

Habitual sleep duration is associated with BMI and macronutrient intake and may be modified by *CLOCK* genetic variants^{1–5}

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ABSTRACT

Background: Short sleep duration has been associated with greater risks of obesity, hypertension, diabetes, and cardiovascular disease. Also, common genetic variants in the human Circadian Locomotor Output Cycles Kaput (*CLOCK*) show associations with ghrelin and total energy intake.

Objectives: We examined associations between habitual sleep duration, body mass index (BMI), and macronutrient intake and assessed whether *CLOCK* variants modify these associations.

Design: We conducted inverse-variance weighted, fixed-effect meta-analyses of results of adjusted associations of sleep duration and BMI and macronutrient intake as percentages of total energy as well as interactions with *CLOCK* variants from 9 cohort studies including up to 14,906 participants of European descent from the Cohorts for Heart and Aging Research in Genomic Epidemiology Consortium.

Results: We observed a significant association between sleep duration and lower BMI ($\beta \pm SE = 0.16 \pm 0.04$, $P < 0.0001$) in the overall sample; however, associations between sleep duration and relative macronutrient intake were evident in age- and sex-stratified analyses only. We observed a significant association between sleep duration and lower saturated fatty acid intake in younger (aged 20–64 y) adults (men: $0.11 \pm 0.06\%$, $P = 0.03$; women: $0.10 \pm 0.05\%$, $P = 0.04$) and with lower carbohydrate ($-0.31 \pm 0.12\%$, $P < 0.01$), higher total fat ($0.18 \pm 0.09\%$, $P = 0.05$), and higher PUFA ($0.05 \pm 0.02\%$, $P = 0.02$) intakes in older (aged 65–80 y) women. In addition, the following 2 nominally significant interactions were observed: between sleep duration and rs12649507 on PUFA intake and between sleep duration and rs6858749 on protein intake.

Conclusions: Our results indicate that longer habitual sleep duration is associated with lower BMI and age- and sex-specific favorable dietary behaviors. Differences in the relative intake of specific macronutrients associated with short sleep duration could, at least in part, explain previously reported associations between short sleep duration and chronic metabolic abnormalities. In addition, the influence of obesity-associated *CLOCK* variants on the association between sleep duration and macronutrient intake suggests that longer habitual sleep duration could ameliorate the genetic predisposition to obesity via a favorable dietary profile. Trials related to this study were registered

at clinicaltrials.gov as NCT00005133 (Cardiovascular Health Study), NCT00005121 (Framingham Offspring Study), NCT01331512 [Invecchiare in Chianti (Aging in the Chianti Area) study], NCT00289237 (Inter99), and NCT00005487 (Multi-Ethnic Study of Atherosclerosis). *Am J Clin Nutr* 2015;101:135–43.

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INTRODUCTION

In 2013, approximately one-third of U.S. workers reported sleep duration ≤ 6 h/night and fewer than 21% of U.S. adults met NIH recommendation of 7–8 h sleep/night (1). The increasing prevalence of short sleep duration raises public health concerns related to both safety and health (2). Short sleep duration has been associated with greater risk of obesity (3), hypertension (4), diabetes (5), cardiovascular disease (6), and all-cause mortality (7). Because cardiometabolic conditions have strong nutritional determinants, links between insufficient sleep and metabolic disruption could be mechanistically mediated through changes in dietary intake.

Studies of experimental sleep restriction showed unfavorable impacts on the appetite-related hormones ghrelin and leptin and on hunger, total energy intake, and weight (8, 9). In short-term, crossover, inpatient trials in adults, sleep restriction was asso-

ciated with increased energy intake (10, 11), increased total fat (11), and SFA (10) intakes and excess consumption of carbohydrate-rich snacks (12). However, habitual sleep duration assesses long-term sleep patterns, which may affect risk for chronic diseases. Self-reported habitual short sleep duration is associated with elevated ghrelin and decreased leptin concentrations in the general population (13), and a recent cross-sectional analysis reported higher energy intake in individuals with self-reported short sleep duration (14). Whether chronic metabolic abnormalities associated with short sleep duration result from differences in relative intakes of macronutrients in addition to reported higher energy intake is not known.

In addition to sleep, the circadian system, which is comprised of transcription factors including Circadian Locomotor Output

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³Any opinions, findings, conclusions, or recommendations expressed in this publication are those of the authors and do not necessarily reflect the views of the USDA.

⁴Supplemental Tables 1–9 and Supplemental Figure 1 are available from the “Supplemental data” link in the online posting of the article and from the same link in the online table of contents at <http://ajcn.nutrition.org>.

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⁶Abbreviations used: CHARGE, Cohorts for Heart and Aging Research in Genomic Epidemiology; *CLOCK*, Circadian Locomotor Output Cycles Kaput; InCHIANTI, Invecchiare in Chianti (Aging in the Chianti Area); SNP, single nucleotide polymorphism; tSNP, tagging single nucleotide polymorphism.

