)	-1 (-1.06, -0.95)	0.56 (-0.44, 0.96)	Reference
Evening snack [h]	Intent-to-treat analysis adjusted for adherence					
0 to 2 times/wk	2.43 (0.18, 4.32)	-1.18 (-1.22, -1.14)	1.8 (-0.42, 3.5)	-1.23 (-1.27, -1.19)	0.65 (0.18, 1.12)	0.05 (0.04, 0.06)
3 to 7 times/wk	3.72 (1.56, 5.29)	Reference	3.14 (1.07, 4.57)	Reference	0.58 (0.16, 1.04)	Reference

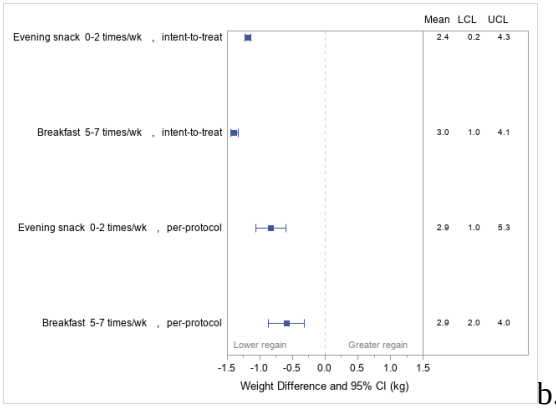
[a] Breakfast frequency is categorized as regular breakfast frequency (consumption of breakfast 5-7 times a week) and irregular to rare breakfast frequency (consumption of breakfast 0-4 times a week)

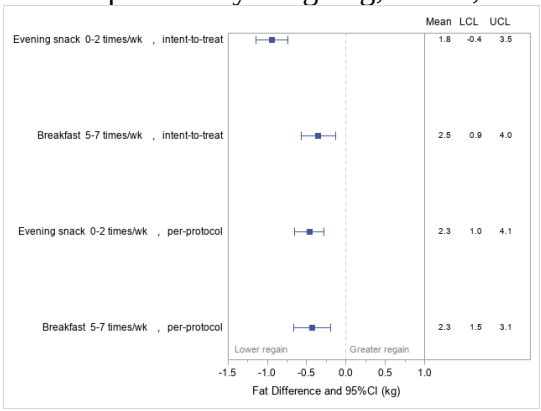
[b] Evening snack frequency is categorized as a frequent to habitual evening snack frequency (consumption of evening snack 3-7 times a week) and avoidance to rare evening snack frequency (consumption of evening snack 0-2 times a week)

[c] Total body weight (kg) change is calculated as (absolute body weight (kg) at 24 months - absolute body weight (kg) at 6 months). A negative estimate means a decrease in absolute body weight during the 18-months follow-up period.

[d] Body fat mass (kg) change is calculated as (body fat mass (kg) at 24 months - body fat mass (kg) at 6 months). A negative estimate means a decrease in body fat mass during the 18-months follow-up period.
[e] Body lean mass (kg) change is calculated as (body lean mass (kg) at 24 months - body lean mass (kg) at 6 months). A negative estimate means a decrease in body lean mass during the 18-months follow-up period.
[g] Estimates are based on MSMs with IPW accounting for selection bias due to censoring and treatment selection. IPWs adjust for pre-baseline covariates (age, sex, ethnicity, income, breakfast frequency, evening snack frequency, education, physical activity, smoking, alcohol consumption, sleep duration, BMI, diet quality, total energy intake, depression, initial body fat change) and time-varying covariates (income, breakfast frequency, evening snack frequency, physical activity, alcohol consumption, sleep duration, diet quality, total energy intake, depression).
[h] All eligible subjects
Abbreviations: IDEA study, the Innovative Approaches to Diet, Exercise and Activity (IDEA) study; CI, confidence interval; MSM, marginal structural model; IPW, inverse-probability weighing.

Figure 5. Estimated mean difference (left pane of the chart) and mean absolute change (right pane of the chart) of a. total body weight (kg), b. body fat mass (kg) and c. body lean mass (kg) during 18-months of the follow-up for dietary strategies compared with no intervention "natural course" in the Innovative Approaches to Diet, Exercise and Activity (IDEA) study. Estimates are based on MSMs with IPW accounting for selection bias due to censoring and treatment selection. IPW adjust for pre-baseline covariates (age, sex, ethnicity, income, breakfast frequency, evening snack frequency, education, physical activity, smoking, alcohol consumption, sleep duration, BMI, diet quality, total energy intake, depression, initial body fat change) and time-varying covariates (income, breakfast frequency, evening snack frequency, physical activity, alcohol consumption, sleep duration, diet quality, total energy intake, depression). The natural course of body weight independent of treatment strategy among all eligible subjects was calculated using MSMs accounting for censoring. IPCWs adjust for age, sex, ethnicity, income, education, physical activity, breakfast, evening snack, smoking, alcohol consumption, sleep duration, BMI, diet quality, total energy intake, and depression. Abbreviations: BMI, body mass index; MSM, marginal structural model; IPW, inverse probability weighing; IPCW, inverse probability censoring weights.

a. 

b. 

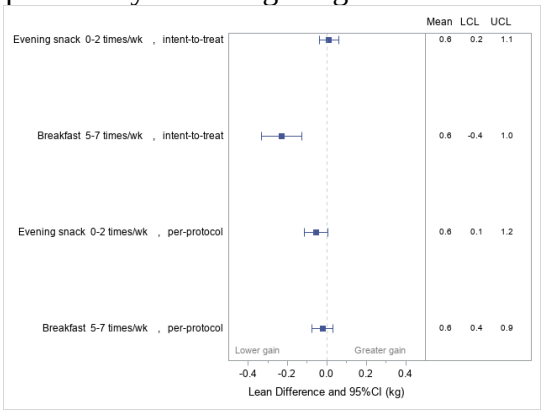
c. 

