Morning diurnal preference and food intake: a Mendelian randomization study

Hassan S Dashti,[1,2,3] *Angela Chen,*[1] *Iyas Daghlas,*[1,2] *and Richa Saxena*[1,2,3,4]

[1]Center for Genomic Medicine, Massachusetts General Hospital, Boston, MA, USA; [2]Broad Institute, Cambridge, MA, USA; [3]Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA; and [4]Division of Sleep Medicine, Harvard Medical School, Boston, MA, USA

ABSTRACT

Background: Poor dietary choices may underlie known associations between having an evening diurnal preference and cardiometabolic diseases. Assessing causal links between diurnal preference and food intake is now possible in Mendelian randomization (MR) analyses.

Objectives: We aimed to use a 2-sample MR to determine potential causal effects of genetic liability to a morning preference on food intake. We also examined potential causal effects of a morning preference on objectively captured response performances to email-administered 24-h diet recalls.

Methods: We used genetic variants associated with a morning preference from a published genome-wide association meta-analysis. Our outcomes included 61 food items with estimates from a food-frequency questionnaire in the UK Biobank (n = 361,194). For significant findings, we repeated the analysis using intake estimates from modified 24-h diet recalls in a subset of overlapping participants (n = 146,086). In addition, we examined 7 response performance outcomes, including the time and duration of responses to 24-h diet recalls (n = 123,035). MR effects were estimated using an inverse-variance weighted analysis.

Results: Genetic liability to a morning preference was associated with increased intake of 6 food items (fresh fruit, alcohol with meals, bran cereal, cereals, dried fruit, and water), decreased intake of 4 food items (beer plus cider, processed meat, other cereals [e.g., corn or frosted flakes], and full cream milk), increased temperature of hot drinks, and decreased variation in diet ($P_{\text{False Discovery Rate}} < 0.05$). There was no evidence for an effect on coffee or tea intake. Findings for fresh fruit, beer plus cider, bran cereal, and cereal were consistent when intakes were estimated by 24-h diet recalls ($P < 0.05$). We also identified potential causal links between a morning preference with earlier timing and a shorter duration for completing email-administered 24-h diet recalls.

Conclusions: Our findings provide evidence for a potentially causal effect of a morning preference with the increased intake of foods known to constitute a healthy diet, suggesting possible health benefits of adopting a more morning diurnal preference. *Am J Clin Nutr* 2020;112:1348–1357.

Keywords: diurnal preference, Mendelian randomization, food intake, chronobiology, UK Biobank

Introduction

The circadian clock governs a wide spectrum of human physiology, including rhythms of body temperature, endogenous melatonin, cortisol, and other hormone secretions (1). The clock also influences human behavior, manifesting in a continuum from morning to evening diurnal preferences (2). Having an evening preference has been consistently associated with diseases, including obesity (3), type 2 diabetes (4), and cardiovascular disease (5). These effects are often attributed to circadian misalignment, when human behavior conflicts with the circadian clock, such as during night shift work (6). However, a direct mediating role of poor dietary choices is possible.

An evening preference has been associated with the timing of food intake (7). We and others have found that an evening preference is cross-sectionally associated with delayed meal times, skipping breakfast, and having larger evening meals, such as larger dinners (8–13). However, it is unlikely that delayed food timing entirely explains the metabolic consequences of having an evening preference (14). For example, the consumption of foods and diets of lower quality may be another pertinent nutritional dimension to consider. There is some evidence indicating that an evening preference is also associated with lower quality diets (15)

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Address correspondence to HSD (e-mail: hassan.dashti@mgh.harvard.edu).

Abbreviations used: FDR, false discovery rate; GWAS, genome-wide association studies; IVW, inverse-variance weighted; MR, Mendelian randomization; MR-PRESSO, Mendelian Randomization Pleiotropy Residual Sum and Outlier; PHESANT, Phenome Scan Analysis Tool; PCs, principal components; SNPs, single nucleotide polymorphisms.

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and less frequent intake of fruits and vegetables (10,16,17) and whole grains (18). This may be driven by perceptions that certain foods, such as whole grain–rich cereals, are suitable morning foods only, whereas desserts are suitable evening foods (19). Collectively, these data suggest that adopting a more morning preference may cause a greater intake of higher quality foods.

Exploring causal links between diurnal preferences and food intake is now possible in Mendelian randomization (MR) analyses (20). MR uses genetic variants that are robustly associated with a trait to explore causal effects on outcomes of interest (20). Unlike conventional cross-sectional studies, MR tends to be less susceptible to measurement error, confounding, and reverse causation. Recently, we identified 351 genetic variants robustly associated with a morning diurnal preference in a large, genome-wide, association meta-analysis (21). Through MR, causal links have been observed between genetic liability to a morning preference and decreased breakfast skipping (11) and health outcomes, including reduced risks of breast cancer (22) and schizophrenia (21). Genetic correlations between a morning preference and food choices—traits with established underlying heritable components (23)—range from -0.14 (r_g) for processed meat to 0.17 (r_g) for fresh fruit (24). Potential causal links with food choices, however, cannot be implied from genetic correlations and have not yet been established.

In the present study, we aimed to use MR to determine potential causal effects of genetic liability to a morning preference on food intake. We first systematically assessed the effects of genetic liability to a morning preference on the intake of 61 food items, estimated from food a frequency questionnaire in the UK Biobank ($n = 361{,}194$); next, we estimated the robustness of the significant findings using intake estimates derived from web-based, modified 24-h diet recalls in a subset of overlapping participants ($n = 146{,}086$). In addition, we explored the potential causal effects of genetic liability to a morning preference on response performance to email- administered, modified 24-h diet recalls ($n = 123{,}035$), in order to understand potential biases in the email administration of dietary assessments.

