



# Gene-Environment Interactions of Circadian-Related Genes for Cardiometabolic Traits

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## OBJECTIVE

Common circadian-related gene variants associate with increased risk for metabolic alterations including type 2 diabetes. However, little is known about whether diet and sleep could modify associations between circadian-related variants (*CLOCK*-rs1801260, *CRY2*-rs11605924, *MTNR1B*-rs1387153, *MTNR1B*-rs10830963, *NR1D1*-rs2314339) and cardiometabolic traits (fasting glucose [FG], HOMA-insulin resistance, BMI, waist circumference, and HDL-cholesterol) to facilitate personalized recommendations.

## RESEARCH DESIGN AND METHODS

We conducted inverse-variance weighted, fixed-effect meta-analyses of results of adjusted associations and interactions between dietary intake/sleep duration and selected variants on cardiometabolic traits from 15 cohort studies including up to 28,190 participants of European descent from the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium.

## RESULTS

We observed significant associations between relative macronutrient intakes and glycemic traits and short sleep duration (<7 h) and higher FG and replicated known *MTNR1B* associations with glycemic traits. No interactions were evident after accounting for multiple comparisons. However, we observed nominally significant interactions (all  $P < 0.01$ ) between carbohydrate intake and *MTNR1B*-rs1387153 for FG with a 0.003 mmol/L higher FG with each additional 1% carbohydrate intake in the presence of the T allele, between sleep duration and *CRY2*-rs11605924 for HDL-cholesterol with a 0.010 mmol/L higher HDL-cholesterol with each additional hour of sleep in the presence of the A allele, and between long sleep duration ( $\geq 9$  h) and *MTNR1B*-rs1387153 for BMI with a 0.60 kg/m<sup>2</sup> higher BMI with long sleep duration in the presence of the T allele relative to normal sleep duration ( $\geq 7$  to <9 h).

## CONCLUSIONS

Our results suggest that lower carbohydrate intake and normal sleep duration may ameliorate cardiometabolic abnormalities conferred by common circadian-related genetic variants. Until further mechanistic examination of the nominally significant interactions is conducted, recommendations applicable to the general population regarding diet—specifically higher carbohydrate and lower fat composition—and normal sleep duration should continue to be emphasized among individuals with the investigated circadian-related gene variants.

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Gene-environment interactions can identify potential opportunities for personalized health interventions for individuals who are genetically susceptible to type 2 diabetes and related chronic diseases (1). During the past decade, researchers have examined lifestyle interventions, particularly those related to diet, physical activity, and sleep, for individuals at increased genetic risk for metabolic alterations such as type 2 diabetes (2,3). For example, dietary changes in carbohydrate (CHO) and fat intake have been shown to attenuate a genetic predisposition to elevated fasting glucose (FG) (4), insulin resistance (5), and type 2 diabetes (6). Sleep duration has also been assessed as a modifying factor in the associations between genetics and type 2 diabetes because of the association of sleep with diet and chronic disease and its effect on the genetic risk for obesity (7). Identifying optimal and personalized therapies for the primary prevention of type 2 diabetes through gene-environment investigations is critical to public health for a disease that affects an estimated 29.1 million Americans (9.3% of the U.S. population) (1,8). In addition, because only 10% of the total heritability of type 2 diabetes is accounted for by genetic variants (9), gene-environment investigations may also reveal novel biological pathways and genetic loci pertinent to this disease.

Glucose homeostasis and insulin secretion are among several biological processes that are controlled by the circadian biological clock, which is maintained endogenously through a transcription-translation feedback loop composed of clock genes (10). Glycemic control is mediated through multiple processes, including circadian regulation of hepatic glucose metabolism (11,12); secretion of adipokines, such as leptin and adiponectin (13,14); and the pancreatic secretion of insulin and glucagon (15). Experiments in clock mutant mice showing disrupted glucose homeostasis, insulin secretion and sensitivity, and other metabolic processes, along with circadian disruption in humans (16), emphasize the importance of circadian control in metabolic control (15,17).

In support of the link between the circadian system and glycemic control in humans are results from genome-wide association studies (GWAS) of FG (18,19) and type 2 diabetes (9,20) that have reported associations with clock gene *CRY2*, encoding cryptochrome 2, and the circadian-related melatonin receptor 1B gene *MTNR1B*. In addition, the circadian locomotor output of clock genes cycles *CLOCK* and, more recently, the nuclear receptor *rev-erb-α NR1D1* have been associated with related metabolic traits, including lower circulating concentrations of HDL-cholesterol (HDL-C) and elevated central

adiposity (21–23). Because metabolic traits are important predictors of type 2 diabetes, these loci may also be relevant to the pathogenesis of type 2 diabetes (24). Thus, investigating whether lifestyle modifications—particularly diet, for its potent role in entraining circadian clocks in metabolic tissues (25), and sleep, for its putative effect on disease risk (7)—attenuate circadian-related genetic predispositions to metabolic disruptions may facilitate the development of personalized recommendations to improve type 2 diabetes prevention strategies.

In cross-sectional meta-analyses of large population-based cohorts from the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium, we tested whether dietary intake (total CHO, total fat, polyunsaturated fatty acid [PUFA], monounsaturated fatty acid [MUFA], and saturated fatty acid [SFA]) and sleep duration (continuous and categorical) modify the associations between five common circadian-related gene variants (*CLOCK*-rs1801260, *CRY2*-rs11605924, *MTNR1B*-rs1387153, *MTNR1B*-rs10830963, and *NR1D1*-rs2314339) and the two glycemic traits of FG and HOMA-insulin resistance (HOMA-IR), as well as related anthropometric (BMI and waist circumference) and lipid (HDL-C) traits. These outcomes are related to cardiovascular disease and have previously been shown to associate with the selected genetic variants.

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\*A list of the CHARGE Nutrition Study Group Investigators can be found in the APPENDIX.

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## RESEARCH DESIGN AND METHODS

### Cohorts

The present cross-sectional meta-analyses include up to 28,190 participants of European descent from the following 15 cohort studies of the CHARGE Consortium Nutrition Working Group (Supplementary Table 1): Coronary Artery Risk Development in Young Adults Study (CARDIA); Corogene Controls; Cardiovascular Health Study (CHS); Dietary, Lifestyle, and Genetic determinants of Obesity and Metabolic syndrome (DILGOM); Family Heart Study (FamHS); Framingham Offspring Study (FOS); Genetics of Lipid Lowering Drugs and Diet Network (GOLDN); GOYA MALE; Helsinki Birth Cohort Study (HBCS); Invecchiare in Chianti (aging in the Chianti area, InCHIANTI); Inter99; Multi-Ethnic Study of Atherosclerosis (MESA); The Rotterdam Study; The Hellenic Study of Interactions between SNPs and Eating in Atherosclerosis Susceptibility (THISEAS); and the Cardiovascular Risk in Young Finns Study (YFS). Participants provided written informed consent, and the study protocols were approved by local institutional review boards and/or oversight committees.

