ORIGINAL RESEARCH

Nutritional Epidemiology and Public Health

CURRENT DEVELOPMENTS IN NUTRITION

Habitual Sleep Duration, Daytime Napping, and Dietary Intake: A Mendelian Randomization Study

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ABSTRACT

Background: Chronic inadequate sleep and frequent daytime napping may inflict deleterious health effects including weight gain, cardiometabolic and psychiatric diseases, and cancer. It is plausible that these relations may be partly influenced by the consumption of suboptimal diets.

Objectives: The study aimed to identify potential causal links of genetically proxied longer habitual sleep duration and more frequent daytime napping on 61 dietary variables derived from an FFQ. In addition, the study aimed to assess potential bidirectional causal links between habitual sleep duration or daytime napping and macronutrient composition.

Methods: Genetic variants robustly associated with habitual sleep duration and daytime napping from published genome-wide association analyses were used. Outcomes included 61 dietary variables estimated from FFQs in the UK Biobank ($n = 361{,}194$). For bidirectional associations with macronutrient composition, genetic variants associated with percentage of energy from carbohydrate, fat, and protein were used. Two-sample Mendelian randomization (MR) effects were estimated with inverse-variance weighted (IVW) analysis.

Results: In 2-sample MR, genetically proxied longer sleep duration was associated with a 0.068 (95% CI: 0.034, 0.103) category increase in salad/raw vegetable intake [$P_{\text{false discovery rate (FDR)}} = 0.006$] per hour of sleep and with "no major dietary changes in the past 5 years" ($P_{FDR} = 0.043$). No associations were evident for daytime napping on dietary variables (all $P_{FDR} > 0.05$). In addition, there were no bidirectional associations between habitual sleep duration or daytime napping with the relative intake of carbohydrate, fat, and protein (all $P_{IVW} > 0.05$).

Conclusions: In this MR study, there was modest evidence for associations between habitual sleep duration with dietary intake and no evidence for associations between daytime napping frequency with dietary intake. These preliminary findings suggest that changes to habitual sleep duration or daytime napping frequency may have limited impact on long-term changes in dietary intake. *Curr Dev Nutr* 2021;5:nzab019.

Keywords: sleep duration, daytime napping, Mendelian randomization, food intake, macronutrient composition, UK Biobank

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Abbreviations used: CHARGE, Cohorts for Heart and Aging Research in Genomic Epidemiology; FDR, false discovery rate; GWAS, genome-wide association study; IVW, inverse-variance weighted; MGB, Mass General Brigham; MR, Mendelian randomization; SNP, single nucleotide polymorphism.

Introduction

Sleep is an unconscious state of decreased motor function and heightened body restoration mechanistically regulated by homeostatic sleep pressure and the circadian clock (1, 2). Daytime napping is a short sleep episode occurring midday conserved across species (3, 4). Studies have shown that chronic inadequate sleep and frequent daytime napping may inflict deleterious health effects, including weight gain, cardiometabolic and psychiatric diseases, and cancer (5–16). It is plausible that the relation between habitual sleep duration or daytime napping and disease outcomes may be partly influenced by the consumption of suboptimal diets (17).

Differences in habitual sleep duration and frequency of daytime napping have been related to dietary intake in epidemiological studies. Both short and long sleep duration show associations with various nutrients and foods (17–20). Among these are associations between lower carbohydrate intake with longer sleep duration (18, 20) and higher fruit and vegetable intake with the recommended sleep duration of 7–9 h/night (21). Studies investigating the link between habitual daytime napping and dietary intake are relatively fewer. Among women, self-reported daytime napping is found to correlate with higher intakes of fats and proteins and lower intakes of caffeine and water (22). In adolescents, cross-sectional associations are evident between daytime napping and higher food cravings (23). Causal relations between

sleep duration and daytime napping with dietary intake remain to be evaluated.

Potential causal links between habitual sleep duration and daytime napping with dietary intake may be established in Mendelian randomization (MR). MR uses genetic variants robustly associated with a trait of interest to uncover potential causal effects on outcomes of interest with limited susceptibility to measurement error, confounding, and reverse causation (23). Habitual self-reported sleep duration and daytime napping have established genetic components [for sleep duration: single nucleotide polymorphism (SNP)–based heritability = 9.8% and twin- and family-based heritability = ≤45%; for daytime napping: SNP-based heritability = 11.9% and twin-based heritability = ≤65%] (7, 16). A total of 78 and 123 genetic variants robustly associate with sleep duration and daytime napping, respectively (7, 16). Through MR, we previously demonstrated potential causal links of genetically proxied morning diurnal preference on increased intake of fresh fruit and cereal and decreased intake of beer plus cider and processed meat (24). Here, using a comparable analytical pipeline and leveraging recent genetic findings for sleep habits, we aimed to identify potential causal links of genetically proxied longer habitual sleep duration and more frequent daytime napping on 61 dietary variables derived from an FFQ. In addition, we aimed to assess potential bidirectional causal links between sleep duration or daytime napping and macronutrient composition (% of total energy from carbohydrate, fat, and protein).

Methods

UK Biobank

The UK Biobank is a population-based cohort of >500,000 participants aimed at determining the relation between genetic and lifestyle exposures and a range of health outcomes (25). Participants are adults aged 37–73 y (mean ± SD = 56.5 ± 8.09 y) who lived in the United Kingdom between 2006 and 2010 (26). The present analysis was limited to participants of European ancestry with sleep, dietary, and genetic data and was conducted using public data from repositories or publications. Previous studies have provided in-depth descriptions of population structure, sample quality control, and genetic quality control and imputation (27, 28). Briefly, the UK Biobank used 2 different genotyping arrays: the UK BiLEVE Axiom Array (Affymetrix) and the UK Biobank Axiom Array (Applied Biosystems) . Variants were imputed using a combined reference panel of UK10K, 1000 Genomes panel, and the Haplotype Reference Consortium panel. Consistency of genotype calling was verified by testing for batch effects, plate effects, departures from Hardy-Weinberg equilibrium ($P < 1 \times 10^{-12}$, chi-square; 1 df), sex effects, array effects, and discordance across control replicates. Participants of European ancestry were identified from clustering participants into 4 ancestry clusters using K-means clustering on the principal components.