Methods

Genetic variants used to proxy morning diurnal preference

Single nucleotide polymorphisms (SNPs) were selected from a meta-analysis of genome-wide data from 697,828 UK Biobank and 23andMe participants with self-reported information on morning-evening diurnal preferences (21). Participants in the UK Biobank were asked, "do you consider yourself to be …?" with possible answers: "definitely a 'morning' person," "more a 'morning' than 'evening' person," "more an 'evening' than a 'morning' person," or "definitely an 'evening' person." Participants in the 23aneMe, Inc. cohort were asked, "are you naturally a night person or a morning person?" All 23andMe participants were customers of the personal genetics company 23andMe, Inc.; were genotyped for the 23andMe Personal Genome Service; and responded to online questionnaires according to 23andMe's human subject protocol (21). A total of 351 SNPs were associated with self-reported diurnal preference at genome-wide significance ($P < 5 \times 10^{-8}$), and a polygenic score of these variants was further associated with an objective assessment of sleep timing (21).

Genetic association with dietary variables

UK Biobank.

Cohort description. The UK Biobank is a large, population-based study established to allow detailed investigations of the genetic and lifestyle determinants of a wide range of phenotypes (25). Data from >500,000 participants living in the United Kingdom aged 37–73 y and living <25 mi. from a study center participated in the study between 2006 and 2010. At baseline assessments, a range of phenotypic data were self-reported by participants using touchscreen questionnaires and were collected in nurse-led interviews, including information on dietary intake and relevant sociodemographic data. The UK Biobank study was approved by the National Health Service National Research Ethics Service (ref. 11/NW/0382), and all participants provided written informed consent to participate.

Genetics. In the UK Biobank, blood samples collected from participants at baseline assessments were used to extract DNA for genotyping ($n = 488{,}377$). Genotyping, pre-imputation quality control, phasing, and imputation were performed centrally by the Biobank and have been described previously (26). In brief, participant DNA was genotyped on 2 arrays—UK BiLEVE and UK Biobank Axiom—with >95% common content, and genotypes for ~800,000 autosomal SNPs were imputed to the Haplotype Reference Consortium panel and the UK10K and 1000 Genomes panel. Genotypes were called with the use of the Affymetrix Power Tools software. Detailed information on sample and SNP quality controls, population structure by principal component analysis, and imputation have been described previously (21, 26). All analyses were restricted to unrelated participants of European ancestry.

Dietary assessment via food-frequency questionnaire and web-based modified 24-h diet recalls. In the UK Biobank, dietary information was gathered through 2 approaches: *1*) a 29-item touchscreen food-frequency questionnaire disseminated to all participants at the baseline assessment; and *2*) an in-depth, web-based, modified 24-h diet recall introduced as an addition to the baseline assessments towards the end of UK Biobank recruitment, and administered via email to enrolled participants with known email addresses.

At the baseline assessment, all enrolled participants ($n > 500{,}000$) were asked 29 questions regarding their diet on a touchscreen food-frequency questionnaire. The questions gathered information on the average frequency of the consumption of selected foods and food groups over the past year (27). Example questions included, "on average how many heaped tablespoons of COOKED vegetables would you eat per DAY?," with integer responses; and "what type of bread do you mainly eat?," with response options including white, brown, wholemeal or whole-grain, or other type of bread. The food-frequency questionnaire also included the following 2 nonfood item questions: "how do you like your hot drinks? (such as coffee or tea)," with response options including very hot, hot, warm, and do not drink hot drinks; and "does your diet vary much from week to week?," with response options including never, rarely, sometimes, and often. Variables from the food-frequency questionnaire were analyzed according to the Phenome Scan

Analysis Tool (PHESANT) rule-based algorithm (28). In brief, negative values denoting missing data—specifically, "prefer not to answer" and "do not know responses"—were recoded as missing (28). Variables with integer field types were either treated as continuous variables (i.e., bread intake) or collapsed to ordinal variables (i.e., cooked vegetable; **Supplementary Table 1**). Continuous variables were also transformed to a normal distribution using an inverse normal rank transformation. Categorical variables were converted to binary variables, each denoting whether a participant indicated their intake for a specific food within that category. For example, bread type (response options of white, brown, wholemeal or whole-grain, or other type of bread) was converted to 4 binary variables indicating intake or non-intake 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) (28). Thus, from the 29 food-frequency questions, a total of 61 food variables were derived (described in Supplementary Table 1).

In-depth dietary information was also collected for a subset of 211,036 participants through the Oxford WebQ: a web-based, modified 24-h diet recall (29). Participants self-reported the frequency of intake of ~200 commonly consumed foods and drinks in the preceding 24 h. Responses from this web-based method generally have good agreement with interviewer-administered 24-h diet recalls (29). The first web-based, modified 24-h diet recall was introduced in assessment centers during the latter part of UK Biobank recruitment (i.e., n = 70,712), and was later readministered electronically in 4 rounds of email mailings (n = 330,998 total known email addresses). Questions included a combination of yes/no questions, such as "did you eat any bread or crackers yesterday? e.g., toast, sandwiches, rice cakes, bread rolls, hotdog roll, crumpets, tortilla wraps," and branched questions, such as "how many slices of sliced bread?," with integer responses. The ~200 questions only partly overlapped with the 61 food variables derived from the food-frequency questionnaire; thus, they were combined, if necessary, to match the food variable from the food-frequency questionnaire (described in **Supplementary Table 2**). For each participant, only responses from the first completed recall were used, in order to limit potential response bias resulting from survey familiarity or fatigue. Responses were further stratified to weekday and weekend responses based on the day of the week when the recall was completed. If multiple recalls were completed by a participant, we used responses from the first weekday and weekend completed recall in analyses stratified by the day of the week, to attain the largest possible sample size.