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Cycles Kaput (*CLOCK*)⁶ and governs the sleep-wake cycle, also influences diet through changes in appetite mediated by endocrine hormones such as leptin, ghrelin, and insulin (15). Common genetic variants in the human *CLOCK* show associations with ghrelin (16), whereas other *CLOCK* variants situated in the 3'-untranslated region show associations with total energy intake (17). These observations are in line with genome-wide association studies that identified 3 *CLOCK* variants rs4864548, rs3736544, and rs1801260 to be associated with obesity and metabolic syndrome (18). Observed differences in appetite-related endocrine hormones and total energy intake related to *CLOCK* variants suggest that *CLOCK* could modify associations between habitual sleep duration and dietary intake.

We hypothesized that habitual short sleep duration is associated with macronutrient composition, specifically with diets higher in relative carbohydrate and SFAs and lower in PUFAs and MUFAs. On the basis of the influence of *CLOCK* on appetite and total energy intake, we further hypothesized that *CLOCK* variants modify the association between habitual short sleep duration and relative macronutrient intake. These hypotheses were tested in large cross-sectional meta-analyses of population-based cohorts from the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium.

SUBJECTS AND METHODS

Cohorts

The cross-sectional meta-analyses included up to 14,906 participants of European descent from the following 9 cohort studies of the CHARGE Consortium Nutrition Working Group (**Supplemental Table 1**): Corogene Controls, the Cardiovascular Health Study (CHS), the Framingham Offspring Study (FOS); the Helsinki Birth Cohort Study (HBCS), Invecchiare in Chianti (aging in the Chianti area, InCHIANTI), Inter99, Multi-Ethnic Study of Atherosclerosis (MESA), The Hellenic Study of Interactions between SNPs and Eating in Atherosclerosis Susceptibility (THISEAS), and the Cardiovascular Disease Risk in Young Finns Study (YFS). Participants provided written informed consent, and the protocol was approved by local institutional review boards and oversight committees.

Dietary assessment and BMI

Habitual dietary intake data were collected via validated food-frequency questionnaires (**Supplemental Table 2**) (19–24). The type of food-frequency questionnaire used in each cohort differed slightly to capture the dietary habits of the population of interest. The current analysis focused on intake as percentages of total energy of protein, carbohydrate, and total fat. In addition, we examined PUFA, MUFA, and SFA intakes as percentages of total energy. Cohort-specific assessment methods for BMI are provided in **Supplemental Table 3**.

Sleep

Data on habitual weekday/workday nighttime sleep duration in hours 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 (**Supplemental Table 3**). Responses were analyzed as

continuous variables. Participants within each cohort were excluded from the analysis if they were shift workers, on a sleep or depression medication, reported bedtimes after 0500 or before 1800, or reported sleep duration ≤ 3 or ≥ 16 h/night.

Genotyping

We selected 9 tagging single nucleotide polymorphisms (tSNPs) that capture variations for *CLOCK* gene and flanking regulatory regions (± 20 kb) by using the web-based service of the Tagger option (aggressive tagging approach) within Haploview software (version 4.2; Broad Institute) (25) with variables on the basis of the Caucasian European Utah analysis panel (HapMap III release 2) with a minor allele frequency ≥ 0.10 and $r^2 \geq 0.80$. Selected tSNPs and single nucleotide polymorphisms (SNPs) in linkage disequilibrium ($r^2 \geq 0.80$) were previously directly genotyped or imputed by participating cohorts before inclusion in this analysis (**Supplemental Table 4**). Not all SNPs were available in all participating cohorts (**Supplemental Table 5**), and as a result, total sample sizes for analyses varied accordingly.

Cohort-specific analyses

All participating cohort-specific statistical analyses followed a uniform analysis plan. First, main associations between sleep duration and BMI were estimated by using linear regression models with adjustment for age, sex, and, when relevant, study site. Main associations between sleep duration and relative dietary intake were estimated similarly with adjustment for age, sex, BMI, and, when relevant, study site. Because sex and age have been reported to modify the association of sleep duration with BMI and total energy intake (11, 26, 27), associations were further explored in stratified age [20–64 y (younger) compared with 65–80 y (older)] and sex groups. Second, main associations between *CLOCK* tSNPs and dietary intake were investigated by using linear fixed-effect regression models or linear mixed-effects models for cohorts with family data in an additive genetic model adjusted for age, sex, BMI, and, when relevant, study site and family or population substructure. Third, the sleep duration \times tSNP effect modification on dietary intake was investigated by including an interaction term in a model adjusted for the aforementioned covariates.

Meta-analyses

We conducted inverse-variance weighted, fixed-effect meta-analyses by using the METAL program (version released 25 March 2011; University of Michigan, Center for Statistical Genetics) (28) for 1) main associations of sleep duration on both BMI and macronutrient intake, 2) main associations of tSNPs on macronutrient intake, and 3) interactions between tSNPs and sleep duration on macronutrient intake.