Genetic variants used to proxy habitual sleep duration and daytime napping

For MR, SNPs were selected from genome-wide association studies (GWASs) for habitual sleep duration ($n = 446{,}118$) and daytime napping ($n = 452{,}633$) (7, 16). In the UK Biobank, participants were asked "How many hours sleep do you get in every 24 h? (please include naps)," with responses in hourly increments, and "Do you have a nap during the day?" with the following responses: Never/rarely, Sometimes, Usually, and Prefer not to answer. A total of 78 and 123 SNPs were associated at genome-wide significance ($P < 5 \times 10^{-8}$) with habitual sleep duration and daytime napping, respectively. The identified variants were partly replicated in independent samples from the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) cohorts ($n = 47{,}180$) and the Mass General Brigham (MGB) Biobank (formerly Partners Biobank; $n = 7155$) for sleep duration and the 23andMe cohort ($n = 541{,}333$) for daytime napping, using similar assessment methods (7, 29).

Dietary variables via FFQ

In the UK Biobank, a total of 61 dietary variables were used to reflect average intake over the past year for a range of food items as measured by a 29-item touchscreen FFQ (24). Briefly, dietary variables included alcohol intake, cooked vegetables, and skimmed milk and are described in detail in **Supplemental Table 1**. Additionally, the following 3 non–food-item-related questions were included: "Have you made any major changes to your diet in the last 5 years?" with response options of No, Yes, because of illness, and Yes, because of other reason; "How do you like your hot drinks? (such as coffee or tea)" with response options of Very hot, Hot, Warm, and Do not drink hot drinks; and "Does your diet vary much from week to week?" with response options of Never/Rarely, Sometimes, and Often. Categorical variables were converted to binary variables denoting intake of a specific food within that corresponding category. For example, composition of bread (with response options of White, Brown, Wholemeal or whole grain, or Other type of bread) was converted to 4 binary variables indicating intake or nonintake of each bread type (i.e., white bread = yes/no; brown bread = yes/no; wholemeal or whole-grain bread = yes/no; other type of bread = yes/no). For binary variables, cases refer to consumers (e.g., "Other type of bread" consumers) and controls refer to nonconsumers (e.g., "Other type of bread" nonconsumers).

Publicly available summary statistics for the 61 outcome dietary variables were derived from the "round 2" version of the UK Biobank GWAS release published by the Neale Lab (30). Each GWAS included a subset of ∼361,194 unrelated participants of European ancestry and included adjustments for the following covariates: age, age-squared, sex, age × sex, age-squared × sex, and principal components 1–20. In addition, genetic correlations between habitual sleep duration and daytime napping with dietary variables in the UK Biobank were extracted from the UKBB Genetic Correlation browser (https://ukbb-rg.hail.is/) and were estimated using linkage disequilibrium (LD) score regression (31). To account for multiple comparison, we present false discovery rate (FDR)–corrected genetic correlation P values (P_{FDR} values).

MR for habitual sleep duration and daytime napping on dietary variables

To conduct 2-sample MR, published effect estimates were derived from replication cohorts (CHARGE cohorts and MGB Biobank for sleep duration; 23andMe cohort for daytime napping) (**Figure 1**). To maximize statistical power, effect estimates for the 78 variants for sleep duration from the CHARGE cohorts and MGB Biobank were meta-analyzed (total $n = 54{,}335$) using METAL by weighting effect

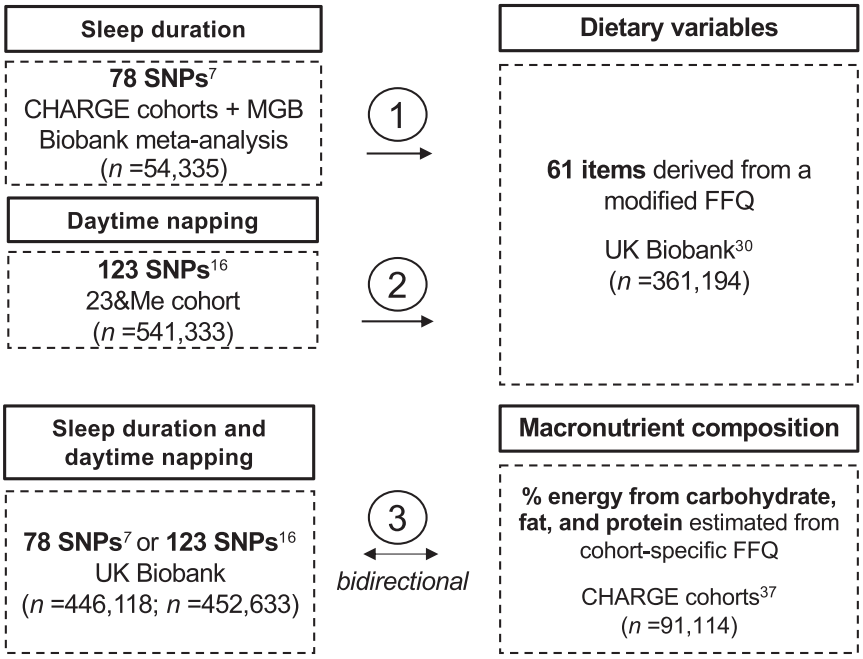

FIGURE 1 Overall framework of the present 2-sample Mendelian randomization study. CHARGE, Cohorts for Heart and Aging Research in Genomic Epidemiology; MGB, Mass General Brigham; SNP, single nucleotide polymorphism.

size estimates using the inverse of the corresponding standard errors squared (version released 25 March 2011) (**Supplemental Table 2**) (32).