Response performance to email-administered, modified 24-h diet recalls. The objective response performance to completed, email-administered, modified 24-h diet recalls was passively captured. Parameters included the hour of the day when the questionnaire was completed, duration in minutes to complete the questionnaire, delay in days between the questionnaire request and completion dates, and day of the week when the questionnaire was completed. From these data, we derived the following questionnaire response performance variables: *1*) time of response (continuous variable); *2*) duration of response (continuous variable; durations >90 min were excluded; excluded n = 1496); *3*) whether the questionnaire was completed on the same day it was requested (same day response; binary variable); and *4*) whether at least 1 questionnaire was completed (questionnaire completed, any; binary variable; described in **Supplementary Table 3**). Only response performance data from the first completed, email-administered, 24-h diet recall were used, in order to limit any potential bias resulting from survey familiarity or fatigue. Response parameters were also stratified by weekday and weekend based on the day of the week when the recall was completed; when multiple email-administered recalls were completed by a participant, we used responses from their first weekday and weekend completed recall. In addition, among the subset of participants who received invitations for all 4 rounds of email mailings, we derived additional response behaviors: *5*) completed all questionnaires (binary variable); *6*) completed no questionnaires (binary variable); and *7*) quantity of completed questionnaires (continuous; described in Supplementary Table 3).

Genetic associations with dietary outcome variables. For the 61 outcome food variables derived from the food-frequency questionnaire, we used publicly available, published, summary statistics from genome-wide association studies (GWAS) from the Neale Lab "round 2" version of the UK Biobank GWAS release (30). GWAS were conducted for a total of 361,194 unrelated samples of European ancestry (n = 194,174 women and n = 167,020 men) and adjusted for the following covariates: age, age^2, sex, age × sex, age^2 × sex, and principal components (PCs) 1–20 (SNP-based heritability listed in Supplementary Table 1). In sex-specific analyses, covariates were age, age^2, and PCs. Additional GWAS details have been previously described (30).

As dietary and response performance outcome variables from the web-based, modified 24-h diet recall were derived specifically for this analysis, we used updated-release UK Biobank genetic data to generate effect estimates, rather than utilizing publicly available data from the Neale Lab. Similarly, for continuous dietary outcomes from the food-frequency questionnaire that were transformed to ordinal variables by the PHESANT rule-based algorithm (Supplementary Table 1) and had significant MR false discovery rate (FDR)–corrected P values (P_{FDR}values), we generated effect estimates for the untransformed, continuous variable for easier interpretation of MR effect estimates (i.e., beer plus cider, dried fruit, cereal, fresh fruit, and water). Outliers that were 2 standard deviations from the mean intake were excluded prior to the analysis of continuous dietary variables. Genetic variants were examined for quality control measures prior to analysis (**Supplementary Table 4**). Association effect estimates were from adjusted PLINK (31) linear (for continuous outcomes) or logistic (for binary outcomes) regression analyses in unrelated participants of white, British ancestry (n = 337,478). We used an additive genetic model adjusted for age, sex, 10 PCs, and genotyping array to determine additive SNP effects on outcome variables. In sensitivity analyses, we excluded participants who reported at baseline that they "sometimes," "usually," or "always" worked night shifts (up to n = 5691 excluded).

Mendelian randomization analyses

We conducted 2-sample MR analyses using the "TwoSampleMR" R package (v 0.5.4) (32). The exposure included SNPs previously associated with morning diurnal preference with effect

estimates from the 23andMe, Inc., cohort (sample 1), representing genetic liability to a morning preference (n = 240,098; log-odds ratio). The units of the exposure SNPs are in log-odds of having a morning diurnal preference. The outcome comprised associations of these SNPs with dietary variables in the UK Biobank (sample 2). We harmonized the exposure and outcome effects to the same effect allele (i.e., an allele associated with a morning preference). Of the 351 genetic variants, 1 variant was excluded for missing effect estimates from the 23andMe cohort and 34 were excluded as a result of linkage disequilibrium with other variants or their absence from a reference panel. In addition, a total of 15 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 data set (23andMe) were excluded, as it was not possible to reconcile ambiguities. The remaining 31 palindromic SNPs were aligned based on their minor allele frequency.

There are 3 necessary assumptions for valid causal inference in MR: *1*) the genetic instrument is strongly associated with the exposure of interest (which is accounted for by limiting the MR analysis to SNPs associated with the exposure at genome-wide significance, or $P < 5 \times 10^{-08}$); *2*) the genetic instrument does not share common causes with the outcome of interest (which is accounted for by using genetic variants, which are 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) (20).

Following data harmonization, we used the inverse-variance weighted (IVW) regression as the primary method to estimate the causal effect of a morning diurnal preference on the outcome (20). Here, we regressed the SNP-outcome associations on the SNP-exposure associations, and weighted the effects by the inverse of the standard error of the SNP-outcome association under a random-effects model. The IVW method yields an unbiased estimate in the absence of horizontal pleiotropy or when horizontal pleiotropy is balanced to the null (20). As a global test for potential balanced or unbalanced horizontal pleiotropy, we calculated Cochran's Q for heterogeneity, which tests the null hypothesis that the causal effects estimated by each variant are equivalent. We then conducted a range of sensitivity analyses that have been developed to address unbalanced horizontal pleiotropy. Specifically, we compared IVW results with other methods: MR Egger (33), the weighted median (34), and, for the food-frequency questionnaire food outcomes, Mendelian Randomization Pleiotropy Residual Sum and Outlier (MR-PRESSO) (35). MR Egger assumes that the association of each genetic variant with the exposure is independent of the pleiotropic effect of the variant (33). The MR Egger intercept indicates directional pleiotropy, and a nonzero intercept indicates that some of the genetic predictors might be acting through a pathway other than the exposure (33). The weighted median method provides consistent MR estimates even when up to 50% of the information comes from invalid instrumental variables (34). MR-PRESSO implements a regression-based outlier detection strategy to select and remove potentially pleiotropic variants (35). We considered consistent effects across multiple methods to strengthen causal evidence.