The heterogeneity across studies was tested by using Cochran's Q statistic and quantified by using the I^2 statistic (29). To assess potential sources of heterogeneity, we conducted a meta-regression of all association and interaction analyses with moderate heterogeneity ($I^2 > 30\%$) to assess the impact of moderator variables on heterogeneity by using the R metafor package (version 1.9-4; Maastricht University) (30). Meta-regression moderators considered included geographic location (United States compared with northern Europe compared with Mediterranean),

TABLE 1
General characteristics of participants by cohort¹

	Corogene Controls	CHS	FOS	HBCS	InCHIANTI	Inter99	MESA	THISEAS	YFS
Characteristics									
<i>n</i>	571	1322	898	1184	912	6514	1670	420	1415
Age, y	53.4 ± 13.5 ²	70.8 ± 3.8	57.7 ± 9.1	69.0 ± 2.9	64.4 ± 14.2	46.2 ± 7.9	65.1 ± 8.8	58.4 ± 12.4	37.8 ± 5.1
Female, %	50.1	62.5	53.3	60.6	53.5	51.4	51.6	39.0	53.6
BMI, kg/m ²	26.7 ± 4.5	26.6 ± 4.2	28.1 ± 5.2	27.5 ± 4.6	27.3 ± 4.2	26.3 ± 4.6	27.8 ± 5.1	28.3 ± 4.5	26.6 ± 4.4
Waist circumference, cm	90.2 ± 13.1	93.3 ± 12.5	97.5 ± 13.6	94.4 ± 13.0	91.5 ± 11.2	86.7 ± 13.4	98.2 ± 14.5	96.5 ± 13.4	87.8 ± 13.0
Sleep duration, ³ h	7.2 ± 1	7.3 ± 1.3	7.1 ± 1.1	7.4 ± 1.1	6.8 ± 1.4	7.3 ± 0.9	7.1 ± 1.1	7.1 ± 1.5	7.4 ± 0.8
Dietary intake									
Total energy, kcal/d	2314 ± 793	2007 ± 610	1854 ± 610	2212 ± 807	2066 ± 603	2330 ± 870	1612 ± 714	2172 ± 1057	2396 ± 772
Total fat, % of total energy	31.0 ± 4.9	32.0 ± 6.1	29.5 ± 6.5	33.4 ± 5.3	31.1 ± 5.2	32.7 ± 7.1	32.1 ± 7.3	35.7 ± 6.0	32.9 ± 4.9
PUFA, % of total energy	5.5 ± 1.1	7.5 ± 2.2	5.7 ± 1.6	5.3 ± 1.3	3.4 ± 0.7	5.3 ± 1.5	6.3 ± 1.8	5.2 ± 1.5	5.3 ± 1.1
MUFA, % of total energy	11.1 ± 2.2	11.5 ± 2.4	11.0 ± 2.6	11.1 ± 2.1	15.7 ± 3.1	10.5 ± 2.7	12.3 ± 3.0	15.7 ± 3.4	11.1 ± 2.0
SFA, % of total energy	11.2 ± 2.4	10.1 ± 2.2	10.1 ± 2.8	12.1 ± 2.6	10.4 ± 2.2	12.3 ± 3.5	10.8 ± 3.4	11.9 ± 3.3	11.8 ± 2.3
Carbohydrate, % of total energy	48.3 ± 6.3	52.1 ± 8.0	51.3 ± 8.3	47.0 ± 6.5	51.3 ± 6.7	47.5 ± 7.9	50.6 ± 9.1	45.0 ± 8.6	44.8 ± 5.8
Protein, % of total energy	17.6 ± 2.6	19.5 ± 3.0	17.2 ± 3.2	17.1 ± 2.5	15.7 ± 2.2	15.1 ± 2.6	15.7 ± 3.4	18.3 ± 3.6	17.5 ± 2.4
Caffeine, mg/d	NA	165.1 ± 177	258.7 ± 207	NA	170.0 ± 143	NA	265.2 ± 232	88.1 ± 53.0	473.9 ± 261

¹Cohort study countries are as follows: Corogene Controls, Finland; CHS, United States; FOS, United States; HBCS, Finland; InCHIANTI, Italy; Inter99, Denmark; MESA, United States; THISEAS, Greece; YFS, Finland. CHS, Cardiovascular Health Study; FOS, Framingham Offspring Study; HBCS, Helsinki Birth Cohort Study; InCHIANTI, Invecchiare in Chianti (Aging in the Chianti Area); MESA, Multi-Ethnic Study of Atherosclerosis; NA, not available; SNP, single nucleotide polymorphism; THISEAS, The Hellenic Study of Interactions between SNPs and Eating in Atherosclerosis Susceptibility; YFS, Cardiovascular Disease Risk in Young Finns Study.

²Mean ± SD (all such values).