### Dietary Assessment

Dietary data were collected via validated food-frequency questionnaires (13 cohorts), dietary recall (1 cohort), and food record (1 cohort) (Supplementary Table 2). The type of food-frequency questionnaire used in each cohort differed slightly to capture the dietary habits of the population of interest. The present analysis quantified total CHO intake and total fat intake as percentages of total energy intake. Additional analyses used percentage of energy from specific fatty acids, including PUFA, MUFA, and SFA. Total energy intake from protein was not included in the present analysis because of the lack of evidence supporting protein intake in gene-environment interactions (3).

### Sleep Assessment

Data on habitual weekday/workday nighttime sleep duration in hours per night were obtained from self-reported responses to questions such as, "How many hours of sleep do you usually get at night?" or were calculated from self-reported weekday/workday bed and rise times (Supplementary Table 3).

Responses were analyzed as continuous and categorical variables. Commonly accepted cutoffs were used to create three sleep duration categories: short (<7 h), normal ( $\geq 7$  to <9 h), and long ( $\geq 9$  h).

### Outcome Measurements

Cohort-specific assessment methods for FG (mmol/L), BMI ( $\text{kg}/\text{m}^2$ ), waist circumference (cm), and HDL-C (mmol/L) are described in detail in Supplementary Table 3. HOMA-IR was estimated from fasting insulin and FG concentrations, using the previously validated equation [ $\text{HOMA-IR} = \text{FG (mmol/L)} \times \text{fasting insulin (mU/L)} / 22.5$ ], and was natural log-transformed to reduce skew before data analysis.

### Genotyping

We selected five single nucleotide polymorphisms (SNPs) in circadian-related genes based on previous reports from GWAS meta-analysis (*CRY2*-rs11605924, *MTNR1B*-rs10830963), replicated candidate gene association studies (*NR1D1*-rs2314339), gene-environment interaction studies (*CLOCK*-rs1801260, *MTNR1B*-rs1387153) that showed associations with type 2 diabetes, FG, and/or BMI (4,9,18–21). SNPs and/or SNPs in linkage disequilibrium ( $r^2 > 0.80$ ; HapMap III release 2 data set) were previously directly genotyped or imputed by participating cohorts before inclusion in this analysis (Supplementary Table 4). SNPs were assessed for quality control: genotyped SNPs were excluded on the basis of low call rate (<95%) and departure from Hardy-Weinberg equilibrium (< $1\text{E-}06$ ), and imputed SNPs were removed on the basis of low imputation quality (MACH:  $R^2 < 0.3$  or IMPUTE: proper info <0.4). Not all SNPs were available in all participating cohorts (Supplementary Table 5), and therefore, total sample sizes for analyses varied.

### Cohort-Specific Analyses

All participating cohort-specific statistical analyses followed a uniform analysis plan. First, main associations between dietary intake or sleep duration and all outcomes were estimated with adjustment for age, sex, BMI (except for BMI outcome), and study site (in CARDIA, CHS, FamHS, GOLDN, InCHIANTI, and MESA) using linear regression models. Second, main

associations between selected SNPs and all outcomes were investigated by using linear regression models and an additive genetic model adjusted for the aforementioned covariates in addition to family or population structure (in Corogene Controls, DILGOM, FamHS, FOS, GOLDN, MESA, The Rotterdam Study, and YFS), and genotype batch (in FamHS). Third, for our primary analysis of interest, 175 interactions (7 environmental variables  $\times$  5 SNPs  $\times$  5 outcomes) between dietary intake or sleep duration (continuous and categorical) and the selected SNPs on all outcomes were tested by using intake/sleep duration  $\times$  SNP cross-product terms and including main-effect terms in linear regression models adjusted for the aforementioned covariates. Participants within each cohort were excluded from the analysis if they were shift workers, on sleep medications or antidepressant medications, reported bedtimes after 5 A.M. or before 6 P.M., and/or reported sleep duration <3 or  $\geq 16$  h. For glycemic outcomes, participants with type 2 diabetes within each cohort were excluded from main association and interaction analyses.

### Meta-analyses

We conducted inverse-variance weighted, fixed-effect meta-analyses using METAL (version released 2011-03-25) for 1) main associations of dietary intake/sleep duration on the outcomes, 2) main associations of the selected SNPs on the outcomes, and 3) interactions between SNPs and dietary intake/sleep duration on the outcomes.

Heterogeneity across studies was tested by using Cochran's  $Q$  statistic and quantified using the  $I^2$  statistic. All association and interaction analyses with moderate heterogeneity ( $I^2 > 30\%$ ) were further assessed for potential sources of heterogeneity by conducting meta-regression and sensitivity analyses. Meta-regression analyses were conducted using the R metafor package (R version 3.1.0) to assess the effect of the following moderator variables on heterogeneity of association/interaction: geographical location (U.S. vs. northern Europe vs. Mediterranean), mean age of cohort (20–64 years vs. 65–80 years), and total energy intake (<2,000 vs.  $\geq 2,000$  kcal/day). Sensitivity analyses assessed the influence of a single cohort on the meta-analyzed estimate by

repeating analyses removing one cohort study at a time in the association and interaction analyses. Statistical significance for each outcome was defined at a level of 0.003, based on Bonferroni correction for 15 total independent interaction tests (3 independent environmental variables [percent energy from CHO, percent energy from total fat, and sleep duration]  $\times$  5 independent SNPs). We performed power calculations using Quanto version 1.2.4 (<http://biostats.usc.edu/software>) for *NR1D1*-rs2314339, which represents the SNP with the least possible power (based on lowest minor allele frequency and sample size). At 80% power, our sample size meets the estimated sample size to detect an interaction effect between dietary macronutrient intake (per 1% intake) and SNPs (per effect allele) on FG.

## RESULTS

General characteristics of participants are reported in Table 1. Mean ages ranged between 32.6 and 70.2 years, and women comprised 37–62% of participants in each cohort, except for GOYA MALE (all men). Mean BMI exceeded 25 kg/m<sup>2</sup> for all cohorts, and there were no substantial variations in waist circumference, FG, HOMA-IR, or HDL-C among cohorts. Total energy intake was generally higher in U.S. cohorts, but relative macronutrient intakes were similar across studies and differed only for MUFA and SFA intakes. The Mediterranean cohorts (InCHIANTI and THISEAS) had higher mean MUFA intake than northern European and U.S. cohorts ( $P < 0.0001$ ), and The Rotterdam Study reported the highest SFA intake ( $P < 0.0001$ ). In addition, the average habitual weekday/workday sleep duration was similar across cohorts, ranging between 6.8 and 8.3 h, the prevalence of short sleep duration (<7 h) ranged between 18.1 and 41.6%, and long sleep duration ( $\geq 9$  h) ranged between 4.0 and 11.9%.