Two-sample MR analyses were conducted using the "TwoSampleMR" R package (version 0.5.4) (33). To assess potential causal links of habitual sleep duration and daytime napping on dietary variables, the exposure comprised 78 SNPs associated with sleep duration with effect estimates from the meta-analysis of CHARGE cohorts and MGB Biobank (sample 1) representing genetically proxied longer habitual sleep duration (**Supplemental Table 3**) or 123 SNPs associated with daytime napping with effect estimates from the 23andMe cohort (sample 1) representing genetically proxied more frequent daytime napping (**Supplemental Table 4**), respectively. The units of the exposure SNPs are in minutes per day for sleep duration and log-odds of increased frequency of daytime napping. The outcome comprised associations of the 78 or 123 SNPs with dietary variables in unrelated participants of European ancestry in the UK Biobank (sample 2). For each exposure, we harmonized the exposure and outcome effects to the same effect allele (i.e., allele associated with longer sleep duration or more frequent daytime napping). For sleep duration, of the 78 genetic variants, 4 variants were excluded as a result of linkage disequilibrium (r^2 at a threshold of 0.8) with other variants, absence from reference panel, or low imputation quality (INFO score < 0.80) in the outcome sample (**Supplemental Table 5**). A total of 4 palindromic SNPs (i.e., SNPs whose alleles correspond to nucleotides that pair in forward and reverse coding, such as A/T or C/G alleles) with minor allele frequencies close to 0.50 (e.g., 0.42 and 0.49) in the exposure dataset were also excluded as it was not possible to reconcile ambiguities (Supplemental Table 5), whereas the remaining palindromic SNPs were aligned based on their minor allele frequency. For daytime napping, of the 123 genetic variants 14 variants were excluded for missing effect estimates from the 23andMe cohort, 11 were excluded as a result of linkage disequilibrium (r^2 at a threshold of 0.8) with other variants or absence from the reference panel, and 4 palindromic SNPs were further excluded (Supplemental Table 5). Thus, the genetic instruments for sleep duration and daytime napping comprised 70 (F-statistic = 3.1) and 94 (F-statistic = 23.4) SNPs, respectively.

When conducting MR, 3 assumptions are necessary to establish valid causal inference: *1*) strong association between the genetic instrument and the exposure of interest (which is accounted for by including SNPs in MR analysis associated with the exposure at genome-wide significance; $P < 5 \times 10^{-8}$), *2*) the genetic instrument and the outcome of interest are not associated with confounders (which is accounted for by using genetic variants randomized at gametogenesis, and by controlling for population stratification), and *3*) the genetic instrument influences the outcome only through the exposure of interest (i.e., no horizontal pleiotropy) (34).

The primary method of analyzing the causal effect of habitual sleep duration or daytime napping on dietary intake was inverse-variance weighted (IVW) (34). The SNP–outcome associations were regressed on the SNP–exposure associations using the inverse of the standard error of the SNP outcome to weight the effects under a random-effects model. The IVW method provides unbiased estimation of the effect assuming the absence of horizontal pleiotropy or when horizontal pleiotropy is balanced to the null (34). To validate this assumption was met, Cochran's Q for heterogeneity was calculated, which tests the null hypothesis that the causal effects estimated by each variant are equivalent. To address potential unbalanced horizontal pleiotropy, additional sensitivity analyses of MR-Egger (35) and weighted median (36) were conducted. MR-Egger assumes an independent association of each

genetic variant with the exposure from the pleiotropic effect of the variant. The MR-Egger intercept indicates directional pleiotropy with a nonzero intercept suggesting that the genetic instrument may be influencing the outcome through a pathway other than the exposure (35). The weighted median method provides consistent MR estimates with ≤50% of the instrument variables being invalid (36). Consistent effects across IVW and both sensitivity analyses strengthen causal evidence.

For interpretation purposes, MR causal effect estimates for sleep duration were multiplied by 60 in order to represent effects per hour of sleep. To account for 61 outcome variables, we present FDR-corrected IVW *P* values (P_{FDR} values). P_{FDR} values <0.05 from the IVW analysis were considered significant.

Genetic variants used to proxy macronutrient composition

To investigate potential bidirectional causal links between the 2 sleep variables and macronutrient composition (% of energy from carbohydrate, fat, and protein), we leveraged genetic variants associated with macronutrient composition in GWASs in >235,000 adults of European ancestry (37). A total of 7, 4, and 5 SNPs were identified to associate with percentage of energy intake from carbohydrate, fat, and protein, respectively (37).

Bidirectional MR for habitual sleep duration and daytime napping with macronutrient composition

To conduct 2-sample MR, effect estimates were retrieved from an independent macronutrient GWAS meta-analysis from the CHARGE cohorts (n = 91,114) (Figure 1) (**Supplemental Table 6**) (38). In the CHARGE cohorts, macronutrient composition was estimated using cohort-specific FFQs. Only 6 of the 7 SNPs for carbohydrate were finally included to represent genetically proxied higher percentage of energy from carbohydrate due to the absence of a robust proxy for rs7502280 (*F*-statistic = 14.6), whereas 4 (*F*-statistic = 12.1) and 5 (*F*-statistic = 16.1) SNPs were included to represent genetically proxied higher percentage of energy from fat and protein, respectively.