Table 20. Estimates[g] of the effect of dietary strategies on the maintenance of total body weight (kg), body fat mass (kg) and body lean mass (kg) relative body fat (%) among restricted populations of participants of the IDEA study during the 18-month follow-up after initial weight loss. Per protocol analysis.

Treatment strategy [a, b]	Total body weight (kg)[c]		Body fat mass (kg)[d]		Body lean mass (kg) [e]	
	Mean change, 95% CI	Mean difference, 95% CI	Mean change, 95% CI	Mean difference, 95% CI	Mean change, 95% CI	Mean difference, 95% CI
Only subjects who consumed breakfast 0-4 times/week at pre-baseline						
Breakfast [n]						
0 to 4 times/wk	3.44 (1.57, 5.64)	Reference	3.05 (1.12, 5.23)	Reference	0.4 (-0.19, 0.94)	Reference
5 to 7 times/wk	2.26 (-2.39, 6.67)	-1.23 (-1.78, -0.67)	1.63 (-2.12, 5.47)	-1.45 (-1.93, -0.98)	0.63 (-0.24, 1.5)	0.24 (0.13, 0.35)
Only subjects who consumed breakfast 5-7 times/week at pre-baseline						
Breakfast [n]						
0 to 4 times/wk	2.86 (0.64, 6.65)	Reference	2.53 (0.54, 5.14)	Reference	0.27 (-0.55, 1.42)	Reference
5 to 7 times/wk	3.01 (2.07, 3.97)	0.04 (-0.34, 0.43)	2.46 (1.55, 3.29)	-0.17 (-0.45, 0.11)	0.56 (0.33, 0.85)	0.27 (0.15, 0.39)
Only subjects who consumed evening snacks 0-2 times/week at pre-baseline						
Evening snack[n]						
0 to 2 times/wk	2.77 (0.02, 5.22)	-1.15 (-1.53, -0.78)	1.95 (-1.03, 4.23)	-1.57 (-1.89, -1.24)	0.83 (0.26, 1.38)	0.44 (0.34, 0.54)
3 to 7 times/wk	3.9 (1.41, 6.33)	Reference	3.5 (1.43, 5.24)	Reference	0.38 (-0.36, 1.05)	Reference

[a] Breakfast frequency is categorized as regular breakfast frequency (consumption of breakfast 5-7 times a week) and irregular to rare breakfast frequency (consumption of breakfast 0-4 times a week)

[b] Evening snack frequency is categorized as a frequent to habitual evening snack frequency (consumption of evening snack 3-7 times a week) and avoidance to rare evening snack frequency (consumption of evening snack 0-2 times a week)

[c] Total body weight (kg) change is calculated as (absolute body weight (kg) at 24 months - absolute body weight (kg) at 6 months). A negative estimate means a decrease in absolute body weight during the 18-months follow-up period.

[d] Body fat mass (kg) change is calculated as (body fat mass (kg) at 24 months - body fat mass (kg) at 6 months). A negative estimate means a decrease in body fat mass during the 18-months follow-up period.
[e] Body lean mass (kg) change is calculated as (body lean mass (kg) at 24 months - body lean mass (kg) at 6 months). A negative estimate means decreased body lean mass during the 18-months follow-up period.
[g] Estimates are based on MSMs with IPW accounting for selection bias due to censoring and treatment selection. IPW adjust for pre-baseline covariates (age, sex, ethnicity, income, breakfast frequency, evening snack frequency, education, physical activity, smoking, alcohol consumption, sleep duration, BMI, diet quality, total energy intake, depression, initial body fat change) and time-varying covariates (income, breakfast frequency, evening snack frequency, physical activity, alcohol consumption, sleep duration, diet quality, total energy intake, depression).
[n] Per-protocol analysis
Abbreviations: IDEA study, the Innovative Approaches to Diet, Exercise and Activity (IDEA) study; CI, confidence interval; MSM, marginal structural model; IPW, inverse-probability weighing; IPCW, inverse probability censoring weights.

Figure 6. Estimated mean difference (left pane of the chart) and mean absolute change (right) of a. total body weight (kg), b. body fat mass (kg) and c. body lean mass (kg) during 18-months of the follow-up for dietary strategies compared with no intervention "natural course" in the Innovative Approaches to Diet, Exercise and Activity (IDEA) study. Estimates are based on MSMs with IPW accounting for selection bias due to censoring and treatment selection. IPW adjust for pre-baseline covariates (age, sex, ethnicity, income, breakfast frequency, evening snack frequency, education, physical activity, smoking, alcohol consumption, sleep duration, BMI, diet quality, total energy intake, depression, initial body fat change) and time-varying covariates (income, breakfast frequency, evening snack frequency, physical activity, alcohol consumption, sleep duration, diet quality, total energy intake, depression). The natural course of body weight independent of treatment strategy among restricted populations of eligible subjects was calculated using MSMs accounting for censoring. IPCWs adjust for age, sex, ethnicity, income, education, physical activity, breakfast, evening snack, smoking, alcohol consumption, sleep duration, BMI, diet quality, total energy intake, and depression. Abbreviations: BMI, body mass index; MSM, marginal structural model; IPW, inverse probability weighing; IPCW, inverse probability censoring weights.