**Associations of Dietary Intake/Sleep Duration With Cardiometabolic Traits** After adjustment for age, sex, BMI, and study site, we identified significant main associations between dietary intake/sleep duration with glycemic traits (Supplementary Fig. 1 and Supplementary Table 6). Each additional 1% of CHO

**Table 1—General characteristics of participating CHARGE cohorts\***

Characteristics	CARDIA <i>n</i> = 1,073	CoroGene Controls <i>n</i> = 549	CHS <i>n</i> = 2,918	DILGOM <i>n</i> = 3,136	FamHS <i>n</i> = 3,326	FOSS <i>n</i> = 917	GOLDN <i>n</i> = 810	GOYA MALE <i>n</i> = 187	HBCS <i>n</i> = 1,184	InCHIANTI <i>n</i> = 922	Inter99 <i>n</i> = 6,000	MESA <i>n</i> = 2,028	Rotterdam <i>n</i> = 2,367	THISEAS <i>n</i> = 931	YFS <i>n</i> = 1,730
Age (years)	32.6 $\pm$ 3.3	51.2 $\pm$ 13.4	71.2 $\pm$ 4	49.9 $\pm$ 13.3	51.4 $\pm$ 13.3	57.5 $\pm$ 9	48.4 $\pm$ 16.3	44.7 $\pm$ 6.5	69 $\pm$ 2.9	64.5 $\pm$ 14.2	46.2 $\pm$ 7.9	61.7 $\pm$ 9.7	70.2 $\pm$ 5	57 $\pm$ 12.4	37.8 $\pm$ 5
Sex (% women)	52.4	54.8	61.9	56.6	53.3	55.4	52.0	0	60.6	53.5	51.4	50.96	58.0	37.1	55.4
BMI (kg/m <sup>2</sup> )	25.7 $\pm$ 5.2	26.5 $\pm$ 4.5	26.4 $\pm$ 4.5	26.7 $\pm$ 4.6	27.7 $\pm$ 5.5	28 $\pm$ 5.2	28.3 $\pm$ 5.6	25.6 $\pm$ 3.2	27.5 $\pm$ 4.6	27.3 $\pm$ 4.2	26.3 $\pm$ 4.6	27.8 $\pm$ 5.1	26.8 $\pm$ 3.9	28.1 $\pm$ 4.3	25.9 $\pm$ 4.6
Waist circumference (cm)	106.9 $\pm$ 36.1	89.4 $\pm$ 13.1	93.2 $\pm$ 12.9	89.5 $\pm$ 12.6	97.3 $\pm$ 15.3	97.3 $\pm$ 15.3	96.6 $\pm$ 16.6	93 $\pm$ 10.6	94.4 $\pm$ 13	91.5 $\pm$ 11.2	86.7 $\pm$ 13.4	98 $\pm$ 14.5	93.1 $\pm$ 11.5	97.3 $\pm$ 13.7	88.2 $\pm$ 13.3
FG (mmol/L)	5.0 $\pm$ 0.7	5.8 $\pm$ 0.5	6 $\pm$ 1.6	5.7 $\pm$ 0.5	5.5 $\pm$ 1.4	5.5 $\pm$ 0.8	5.6 $\pm$ 1	5.7 $\pm$ 0.6	5.7 $\pm$ 1.2	5.2 $\pm$ 1.5	5.6 $\pm$ 1.1	5.1 $\pm$ 1.2	5.6 $\pm$ 0.9	5.9 $\pm$ 1.8	5.3 $\pm$ 0.9
Fasting insulin (pmol/L)	30.4 $\pm$ 29.5	42.9 $\pm$ 26.2	108.1 $\pm$ 125	43.9 $\pm$ 29.7	79.4 $\pm$ 94.7	NA	95.4 $\pm$ 56.7	37.4 $\pm$ 26.7	70.9 $\pm$ 56	77.2 $\pm$ 42.8	42.9 $\pm$ 29.6	63.2 $\pm$ 38.2	77.9 $\pm$ 54.7	NA	61.4 $\pm$ 60.1
HOMA-IR	2.9 $\pm$ 4.2	1.6 $\pm$ 1.1	4.5 $\pm$ 9.2	1.7 $\pm$ 1.3	3.1 $\pm$ 6.1	NA	3.5 $\pm$ 2.5	1.4 $\pm$ 1.1	2.6 $\pm$ 2.3	2.6 $\pm$ 1.9	1.9 $\pm$ 1.7	1.4 $\pm$ 1.3	2.9 $\pm$ 2.5	NA	2.2 $\pm$ 3.3
HDL-C (mmol/L)	1.3 $\pm$ 0.4	1.5 $\pm$ 0.3	1.4 $\pm$ 0.4	1.5 $\pm$ 0.3	1.3 $\pm$ 0.4	1.3 $\pm$ 0.4	1.2 $\pm$ 0.3	1.3 $\pm$ 0.3	1.6 $\pm$ 0.4	1.5 $\pm$ 0.4	1.4 $\pm$ 0.4	1.4 $\pm$ 0.4	1.4 $\pm$ 0.4	1.3 $\pm$ 0.4	1.3 $\pm$ 0.3
Sleep duration (h) <sup>†</sup>	NA	7.2 $\pm$ 1	7.2 $\pm$ 1.3	7.3 $\pm$ 1	NA	7.1 $\pm$ 1.1	NA	NA	7.4 $\pm$ 1.1	6.8 $\pm$ 1.4	7.3 $\pm$ 0.9	7 $\pm$ 1.2	NA	7.1 $\pm$ 1.5	7.4 $\pm$ 0.8
Short <7 h, <i>n</i> (%)	NA	99 (18.1)	389 (26.8)	568 (18.2)	NA	231 (25.7)	NA	NA	492 (41.6)	NA	851 (20.0)	586 (29.3)	NA	198 (36.1)	330 (19.1)
Normal $\geq 7$ to <9 h, <i>n</i> (%)	NA	406 (74.4)	892 (61.3)	2324 (74.3)	NA	613 (68.2)	NA	NA	651 (55.0)	NA	3174 (74.7)	1281 (52.4)	NA	287 (52.4)	1330 (76.9)
Long $\geq 9$ h, <i>n</i> (%)	NA	41 (7.5)	173 (11.9)	234 (7.5)	NA	55 (6.1)	NA	NA	41 (5.3)	NA	225 (5.3)	130 (11.5)	NA	63 (11.5)	70 (4.0)
Dietary intake															
Total energy (kcal/day)	2,587 $\pm$ 928	2,302 $\pm$ 776	1,999 $\pm$ 613	2,538 $\pm$ 903	1,755 $\pm$ 619	1,878 $\pm$ 616	2,115 $\pm$ 1,181	2,490 $\pm$ 598	2,212 $\pm$ 807	2,066 $\pm$ 601	2,332 $\pm$ 870	1,602 $\pm$ 705	2,007 $\pm$ 520	1,922 $\pm$ 1,046	2,383 $\pm$ 761
Total fat (% total energy)	34 $\pm$ 6.7	31.2 $\pm$ 4.9	32.3 $\pm$ 6	31.3 $\pm$ 4.8	30.8 $\pm$ 7.4	29.5 $\pm$ 6.4	35.4 $\pm$ 6.9	32.4 $\pm$ 4.6	32.5 $\pm$ 5.2	31 $\pm$ 5.2	32.6 $\pm$ 7	32.1 $\pm$ 7.3	36.0 $\pm$ 6	36.1 $\pm$ 6	32.9 $\pm$ 4.8
PUFA (% total energy)	6.9 $\pm$ 2	5.5 $\pm$ 1.2	7.5 $\pm$ 2.2	5.4 $\pm$ 1.1	4.5 $\pm$ 1.4	5.7 $\pm$ 1.6	6.9 $\pm$ 2.2	4.1 $\pm$ 0.7	5.2 $\pm$ 1.2	3.4 $\pm$ 0.7	5.3 $\pm$ 1.5	6.3 $\pm$ 1.8	6.9 $\pm$ 2.7	5 $\pm$ 1.4	5.3 $\pm$ 1.1
MUFA (% total energy)	12.5 $\pm$ 2.8	11.1 $\pm$ 2.2	11.6 $\pm$ 2.5	11.1 $\pm$ 2.1	12 $\pm$ 3.2	11 $\pm$ 2.6	13.3 $\pm$ 2.8	9.8 $\pm$ 1.7	10.8 $\pm$ 2.1	15.6 $\pm$ 3.2	10.6 $\pm$ 2.7	12.3 $\pm$ 3	12.3 $\pm$ 2.6	16.2 $\pm$ 3.6	11.1 $\pm$ 2
SFA (% total energy)	11.9 $\pm$ 3.2	11.3 $\pm$ 2.4	10.3 $\pm$ 2.2	11.8 $\pm$ 2.5	11.3 $\pm$ 3.2	10.1 $\pm$ 2.8	11.8 $\pm$ 2.8	13.5 $\pm$ 2.4	11.8 $\pm$ 2.5	10.4 $\pm$ 2.2	12.3 $\pm$ 7.9	10.8 $\pm$ 3.4	14.1 $\pm$ 3	11.8 $\pm$ 3.2	11.8 $\pm$ 2.4
CHO (% total energy)	50.2 $\pm$ 7.8	48.1 $\pm$ 6.2	52.2 $\pm$ 7.9	49 $\pm$ 6.1	50.8 $\pm$ 10.1	51.6 $\pm$ 8.2	48.9 $\pm$ 8.7	41.8 $\pm$ 6.6	47 $\pm$ 6.5	51.4 $\pm$ 6.7	47.5 $\pm$ 7.9	50.7 $\pm$ 9	43.3 $\pm$ 6.9	44.5 $\pm$ 8.7	45.9 $\pm$ 5.8
Proteins (% total energy)	15 $\pm$ 2.6	17.6 $\pm$ 2.6	19.1 $\pm$ 3.2	17.7 $\pm$ 2.5	18.3 $\pm$ 4.1	17.1 $\pm$ 3.1	15.8 $\pm$ 2.9	15.2 $\pm$ 2.3	17.1 $\pm$ 2.5	15.7 $\pm$ 2.1	15.1 $\pm$ 2.6	15.7 $\pm$ 3.3	16.9 $\pm$ 3	17.9 $\pm$ 2.4	17.5 $\pm$ 2.4