To evaluate potential causal links of habitual sleep duration and daytime napping on macronutrient composition, the exposure (sample 1) composed of 78 SNPs associated with sleep duration (Supplemental Table 3) or 123 SNPs associated with daytime napping (Supplemental Table 4) with effect estimates derived from the UK Biobank (7, 16). The outcome (sample 2) comprised associations of the 78 or 123 SNPs with the percentage of energy from carbohydrate, fat, and protein with effect estimates from the CHARGE cohorts GWAS meta-analysis (38). For each sleep exposure, we harmonized the exposure and outcome effects to the same effect allele. Of the 78 SNPs for sleep duration, 5 variants were excluded as a result of linkage disequilibrium (r^2 at a threshold of 0.8) with other variants or absence from the reference panel, and 4 palindromic SNPs were excluded (Supplemental Table 5). Of the 123 SNPs for daytime napping, 15 variants were excluded as a result of linkage disequilibrium (r^2 at a threshold of 0.8) with other variants or absence from the reference panel, 2 variants for carbohydrate and protein and 3 variants for fat were excluded due to missing data in the CHARGE cohorts, and 4 palindromic SNPs were excluded (Supplemental Table 5). Thus for macronutrient composition, genetic instruments for sleep duration and daytime napping comprised 69 (*F*-statistic = 28.8) and 102 (*F*-statistic = 45.3) SNPs, respectively. Units of the exposure SNPs were in minutes per day for sleep duration and log-odds of increased frequency of daytime napping, and units of the outcome SNPs were in percentage of energy.

Next, to evaluate potential reverse causal links of macronutrient composition on habitual sleep duration or daytime napping, the exposure (sample 1) composed of SNPs associated with percentage of energy from carbohydrate, fat, and protein with effect estimates derived from the CHARGE cohorts (Supplemental Table 6). The outcome (sample 2) comprised associations of the SNPs with habitual sleep duration or daytime napping with effect estimates from the respective UK Biobank GWASs retrieved from the Sleep Disorder Knowledge Portal (https://sleep.hugeamp.org/) (7, 16). Units of the exposure SNPs were in percentage of energy and units of the outcome SNPs were in minutes per day for sleep duration and log-odds of increased frequency of daytime napping. IVW was used for the primary analysis and MR-Egger and weighted medians were used as sensitivity analyses.

For interpretation purposes, all MR causal effect estimates for habitual sleep duration were scaled to represent effects per hour of sleep. For the bidirectional MR between sleep habits and macronutrient composition, *P* values <0.05 from the IVW analysis were considered significant.

Results

Genome-wide genetic correlations (r_g) between habitual sleep duration or daytime napping and dietary variables, traits with established underlying heritable components (39), ranged from −0.3 to 0.3, and thus are generally modest (**Figure 2**). For sleep duration, correlations ranged from −0.22 (r_g) for semi-skimmed milk to 0.20 (r_g) for never have milk (40), and for daytime napping correlations ranged from −0.11 (r_g) for wholemeal or whole-grain bread to 0.15 (r_g) for alcohol intake (40).

First, we conducted 2-sample MR between genetically proxied longer habitual sleep duration and 61 dietary variables from an FFQ in the UK Biobank (**Supplemental Table 7**). We found evidence ($P_{FDR} < 0.05$) that genetically proxied longer sleep duration was associated with a 0.068 (95% CI: 0.034, 0.103) category increase in salad/raw vegetable intake ($P_{FDR} = 0.006$) per hour of sleep (**Figure 3**). In addition, we found evidence that genetically proxied longer sleep duration was associated with "no major dietary changes in the past 5 years" ($P_{FDR} = 0.043$). Effects for both dietary variables remained robust in sensitivity analyses (Supplemental Table 7). An additional 10 associations were evident at $P_{IVW} < 0.05$, including the intake of muesli, alcohol, decaffeinated coffee, and cheese (**Table 1**).

Next, we conducted 2-sample MR between genetically proxied more frequent habitual daytime napping and 61 dietary variables from an FFQ in the UK Biobank (**Supplemental Table 8**). Overall, we found no significant evidence that suggests causal links of daytime napping on dietary variables at $P_{FDR} < 0.05$ and 7 associations at $P_{IVW} < 0.05$ (**Table 2**, Supplemental Table 8). Notably, the 2 strongest, albeit nonsignificant, associations were related to variables assessing major dietary changes within the last 5 y. The strongest positive association was observed for "major dietary change due to illness" ($P_{FDR} = 0.13$), and the strongest negative association was observed for "no major dietary change in the last 5 years" ($P_{FDR} = 0.13$).