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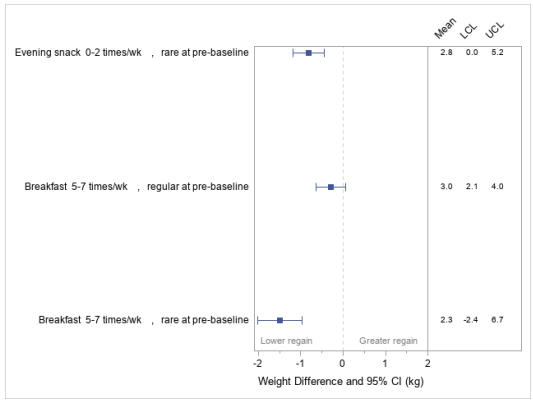

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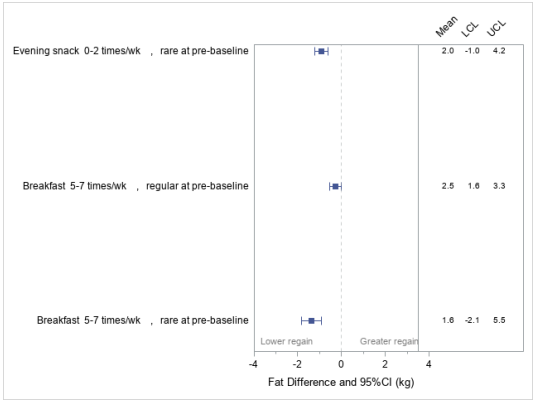

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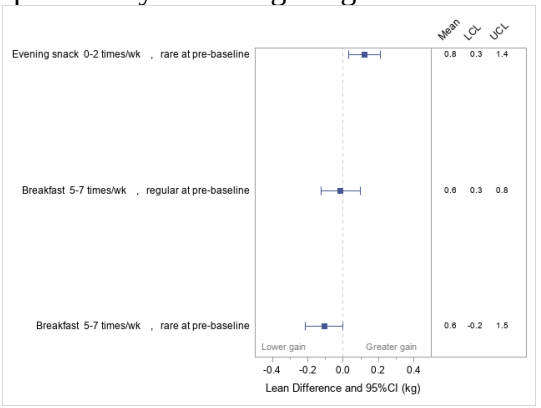
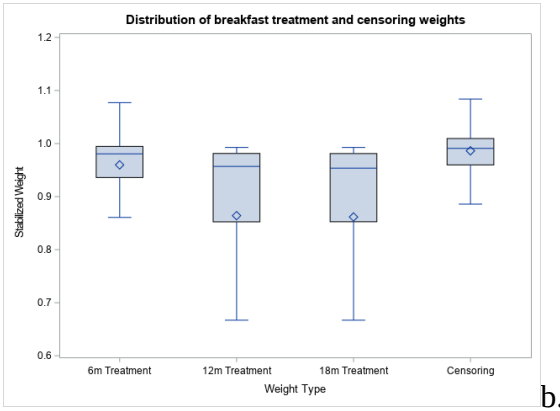
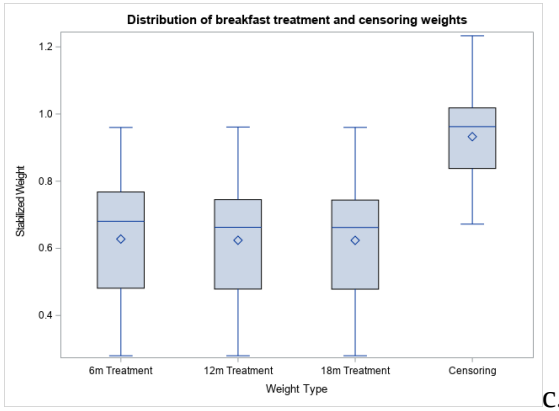
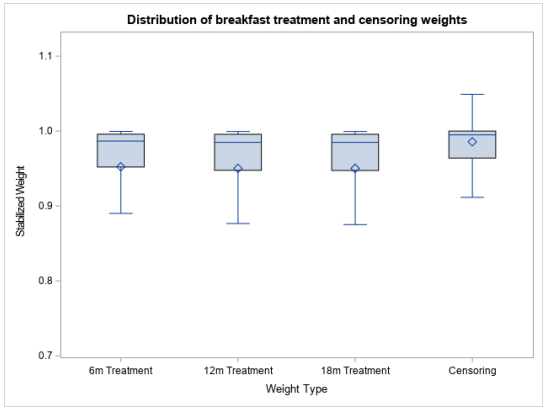
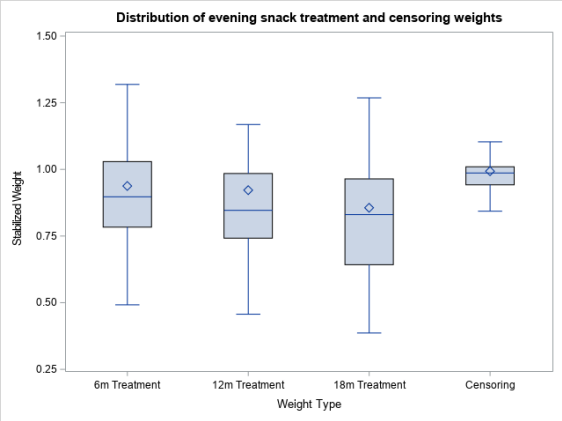


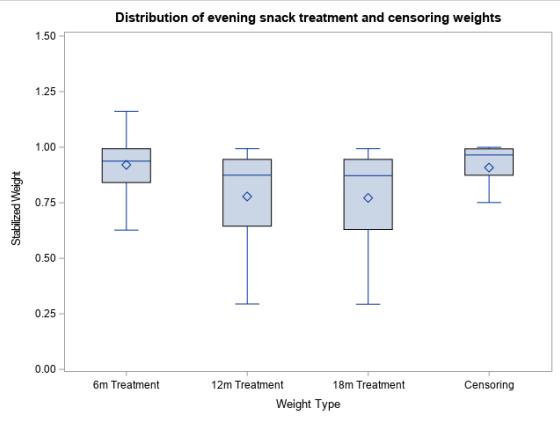
a. 

b. 

c. 

Supplementary Figure 1. Distribution of stabilized treatment and censoring weights for per-protocol breakfast treatment strategies a. among all eligible participants, b. per-protocol breakfast intervention among participants who consumed irregularly to rare breakfast at pre-baseline, c. per-protocol breakfast intervention among participants who consumed regular breakfast at pre-baseline.