³Sleep duration was defined as weekday/workday self-reported sleep duration as usual hours of sleep per night.

mean age of cohort (20–64 compared with 65–80 y), and total energy intake (<2000 compared with ≥2000 kcal/d). In addition, we conducted sensitivity analyses to assess the influence on the meta-analyzed estimate of any single cohort study by repeating analyses with the removal of one cohort study at a time in both association and interaction analyses. Statistical significance was defined at $\alpha = 0.002$ on the basis of Bonferroni correction for 27 total independent interaction tests (3 independent macronutrients \times 9 independent tSNPs).

RESULTS

General characteristics of participants are shown in **Table 1**. Average habitual sleep duration was consistent in the 9 cohorts and remained similar when stratified by sex and age group [20–64 y (younger) compared with 65–80 y (older)] (**Supplemental Figure 1**). In older adults, however, we observed that women had lower sleep duration than that of men ($P < 0.0001$). Mean dietary intakes were not significantly different across studies and differed only for MUFA intake; the Mediterranean cohorts (InCHIANTI and THISEAS) had higher mean MUFA intakes than northern European and U.S. cohorts ($P < 0.0001$).

Associations of sleep duration with BMI and macronutrient intake

After adjustment for age, sex, and study site, we identified a significant association between sleep duration and BMI (**Table 2, Supplemental Table 6**). Each additional hour of sleep was associated with 0.16 lower BMI ($\beta \pm SE = -0.16 \pm 0.04$, $P < 0.0001$). In sex-stratified analyses, the magnitude of this association was approximately twice as great in men as women and was significant in men only with slight differences by age group; each additional hour of sleep was associated with 0.23 ± 0.07 lower BMI ($P < 0.001$) and 0.19 ± 0.07 lower BMI ($P < 0.01$) in younger and older men, respectively.

There were no significant associations between sleep duration and relative macronutrient intake adjusted for age, sex, BMI, and study site in the overall sample. However, associations between sleep duration and intake were evident in age- and sex-stratified analyses (Table 2). We observed a significant association between sleep duration and SFA intake in younger adults whereby, per each additional hour of sleep, SFA intake was $0.11 \pm 0.06\%$ ($P = 0.03$) and $0.10 \pm 0.05\%$ ($P = 0.04$) lower in younger men and women, respectively. In addition, in older women, each additional hour of sleep was associated with $-0.31 \pm 0.12\%$ ($P < 0.01$), $0.18 \pm 0.09\%$ ($P = 0.05$), and $0.05 \pm 0.02\%$ ($P = 0.02$) differences in percentages of energy from carbohydrate, total fat, and PUFAs, respectively. Results from both meta-regressions and sensitivity analyses did not substantively affect these results or reveal any clear sources of heterogeneity between sleep duration and BMI and dietary intake (results not shown).

Associations of CLOCK variants with macronutrient intake

Meta-analyzed estimates of SNP associations with macronutrient intake are presented in **Table 3**. No associations met the prespecified Bonferroni-corrected significance level of $P < 0.002$. A nominally significant (i.e., $P < 0.05$) association with rs10462028 ($\beta \pm SE = -0.07 \pm 0.03\%$ per additional C allele,

TABLE 2
Meta-analyzed associations between sleep duration, BMI, and macronutrient intake and stratified by age and sex¹

Participants	N ²	BMI, kg/m ²			PUFA, % of total energy			MUFA, % of total energy			SFA, % of total energy			Total fat, % of total energy			Total carbohydrate, % of total energy			Total protein, % of total energy		
		$\beta \pm SE$	P	I ²	$\beta \pm SE$	P	I ²	$\beta \pm SE$	P	I ²	$\beta \pm SE$	P	I ²	$\beta \pm SE$	P	I ²	$\beta \pm SE$	P	I ²	$\beta \pm SE$	P	I ²
All	14,906	-0.16 \pm 0.04	2.06×10^{-5}		0.01 \pm 0.01	0.37*		0.01 \pm 0.02	0.54*		-0.02 \pm 0.02	0.40*		0.02 \pm 0.05	0.99*		-0.07 \pm 0.06	0.23*		0.001 \pm 0.02	0.96	
M, aged 20–64 y	5022	-0.23 \pm 0.07	0.0007		-0.01 \pm 0.02	0.64		-0.05 \pm 0.04	0.30		-0.11 \pm 0.05	0.03		-0.17 \pm 0.11	0.11		0.08 \pm 0.12	0.52		-0.04 \pm 0.05	0.32	
F, aged 20–64 y	5297	-0.10 \pm 0.08	0.26*		0.01 \pm 0.02	0.83*		0.01 \pm 0.04	0.88*		-0.10 \pm 0.05	0.04		-0.09 \pm 0.10	0.38		0.04 \pm 0.12	0.76		-0.03 \pm 0.05	0.54	
M, aged 65–80 y	1958	-0.19 \pm 0.07	0.005		-0.02 \pm 0.02	0.42		0.03 \pm 0.05	0.60*		0.03 \pm 0.05	0.47		0.02 \pm 0.10	0.85*		-0.13 \pm 0.14	0.36		0.01 \pm 0.05	0.80	
F, aged 65–80 y	2629	-0.11 \pm 0.08	0.16		0.05 \pm 0.04	0.20*		0.05 \pm 0.04	0.20*		0.05 \pm 0.04	0.20*		0.18 \pm 0.09	0.05*		-0.31 \pm 0.12	0.007		0.07 \pm 0.04	0.09	