In addition, to assess sex and day of the week differences in the causal effects on food intake, as suggested in prior research (36, 37), we tested for heterogeneity across sex and weekday/weekend stratified analyses. MR results for binary outcomes (as indicated in Supplementary Table 1) were divided by [prevalence x (1-prevalence)] to convert linear regression coefficients to log-odds. In order to scale MR effects to a more clinically meaningful scale, we used genetic associations from a GWAS of accelerometer-derived sleep midpoint (hours) conducted in the UK Biobank (n = 85,502) (38). Here, sleep midpoint was defined as the midpoint between the start and end of a sleep period, and is reported as hours since the previous midnight. We first tested the effect of a morning diurnal preference on sleep midpoint to estimate the effect of a log-odds increase in a morning diurnal preference on an earlier sleep midpoint. We refer to the beta coefficient from this regression as the "scaling factor." For analyses presented in the main manuscript text, we divided the beta coefficient of the causal effect (effect on outcome per log-odds increase in morning diurnal preference) by the scaling factor (hour advance in sleep midpoint per log-odds increase in morning diurnal preference) to obtain the effect of a morning diurnal preference on the outcome scaled to a sleep midpoint of 1 h earlier.

We used a P_{FDR} of <0.05 from the IVW analysis to prioritize food items from the food-frequency questionnaire to test with modified 24-h diet recalls. MR results from the modified 24-hour diet recalls with P values < 0.05 were considered significant. All analyses were conducted using R software (version 3.6.2).

Results

We first conducted a 2-sample MR between genetic liability to a morning diurnal preference and 61 food variables derived from a food-frequency questionnaire (**Figure 1**). In total, 301 SNPs were used to instrument a morning preference after data harmonization (Supplementary Table 4), consistent with earlier studies (22). We found evidence ($P_{\text{FDR}} < 0.05$) that genetic liability to a morning preference was associated with increased intake of 6 food items (fresh fruit, alcohol with meals, bran cereal, cereals, dried fruit, and water), decreased intake of 4 food items [beer plus cider, processed meat, other cereals (e.g., corn or frosted flakes), and full cream milk], increased temperature of hot drinks, and decreased variation in diet (**Figure 2**; **Table 1**; **Supplementary Table 5**). The strongest positive association was observed for increased fresh fruit intake, where a morning preference (scaled to a sleep midpoint of 1 h earlier) was associated with a 0.49-piece (standard error = 0.07) increase in fresh fruit per day ($P_{\text{FDR}} = 3.40 \times 10^{-10}$), and the strongest negative association was observed for decreased beer plus cider intake, where a morning preference was associated with an 0.80 (standard error = 0.18) decrease in pints per week ($P_{\text{FDR}} = 5.48 \times 10^{-5}$). We found no evidence of heterogeneity in the causal effect by sex for the significant food items (**Supplementary Table 6**). Among the nonsignificant food items, in sex-stratified MR, we found evidence of other sex-specific causal links with a morning preference, including increased intake of red wine for men (n = 167,020) and increased intake of beef and non-oily fish for women (n = 194,174; Supplementary

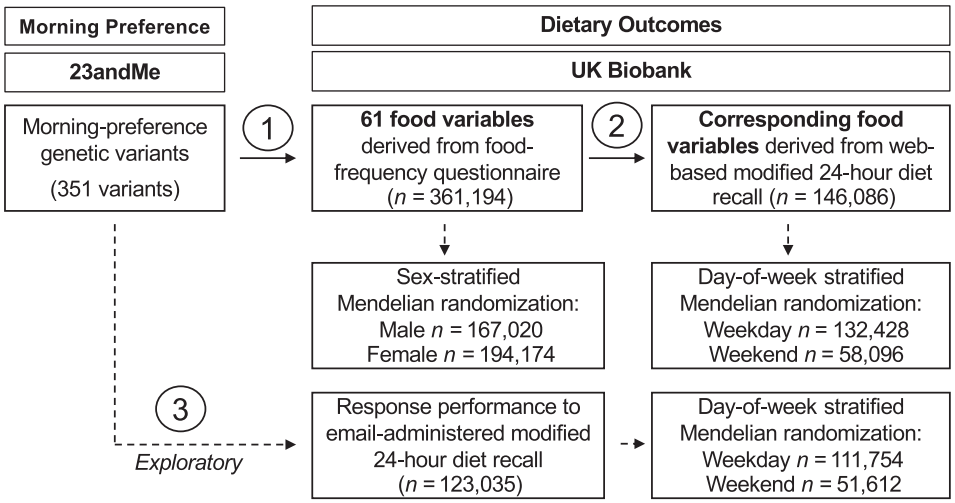

FIGURE 1 Workflow of present Mendelian randomization study.

Table 6). Notably, there was no evidence for an effect of a morning preference on the consumption of caffeinated beverages, including coffee or tea.