Supplementary Figure 2. Distribution of stabilized treatment and censoring weights for per-protocol evening snack treatment strategies a. among all eligible participants, b. among participants who avoided or rarely consumed evening snacks at pre-baseline, c. among participants who consumed frequent and habitual evening snacks at pre-baseline.

Supplementary Table 4. Cumulative Percent of Participants Intervened on Under Strategies in Main Tables 2, 3: Estimates[a] of the effect of breakfast/evening snack frequency on the difference in body weight and composition among eligible participants of the IDEA study. All Strategies are followed by participants at 6, 12, and 18 months of the follow-up.

Strategy	**A cumulative % of participants intervened on**
Breakfast[n]	
0 to 4 times/wk	14
5 to 7 times/wk	50
7 times/wk	27
Evening snack [n]	
0 times/wk	3
0 to 2 times/wk	21
3 to 7 times/wk	30
Breakfast [m]	
0 to 4 times/wk	23
5 to 7 times/wk	72
7 times/wk	48
Evening snack,[m]	
0 times/wk	6
0 to 2 times/wk	37
3 to 7 times/wk	57

[a] Estimates based on the marginal structural models with IPW accounting for selection bias due to censoring and treatment selection. IPW adjust for baseline covariates (age, sex, ethnicity, income, breakfast frequency, evening snack frequency, education, physical activity, smoking, alcohol consumption, sleep duration, BMI, diet quality, total energy intake, depression) and time-varying covariates (income, breakfast frequency, evening snack frequency, education, physical activity, alcohol consumption, sleep duration, BMI, diet quality, total energy intake, depression weight/fat change). Weights for treatment at 6M, 12M, and 18M were derived, accounting for time-varying confounders at 0-6M, 0-12M, and 0-18M, respectively. Component weight truncation at the 95th percentile of the distribution for breakfast and evening snack intervention improves the IPTW estimators.

[b] Proportion of eligible participants (out of n=372) who adhered to treatment at 6, 12, and 18 months of the follow-up

[h] All eligible subjects

[m] Intent-to-treat analysis adjusted for adherence

[n] Per-protocol analysis

Supplementary Table 5. Estimates[g] of the effect of dietary strategies on the maintenance of relative body weight (%) and relative body fat (%) among all eligible participants of the IDEA study during the 18-month follow-up after initial weight loss. Per protocol and intent-to-treat analysis.

Treatment strategy [a, b]	Relative body weight (%)[d]		Relative body fat (%)[e]	
	Mean change, 95% CI	Mean difference, 95% CI	Mean change, 95% CI	Mean difference, 95% CI
Breakfast [h, n]				
0 to 4 times/wk	1.73 (-0.25, 3.37)	. (., .)	4.35 (0.6, 7.24)	. (., .)
5 to 7 times/wk	1.35 (0.75, 1.91)	-0.36 (-0.55, -0.18)	3.57 (2.54, 4.59)	-0.74 (-1.1, -0.39)
Evening snack [h,n]				
0 to 2 times/wk	1.35 (0.52, 2.43)	-0.22 (-0.34, -0.09)	3.48 (1.12, 6.06)	-0.87 (-1.15, -0.59)
3 to 7 times/wk	1.58 (0.5, 2.17)	. (., .)	4.37 (2.62, 5.72)	. (., .)
Breakfast [h,m]				
0 to 4 times/wk	2.02 (0.35, 3.81)	. (., .)	4.89 (2.24, 7.63)	. (., .)
5 to 7 times/wk	1.4 (0.37, 2.59)	-0.65 (-0.69, -0.61)	3.59 (1.2, 4.87)	-1.68 (-1.75, -1.62)
Evening snack [h,m]				
0 to 2 times/wk	0.86 (-0.72, 2.13)	-0.93 (-0.96, -0.9)	2.89 (0.32, 5.23)	-1.48 (-1.53, -1.42)
3 to 7 times/wk	1.9 (0.52, 2.95)	. (., .)	4.49 (1.98, 6.34)	. (., .)

[a] Breakfast frequency is categorized as regular breakfast frequency (consumption of breakfast 5-7 times a week) and irregular to rare breakfast frequency (consumption of breakfast 0-4 times a week)

[b] Evening snack frequency is categorized as a frequent to habitual evening snack frequency (consumption of evening snack 3-7 times a week) and avoidance to rare evening snack frequency (consumption of evening snack 0-2 times a week)

[d] Relative body weight (%) change is calculated as (100x(absolute body weight (kg) at 24 months - absolute body weight (kg) at 6 months)/ absolute body weight (kg) at 6 months). A negative estimate means a decrease in body weight during the follow-up period.

[e] Relative body fat (%) change is calculated as (relative body fat (%) at 24 months – relative body fat (%) at 6 months). A negative estimate means a decrease in relative body fat during the 18-months follow-up period.

[g] Estimates are based on MSMs with IPW accounting for selection bias due to censoring and treatment selection. IPW adjust for pre-baseline covariates (age, sex, ethnicity, income, breakfast frequency, evening snack frequency, education, physical activity, smoking, alcohol consumption, sleep duration, BMI, diet quality, total energy intake, depression, initial body fat change) and time-varying covariates (income, breakfast frequency, evening snack frequency,

physical activity, alcohol consumption, sleep duration, diet quality, total energy intake, depression).
[h] All eligible subjects
[m] Intent-to-treat analysis adjusted for adherence
[n] Per-protocol analysis
Abbreviations: IDEA study, the Innovative Approaches to Diet, Exercise and Activity (IDEA) study; CI, confidence interval; MSM, marginal structural model; IPW, inverse-probability weighing.

Supplementary Table 6. Estimates[g] of the effect of dietary strategies on the maintenance of relative body weight (%) and relative body fat (%) among restricted populations of participants of the IDEA study during the 18-month follow-up after initial weight loss. Per protocol analysis.