Values are means  $\pm$  SD or percentages. NA, not available. \*Cohort study name (study acronym) (country): Coronary Artery Risk Development in Young Adults (CARDIA) (U.S.); CoroGene Controls (Finland); Cardiovascular Health Study (CHS) (U.S.); Dietary Lifestyle and Genetic Determinants of Obesity and Metabolic Syndrome (DILGOM) (Finland); Family Heart Study (FamHS) (U.S.); Framingham Offspring Study (FOSS) (U.S.); Genetics of Lipid Lowering Drugs and Diet Network (GOLDN) (U.S.); GOYA MALE (Denmark); Helsinki Birth Cohort Study (HBCS) (Finland); Invechiare in Chianti (aging in the Chianti Area, InCHIANTI) (Italy); Inter99 (Denmark); Multi-Ethnic Study of Atherosclerosis (MESA) (U.S.); The Rotterdam Study (the Netherlands); The Helenic Study of Interactions between SNPs and Eating in Atherosclerosis Susceptibility (THISEAS) (Greece); Cardiovascular Risk in Young Finns Study (YFS) (Finland); †Weekday or workday self-reported sleep duration as usual hours of sleep per night.

intake was associated with 0.007 mmol/L lower FG ( $\beta \pm SE = -0.007 \pm 0.001$  mmol/L,  $P = 2.7E-29$ ) and a 0.001 lower HOMA-IR ( $\beta \pm SE = -0.001 \pm 0.0004$  [In],  $P = 0.002$ ). Each additional 1% of total fat intake was associated with a 0.01 mmol/L higher FG ( $\beta \pm SE = 0.01 \pm 0.001$  mmol/L,  $P = 8.36E-13$ ) and a 0.005 higher HOMA-IR ( $\beta \pm SE = 0.005 \pm 0.0005$  [In],  $P = 2.76E-16$ ). Similar trends were evident for MUFA and SFA intakes: each additional 1% of MUFA intake was associated with a 0.01 mmol/L higher FG ( $\beta \pm SE = 0.01 \pm 0.001$  mmol/L,  $P = 4.23E-12$ ) and a 0.01 higher HOMA-IR ( $\beta \pm SE = 0.01 \pm 0.001$  [In],  $P = 1.12E-13$ ), whereas each additional 1% of SFA intake was associated with a 0.01 mmol/L higher FG ( $\beta \pm SE = 0.01 \pm 0.001$  mmol/L,  $P = 9.26E-13$ ) and a 0.01 higher HOMA-IR ( $\beta \pm SE = 0.01 \pm 0.001$  [In],  $P = 1.66E-19$ ). However, no associations were evident for PUFA intake.

When sleep was assessed linearly, we observed a marginal association between sleep duration and FG: each additional hour of sleep was associated with 0.01 mmol/L lower FG ( $\beta \pm SE = -0.01 \pm 0.005$  mmol/L,  $P = 0.05$ ). However, when sleep was categorical, we observed a significant association between short sleep duration (<7 h) and FG: short sleep duration was associated with a 0.03 mmol/L higher FG ( $\beta \pm SE = 0.03 \pm 0.01$  mmol/L,  $P = 0.01$ ) and with a 0.45 kg/m<sup>2</sup> higher BMI ( $\beta \pm SE = 0.45 \pm 0.09$  kg/m<sup>2</sup>,  $P < 0.001$ ) relative to normal sleep duration ( $\geq 7$  to <9 h). In addition, long sleep duration ( $\geq 9$  h) was associated with a 0.33 kg/m<sup>2</sup> higher BMI ( $\beta \pm SE = 0.33 \pm 0.14$  kg/m<sup>2</sup>,  $P = 0.02$ ) and a 0.76 cm higher waist circumference ( $\beta \pm SE = 0.76 \pm 0.18$  cm,  $P < 0.001$ ) and was marginally associated with a higher HOMA-IR ( $\beta \pm SE = 0.03 \pm 0.02$  [In],  $P = 0.05$ ), relative to normal sleep duration ( $\geq 7$  to <9 h).