¹Adjusted for age, sex, BMI (except for BMI outcome), and study site (in the CHS, InCHIANTI, and MESA). Sleep duration defined as weekday/workday self-reported sleep duration as usual hours of sleep per night. Association coefficients are shown as β s \pm SEs. β represents the change in BMI (in kg/m²) or macronutrient intake (percentage of total energy) per each additional hour of sleep. Heterogeneity statistics (I²) are presented in Supplemental Table 6. *I² > 30%. CHS, Cardiovascular Health Study; InCHIANTI, Invecchiare in Chianti (Aging in the Chianti Area); MESA, Multi-Ethnic Study of Atherosclerosis.

²Number of independent observations in each association analysis.

TABLE 3
Meta-analyzed associations between SNPs and macronutrient intake¹

SNP	Alleles, minor/major	Position	Location	Minor allele frequency	N ²	PUFA, % of total energy		MUFA, % of total energy		SFA, % of total energy		Total fat, % of total energy		Total carbohydrate, % of total energy		Total protein, % of total energy	
						$\beta \pm SE$	P	$\beta \pm SE$	P	$\beta \pm SE$	P	$\beta \pm SE$	P	$\beta \pm SE$	P	$\beta \pm SE$	P
rs504836	C/T	55980062	Intronic ³	0.26	7417	-0.002 ± 0.03	0.96	0.01 ± 0.06	0.92*	0.01 ± 0.05	0.93	0.06 ± 0.13	0.63	0.17 ± 0.15	0.25*	0.13 ± 0.06	0.04*
rs6858749	T/C	55985194	Intronic ³	0.41	8316	0.02 ± 0.02	0.43	0.02 ± 0.04	0.63	0.003 ± 0.04	0.95	0.09 ± 0.095	0.33	0.05 ± 0.11	0.62*	0.06 ± 0.05	0.18*
rs1047354	G/A	55990340	Intergenic	0.34	14,274	-0.03 ± 0.02	0.15	-0.003 ± 0.03	0.92	0.01 ± 0.04	0.84	-0.03 ± 0.08	0.71	0.08 ± 0.09	0.38	0.12 ± 0.03	0.0002** ⁴
rs10462028	G/A	55993057	Downstream	0.34	14,305	-0.02 ± 0.02	0.25** ⁵	-0.07 ± 0.03	0.05	-0.02 ± 0.04	0.64	-0.12 ± 0.08	0.13	0.09 ± 0.09	0.34	0.02 ± 0.04	0.69
rs1801260	C/T	55996126	3'UTR	0.31	8316	0.02 ± 0.02	0.34	0.04 ± 0.04	0.33	0.03 ± 0.04	0.54	0.10 ± 0.11	0.33	-0.09 ± 0.11	0.41	0.09 ± 0.05	0.85
rs3792603	G/A	55996815	Intronic	0.18	8313	0.002 ± 0.03	0.93	-0.02 ± 0.06	0.78	0.01 ± 0.06	0.86	0.02 ± 0.12	0.88	-0.10 ± 0.14	0.47	-0.10 ± 0.06	0.09
rs11932595	C/T	56018354	Intronic	0.36	7007	0.01 ± 0.02	0.79*	0.003 ± 0.05	0.95	-0.01 ± 0.05	0.90	0.08 ± 0.11	0.50	-0.17 ± 0.14	0.22	-0.04 ± 0.05	0.51
rs12649507	A/G	56075241	Intronic	0.17	7748	-0.03 ± 0.02	0.16	-0.02 ± 0.05	0.66	0.02 ± 0.05	0.71	-0.03 ± 0.11	0.80	-0.04 ± 0.12	0.74	-0.03 ± 0.05	0.62*
rs11726609	A/T	56095626	Intronic	0.38	14,215	-0.001 ± 0.02	0.97*	-0.06 ± 0.03	0.09	-0.03 ± 0.04	0.49	-0.11 ± 0.08	0.19	0.06 ± 0.09	0.54	0.03 ± 0.04	0.47

¹Additive allele model was adjusted for age, sex, BMI, study site (in the CHS, InCHIANTI, and MESA) and family or population structure (in the Corogene Controls, FOS, and MESA). Association coefficients are shown as β ± SEs. β represents the change in macronutrient intake (percentage of total energy) per each additional minor allele. Prespecified Bonferroni-corrected significance level of $P < 0.002$. Heterogeneity statistics (I^2) are presented in Supplemental Table 8. * $I^2 > 30\%$. CHS, Cardiovascular Health Study; FOS, Framingham Offspring Study; HBCS, Helsinki Birth Cohort study; InCHIANTI, Invecchiare in Chianti (Aging in the Chianti Area); MESA, Multi-Ethnic Study of Atherosclerosis; SNP, single nucleotide polymorphism; 3'UTR, 3'-untranslated region.