Treatment strategy [a, b]	Relative body weight (%)[d]		Relative body fat (%)[e]	
	Mean change, 95% CI	Mean difference, 95% CI	Mean change, 95% CI	Mean difference, 95% CI
Breakfast [i,n]				
0 to 4 times/wk	1.81 (0.45, 3.46)	. (., .)	3.9 (1.63, 6.62)	. (., .)
5 to 7 times/wk	0.56 (-1.77, 3.02)	-1.27 (-1.57, -0.97)	2.98 (-2.28, 8)	-0.97 (-1.61, -0.34)
Breakfast [j,n]				
0 to 4 times/wk	1.87 (0.44, 2.59)	. (., .)	2.97 (0.73, 5.67)	. (., .)
5 to 7 times/wk	1.49 (0.82, 2.15)	-0.43 (-0.57, -0.29)	3.66 (2.58, 4.75)	0.59 (0.29, 0.89)
Evening snack [k,n]				
0 to 2 times/wk	0.84 (-0.93, 2.16)	-1.94 (-2.17, -1.71)	3.12 (0.34, 5.79)	-1.83 (-2.26, -1.4)
3 to 7 times/wk	2.78 (1.08, 4.33)	. (., .)	4.94 (1.9, 7.96)	. (., .)

[a] Breakfast frequency is categorized as regular breakfast frequency (consumption of breakfast 5-7 times a week) and irregular to rare breakfast frequency (consumption of breakfast 0-4 times a week)

[b] Evening snack frequency is categorized as a frequent to habitual evening snack frequency (consumption of evening snack 3-7 times a week) and avoidance to rare evening snack frequency (consumption of evening snack 0-2 times a week)

[d] Relative body weight (%) change is calculated as (100x(absolute body weight (kg) at 24 months - absolute body weight (kg) at 6 months)/ absolute body weight (kg) at 6 months). A negative estimate means a decrease in body weight during the follow-up period.

[e] Relative body fat (%) change is calculated as (relative body fat (%) at 24 months – relative body fat (%) at 6 months). A negative estimate means a decrease in relative body fat during the 18-months follow-up period.

[g] Estimates are based on MSMs with IPW accounting for selection bias due to censoring and treatment selection. IPW adjust for pre-baseline covariates (age, sex, ethnicity, income, breakfast frequency, evening snack frequency, education, physical activity, smoking, alcohol consumption, sleep duration, BMI, diet quality, total energy intake, depression, initial body fat change) and time-varying covariates (income, breakfast frequency, evening snack frequency, physical activity, alcohol consumption, sleep duration, diet quality, total energy intake, depression).

[i] Only subjects who consumed breakfast 0-4 times/week at pre-baseline

[j] Only subjects who consumed breakfast 5-7 times/week at pre-baseline

[k] Only subjects who consumed evening snacks 0-2 times/week at pre-baseline

[n] Per-protocol analysis

Abbreviations: IDEA study, the Innovative Approaches to Diet, Exercise and Activity (IDEA) study; CI, confidence interval; MSM, marginal structural model; IPW, inverse-probability weighing; IPCW, inverse probability censoring weights.

Supplementary Table 7. Estimates[g] of the effect of extreme dietary strategies on the maintenance of total body weight (kg), body fat mass (kg) and body lean mass (kg) relative body fat (%) among all eligible participants of the IDEA study during the 18-month follow-up after initial weight loss. Per protocol and intent-to-treat analysis.

Treatment strategy [a, b]	Total body weight (kg)[c]		Body fat mass (kg)[d]		Body lean mass (kg) (%)[e]	
	Mean change, 95% CI	Mean difference, 95% CI	Mean change, 95% CI	Mean difference, 95% CI	Mean change, 95% CI	Mean difference, 95% CI
Breakfast [h, n]						
0 to 6 times/wk	3.04 (2.03, 4.38)	Reference	2.59 (1.66, 3.75)	Reference	0.45 (0.17, 0.79)	Reference
7 times/wk	2.95 (1.79, 4.24)	-0.08 (-0.25, 0.09)	2.39 (1.36, 3.34)	-0.19 (-0.34, -0.04)	0.56 (0.25, 0.99)	0.12 (0.07, 0.17)
Breakfast [h,m]						
0 to 6 times/wk	3.22 (0.21, 5.03)	Reference	2.44 (-0.56, 4.02)	Reference	0.77 (0.38, 1.41)	Reference
7 times/wk	3.86 (2.17, 6.92)	1.26 (1.2, 1.33)	3.27 (1.72, 6.36)	1.56 (1.5, 1.63)	0.59 (-0.12, 1.05)	-0.17 (-0.2, 0.01)

[a] Breakfast frequency is categorized as regular breakfast frequency (consumption of breakfast 7 times a week) and rare to irregular breakfast frequency (consumption of breakfast 0-6 times a week)

[c] Total body weight (kg) change is calculated as (absolute body weight (kg) at 24 months - absolute body weight (kg) at 6 months). A negative estimate means a decrease in absolute body weight during the 18-months follow-up period.

[d] Body fat mass (kg) change is calculated as (body fat mass (kg) at 24 months - body fat mass (kg) at 6 months). A negative estimate means a decrease in body fat mass during the 18-months follow-up period.

[e] Body lean mass (kg) change is calculated as (body lean mass (kg) at 24 months - body lean mass (kg) at 6 months). A negative estimate means decreased body lean mass during the 18-months follow-up period.

[g] Estimates are based on MSMs with IPW accounting for selection bias due to censoring and treatment selection. IPW adjust for pre-baseline covariates (age, sex, ethnicity, income, breakfast frequency, evening snack frequency, education, physical activity, smoking, alcohol consumption, sleep duration, BMI, diet quality, total energy intake, depression, initial body fat change) and time-varying covariates (income, breakfast frequency, evening snack frequency, physical activity, alcohol consumption, sleep duration, diet quality, total energy intake, depression).