Additional main associations of dietary intake and sleep duration on anthropometric and lipid traits are presented in Supplementary Table 6.

#### Associations of SNPs With Cardiometabolic Traits

Sensitivity analyses indicated that substantial heterogeneity ( $I^2 > 30\%$ ) was introduced by one cohort (GOLDN) for glycemic trait outcomes; consequently, GOLDN was excluded from the association

and interaction meta-analyses for glycemic traits.

Main associations of selected SNPs on cardiometabolic traits are presented in Supplementary Table 7. We replicated previously published associations between *MTNR1B* variants and glycemic traits in the present meta-analysis (18,19). In short, *MTNR1B*-rs1387153 was associated with FG ( $\beta \pm SE = 0.058 \pm 0.007$  mmol/L per additional T allele,  $P = 1.7E-17$ ), whereas *MTNR1B*-rs10830963 was associated with FG ( $\beta \pm SE = 0.1 \pm 0.008$  mmol/L per additional G allele,  $P = 4.2E-35$ ) and HOMA-IR ( $\beta \pm SE = 0.016 \pm 0.004$  [In] per additional G allele,  $P = 0.004$ ). We did not replicate previous associations between *CRY2*-rs11605924 and FG ( $P = 0.06$ ) (18,19). Consistent with previous findings, no associations were observed for *CLOCK*-rs1801260 or *NR1D1*-rs2314339 on glycemic traits. Main associations of selected SNPs on anthropometric and lipid traits are presented in Supplementary Table 7.

#### Interactions Between Dietary Intake and Selected SNPs on Cardiometabolic Traits

Meta-analyzed estimates of the interactions between dietary intake and selected SNPs on cardiometabolic traits are presented in Table 2. We observed no interactions at the prespecified Bonferroni-corrected significance level of  $P < 0.003$ . We observed a nominal interaction (i.e.,  $P < 0.05$ ) between CHO intake and *MTNR1B*-rs1387153 for FG ( $\beta \pm SE = 0.003 \pm 0.001$  mmol/L,  $P = 0.01$ ), which suggests a 0.003 mmol/L higher FG with each additional 1% of CHO intake in the presence of the effect T allele (Supplementary Fig. 2A and Supplementary Fig. 3A). In other words, although higher CHO intake is associated with lower FG when evaluated independently of genotype, the protective association of a higher CHO intake was 0.003 mmol/L weaker (per 1% difference in CHO intake) in the presence of each additional T allele, implying that the T allele attenuates the inverse association between CHO intake and FG. Another nominal interaction was evident for MUFA intake and the same *MTNR1B* variant for FG ( $\beta \pm SE = -0.007 \pm 0.003$  mmol/L,  $P = 0.02$ ), which suggests 0.007 mmol/L lower FG with each additional 1% of MUFA intake in the presence

of the effect T allele (Supplementary Fig. 2B). In addition, a nominal interaction was present between total fat intake and *NR1D1*-rs2314339 on HOMA-IR ( $\beta \pm SE = 0.0024 \pm 0.001$  [In],  $P = 0.04$ ) (Supplementary Fig. 2C), suggesting a 0.0024 higher HOMA-IR with each additional 1% of total fat intake in the presence of the effect T allele.

For anthropometric and lipid traits, we observed nominal interactions (i.e.,  $P < 0.05$ ), including that between SFA intake and *NR1D1*-rs2314339 for BMI ( $\beta \pm SE = 0.005 \pm 0.002$  kg/m<sup>2</sup>,  $P = 0.01$ ); the interaction suggests a 0.005 kg/m<sup>2</sup> higher BMI with each additional 1% of SFA intake in the presence of the effect T allele (Supplementary Fig. 1D).

#### Interactions Between Sleep Duration and Selected SNPs on Cardiometabolic Traits

Meta-analyzed estimates of the interactions between sleep duration (continuous and categorical) and selected SNPs on cardiometabolic traits are presented in Table 3. We observed no interactions at the prespecified Bonferroni-corrected significance level of  $P < 0.003$ . A nominal interaction was evident between sleep duration and *CRY2*-rs11605924 for HDL-C ( $\beta \pm SE = 0.010 \pm 0.004$  mmol/L,  $P = 0.005$ ), suggesting a 0.010 mmol/L higher HDL-C with each additional hour of sleep in the presence of the effect A allele (Supplementary Fig. 2E and Supplementary Fig. 3B). That is, in the presence of each additional A allele, the protective association of higher sleep duration on HDL-C was 0.01 mmol/L stronger (per 1 h of additional sleep), such that the A allele appears to strengthen the positive association observed with longer sleep duration. No interactions were evident between categories of sleep duration and this variant for HDL-C (short sleep duration,  $P = 0.15$ ; long sleep duration,  $P = 0.21$ ).

Finally, we observed a nominal interaction between short sleep duration (<7 h) and *MTNR1B*-rs1387153 for BMI ( $\beta \pm SE = 0.25 \pm 0.12$  kg/m<sup>2</sup>,  $P = 0.04$ ) (Supplementary Fig. 2F) and a stronger interaction between long sleep duration ( $\geq 9$  h) and the same variant for BMI ( $\beta \pm SE = 0.60 \pm 0.20$  kg/m<sup>2</sup>,  $P = 0.003$ ) (Supplementary Fig. 2G); these interactions suggest 0.25 and 0.60 kg/m<sup>2</sup> higher BMIs with short and long sleep durations, respectively, in the

