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Behavioral Circadian Timing System Disruptors and Incident Type 2 Diabetes in a Nonshift Working Multiethnic Population

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Objective: This study aimed to describe distributions of behavioral circadian disruptors in a free-living setting among a nonshift working multiethnic population, estimate the associated risk of type 2 diabetes (T2D), and determine whether disruptors account for ethnic differences in T2D.

Methods: Participants from six ethnic groups were included (Amsterdam, the Netherlands; $n=1,347-3,077$ per group). Multinomial logistic regression was used to estimate ethnic differences in disruptors, such as skipping breakfast, eating erratically, and sleep duration. Associations between disruptors and incident T2D and the interaction by ethnicity were studied by Cox regression.

Results: Ethnic minority populations skipped breakfast more often, timed meals differently, had longer periods of fasting, ate more erratically, and had more short/long sleep durations than the Dutch. Night snacking from 4 AM to 6 AM (HR: 5.82; 95% CI: 1.42-23.91) and both short (HR: 1.48; 95% CI: 1.03-2.12) and long sleep (HR: 3.09; 95% CI: 1.54-6.22), but no other disruptors, were associated with T2D. The higher T2D risk among ethnic minority populations compared with Dutch did not decrease after adjustment for last snack or length of sleep.

Conclusions: Although prevalence of circadian disruptors was higher among ethnic minority populations and some disruptors were associated with T2D, disruptors did not account for ethnic differences in T2D risk.

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Introduction

More than 425 million people are affected by type 2 diabetes (T2D) worldwide, and this number is expected to grow to 629 million by 2045 (1). The burden of T2D differs greatly across ethnic groups (2); disparities were, for instance, observed between groups of Dutch, Ghanaian, Turkish, Moroccan, South-Asian Surinamese, and African Surinamese ethnicities living in the Netherlands (3-5). People of South Asian origin especially are at much higher risk for T2D and its complications than Europeans (5,6). Conventional risk factors, such as obesity, cannot explain the excessive burden among ethnic minority populations compared with Europeans (5,6). A potential novel risk factor that may be

involved in the high risk among ethnic minority groups living in the Netherlands is the disruption of the circadian timing system (7-10).

The circadian timing system in humans consists of a central brain clock that regulates the sleep-wake cycle, locomotor activity, and preparation for food availability as well as peripheral clocks that regulate local rhythms in most peripheral organs and tissues. The circadian rhythm generated by the central clock is entrained to the 24-hour rhythm of the outside world by light information received via a direct input from the retina. The central brain clock subsequently synchronizes the peripheral clocks in metabolic tissues, such as liver, muscle, pancreas, and adipose tissue (7-8,11-14). Recent studies have shown that disturbances of the

Study Importance

What is already known?

- ▶ Ethnic minority populations are at increased risk for type 2 diabetes compared with the Dutch.
- ▶ Disturbances of the circadian timing system increase the risk for type 2 diabetes.

What does this study add?

- ▶ Prevalence of circadian disruptors is higher among ethnic minority populations compared with the Dutch.
- ▶ Although night snacking and sleep duration were associated with type 2 diabetes across ethnic groups, circadian disruptors do not account for ethnic differences in incidence of type 2 diabetes.

How might the results change the focus of clinical practice?

- ▶ Night snacking and sleep duration may represent potential targets to prevent type 2 diabetes across populations of various ethnicities.

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circadian timing system increase the risk for T2D, most likely because of a mismatch between the timing information received by the central and peripheral clocks. Factors such as timing of meals, sleep duration, and social jetlag may have an effect on circadian rhythms in insulin sensitivity and plasma glucose levels (9-10,15-17). The negative health effects of circadian disruptors were, however, predominantly observed in animal studies, while there is a paucity of human studies, especially among different ethnicities (17). Nevertheless, the very limited evidence available has suggested that there may be a higher prevalence of circadian disruptors in ethnic minority populations compared with Europeans. For instance, short sleep (18) and low breakfast consumption (19) occurred more often in minority ethnic groups living in the Netherlands and might increase T2D risk (20,21).

Our study set out to investigate the prevalence and association of behavioral circadian disruptors, including short or long sleep duration and eating erratically, with incident T2D in a free-living environment. First, we described the prevalence of behavioral circadian disruptors among various ethnic groups. Second, we investigated the association of behavioral circadian disruptors with incident T2D. Finally, we investigated whether the higher prevalence of circadian disruptors accounted for ethnic differences in T2D risk.