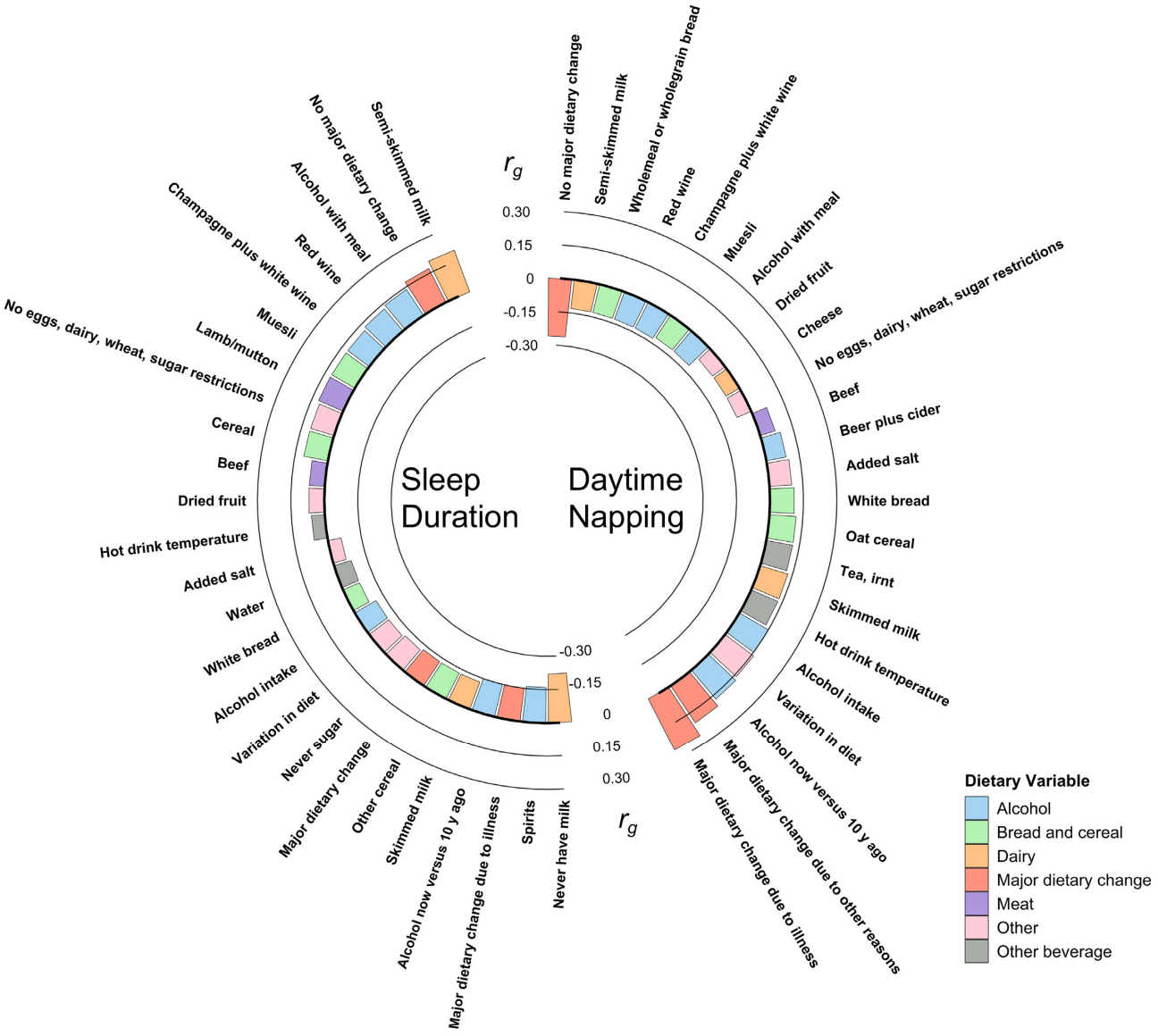

FIGURE 2 Genetic correlations between habitual sleep duration and daytime napping with dietary variables in the UK Biobank. Correlation estimates were estimated using LD score regression and were extracted from the UKBB Genetic Correlation browser (https://ukbb-rg.hail.is/). Only correlations with $P_{FDR} < 0.05$ accounting for 61 dietary variables are shown; full correlation results for all dietary variables are shown in Supplemental Table 1. Correlation values >0 (e.g., $r_g > 0$) indicate positive relations between longer habitual sleep duration or more frequent daytime napping and dietary variable, whereas correlation values <0 (e.g., $r_g < 0$) indicate negative relations between longer habitual sleep duration or more frequent daytime napping and dietary variable. In the UK Biobank, habitual sleep duration and daytime napping were self-reported and dietary variables were derived from a modified FFQ. A detailed description of dietary variables can be found in Supplemental Table 1. FDR, false discovery rate; irnt, rank-normalized; LD, linkage disequilibrium.

Last, we conducted bidirectional 2-sample MR between habitual sleep duration or daytime napping and macronutrient composition (% of energy from carbohydrate, protein, and fat) (**Figure 4**, **Supplemental Table 9**). Overall, we found no evidence for causal links of sleep duration or daytime napping on the relative intakes of carbohydrate, fat, and protein (all $P_{IVW} > 0.05$) and no evidence ($P_{IVW} < 0.05$) for causal links of macronutrient composition on habitual sleep duration or daytime napping.

Discussion

In this study we investigated the relations between habitual sleep duration and daytime napping with dietary variables through 2-sample MR. We identified associations of genetically proxied longer habitual sleep duration with increased intake of salad/raw vegetables and an increased effect on "no major dietary change in the past 5 years." In addition, we observed no evidence of associations between genetically proxied

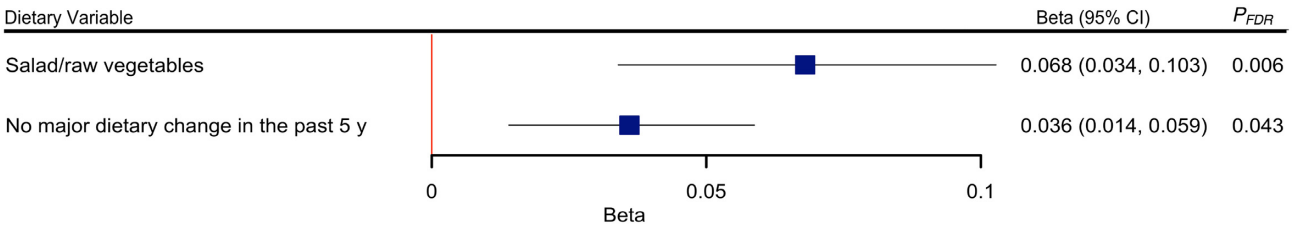

FIGURE 3 Potential causal effects of genetically proxied longer habitual sleep duration on dietary variables. Only significant results with $P_{FDR} < 0.05$ are shown; full results and sensitivity analyses are presented in Supplemental Table 7. The effect of the habitual sleep duration genetic instrument ($n = 70$) on each dietary variable was calculated using random-effects IVW regression. The exposure was scaled to represent a 1-h longer habitual sleep duration. A positive B (beta) represents per 1-h longer sleep duration increase per category (for ordinal variables: salad/raw vegetables) or log-odds (for binary variables: no major dietary change). To account for 61 outcome variables, we present FDR-corrected IVW *P* values (P_{FDR}). P_{FDR} values <0.05 from the IVW analysis were considered significant. Detailed description of dietary variables can be found in Supplemental Table 1. FDR, false discovery rate; IVW, inverse-variance weighted.

daytime napping frequency and dietary variables and no bidirectional associations between habitual sleep duration or daytime napping and macronutrient composition (% of energy from carbohydrate, fat, and protein).