**Table 2—Meta-analyzed interactions between dietary intake and SNPs on cardiometabolic traits\***

SNP	Gene	Alleles†	n‡	Glycemic traits			Anthropometric traits			Lipid trait			
				β ± SE	P	β ± SE	P	β ± SE	P	β ± SE	P		
<b>Total fat (% total energy)</b>													
rs1801260	CLOCK	C/T	18,401	0.003 ± 0.002	0.12	0.0013 ± 0.001	0.29	0.0006 ± 0.001	0.33	0.0002 ± 0.0003	0.55	-2.6E-05 ± 2.1E-05	0.14
rs11605924	CRY2	A/C	18,389	-0.001 ± 0.001	0.28	0.0012 ± 0.001	0.09§	-0.0005 ± 0.001	0.40§	0.0001 ± 0.0002	0.93	-1.3E-05 ± 1.8E-05	0.51§
rs1387153	MTNR1B	T/C	26,532	-0.002 ± 0.001	0.09	0.0006 ± 0.001	0.46§	-0.0010 ± 0.001	0.09§	-0.0001 ± 0.0003	0.58	<b>5.2E-05 ± 2.1E-05</b>	<b>0.02</b>
rs10830963	MTNR1B	G/C	27,607	-0.001 ± 0.002	0.72	-0.0005 ± 0.001	0.60	-0.0004 ± 0.001	0.52	-0.0003 ± 0.0003	0.31	<b>4.7E-05 ± 2.1E-05</b>	<b>0.02</b>
rs2314339	NR1D1	T/C	25,016	-0.002 ± 0.002	0.39	<b>0.0024 ± 0.001</b>	<b>0.04</b>	0.0010 ± 0.001	0.09	0.0002 ± 0.0003	0.58	1.6E-05 ± 2.6E-05	0.55
<b>PUFA (% total energy)</b>													
rs1801260	CLOCK	C/T	18,401	0.005 ± 0.005	0.39§	-0.0003 ± 0.004	0.95	0.0022 ± 0.002	0.25	0.0011 ± 0.0010	0.15	-5.2E-05 ± 5.2E-05	0.49§
rs11605924	CRY2	A/C	18,389	-0.003 ± 0.004	0.41	0.0002 ± 0.003	0.94	-0.0014 ± 0.002	0.39§	0.0001 ± 0.0010	0.94	-4.1E-05 ± 5.2E-05	0.46
rs1387153	MTNR1B	T/C	26,532	0.001 ± 0.004	0.91§	0.0013 ± 0.003	0.66§	-0.0009 ± 0.002	0.65	0.0004 ± 0.0010	0.64	1.0E-04 ± 5.2E-05	0.06
rs10830963	MTNR1B	G/C	27,607	0.003 ± 0.005	0.61	-0.0002 ± 0.003	0.96	0.0001 ± 0.002	0.97	-0.0002 ± 0.0010	0.74	7.8E-05 ± 5.2E-05	0.17
rs2314339	NR1D1	T/C	25,016	-0.001 ± 0.008	0.89	0.0047 ± 0.005	0.30	0.0010 ± 0.003	0.59	0.0004 ± 0.0010	0.69	6.5E-05 ± 7.8E-05	0.42
<b>MUFA (% total energy)</b>													
rs1801260	CLOCK	C/T	18,401	0.006 ± 0.004	0.11	0.0047 ± 0.003	0.09	0.0008 ± 0.002	0.58	0.0002 ± 0.0010	0.79	-6.5E-05 ± 5.2E-05	0.19
rs11605924	CRY2	A/C	18,389	-0.001 ± 0.003	0.60	0.0019 ± 0.002	0.31	-0.0016 ± 0.001	0.21	0.0002 ± 0.0010	0.78	-1.6E-05 ± 5.2E-05	0.69§
rs1387153	MTNR1B	T/C	26,532	<b>-0.007 ± 0.003</b>	<b>0.02</b>	0.0008 ± 0.002	0.67§	<b>-0.0035 ± 0.002</b>	<b>0.02§</b>	-0.0003 ± 0.0010	0.67	<b>1.0E-04 ± 5.2E-05</b>	<b>0.01</b>
rs10830963	MTNR1B	G/C	27,607	-0.002 ± 0.003	0.58	-0.0015 ± 0.002	0.50	-0.0020 ± 0.002	0.31	-0.0007 ± 0.0010	0.30	<b>1.0E-04 ± 5.2E-05</b>	<b>0.02</b>
rs2314339	NR1D1	T/C	25,016	-0.005 ± 0.006	0.35	0.0038 ± 0.003	0.16	0.0026 ± 0.002	0.17	0.0003 ± 0.0010	0.71	5.2E-05 ± 5.2E-05	0.52
<b>SFA (% total energy)</b>													
rs1801260	CLOCK	C/T	18,401	0.006 ± 0.004	0.13§	0.0025 ± 0.003	0.35	0.0020 ± 0.002	0.31	0.0001 ± 0.0010	0.92	-8.5E-05 ± 5.2E-05	0.11§
rs11605924	CRY2	A/C	18,389	-0.003 ± 0.002	0.21	-0.0001 ± 0.002	0.97§	0.0003 ± 0.001	0.84§	0.0001 ± 0.0010	0.99	-1.0E-05 ± 5.2E-05	0.82
rs1387153	MTNR1B	T/C	26,532	-0.003 ± 0.003	0.21	0.0013 ± 0.002	0.45	<b>-0.0030 ± 0.002</b>	<b>0.04§</b>	-0.0009 ± 0.0010	0.17	7.5E-05 ± 5.2E-05	0.15
rs10830963	MTNR1B	G/C	27,607	-0.001 ± 0.003	0.66	-0.0016 ± 0.002	0.41	-0.001 ± 0.002	0.38	-0.0007 ± 0.0010	0.26§	9.6E-05 ± 5.2E-05	0.06
rs2314339	NR1D1	T/C	25,016	-0.005 ± 0.005	0.29	0.0045 ± 0.003	0.09	<b>0.0050 ± 0.002</b>	<b>0.01</b>	0.0007 ± 0.0010	0.42	1.3E-05 ± 7.8E-05	0.87
<b>CHO (% total energy)</b>													
rs1801260	CLOCK	C/T	18,401	-0.002 ± 0.001	0.15	-0.0012 ± 0.001	0.19	-0.0003 ± 0.001	0.53	-0.0002 ± 0.0002	0.47	8.0E-06 ± 1.6E-05	0.64
rs11605924	CRY2	A/C	18,389	0.001 ± 0.001	0.57	-0.0007 ± 0.001	0.24§	-0.0001 ± 0.001	0.81§	0.0001 ± 0.0002	0.86	1.0E-05 ± 1.6E-05	0.49
rs1387153	MTNR1B	T/C	26,532	<b>0.003 ± 0.001</b>	<b>0.008</b>	-0.0001 ± 0.001	0.87	0.0010 ± 0.001	0.18	0.0001 ± 0.0002	0.97§	-2.8E-05 ± 1.6E-05	0.07
rs10830963	MTNR1B	G/C	27,607	0.002 ± 0.001	0.08	0.0008 ± 0.001	0.24	0.0001 ± 0.001	0.76	0.0001 ± 0.0002	0.80§	-2.6E-05 ± 1.6E-05	0.08
rs2314339	NR1D1	T/C	25,016	0.001 ± 0.002	0.59	-0.0017 ± 0.001	0.05§	<b>-0.0010 ± 0.001</b>	<b>0.03</b>	-0.0002 ± 0.0003	0.51	<b>-4.4E-05 ± 2.1E-05</b>	<b>0.03</b>

\*Additive allele mode, adjusted for age, sex, BMI (except when assessing BMI outcome), study site (in CARDIA; CHS; FamHS; GOLDN; InCHIANTI; MESA), family or population structure (in Corogene Controls; DILGOM; FamHS; FOS; GOLDN; MESA; The Rotterdam Study; YFS), and genotype batch (in FamHS). Interaction coefficients are shown as β ± SE. β represents the direction and magnitude of the change in outcome trait with each additional minor allele, per each additional % of macronutrient intake. Boldface type indicates nominally significant values (P < 0.05). †Alleles presented as effect/non-effect alleles. ‡The number of independent observations in each interaction analysis. Exact numbers of observations vary depending on availability of phenotype and genotype information and are presented in Supplementary Table 8. §P > 30%, where P represents the heterogeneity statistic presented as percent. Exact P is presented in Supplementary Table 8.

presence of the effect T allele, relative to normal sleep duration ( $\geq 7$  to  $< 9$  h).