To account for inherent limitations of food-frequency questionnaires, such as recall bias, we repeated the 2-sample MR for food items with significant findings, using the same food item with the intake estimated from modified 24-h diet recalls in a subset of overlapping participants (Figure 1). Of the 9 tested food items (i.e., captured in both the food-frequency questionnaire and 24-h diet recall), fresh fruit, beer plus cider, bran cereal, and cereal showed consistent evidence of causal effects with a morning preference ($P < 0.05$; Figure 2; **Supplementary Table 7**). We found no evidence of a statistical interaction with the day of the week when comparing estimates between weekday ($n = 132{,}428$) and weekend ($n = 58{,}096$) responses in the stratified MR, and no difference in the findings when excluding participants involved in night shift work (Supplementary Table 7).

Finally, we leveraged objective response performance data from email-administered 24-h diet recalls ($n = 123{,}035$), and found that a morning preference was associated with earlier timing and a shorter duration in completing the recall (Figure 1; **Figure 3**; **Table 2**; **Supplementary Table 8**). Scaled to a sleep midpoint of 1 h earlier, a morning preference was associated with a 2.45-h (standard error = 0.32) earlier response time ($P_{IVW} = 9.33 \times 10^{-15}$) and a 3.35-min (standard error = 0.68) shorter duration ($P_{IVW} = 8.21 \times 10^{-7}$) to complete the recalls. Effects were modestly larger for the time of response on weekends and for the duration of response on weekdays. We also observed an association between a morning preference and an increased likelihood of a same-day response, on weekdays only. Among participants receiving invitations to all 4 rounds of email mailings, we did not observe differences in the number of completed questionnaires or likelihood of completing all or none of the questionnaires (Figure 3; Table 2). Effects remained similar in sensitivity analyses after excluding participants involved in night shift work (Supplementary Tables 7 and 8).

Discussion

In this 2-sample MR study, we provide evidence for potential causal effects between a morning diurnal preference and the intake of fresh fruit, cereal, and beer, among other foods. Findings for several foods were consistent when intake was estimated by a food-frequency questionnaire and a modified 24-h diet recall, and remained robust in sensitivity analyses. In exploratory analyses, we found potential causal links between a morning preference and both earlier timing and a shorter duration in completing email-administered, modified 24-h diet recalls, but no link between a morning preference and the likelihood of responding to the diet recalls.

Overall, our findings provide evidence that morning preference possibly increases intake of foods known to constitute a healthy diet. With morning preference, we observed higher intake of fresh fruits and bran (fiber-rich) cereals, foods previously associated with lower risk of cardiovascular disease and mortality (39–41), extending cross-sectional evidence (42). Our MR results also distinguished between fiber-rich cereals and refined-grain cereals (i.e., corn or frosted flakes). Our systematic interrogation of several foods also indicated possible novel causal links of morning preference with decreased intake of beer plus cider and processed meat, foods generally recommended in moderation (43). Although consistent in direction, null associations with processed meat estimated from modified 24-h diet recalls may be due to a more modest sample size in the subset with recall data or difference in the derivation of intake. Genetic liability to an evening preference was also observed to increase variation in diet and increase alcohol with meals, aspects which may reflect meal skipping tendencies or erratic eating behaviors of adults with evening preference (42). The health implications of limiting day-to-day variation in diet and maintaining consistency in food intake remains to be elucidated (44–46). Overall, these links propose that a morning preference may facilitate adherence to key recommendations from dietary guidelines to promote health and prevent chronic disease (43).

Our findings suggest the potential temporality in the consumption of certain foods across 24 h of the day. Studies have