While our findings provide some evidence that longer sleep duration potentially increases intake of some foods, overall these relations were few. We observed a higher intake of salad/raw vegetables with longer sleep duration, extending epidemiological evidence (21). In addition, we observed that genetically proxied longer sleep duration increases "no major dietary change in the past 5 years," suggesting that longer sleep duration prevents substantial changes in diet. An analysis of the UK Biobank identified that participants reporting major dietary changes were more likely to have diabetes and cardiovascular disease (41). Epidemiological studies also suggested associations between short sleep duration and irregular eating behaviors, aspects that may reflect inconsistent dietary habits (17). Thus, it is possible that consistent dietary intake associated with longer sleep duration reflects aspects of an overall healthy lifestyle. Notably, none of the dietary variables that genetically correlated with sleep duration, with the exception of no major dietary change in the past 5 y, showed evidence of causal effects, suggesting that genetic correlations should not be used to prioritize subsequent MR analyses. However, results for sleep duration should be considered preliminary considering the modest *F*-statistic (i.e., <10) and thus the potential for weak instrument bias (42). Follow-up 2-sample MR analyses are necessary as larger replication cohorts with sleep-duration data become available.

We observed no evidence of associations of daytime napping on dietary variables and macronutrient composition. Few epidemiological studies have suggested associations between daytime napping and dietary intake. The largest is a study of 423 women from the Women's Health Initiative that investigated the relation between actigraphic and subjective daytime napping and 88 dietary nutrient variables estimated from a semi-quantitative FFQ. Partial correlations were only evident for subjective daytime napping after adjusting for confounders and included positive correlations with various fats and amino acids and negative correlations with caffeine and water (22). Contrary to those findings, our MR study does not support associations between the frequency of daytime napping and the intake of caffeinated beverages, water, relative fat, and protein compositions in the diet. It is possible that the correlations identified in the Women's Health Initiative study may be confounded by daytime sleepiness or fatigue. In another study of 85 adolescents, longer durations of daytime napping were associated with increased food cravings (23). As our analysis was restricted to variables derived from an FFQ, we were unable to investigate causal links with hunger and satiety. The continued evaluation of potential relations with dietary patterns, hunger, and satiety and daytime napping duration is warranted.

Because of the expected soporific effects of some foods and the association of some macronutrients with sleep architecture (43), we examined in MR whether macronutrient composition directly influences habitual sleep duration or daytime napping. Overall, we found no associations between the relative composition of carbohydrate, fat, and protein in the diet on either habitual sleep duration or daytime napping. Earlier short-term experimental studies found that high-carbohydrate diets are associated with higher sleep quality and high-fat diets are associated with lower sleep quality (43). Our findings, however, suggest that increasing or decreasing the percentage of carbohydrate, fat, or protein in the diet has no direct impact on the long-term duration of sleep or the long-term frequency of daytime napping. Future MR analyses examining other dimensions of sleep beyond duration, such as quality, and investigating specific sleep-promoting foods, such as milk, fatty fish, cherries, and kiwifruit, are warranted (43).

It is worth mentioning that our analytical approach was limited to habitual sleep habits. So far, GWASs have focused primarily on unraveling the genetic architecture of habitual sleep habits, such as usual sleep duration and usual daytime napping (7, 16). However, short-term experimental sleep trials in adults, including sleep-restriction and sleep-extension studies, indicate sizable effects of sleep duration on dietary intake. For example, a meta-analysis of sleep-restriction trials (~1 wk of restriction to 3.5–5.5 h/night) identified that partial sleep deprivation was associated with an ~400-kcal increase in total energy intake (44). Other sleep-restriction trials have identified similar increases in the intake of total fats, carbohydrate-rich snacks, and dessert (17). Conversely, a 1- to 1.5-h/night sleep extension for 28 d in free-living adults showed a decrease in free sugar intake (45). As our MR evaluated habitual sleep architecture, our findings suggest that changes observed in short-term controlled experiments are possibly not sustained over the long term in free-living conditions.

Several limitations need to be considered in the interpretation of these MR results. First, the genetic variants are derived from GWASs for