[h] All eligible subjects

[m] Intent-to-treat analysis adjusted for adherence
[n] Per-protocol analysis
Abbreviations: IDEA study, the Innovative Approaches to Diet, Exercise and Activity (IDEA) study; CI, confidence interval; MSM, marginal structural model; IPW, inverse-probability weighing.

Supplementary Table 8. Estimates[g] of the effect of extreme dietary strategies on the maintenance of relative body weight (%) and relative body fat (%) among all eligible participants of the IDEA study during the 18-month follow-up after initial weight loss. Per protocol and intent-to-treat analysis.

Treatment strategy [a, b]	Relative body weight (%)[d]		Relative body fat (%)[e]	
	Mean change, 95% CI	Mean difference, 95% CI	Mean change, 95% CI	Mean difference, 95% CI
Breakfast [h, n]				
0 to 6 times/wk	1.66 (1.01, 2.45)	Reference	3.75 (2.56, 5.27)	Reference
7 times/wk	1.43 (0.62, 2.13)	-0.22 (-0.33, -0.12)	3.56 (1.89, 5.06)	-0.19 (-0.4, 0.02)
Breakfast [h,m]				
0 to 6 times/wk	1.34 (-0.72, 2.39)	Reference	3.88 (0.23, 6.17)	Reference
7 times/wk	1.88 (0.83, 3.91)	0.96 (0.92, 1)	4.46 (2.28, 7.96)	1.23 (1.15, 1.31)

[a] Breakfast frequency is categorized as regular breakfast frequency (consumption of breakfast 7 times a week) and rare to irregular breakfast frequency (consumption of breakfast 0-6 times a week)

[d] Relative body weight (%) change is calculated as (100x(absolute body weight (kg) at 24 months - absolute body weight (kg) at 6 months)/ absolute body weight (kg) at 6 months). A negative estimate means a decrease in body weight during the follow-up period.

[e] Relative body fat (%) change is calculated as (relative body fat (%) at 24 months – relative body fat (%) at 6 months). A negative estimate means a decrease in relative body fat during the 18-months follow-up period.

[g] Estimates are based on MSMs with IPW accounting for selection bias due to censoring and treatment selection. IPW adjust for pre-baseline covariates (age, sex, ethnicity, income, breakfast frequency, evening snack frequency, education, physical activity, smoking, alcohol consumption, sleep duration, BMI, diet quality, total energy intake, depression, initial body fat change) and time-varying covariates (income, breakfast frequency, evening snack frequency, physical activity, alcohol consumption, sleep duration, diet quality, total energy intake, depression).

[h] All eligible subjects

[m] Intent-to-treat analysis adjusted for adherence

[n] Per-protocol analysis

Abbreviations: IDEA study, the Innovative Approaches to Diet, Exercise and Activity (IDEA) study; CI, confidence interval; MSM, marginal structural model; IPW, inverse-probability weighing.

Supplementary Table 9. Estimates[g] of the effect of extreme dietary strategies on the maintenance of total body weight (kg), body fat mass (kg) and body lean mass (kg) relative body fat (%) among restricted populations of participants of the IDEA study during the 18-month follow-up after initial weight loss. Per protocol analysis.

Treatment strategy [a, b]	Total body weight (kg)[c]		Body fat mass (kg)[d]		Body lean mass (kg) (%)[e]	
	Mean change, 95% CI	Mean difference, 95% CI	Mean change, 95% CI	Mean difference, 95% CI	Mean change, 95% CI	Mean difference, 95% CI
Breakfast [i,n]						
0 to 6 times/wk	2.85 (1.29, 3.96)	Reference	2.52 (1.08, 3.62)	Reference	0.33 (0.02, 0.67)	Reference
7 times/wk	1.69 (-0.69, 4.19)	-1.17 (-1.46, -0.88)	1.36 (-0.54, 3.75)	-1.18 (-1.43, -0.92)	0.35 (-0.41, 1.08)	0.02 (-0.06, 0.1)
Breakfast [j,n]						
0 to 6 times/wk	2.74 (0.35, 4.99)	Reference	1.67 (0.76, 2.57)	Reference	1.03 (-0.8, 2.42)	Reference
7 times/wk	2.57 (1.51, 3.81)	-0.24 (-0.51, 0.03)	2.19 (1.02, 3.45)	0.52 (0.36, 0.68)	0.39 (0.02, 0.77)	-0.72 (-0.89, -0.54)

[a] Breakfast frequency is categorized as regular breakfast frequency (consumption of breakfast 7 times a week) and rare to irregular breakfast frequency (consumption of breakfast 0-6 times a week)

[c] Total body weight (kg) change is calculated as (absolute body weight (kg) at 24 months - absolute body weight (kg) at 6 months). A negative estimate means a decrease in absolute body weight during the 18-months follow-up period.

[d] Body fat mass (kg) change is calculated as (body fat mass (kg) at 24 months - body fat mass (kg) at 6 months). A negative estimate means a decrease in body fat mass during the 18-months follow-up period.

[e] Body lean mass (kg) change is calculated as (body lean mass (kg) at 24 months - body lean mass (kg) at 6 months). A negative estimate means decreased body lean mass during the 18-months follow-up period.

[g] Estimates are based on MSMs with IPW accounting for selection bias due to censoring and treatment selection. IPW adjust for pre-baseline covariates (age, sex, ethnicity, income, breakfast frequency, evening snack frequency, education, physical activity, smoking, alcohol consumption, sleep duration, BMI, diet quality, total energy intake, depression, initial body fat change) and time-varying covariates (income, breakfast frequency, evening snack frequency, physical activity, alcohol consumption, sleep duration, diet quality, total energy intake, depression).

[i] Only subjects who consumed breakfast 0-6 times/week at pre-baseline

[j] Only subjects who consumed breakfast 7 times/week at pre-baseline

[n] Per-protocol analysis

Abbreviations: IDEA study, the Innovative Approaches to Diet, Exercise and Activity (IDEA) study; CI, confidence interval; MSM, marginal structural model; IPW, inverse-probability weighing; IPCW, inverse probability censoring weights.