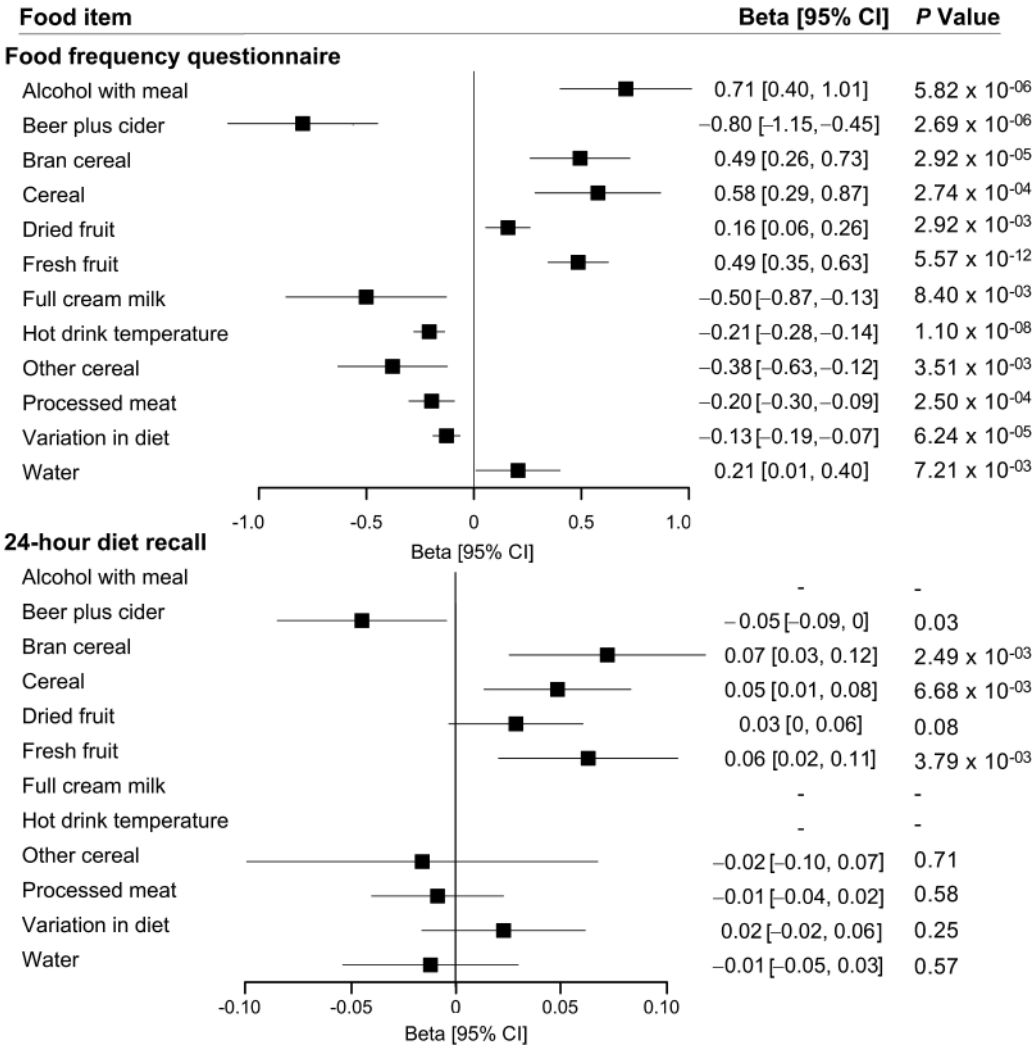

FIGURE 2 Potential causal effect of increased genetic liability to a morning preference and food items, derived from food-frequency questionnaire and modified 24-h diet recall. Only results from FFQ with $P_{FDR} < 0.05$ are shown. The results (beta, 95% CI and *P* value) of the morning preference genetic instrument for each food item were calculated using random-effects inverse-variance weighted regression. The morning preference exposure was scaled to represent a sleep midpoint of 1 h earlier. A positive beta represents increased intake (or lower temperature or increased variation) in pieces per day (for fresh and dried fruit), pints per week (for beer plus cider), bowls per week (for cereal), glasses per day (for water), per category (for ordinal variables: processed meat, variation in diet), or log-odds (for binary variables: alcohol with meal, bran cereal, brown bread, full cream milk, hot drink temperature, and other cereal; variable description in Supplementary Table 1). Full results are shown in Supplementary Table 5. Abbreviations: FDR, false discovery rate; FFQ, food-frequency questionnaire.

shown that hunger peaks in the biological evening and troughs in the biological morning (47). In addition to total and subtypes of cereals, which have known morning peaks of consumption (48), our findings suggest the possibility that other noncereal foods may also exhibit similar temporality in their consumption. The precise timing of these peaks cannot be determined from the present analysis. Also notable are null findings with other presumed breakfast foods, such as eggs, muesli, and some breads, suggesting equivalent consumption across the spectrum of diurnal preferences. Similarly, our findings for hot beverage temperatures, but not amounts (49), suggest that hot beverages, such as tea and coffee, are also consumed in equal amounts across the diurnal preference strata. Thus, it is possible that our analysis is only able to discriminate foods that have early morning peaks in consumption.

In addition to the possible temporality in food consumption, other mechanisms may also be implicated in these findings. Some associations may reflect learned behaviors and beliefs driven by extrinsic contextual factors, such as society or marketing (19). Revising possible misconceptions that may limit the selection or availability of healthier food options around the clock may be a public health initiative worth exploring. It is also plausible that our findings may be biologically driven. For example, it is possible that the selection of energy-dense foods with lower quality may be driven by impaired decision-making or enhanced food stimuli in the evenings among adults with an evening preference (50, 51).

We further leveraged unique, objective data from email-administered, modified 24-h diet recalls to determine potential causal links between a morning diurnal preference and response

TABLE 1 Potential causal effect of increased genetic liability to a morning preference and food items, derived from the food-frequency questionnaire

Food item	Total *n* or *n* cases/*n* controls	P_{FDR}, IVW	IVW			MR Egger			Weighted median		
			Beta	SE	*P* value	Beta	SE	*P* value	Beta	SE	*P* value
Fresh fruit	348,284	3.40×10^{-10}	0.49	0.07	5.57×10^{-12}	0.17	0.17	2.63×10^{-01}	0.18	0.09	5.14×10^{-04}
Hot drink temperature	357,256	3.36×10^{-07}	-0.21	0.04	1.10×10^{-08}	-0.09	0.09	2.99×10^{-01}	-0.13	0.04	7.23×10^{-04}
Beer plus cider	258,256	5.48×10^{-05}	-0.80	0.18	2.69×10^{-06}	-1.09	0.43	1.35×10^{-03}	-0.87	0.22	1.26×10^{-03}
Alcohol with meal	125,164/59,552	8.87×10^{-05}	0.71	0.16	5.82×10^{-06}	0.93	0.37	1.27×10^{-02}	0.70	0.19	2.85×10^{-04}
Bran cereal	50,609/249,289	3.56×10^{-04}	0.49	0.12	2.92×10^{-05}	0.40	0.28	1.55×10^{-01}	0.38	0.18	3.10×10^{-02}
Variation in diet	359,752	6.35×10^{-04}	-0.13	0.03	6.24×10^{-05}	-0.13	0.08	8.68×10^{-02}	-0.11	0.04	4.55×10^{-03}
Processed meat	360,468	2.09×10^{-03}	-0.20	0.05	2.50×10^{-04}	-0.18	0.13	1.59×10^{-01}	-0.22	0.06	4.22×10^{-04}
Cereal	345,019	2.09×10^{-03}	0.58	0.15	2.74×10^{-04}	0.59	0.36	3.11×10^{-02}	0.69	0.19	3.36×10^{-05}
Dried fruit	329,134	1.98×10^{-02}	0.16	0.05	2.92×10^{-03}	0.20	0.13	1.42×10^{-01}	0.12	0.07	4.17×10^{-02}
Other cereal	58,105/241,793	2.14×10^{-02}	-0.38	0.13	3.51×10^{-03}	-0.23	0.31	4.62×10^{-01}	-0.33	0.17	5.23×10^{-02}
Water	333,363	4.00×10^{-02}	0.21	0.10	7.21×10^{-03}	0.27	0.24	9.41×10^{-02}	0.10	0.12	6.25×10^{-02}
Full cream milk	22,902/337,904	4.27×10^{-02}	-0.50	0.19	8.40×10^{-03}	-0.60	0.46	1.90×10^{-01}	-0.25	0.25	3.25×10^{-01}
Brown bread	41,518/306,906	1.56×10^{-01}	0.28	0.14	4.61×10^{-02}	-0.62	0.33	5.69×10^{-02}	-0.08	0.19	6.58×10^{-01}