Results from meta-regressions and sensitivity analyses did not substantively ( $P > 0.05$ ) affect association or interaction results, neither did they reveal any clear sources of heterogeneity between dietary intake/sleep duration on glycemic, anthropometric, or lipid traits (results not shown).

**CONCLUSIONS**

Our meta-analyses of 15 cohorts did not identify statistically significant gene-environment interactions between modifiable lifestyle factors (relative CHO and fat intakes and sleep duration) and common circadian-related gene variants on glycemic and related metabolic traits. However, the observed nominally significant interactions suggest that lower CHO intake and normal sleep duration may ameliorate cardio-metabolic abnormalities conferred by the investigated variants. Until further examination of these interactions is conducted, recommendations should continue to emphasize favorable lifestyle behaviors applicable to the general population, namely, maintaining a healthy diet and obtaining sufficient sleep ( $\geq 7$  to  $< 9$  h) for reducing the risk of metabolic disorders associated with these variants.

The dietary intake associations we observed suggest that diets with a higher percentage of total energy intake from CHO and a lower percentage of total energy intake from total fat, MUFA, and SFA are associated with lower FG. The FG-raising associations of MUFA and SFA intakes observed in the current study are twice the magnitude of the FG-lowering effect of CHO intake, emphasizing the importance of limiting fat intake and in line with current dietary recommendations for individuals with diabetes (26). The similar associations of MUFA and SFA on FG may be partly driven by the strong correlation between the two macronutrients in some cohorts rather than the intake of each dietary component independently. Despite not taking CHO quality into account, our observations that diets higher in relative CHO intake are associated with lower FG are consistent with results from meta-analyses for whole grains (27). Furthermore, the association observed between short sleep

**Table 3—Meta-analyzed interactions between sleep duration (continuous and categorical) and SNPs on cardiometabolic traits\***

SNP	Gene	Allele†	n‡	Glycemic traits			Anthropometric traits			Lipid trait					
				FG (mmol/L)			BMI (kg/m <sup>2</sup> )			Waist circumference (cm)			HDL-C (mmol/L)		
				$\beta \pm SE$	P		$\beta \pm SE$	P		$\beta \pm SE$	P		$\beta \pm SE$	P	
<b>Continuous, h</b>															
rs1801260	CLOCK	C/T	10,707	0.005 ± 0.02	0.67§	-0.004 ± 0.01	0.61	-0.07 ± 0.07	0.32	0.08 ± 0.09	0.38	0.001 ± 0.005	0.82§		
rs11605924	CRY2	A/C	10,706	-0.001 ± 0.01	0.85	-0.004 ± 0.01	0.52	0.02 ± 0.05	0.66	-0.07 ± 0.06	0.24	<b>0.010 ± 0.004</b>	<b>0.005</b>		
rs1387153	MTNR1B	T/C	19,911	0.006 ± 0.01	0.42	0.007 ± 0.01	0.23	0.04 ± 0.05	0.35	0.09 ± 0.06	0.14	-0.001 ± 0.004	<b>0.78</b>		
rs10830963	MTNR1B	G/C	19,913	0.002 ± 0.01	0.85§	-0.004 ± 0.01	0.63	-0.03 ± 0.06	0.58	0.06 ± 0.07	0.41	-0.006 ± 0.004	0.13		
rs2314339	NR1D1	T/C	18,404	0.007 ± 0.02	0.64	0.015 ± 0.01	0.19§	-0.14 ± 0.08	0.10	0.03 ± 0.11	0.78	0.002 ± 0.006	0.79		
<b>Short (&lt;7 h)</b>															
rs1801260	CLOCK	C/T	2,158	-0.010 ± 0.03	0.70§	0.005 ± 0.23	0.82	-0.06 ± 0.19	0.60	-0.11 ± 0.23	0.65	-0.008 ± 0.01	0.57		
rs11605924	CRY2	A/C	3,294	-0.002 ± 0.02	0.92§	0.006 ± 0.01	0.66§	0.02 ± 0.12	0.89§	-0.08 ± 0.15	0.58	0.010 ± 0.01	0.15		
rs1387153	MTNR1B	T/C	2,158	0.010 ± 0.02	0.49	-0.001 ± 0.01	0.92§	<b>0.25 ± 0.12</b>	<b>0.04</b>	-0.23 ± 0.15	0.13	0.005 ± 0.01	0.62		
rs10830963	MTNR1B	G/C	3,525	0.020 ± 0.02	0.38§	0.020 ± 0.02	0.13§	-0.08 ± 0.15	0.18§	-0.11 ± 0.18	0.53	-0.005 ± 0.01	0.62		
rs2314339	NR1D1	T/C	3,525	0.0004 ± 0.04	0.88	-0.030 ± 0.03	0.26	0.45 ± 0.23	0.05	0.35 ± 0.28	0.22	-0.003 ± 0.02	0.86		
<b>Long (<math>\geq 9</math> h)</b>															
rs1801260	CLOCK	C/T	522	-0.006 ± 0.04	0.89	-0.030 ± 0.04	0.48	0.14 ± 0.31	0.65	-0.30 ± 0.41	0.47	-0.020 ± 0.02	0.45		
rs11605924	CRY2	A/C	906	0.002 ± 0.03	0.95	0.010 ± 0.02	0.68	0.27 ± 0.21	0.19	-0.03 ± 0.27	0.92	-0.010 ± 0.02	0.21		
rs1387153	MTNR1B	T/C	522	0.020 ± 0.03	0.54	0.010 ± 0.02	0.70	<b>0.60 ± 0.20</b>	<b>0.003</b>	-0.40 ± 0.25	0.10§	0.010 ± 0.03	0.57		
rs10830963	MTNR1B	G/C	961	0.008 ± 0.03	0.79	0.030 ± 0.03	0.30	-0.20 ± 0.24	0.42§	0.20 ± 0.30	0.50§	-0.020 ± 0.02	0.64		
rs2314339	NR1D1	T/C	961	0.070 ± 0.06	0.49	-0.040 ± 0.05	0.50§	0.44 ± 0.40	0.28	0.58 ± 0.50	0.25	0.010 ± 0.02	0.83		

\*Additive allele mode, adjusted for age, sex, BMI (except when assessing BMI outcome), study site (in CHS; InCHIANTI; MESA), family or population structure (in Corogene Controls; DILGOM; FOS; MESA; YFS), and genotype batch (in FamHS). Interaction coefficients are shown as  $\beta \pm SE$ .  $\beta$  represents the direction and magnitude of the change in outcome trait with each additive minor allele, per each additional hour of sleep or compared with the reference sleep group ( $\geq 7$  to  $< 9$  h). Boldface type indicates nominally significant values ( $P < 0.05$ ). †Alleles presented as effect/non-effect alleles. ‡The number of independent observations in each interaction analysis. Exact numbers of observations vary depending on availability of phenotype and genotype information and are presented in Supplementary Table 8. § $r^2 > 30\%$ , where  $r^2$  represents the heterogeneity statistic presented as percent. Exact  $r^2$  is presented in Supplementary Table 8.

duration (<7 h) and higher FG supports previously reported associations in single cohorts (28) and supports previously reported associations between short sleep duration and type 2 diabetes (7). As such, lifestyle recommendations should include dietary modifications related to higher CHO and lower fat composition and achieving normal sleep durations ( $\geq 7$  to <9 h).