²Number of independent observations in each association analysis. Exact numbers of observations varied for each outcome and are presented in Supplemental Table 8.

³Transmembrane protein 165, *TMEM165*.

⁴Sensitivity analysis (removal of the HBCS); $\beta \pm SE = 0.03 \pm 0.03\%$, $P = 0.46$, $I^2 = 52\%$.

⁵Sensitivity analysis (removal of the InCHIANTI); $\beta \pm SE = -0.05 \pm 0.02\%$, $P = 0.03$, $I^2 = 23\%$.

$P = 0.05$), and percentage of energy from protein at rs504836 ($\beta \pm SE = 0.13 \pm 0.06\%$ per additional C allele, $P = 0.04$). Although overall meta-analyzed estimates of SNP associations show little evidence of heterogeneity (Supplemental Table 7), results of the meta-regression revealed that geographic location ($P < 0.05$) might be a source of heterogeneity for several of the associations between tSNPs and PUFAs; these subgroup meta-analyzed estimates by geographic location (United States compared with northern Europe compared with Mediterranean) are presented in Supplemental Table 8. Sensitivity analyses showed that the association for rs1047354 with protein ($I^2 = 96\%$) was driven by one cohort (HBCS); the removal of the cohort from the meta-analysis resulted in a weaker and non-significant association ($\beta \pm SE = 0.03 \pm 0.03\%$ per additional G allele, $P = 0.46$, $I^2 = 52\%$). Sensitivity analyses also altered the association of rs10462028 with PUFA such that the association became nominally significant when the outlying cohort (InCHIANTI) was excluded ($\beta \pm SE = -0.05 \pm 0.02\%$ per additional C allele, $P = 0.03$, $I^2 = 23\%$).

Sleep duration × CLOCK variants on macronutrient intake

Meta-analyzed estimates of interactions between sleep duration and tSNPs on macronutrient intake are presented in Table 4. There were no significant interactions evident on intake after correction for multiple testing (i.e., at corrected $P < 0.002$). The following 2 nominally significant interactions were observed: 1) between sleep duration and rs12649507 for PUFA ($\beta \pm SE = 0.05 \pm 0.02\%$, $P = 0.01$), which suggested higher PUFA intake with each additional hour of sleep in the presence of the minor G allele, and 2) between sleep duration and rs6858749 for energy from protein ($\beta \pm SE = -0.08 \pm 0.04\%$, $P = 0.04$), which suggested lower protein intake with each additional hour of sleep in the presence of the minor T allele. Meta-analyzed estimates of interactions showed little evidence of heterogeneity (Supplemental Table 9), and results of meta-regressions and the sensitivity analyses did not substantively affect our results or reveal any clear sources of heterogeneity (results not shown).

DISCUSSION

In meta-analyses of 9 cohorts, we showed that sleep duration was associated with BMI in the overall sample and relative macronutrient intake in specific age and sex groups. We also identified several nominal associations between CLOCK variants and intake, some of which appeared to be region specific. Finally, we observed that CLOCK variants could modify the associations between sleep duration and dietary intake; however, these results were only nominally significant.

Our large-scale, multinational assessment of habitual sleep duration and BMI was consistent with previous literature whereby adults who reported habitually longer sleep durations had significantly lower BMI than that of those with habitually shorter sleep durations (31). No associations were evident between sleep duration and relative macronutrient intake in the overall sample; however, stratified exploratory analyses indicated that associations between sleep duration and intake tended to be age- and sex-specific; longer sleep duration was associated with lower SFA intake in younger adults and higher total fat intake, primarily driven by higher PUFA intake, as well as lower

TABLE 4
Meta-analyzed interactions between sleep duration and SNPs on macronutrient intake¹