Only results with $P_{FDR} < 0.05$ are shown. The effect of the morning preference genetic instrument (*n* of SNPs =301) on each food item was calculated using random-effects inverse-variance weighted regression. The morning preference exposure was scaled to represent a sleep midpoint of 1 h earlier. A positive beta represents increased intake (or lower temperature or increased variation) in pieces per day (for fresh and dried fruit), pints per week (for beer plus cider), bowls per week (for cereal), glasses per day (for water), per category (for ordinal variables: processed meat, variation in diet), or log-odds (for binary variables: alcohol with meal, bran cereal, brown bread, full cream milk, hot drink temperature, and other cereal; variable description in Supplementary Table 1). Sensitivity analyses and results with unscaled exposure, representing a 1-unit category increase in morning preference, are shown in Supplementary Table 5. Abbreviations: FDR, false discovery rate; IVW, inverse variance weighted; MR, Mendelian randomization; SNPs, single nucleotide polymorphisms.

performance to online surveys. As expected, genetic liability to a morning preference was associated with earlier response times, with larger effect estimates on weekends, when behaviors are generally presumed to not be constrained by work obligations. Findings pertaining to the response duration may be less intuitive. When completing the web-based recalls, participants were able to stop and resume questionnaires at a later time, and longer response durations are assumed to reflect this feature, rather than continuous use. Thus, it is possible that the longer durations associated with an evening preference reflect the procrastination habits associated with an evening preference (52). This is supported by the finding related to decreased same-day responses on weekends for those with an evening preference. The null findings with the number of completed questionnaires and the likelihood of completing any, all, or none of the 24-h diet recalls indicate that a selection bias due to diurnal preferences is unlikely to exist in online surveys. Overall, these findings suggest that the flexibility of online surveys may capture a wider range of individuals with more extreme morning or evening preferences, who may be at a disadvantage from attending in-person assessments during regular business hours.

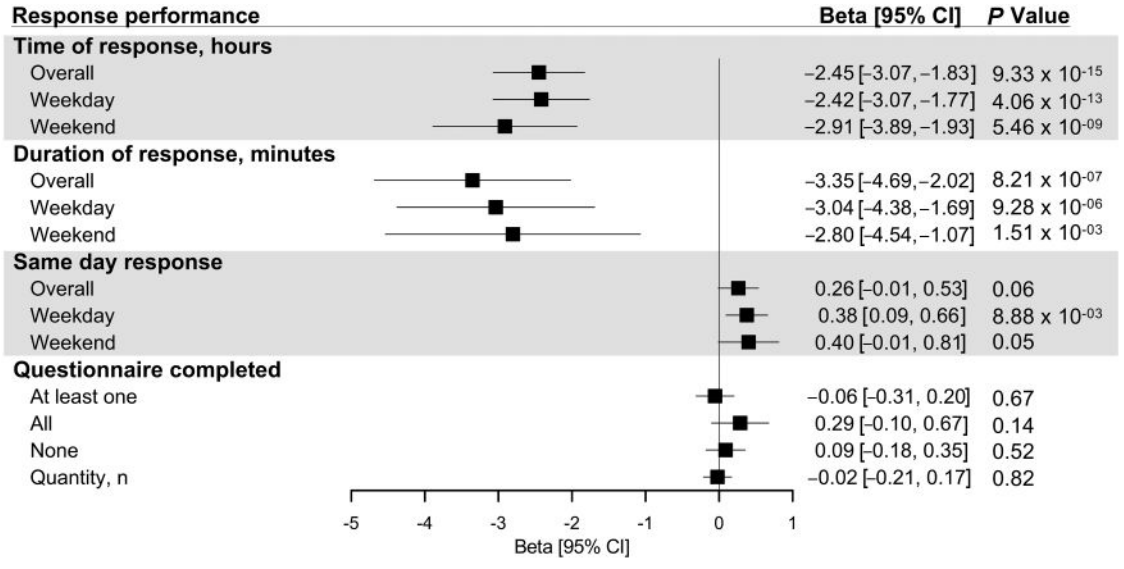

FIGURE 3 Potential causal effect of increased genetic liability to a morning preference and response performance to email-administered, modified 24-h diet recall. The results (beta, 95% CI and *P* value) of the morning preference genetic instrument on each response performance were calculated using random-effects inverse-variance weighted regression. The morning preference exposure was scaled to represent a sleep midpoint of 1 h earlier. Binary outcomes: same-day response, questionnaire completed (at least 1, all, or none).