Supplementary Table 10. Estimates[g] of the effect of extreme dietary strategies on the maintenance of relative body weight (%) and relative body fat (%) among restricted populations of participants of the IDEA study during the 18-month follow-up after initial weight loss. Per protocol analysis.

Treatment strategy [a, b]	Relative body weight (%)[d]		Relative body fat (%)[e]	
	Mean change, 95% CI	Mean difference, 95% CI	Mean change, 95% CI	Mean difference, 95% CI
Breakfast [i,n]				
0 to 6 times/wk	1.61 (0.75, 2.48)	Reference	3.5 (1.77, 4.84)	Reference
7 times/wk	0.96 (-0.4, 2.49)	-0.67 (-0.83, -0.5)	2.41 (-0.26, 5.33)	-1.12 (-1.45, -0.79)
Breakfast [j,n]				
0 to 6 times/wk	0.82 (0.12, 1.51)	Reference	3.6 (0.47, 6.6)	Reference
7 times/wk	1.41 (0.55, 2.53)	0.62 (0.49, 0.75)	3.03 (1.75, 4.5)	-0.67 (-1.01, -0.33)

[a] Breakfast frequency is categorized as regular breakfast frequency (consumption of breakfast 7 times a week) and irregular to rare breakfast frequency (consumption of breakfast 0-6 times a week)

[d] Relative body weight (%) change is calculated as (100x(absolute body weight (kg) at 24 months - absolute body weight (kg) at 6 months)/ absolute body weight (kg) at 6 months). A negative estimate means a decrease in body weight during the follow-up period.

[e] Relative body fat (%) change is calculated as (relative body fat (%) at 24 months – relative body fat (%) at 6 months). A negative estimate means a decrease in relative body fat during the 18-months follow-up period.

[g] Estimates are based on MSMs with IPW accounting for selection bias due to censoring and treatment selection. IPW adjust for pre-baseline covariates (age, sex, ethnicity, income, breakfast frequency, evening snack frequency, education, physical activity, smoking, alcohol consumption, sleep duration, BMI, diet quality, total energy intake, depression, initial body fat change) and time-varying covariates (income, breakfast frequency, evening snack frequency, physical activity, alcohol consumption, sleep duration, diet quality, total energy intake, depression).

[i] Only subjects who consumed breakfast 0-6 times/week at pre-baseline

[j] Only subjects who consumed breakfast 7 times/week at pre-baseline

[n] Per-protocol analysis

Abbreviations: IDEA study, the Innovative Approaches to Diet, Exercise and Activity (IDEA) study; CI, confidence interval; MSM, marginal structural model; IPW, inverse-probability weighing; IPCW, inverse probability censoring weights.

Supplementary Table 11. Estimates[g] of the effect of extreme dietary strategies on the maintenance of relative body weight (%) and relative body fat (%) among restricted populations of participants of the IDEA study during the 18-month follow-up after initial weight loss. Per protocol analysis.

Variable	Missing (%)[a]	The month of follow up
Alcohol, days/month	11%	0
Moderate-intensity physical activity, min/week	49%	0
Vigorous-intensity physical activity, min/week	53%	0
Alcohol, days/month	15%	6
Moderate-intensity physical activity, min/week	23%	6
Vigorous-intensity physical activity, min/week	29%	6
Alcohol, days/month	14%	12
Sleep on weekdays, hrs/day	3%	12
Total energy intake, calories	13%	12
Diet quality, HEI out of 100	13%	12
Income	13%	12
Smoking	13%	12
Moderate-intensity physical activity, min/week	29%	12
Vigorous-intensity physical activity, min/week	35%	12
Weight reducing diets[b]	13%	12
Alcohol, days/month	14%	18
Sleep on weekdays, hrs/day	2%	18
Total energy intake, calories	23%	18
Diet quality, HEI out of 100	23%	18
Income	23%	18
Smoking	23%	18
Moderate-intensity physical activity, min/week	27%	18
Vigorous-intensity physical activity, min/week	30%	18
Weight reducing diets[b]	23%	18
Depression	1%	18

[a] Out of 372 eligible subjects.
[b]Subject responded to the following statement: “Since my weight goes up and down, I have gone on reducing diets more than once.”

SUPPLEMENTARY METHODS

The main text presented estimates of the 18-months change in body weight and composition under each dietary strategy of interest in the IDEA study cohort. We attempted to reproduce the body weight, body fat, and lean body mass change estimates that would have been obtained in a (hypothetical) target trial in which individuals had been randomly assigned and adhered to these dietary strategies over 18 months. We then compared those estimates with the estimates under no dietary intervention. Our approach had two stages: 1) specification of the components of the protocol of the target trial, including the sustained dietary strategies, and 2) emulation of each component, including the use of the MSMs for confounding adjustment via IPWs. If our emulation procedures had been successful, the estimates would have a straightforward interpretation because the target trial is well defined. However, our estimates are only valid under strong assumptions of no unmeasured confounding, measurement error, and model misspecification.