SNP	Alleles, minor/major	N ²	PUFA, % of total energy		MUFA, % of total energy		SFA, % of total energy		Total fat, % of total energy		Total carbohydrate, % of total energy		Total protein, % of total energy	
			$\beta \pm SE$	P	$\beta \pm SE$	P	$\beta \pm SE$	P	$\beta \pm SE$	P	$\beta \pm SE$	P	$\beta \pm SE$	P
rs504836	C/T	7417	-0.02 ± 0.02	0.35	-0.07 ± 0.05	0.14	0.03 ± 0.05	0.58	-0.80 ± 0.11	0.47	0.12 ± 0.12	0.32	-0.04 ± 0.05	0.44
rs658749	T/C	8316	-0.03 ± 0.02	0.12	-0.06 ± 0.08	0.08	0.02 ± 0.03	0.50	-0.09 ± 0.08	0.27	0.08 ± 0.09	0.37	-0.08 ± 0.04	0.04
rs1047354	G/A	14,274	0.03 ± 0.01	0.06	0.02 ± 0.03	0.55	-0.04 ± 0.03	0.24	0.04 ± 0.07	0.63	-0.11 ± 0.08	0.17	0.02 ± 0.03	0.59
rs10462028	G/A	14,305	0.01 ± 0.02	0.41	0.02 ± 0.03	0.54	-0.03 ± 0.04	0.41	0.03 ± 0.08	0.75	0.04 ± 0.09	0.69	-0.04 ± 0.04	0.21
rs1801260	C/T	8316	-0.01 ± 0.02	0.52	-0.04 ± 0.04	0.37	0.02 ± 0.04	0.60	-0.05 ± 0.10	0.64	0.05 ± 0.10	0.65	-0.03 ± 0.05	0.46
rs3792603	G/A	8316	-0.002 ± 0.02	0.89	0.04 ± 0.05	0.45	0.03 ± 0.05	0.60	0.09 ± 0.10	0.37	-0.14 ± 0.11	0.22	-0.05 ± 0.05	0.32
rs11932595	C/T	7007	-0.0002 ± 0.02	0.99	-0.02 ± 0.04	0.72	-0.002 ± 0.04	0.96*	-0.02 ± 0.09	0.86*	0.06 ± 0.11	0.61	-0.04 ± 0.04	0.35
rs12649507	A/G	7748	0.05 ± 0.02	0.01	0.07 ± 0.04	0.07	-0.03 ± 0.04	0.40	0.14 ± 0.09	0.12	-0.07 ± 0.09	0.45	-0.01 ± 0.04	0.88*
rs11726609	A/T	14,215	-0.03 ± 0.02	0.05*	-0.02 ± 0.03	0.53	0.02 ± 0.03	0.54*	-0.05 ± 0.08	0.53	0.11 ± 0.08	0.19	-0.03 ± 0.03	0.45

¹Additive allele model was adjusted for age, sex, BMI, study site (in the CHS, InCHIANTI, and MESA) and family or population structure (in the Corogene Controls, FOS, and MESA). Interaction coefficients are shown as β s ± SEs. β represents the direction and magnitude of the change in macronutrient intake (percentage of total energy) with each additional hour of sleep per each additional minor allele. Prespecified Bonferroni-corrected significance level of $P < 0.002$. Heterogeneity statistics (I^2) are presented in Supplemental Table 9. * $I^2 > 30\%$. CHS, Cardiovascular Health Study; FOS, Framingham Offspring Study; InCHIANTI, Invecchiare in Chianti (Aging in the Chianti Area); MESA, Multi-Ethnic Study of Atherosclerosis; SNP, single nucleotide polymorphism.

²Number of independent observations in each interaction analysis. Exact numbers of observations varied for each outcome and are presented in Supplemental Table 9.

carbohydrate intake in older women. The mechanisms that underlie these sex-specific associations were unclear but could have included sex-specific hormonal differences, differences in self-reporting behaviors (32), or differences in sleep duration between older adult men and women identified in the current study. Sex-specific associations of short sleep duration were also shown for other outcomes such as hypertension (4).

The 2010 Dietary Guidelines for Americans emphasized the cardioprotective benefits of consuming diets lower in SFAs by replacing them with MUFAs and PUFAs (33). On the basis of our observation of associations between habitual sleep duration and dietary fat intake in younger adults and older females, our findings suggest that longer sleep duration may facilitate compliance to the current recommendations for healthier eating behaviors. Together with previously reported differences in total energy intake with sleep duration (9), our results may support the hypothesis that metabolic differences associated with sleep duration can be mediated in part by differences in dietary intake, specifically differences in SFA, PUFA, and carbohydrate intakes.

For associations between *CLOCK* variants and macronutrient intake, results from both sensitivity and meta-regression analyses indicated various sources of heterogeneity. Meta-regression results indicated that geographic location could have influenced these associations, particularly between *CLOCK* and PUFA. When stratified by geographic location, meta-analyses results showed nominally significant SNP-PUFA associations. Although region-specific observations could result from mechanistically plausible effects of geographic variation on the entrainment of circadian rhythms (34), whether the SNP-diet associations are truly region specific or confounded by other factors such as differences in dietary assessment tools and dietary patterns across the meta-analyzed cohorts could not be elucidated in our analysis. Likewise, by the sequential removal of single cohorts from the meta-analyses, sensitivity analyses suggested the strong influence of single cohorts on some of these associations. Single cohort-driven results are possibly attributable to differences in intakes across cohorts as evident for the association between rs10462028 and PUFAs for which heterogeneity was substantially reduced after the removal of InCHIANTI, which was a Mediterranean cohort with the lowest PUFA intake. Overall, we report no associations between *CLOCK* variants and macronutrient composition; however, our results suggest that differences in intakes across geographic regions should be accounted for in future studies of the genetic component of dietary intake.