TABLE 2 Potential causal effect of increased genetic liability to a morning preference response performance to email-administered, modified 24-h diet recalls

Response performance	Total *n* or *n* cases/*n* controls	Inverse variance weighted			MR Egger			Weighted median		
		Beta	SE	*P* value	Beta	SE	*P* value	Beta	SE	*P* value
Time of response, hours	123,035	-2.45	0.32	9.33×10^{-15}	-2.02	0.76	8.01×10^{-03}	-2.13	0.47	6.01×10^{-06}
Weekday	111,754	-2.42	0.33	4.06×10^{-13}	-2.23	0.80	5.62×10^{-03}	-2.10	0.56	1.67×10^{-04}
Weekend	51,612	-2.91	0.50	5.46×10^{-09}	-2.83	1.20	1.89×10^{-02}	-2.32	0.75	2.02×10^{-03}
Duration of response, minutes	122,049	-3.35	0.68	8.21×10^{-07}	-0.73	1.62	6.51×10^{-01}	-1.56	0.97	1.09×10^{-01}
Weekday	110,866	-3.04	0.68	9.28×10^{-06}	-0.27	1.63	8.70×10^{-01}	-2.55	0.98	9.29×10^{-03}
Weekend	51,249	-2.80	0.88	1.51×10^{-03}	-2.70	2.12	2.04×10^{-01}	-1.88	1.30	1.49×10^{-01}
Same day response	75,235/47,800	0.26	0.14	5.89×10^{-02}	0.29	0.33	3.77×10^{-01}	0.31	0.23	1.72×10^{-01}
Weekday	61,261/42,493	0.38	0.14	8.88×10^{-03}	0.31	0.34	3.63×10^{-01}	0.21	0.23	3.68×10^{-01}
Weekend	29,454/22,158	0.40	0.21	5.45×10^{-02}	0.33	0.50	5.17×10^{-01}	0.65	0.34	5.77×10^{-02}
Questionnaire completed, any	123,035/103,502	-0.06	0.13	6.74×10^{-01}	-0.04	0.31	9.02×10^{-01}	0.00	0.17	1.00
Questionnaire completed, all	17,900/18,4648	0.29	0.20	1.48×10^{-01}	0.78	0.47	9.95×10^{-02}	0.57	0.30	5.29×10^{-02}
Questionnaire completed, none	92,556/109,992	0.09	0.14	5.16×10^{-01}	0.09	0.32	7.78×10^{-01}	0.00	0.17	1.00
Questionnaire completed, quantity	202,548	-0.02	0.10	8.17×10^{-01}	0.14	0.23	5.48×10^{-01}	0.15	0.12	2.03×10^{-01}

The effect of the morning preference genetic instrument (*n* of SNPs =298) on each response performance was calculated using random-effects inverse-variance weighted regression. The morning preference exposure was scaled to represent a sleep midpoint of 1 h earlier. Binary outcomes: same-day response, questionnaire completed (at least 1, all, or none). Unscaled exposure, representing a 1-unit category increase in morning preference, is shown in Supplementary Table 8. Abbreviations: IVW = inverse variance weighted; MR = Mendelian randomization; SNPs, single nucleotide polymorphisms.

Strengths of this study include the use of multiple approaches to assess dietary intake, including a modified 24-h diet recall and food-frequency questionnaires, that included food and nonfood items, such as diet variations. We leveraged publicly available genetic data for heritable dietary traits from a large biobank, thus providing a framework for cost-effective strategies for advancing nutritional genomics research. Our MR results were largely robust to sensitivity analyses for horizontal pleiotropy. Furthermore, we were able to harness unique data to assess web-based, objective response performance information, highlighting potential strengths in the use of online nutritional surveys for data collection. The MR analyses used the largest number of genetic variants identified in a genome-wide association meta-analysis for a morning preference, enabling robust genetic instruments for analysis.

There are also limitations to consider in interpreting these results. First, these analyses were restricted to participants of European ancestry, and thus require replication in populations of other ancestries. Second, as the UK Biobank constitutes a biased sample of healthy, older adults in the United Kingdom, the generalizability of findings to other populations with different patterns of dietary intake, medication use, or disease prevalence may be limited (53). Third, analyses were restricted to 61 food items that were derived from the food-frequency questionnaire disseminated to all UK Biobank participants, in order to gain the statistical power necessary for robust MR, but this also limited the number of food items and the diet quality and timing metrices considered (54). Fourth, relying on the publicly available genetic data for dietary traits hindered the interpretation of effect estimates from MR for continuous traits as a result of systematic data transformation by PHESANT (28), thus requiring some additional re-analysis of the untransformed data for easier interpretation. Lastly, our results do not inform the mechanisms mediating the effect of diurnal preferences on consumption.

Overall, we provide evidence for potential causal links between diurnal preferences and both food choices and online survey response performances. Our findings suggest that having a morning preference results in increased intake of foods of known higher quality and decreased intake of foods of known lower quality. Potential causal links with other foods and indices of diet quality remain to be examined. Our results may reflect temporality in the consumption of foods and may warrant the systematic assessment of diurnal preferences in health assessments, with an emphasis on healthy food selection, particularly for adults with an evening preference. In addition, our results suggest that email-administered dietary assessments may allow for diurnal-preferred optimal response conditions, including the time of day and duration of responses, which may be constrained by in-person assessments.

This research was conducted using the UK Biobank Resource (application 6818). We would like to thank the participants and researchers from the UK Biobank who contributed or collected data. Data described in the manuscript, code book, and analytic code will be made available upon request pending application and approval.

The authors' responsibilities were as follows — all authors: designed the study and participated in the acquisition, analysis, and/or interpretation of data; HSD: wrote the manuscript; AC, ID, RS: reviewed and edited the manuscript; and all authors: read and approved the final version. HSD is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. The authors report no conflicts of interest.

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