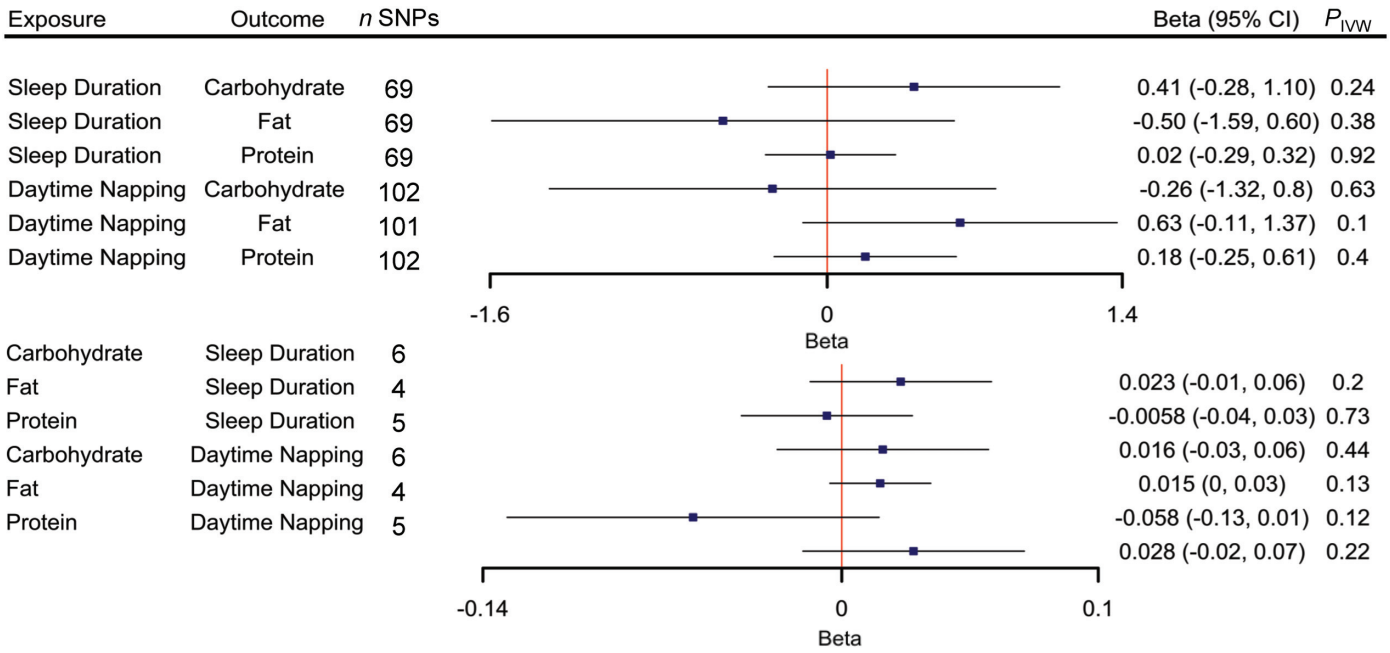

FIGURE 4 Potential bidirectional causal effects between habitual sleep duration or daytime napping and macronutrient composition (% of energy from carbohydrate, fat, and protein). Effects were calculated using random-effects IVW regression. Sensitivity analyses are presented in Supplemental Table 9. The effect of the sleep duration genetic instrument represents a 1-h increase in sleep duration. The effect of the daytime napping genetic instrument represents a 1-unit category increase in daytime napping. The effect of the macronutrient genetic instrument represents the percentage of energy increase in carbohydrate, fat, or protein. FDR, false discovery rate; IVW, inverse-variance weighted; SNP, single nucleotide polymorphism.

continuous sleep duration in minutes per day and ordinal categories for daytime napping preference and thus assumes linear relations between sleep habits and dietary intake. Considering the limited number of distinct genetic variants for short and long sleep duration, we restricted our MR to continuous sleep duration, but future MR analyses of short and long sleep duration should be considered as more robust genetic instruments are identified for these traits. In addition, although the genetic variants for self-reported sleep duration and daytime napping have been partly validated with accelerometer-derived sleep estimates, variance explained by these variants is modest (e.g., <5%) (7, 16). Future studies should also consider variants identified from GWASs for objective sleep measures, which so far have a too limited number of variants and modest sample sizes in their replication cohorts to allow 2-sample MR (46). Second, our analysis was restricted to 61 dietary variables derived from a modified FFQ in the UK Biobank (47). Despite validation of responses from this modified questionnaire against 24-h dietary recalls in the UK Biobank (48), validation of non–food-related questions, including major dietary changes, remains missing. Findings pertaining to nonfood items are liable to recall bias and should be interpreted cautiously. In addition, associations may exist for other food items or dietary patterns that show association effects in epidemiological studies, such as fiber, but are not adequately captured by the UK Biobank dietary assessment tool. Third, our analyses were restricted to generally healthy older adults (ages 37–73 y) of European ancestry from the UK Biobank, which limits generalizability, particularly to other age groups and ancestries with different sleep architecture and dietary patterns (7, 16). Despite evidence of replication of sleep duration and daytime napping genetic signals in independent studies with different demographic characteristics, the MR effects reported here may still be biased (49). Therefore, continued evaluation in other demographics, including younger age groups (50, 51), is necessary.

Strengths of the present study include our 2-sample MR approach, which provides several advantages in comparison to epidemiological studies. Epidemiological studies cannot address causality or directionality in their assessment of the relation between sleep and dietary variables. Thus, our use of robust genetic instruments associated with habitual sleep duration and daytime napping derived from large GWASs with signals validated against accelerometer-derived objective measures of sleep (16, 36) and with acceptable levels of relative bias (42) (except for sleep duration on dietary variables) allowed us to directly assess causal links of sleep habits on dietary intake. Compared with epidemiological studies, this 2-sample MR approach has decreased susceptibility to confounding, as demonstrated previously (7, 9, 11, 16), measurement error, and reverse causation, but does not inform mechanisms mediating these effects. While signals for sleep duration were directionally concordant in the independent datasets used in the present analysis and the UK Biobank (binomial $P = 0.048$), findings pertaining to sleep duration should be considered preliminary and later re-evaluated as larger independent datasets (e.g., $n > 54{,}335$) become available for more robust 2-sample MR analyses.

Overall, we provide some evidence for associations of habitual sleep duration with dietary intake and no evidence for associations of daytime napping frequency with dietary intake. Thus, our MR findings suggest that changes to habitual sleep duration or daytime napping

TABLE 1 Potential causal effects of genetically proxied longer habitual sleep duration on dietary variables[1]