A potential mechanistic overlap between effects of *CLOCK* and sleep duration on dietary intake led us to investigate potential gene × sleep duration interactions. Our interaction analyses failed to identify interactions that met prespecified criteria for statistical significance. However, they did identify potentially interesting and nominally significant interactions. One of these interactions was between sleep duration and rs12649507, which is an intronic variant, that indicated that, in individuals with the minor A allele, longer sleep duration was associated with a more favorable dietary profile through greater increases in PUFA intake. The minor allele was associated with shorter sleep duration in an earlier meta-analysis (35). In addition, this variant is in linkage disequilibrium with rs6843722 ($r^2 = 1.00$ in Caucasian European Utah by using the HapMap II dataset), which is a variant previously associated with obesity

(36). Taken together, the interaction suggests that longer sleep duration could result in an increase in PUFA consumption in individuals at risk for obesity.

Our meta-analysis of data from 9 cohort studies had several strengths. To our knowledge, this was the largest observational study to investigate sleep duration with both BMI and dietary composition and the largest meta-analysis to investigate associations of *CLOCK*, as well as its interactions with sleep duration, with dietary intake. With the investigation of habitual lifestyle, including sleep and diet, our findings are potentially relevant to chronic diseases (14). Our standardized analytic plan and uniform analysis across all participating cohorts reduced errors and biases often associated with meta-analyses, including selection and publication biases. Although the associations we observed between sleep duration and BMI and dietary behavior were small in terms of the size, they were consistent in direction with those reported in single cohorts that investigated similar relations, but more importantly, they are relevant to elucidating the potential underlying biology of very complex human dietary and sleep behaviors. The small size of these associations could have also resulted from a potential U-shaped relation between sleep duration and dietary intake, which was not investigated in the current analysis. Finally, we observed, overall, little evidence of heterogeneity in our analyses despite the wide range of cohorts investigated.

The implications of our current study were limited to individuals of European descent, and additional analysis in other ethnic groups is warranted to generalize these findings. Although our analysis examined associations and interactions of a single circadian gene on dietary intake because of well-established biological pathways linking *CLOCK* to dietary intake, it is likely there are potentially important interactions elsewhere in the genome. Our use of self-reported habitual sleep duration and dietary intake was susceptible to reporting bias, and objective measures of sleep duration may be required for future studies (37). Likewise, the use of different assessment tools across cohorts could affect these findings. Although our investigation focused on nighttime sleep duration, which is a commonly surveyed sleep variable in large observational studies, the assessment of other dimensions of sleep, such as sleep quality, in addition to napping, which may have important effects on dietary intake, should also be considered (38–40). The current cross-sectional meta-analyses of observational studies could not inform us about the temporal relation or the causal pathway linking *CLOCK*, sleep, and diet. Therefore, whether sleep duration directly influenced dietary intake or indirectly moderated macronutrient effects on BMI, potentially through changes in substrate utilization, cannot be inferred from this investigation, and other studies are necessary to establish these mechanistic links.

In conclusion, given the declining trends in habitual sleep duration and rising trends in metabolic abnormalities, our findings may have public health implications by providing recommendations to individuals at risk for chronic diseases. Our results indicate that an increase in habitual sleep duration is associated with desirably lower BMI and age- and sex-specific favorable dietary behaviors. Furthermore, differences in the relative intake of specific macronutrients associated with short sleep duration could provide a partial basis for previously reported associations between short sleep duration and chronic metabolic abnormalities. In addition, the nominal evidence for the influence of an

obesity-associated *CLOCK* variant on the association between sleep duration and macronutrient intake suggests that an increase in habitual sleep duration could ameliorate a genetic predisposition to obesity via a more favorable dietary profile. The identified interaction provides preliminary findings for personalized sleep recommendations for individuals at increased genetic risk for obesity aimed at attenuating this risk, and additional exploration of these interactions in age- and sex-specific groups is warranted.

The authors' responsibilities were as follows—HSD, CES, TT, DJG, FAJLS, and JMO: designed the study; VM, TP, RNL, JL, DGH, UT, WCJ, SK, OTR, MP, BMP, LF, NG, HMH, LR, MK, ASH, DSS, KR, TJ, JIR, PD, JSAV, DM, AL, IS, TH, VS, SAG, JGE, SB, OP, SSR, GD, and TL: conducted research; HSD, JLF, TT, LK, TMB, M-MP, AJ, ACF-W, and I-PK: contributed to statistical analyses; HSD, JLF, CES, TT, BEC, SL-F, DJG, AH, PFJ, KR, RS, FAJLS, and JMO: interpreted data and wrote the manuscript; and all authors: read and approved the final version of the manuscript. None of the authors declared a conflict of interest.

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