Traditionally, dietary analysis of observational cohort has not been based on the exact emulation of a target trial. Instead, a conventional analysis estimates an 18-month change in body weight and composition for one dietary exposure level vs. another, conditional on covariates. For example, we considered the following conventional analysis to study the exposure to different breakfast and evening snack frequencies in the IDEA study cohort. The body weight, fat, and lean body mass change were estimated using linear mixed models (LMMs). LMMs with participant-level random intercepts were fitted to compare the evolution of body weight and composition over the period between 0 and 24 months according to breakfast and evening snack intake frequency groups, controlling for age, sex, race, smoking, education, BMI, vigorous and moderate physical activity, alternative eating occasion (breakfast frequency or evening snack frequency), energy intake, diet quality, alcohol intake, sleep duration, depression. When using

this approach, the mean difference (95% CI) estimates were 3.79 kg (1.07, 6.51) increase in body weight, 2.95 kg (1.07, 4.83) kg increase in body fat, and 0.83 kg (-0.96, 2.63) increase lean body mass among those who were consuming regular breakfast in comparison to 1.97 kg (-3.59, 7.54) increase in body weight, 1.15 kg (-2.29, 4.59) kg increase in body fat and 0.77 kg (-3.20, 4.74) increase in lean body mass among those who were consuming irregular to rare breakfast between 6 and 24 months of the follow-up. The mean difference (95% CI) estimates were a 2.41 kg (0.07, 4.75) increase in body weight, a 2.28 kg (-1.31, 5.88) kg increase in body fat, and 0.13 kg (-2.60, 2.34) decrease in lean body mass among those who were avoiding or rarely consuming evening snack in comparison to 2.72 kg (0.39, 5.06) increase in body weight, 4.46 kg (1.09, 7.83) kg increase in body fat and 1.71 kg (-0.52, 3.94) increase lean body mass among those who were consuming frequent evening snack between 6 and 24 months of the follow-up.

The interpretation of these estimates is not straightforward, even if we assume no unmeasured confounding, no measurement error, and no model misspecification. One could view these 18-year difference estimates as an attempt to estimate the causal effect of recent diet on weight and body composition. This interpretation would be justified if the dietary exposure were defined as the most recently available values at the start of the interval and previous values of dietary exposure and the other covariates were included in the model as potential confounders. However, prior dietary history is not included in many conventional analyses. In addition, adjustment for confounding due to diet before the start of follow-up is required when the diet is expected to have long-term effects.

Therefore, a conventional analysis targets the effect of recent exposure or an association among subjects who were not lost to follow-up (subject to selection bias and confounding), cannot readily consider sustained dietary strategies that may be dynamic, and do not use the usual diet

as the comparison group. Hence, it is impossible to directly compare conventional estimates with those based on an explicit emulation of a target trial of sustained dietary strategies. Specifically, the above conventional estimates cannot be interpreted as the effect on body weight and composition of adhering to breakfast and evening snack consumption strategies over 18 months. Note that the assumptions required by our target trial emulation—no unmeasured confounding, no measurement error, no model misspecification—are also required by conventional analyses. In the presence of unmeasured confounding, measurement error, or misspecification of the outcome model, both our analysis and conventional analyses would yield biased estimates of their respective estimands.

We implemented parametric marginal structural models (MSMs) to estimate the causal effect of each dietary strategy on body fat and weight maintenance between 6 and 24 months.[87], [115] The MSMs appropriately handle treatment-confounder feedback when the measured time-varying confounders are affected by prior exposure to dietary strategy and, under the assumptions of no unmeasured confounding and no model misspecification.[87], [115] This modeling approach attempts to create a pseudo-population in which the following assumptions hold: exchangeability (no unmeasured confounding); consistency (unambiguously defined exposure); positivity (nonzero probability of each possible exposure value at each possible confounder value); and correct model specification of the marginal structural model and weights. 12 This approach allows one to estimate a causal effect (assuming the above assumptions hold) in the overall population.

Briefly, each patient's data were expanded into 6 months intervals, and pooled logistic regression models were fitted to estimate stabilized IPTW.[85], [87] The probability of treatment strategy was estimated at 6 (baseline), 12, and 18 months of the follow-up. Subjects who had a missing

measure of the outcome or nonresponse to the breakfast or evening snack frequency questionnaire were censored at the time of nonresponse or 18 months follow-up. The model for the denominator of the weight included baseline covariates measured at pre-baseline (month 0): age, sex, race, smoking, education, BMI, vigorous and moderate physical activity, breakfast frequency, evening snack frequency, energy intake, diet quality, alcohol intake, sleep duration, depression; and the following time-varying covariates measured at all previous time-points and at the times of treatment: vigorous and moderate physical activity, body mass/body fat change since pre-baseline, breakfast frequency, evening snack frequency, energy intake, diet quality, alcohol intake, sleep duration, depression.

The MSMs have been previously applied to estimate the effects of lifestyle interventions on risk type 2 diabetes[116]–[119], abdominal obesity[120], current asthma[121], the aging process[61], [122], functional limitations in elderly[123].

SUMMARY AND CONCLUSIONS

Several studies have demonstrated an association between timing of eating, circadian rhythms, metabolism, and chronic disease risk. However, a long-term relationship between the timing of eating and disease remains unclear due to the length of time required to study this association, among other reasons. The objective of this dissertation is to explore further the relationship between the time, type 2 diabetes risk, breast cancer risk, and weight loss maintenance over time by using breakfast and after-dinner snacks as proxies of eating timing.

This dissertation consisted of three separate research projects aiming to 1) examine the association between the consumption of breakfast and after-dinner snack patterns and breast cancer risk among post-menopausal; 2) estimate the causal effect of long-term breakfast consumption and night snacking on type 2 diabetes risk via causal inference modeling among young adults; 3) investigate if consuming breakfast and evening snacks have a differential effect on weight loss maintenance among individuals with obesity undergoing a standard weight loss intervention.

The analyses showed no association between breakfast meals or after-dinner snack habits and the risk of breast cancer in post-menopausal women. In addition, the estimates from causal inference analysis supported that avoiding post-dinner snacks might be beneficial in reducing the long-term risk of diabetes; however, the role of starting regular breakfast consumption in midlife may have no major impact on the 20-y risk of diabetes. Finally, regular breakfast consumption and minimizing evening snacking may have a modest impact on lessening weight and body fat regain over 18 months after initial weight loss. In conclusion, the frequency of breakfast and after-dinner snacks is associated with metabolic disease risk and body weight maintenance.

It is essential to note that breakfast and after-dinner snack frequency could serve as a proxy for circadian rhythms that are the actual correlates of cancer and diabetes development and that these

also depend on many other lifestyle and environmental factors.

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