Dietary variable	Total *n* or *n* cases/*n* controls	P_{FDR}	IVW		MR-Egger		Weighted median	
			B (95% CI)	*P*	B (95% CI)	*P*	B (95% CI)	*P*
Salad/raw vegetables	339,601	0.006	0.068 (0.034, 0.103)	9.72×10^{-5}	0.096 (0.047, 0.146)	2.98E-04	0.044 (0.005, 0.083)	0.027
No major dietary change	221,368/138,926	0.043	0.036 (0.014, 0.059)	0.0014	0.031 (−0.002, 0.063)	0.069	0.006 (−0.025, 0.038)	0.69
Major dietary change due to illness	38,051/322,243	0.11	−0.03 (−0.051, −0.009)	0.0055	−0.033 (−0.064, −0.002)	0.038	−0.01 (−0.038, 0.018)	0.49
Muesli	61,523/238,375	0.16	0.036 (0.008, 0.065)	0.012	0.019 (−0.022, 0.06)	0.37	−0.008 (−0.045, 0.029)	0.66
Hot drink temperature	357,256	0.16	0.029 (0.006, 0.052)	0.013	0.023 (−0.01, 0.056)	0.18	0.002 (−0.026, 0.03)	0.89
Major dietary change due to other reason	100,875/259,419	0.18	−0.01 (−0.018, −0.002)	0.020	−0.008 (−0.02, 0.004)	0.22	−0.005 (−0.017, 0.006)	0.38
Beer plus cider	258,256	0.18	−0.016 (−0.03, −0.002)	0.023	−0.016 (−0.036, 0.004)	0.13	−0.006 (−0.026, 0.013)	0.51
Other bread	14,441/333,983	0.18	−0.02 (−0.038, −0.003)	0.023	−0.015 (−0.041, 0.011)	0.26	−0.019 (−0.046, 0.009)	0.19
Alcohol	360,726	0.19	0.076 (0.008, 0.145)	0.029	0.061 (−0.039, 0.16)	0.24	0.001 (−0.078, 0.079)	0.99
Decaffeinated coffee	55,310/228,139	0.20	0.049 (0.003, 0.094)	0.035	0.026 (−0.04, 0.091)	0.45	0.012 (−0.042, 0.067)	0.66
Cheese	352,458	0.20	0.042 (0.003, 0.082)	0.037	0.082 (0.025, 0.139)	0.62	0.037 (−0.015, 0.088)	0.16
Dried fruit	329,134	0.20	−0.093 (−0.182, −0.004)	0.040	−0.192 (−0.318, −0.067)	0.37	−0.036 (−0.132, 0.06)	0.46

[1]Only results with $P_{IVW} < 0.05$ are shown. The effect of the habitual sleep duration genetic instrument ($n = 70$) on each dietary variable was calculated using random-effects IVW regression for the primary analysis and MR-Egger and weighted median as sensitivity analyses. The exposure was scaled to represent a 1-h longer habitual sleep duration. A positive B represents an increase per category (for ordinal variables: salad/raw vegetables, hot drink temperature, beer plus cider, alcohol, cheese, and dried fruit) or log-odds (for binary variables: no major dietary change, major dietary change due to illness, major dietary change due to other reasons, muesli, other bread, decaffeinated coffee). For binary variables, *n* cases refer to *n* of consumers of that dietary variable, and *n* controls refer to *n* of nonconsumers of that dietary variable. To account for 61 outcome variables, we present FDR-corrected IVW *P* values (P_{FDR}). P_{FDR} values <0.05 from the IVW analysis were considered significant. Only results with $P_{IVW} < 0.05$ are shown in the table; full results are presented in Supplemental Table 7. A detailed description of dietary variables can be found in Supplemental Table 1. FDR, false discovery rate; IVW, inverse-variance weighted; MR, Mendelian randomization.

TABLE 2 Potential causal effect of genetically proxied habitual daytime napping on dietary variables[1]

Dietary variable	Total *n* or *n* cases/*n* controls	P_{FDR}	IVW		MR-Egger		Weighted median	
			B (95% CI)	*P*	B (95% CI)	*P*	B (95% CI)	*P*
Major dietary change due to illness	38,051/322,243	0.13	0.048 (0.016, 0.079)	0.0033	0.014 (−0.048, 0.076)	0.66	0.027 (−0.014, 0.068)	0.20
Skim milk	74,087/286,719	0.13	0.056 (0.016, 0.095)	0.0056	0.031 (−0.047, 0.108)	0.44	0.028 (−0.026, 0.082)	0.31
No major dietary change	221,368/138,926	0.13	−0.079 (−0.135, −0.022)	0.0062	−0.032 (−0.143, 0.079)	0.57	−0.06 (−0.13, 0.01)	0.10
Added salt	360,954	0.18	0.147 (0.033, 0.261)	0.0012	0.206 (−0.019, 0.432)	0.76	0.061 (−0.057, 0.179)	0.31
Never have milk	11,587/349,219	0.24	−0.02 (−0.036, −0.003)	0.019	−0.018 (−0.05, 0.015)	0.29	−0.014 (−0.037, 0.008)	0.21
Alcohol	360,726	0.33	0.236 (0.02, 0.453)	0.032	0.133 (−0.293, 0.559)	0.54	0.226 (0.013, 0.438)	0.04
Processed meat	360,468	0.40	0.109 (0.001, 0.217)	0.047	0.008 (−0.203, 0.219)	0.94	0.074 (−0.063, 0.211)	0.29

[1]Only results with $P_{IVW} < 0.05$ are shown. The effect of the habitual daytime napping genetic instrument ($n = 94$) representing a 1-unit category increase in daytime napping frequency on each dietary variable was calculated using random-effects IVW regression for the primary analysis and MR-Egger and weighted median as sensitivity analyses regression. A positive B represents an increase per category (for ordinal variables: added salt, alcohol, processed meat) or log-odds (for binary variables: major dietary change due to illness, skim milk, no major dietary change, never have milk). For binary variables, *n* cases refer to *n* of consumers of that dietary variable, and *n* controls refer to *n* of nonconsumers of that dietary variable. To account for 61 outcome variables, we present FDR-corrected IVW *P* values (P_{FDR}). P_{FDR} values <0.05 from the IVW analysis were considered significant. Only results with $P_{IVW} < 0.05$ are shown in the table; full results are presented in Supplemental Table 8. A detailed description of dietary variables can be found in Supplemental Table 1. FDR, false discovery rate; IVW, inverse-variance weighted; MR, Mendelian randomization.

frequency may have limited impact on long-term changes in dietary intake.

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Data Availability

Data described in the manuscript, code book, and analytic code will be made available upon request pending application and approval.

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