Our evaluation of gene-environment interactions suggest novel putative interactions that fell short of our Bonferroni-corrected cut point but are supported by biological plausibility and may be important for understanding the etiology of type 2 diabetes. The strongest nominal interaction for glycemic traits was an interaction of CHO intake and the *MTNR1B*-rs1387153 variant on FG, which suggests that every 1% increase in CHO intake exacerbates the FG-raising effect of the T allele that interacts similarly with CHO as another clock variant in *CRY1* (5). Along with other nominal interactions observed for *MTNR1B*-rs1387153, these findings suggest lower CHO and higher MUFA intakes for lower FG among those with the effect T allele. The high frequency of the effect T allele among individuals of European descent (minor allele frequency = 0.28) and the consistency of the rs1387153-FG association across different ethnicities (29) warrant further investigation of this interaction and examination of the potential role of CHO quality in the FG-raising effect of the T allele. These nominal findings, in conjunction with confirmed associations between two common *MTNR1B* variants and FG of effect sizes similar to those reported earlier (18,30), indicate that continuing efforts to identify lifestyle modifications that offset this genetic risk should remain an important area of active research. Consistent with previous findings, no interactions were evident between sleep duration and the selected variants on glycemic traits (7).

Our previous work suggests that variants identified through GWAS or candidate gene association studies for type 2 diabetes may show gene-environment interactions for related metabolic traits beyond glycemic traits (3). We identified three nominal interactions that are supported by previous reports and biological plausibility. The first is a nominal interaction between SFA intake and *NR1D1*-rs2314339 on BMI. The obesity-

associated *NR1D1* gene encodes the nuclear receptor rev-erb- $\alpha$ , which plays a critical role in metabolism and was reported to respond to dietary MUFA for the outcome of BMI (21,31,32). The second is a nominal interaction between FG-associated *CRY2*-rs11605924 and sleep duration for HDL-C. We observed a positive association between HDL-C and sleep only when considered in the context of *CRY2*, a clock gene that inhibits *CLOCK:BMAL1*-mediated transcription of genes involved in lipid metabolism (33). Supporting the circadian control of HDL-C are results from the Global Lipids Genetics Consortium GWAS for HDL-C for this *CRY2* variant ( $\beta \pm SE = 0.0004 \pm 0.0001$  mmol/L per additional A allele,  $P < 0.001$ ) (34), which suggest marginal associations between *CRY2* and HDL-C (Supplementary Fig. 4). The *CRY2* variant is in linkage disequilibrium with rs6843722 ( $r^2 = 1.00$  in the 1000 Genomes Project data set), a *CRY2* intronic variant that was shown to abolish the upregulation of *CRY2* expression in human peripheral blood mononuclear cells after sleep restriction and has functional evidence to affect transcriptional regulation of CCCTC-binding factor and glucocorticoid receptor, two transcription factors associated with HDL-C (35–37). Therefore, it is possible that short sleep duration results in differences in *CRY2* expression, influencing *CRY2* control of downstream pathways, namely HDL-C. Finally, we observed nominal interactions between short and long sleep duration, both of which are associated with higher BMI, and *MTNR1B*-rs1387153 on BMI, suggesting even higher BMI with short and long sleep duration among carriers of the effect T allele. This interaction provides additional support for the potential role of sleep duration in modifying the associations between circadian-related genetic variants and cardiometabolic outcomes (38) and the importance of normal sleep duration ( $\geq 7$  to <9 h) for optimal health.

The strengths of the present observational study from 15 cohorts include a large sample size necessary to detect gene-environment interactions. Our collaborative approach enabled us to standardize our analytic approach across cohorts, and despite the wide range of cohorts included in the study, we observed little evidence of heterogeneity

in our overall analysis. However the present investigation also has limitations. The reported findings are limited to individuals of European descent, and exploring the interaction in other populations is warranted considering replication of the SNP associations in different ethnicities (29,39).

Our use of self-reported dietary intake and sleep duration was susceptible to reporting bias, and the use of different assessment tools across cohorts could have increased measurement error, biasing our results toward the null (40). In addition, we failed to replicate a previously reported significant association between *CRY2* variant and FG, although we observed an effect size similar to that of the discovery GWAS of up to 46,000 individuals (18); it is possible our sample size was too small to replicate the significant associations. Although we have selected circadian-related gene variants showing strong associations with metabolic traits from GWAS and candidate-gene studies, it is possible that interactions might be observable for other circadian-related variants.

Lastly, these cross-sectional meta-analyses of observational studies can only lead us toward hypotheses rather than demonstrate the temporal relationships or causal pathways linking clock genes, diet, or sleep, with glycemic, anthropometric, and lipid traits. Other studies are required to establish these mechanistic links, including studies of genetic modification of the effects of experimental changes in diet composition or sleep duration.

Our findings contribute to the understanding of how lifestyle can reduce the risk of type 2 diabetes and cardiometabolic disorders in genetically susceptible individuals. Results from the present large observational study from 15 cohorts suggest the potential presence of selected common circadian-related gene-environment interactions on metabolic traits. The nominal interaction between CHO intake and the *MTNR1B* variant on FG, suggesting that CHO intake could exacerbate the FG-raising effects of this well-studied *MTNR1B* variant, the evidence supporting the role for *CRY2* in HDL-C control and its responsiveness to sleep duration, and the interaction between long sleep duration and *MTNR1B* variant on BMI,



suggesting that the association between long sleep duration and higher BMI is exacerbated among carriers of the *MTNR1B* variant, are interesting and merit further study. Mechanistic examinations of the novel nominal interactions and further investigations in larger cohorts are necessary before personalized recommendations are framed for individuals at genetic risk for metabolic disruption. Moreover, the observed associations between diet—specifically, higher CHO and lower fat composition—and normal sleep duration ( $\geq 7$  to  $< 9$  h) on glycemic traits—particularly FG—suggest that emphasis should be placed on these modifiable lifestyle factors to offset the growing prevalence of type 2 diabetes and cardiovascular disease.

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