Methods

Population

We used baseline data from the healthy life in an urban setting (HELIUS) study, which were collected between 2011 and 2015. HELIUS is a multiethnic cohort among six ethnic groups living in Amsterdam; a detailed description of the design is available elsewhere (22,23). In brief, participants were randomly sampled from the municipality registry and stratified by ethnicity. Full data were collected among 22,165 participants; questionnaires, physical examinations, and biological samples were obtained (23). Participants who did shift work or who had missing data on this variable were excluded ($n=4,281$ and 642 , respectively), as shift work has frequently been associated with circadian misalignment (24). Thereafter, participants with prevalent T2D ($n=2,025$) or missing T2D prevalence data ($n=75$) at baseline were excluded. From the remaining participants, 3,077 were of Dutch, 1,575 of South Asian Surinamese, 2,174 of African Surinamese, 1,347 of Ghanaian, 2,237 of Turkish, and 2,364 of Moroccan ethnicity; those from different ethnic backgrounds were excluded ($n=324$). Finally, 12,774 participants were included in the current study. HELIUS was approved by the Institutional Review Board of the Amsterdam Medical Center (MREC 10/100# 17.10.1729). All participants provided written informed consent.

Measurements

There is no existing consensus for the definitions of behavioral circadian disruptors; therefore, we *a priori* defined these ourselves based on previous literature combined with expert knowledge (25,26). Behavioral circadian disruptors selected included skipping breakfast, eating erratically, timing of the hot (largest) meal, timing of the last snack, and sleep duration; this selection was based on data availability within the HELIUS study. For timing of meals, the most prevalent category was set as the reference category. For the other variables, the category usually associated with decreased risk for T2D was set as the reference category. All variables were derived from a questionnaire filled out by participants at baseline. Participants who were unable to complete the

questionnaire themselves were offered assistance from a trained ethnically matched same-sex interviewer speaking their preferred language (23).

Variables

In the questionnaire, participants were asked to report on how many days of the week they used breakfast, as defined by anything eaten within 1.5 hours after getting up. Skipping breakfast (25) was then divided into the following categories: “never or almost never,” “regularly,” and “often.” These categories were defined as having breakfast six or seven times a week, three to five times a week, or never up to maximum two times a week, respectively.

Eating erratically (25) was categorized into three subcategories based on self-reported amount of days of the week they consumed breakfast, lunch, and dinner, respectively. Eating “not erratically” was defined as consuming two out of three meals (breakfast, lunch, dinner) 6 to 7 days a week and was set as the reference category. “Very erratically” was defined as using two out of three meals three to five times a week, while other patterns were categorized as “somewhat erratically.” If no data were available on either breakfast, lunch, or dinner consumption, the variable of eating erratically was set to missing.

Timing of the hot (largest) meal and timing of the last snack were grouped in blocks of 2 hours. Because of power, time blocks for which a reasonable number of participants reported to have their meals were compared (12-24 hours for timing hot meal; 16-6 hours for timing last snack). Data from participants who reported to have their meals or snacks in the morning were converted to evening meals because people commonly make the mistake to answer a questionnaire based on the 12-hour clock instead of the 24-hour clock; for example, someone who reported to have the hot (largest) meal at 6 hours was converted to 18 hours.

We compared short and long periods of fasting; these were considered because longer periods of fasting, also known as time-restricted feeding, may prevent T2D (25,27). A subgroup of each population was selected for these analyses. Participants were selected for the long period of fasting if they never or a maximum of once a week consumed breakfast and had their last snack of the day between 12 hours and 20 hours ($n=176$), whereas participants were selected for the short period of fasting if they always consumed breakfast and had their last snack of the day between 22 hours and 4 hours ($n=2,291$).

Sleep duration was based on self-report in the questionnaire and categorized in to “short” (≤ 7 hours/night), “intermediate” (7-9 hours/night), and “long” (>9 hours/night) sleep (18,26). Intermediate sleep was defined as the reference category.

Incident T2D cases were identified through record linkage with two health care registrations (Supporting Information). We first linked HELIUS data by Citizen Service number to the Achmea Health Database, containing reimbursement data from the Achmea insurance company with registrations from January 1, 2010, until April 30, 2016. Second, HELIUS data were linked to Vektis, a business intelligence center for health care collecting reimbursement data for all insurance companies in the Netherlands, including probabilistic linkage based on data of birth, sex, and postal code, with registrations from January 1, 2011, until December 31, 2017. We defined incident T2D as a registration of one of the considered codes in either one of the databases and not having T2D at baseline based on

self-report, medication use, glucose, or HbA1c levels. Follow-up duration was determined from inclusion date within HELIUS until the moment of data linkage or the year that a participant developed T2D.

Covariates

Ethnicity was defined by the individual's country of birth combined with the parental countries of birth (28). For the Dutch sample, we invited people who were born in the Netherlands and of whom both parents were born in the Netherlands. Non-Dutch ethnic origin was assigned to participants born abroad with at least one parent born abroad (first generation) or born in the Netherlands with both parents born abroad (second generation). After data collection, the Surinamese group was further classified according to self-reported ethnic origin into "African," "South-Asian," "Javanese," or "other."

Season was derived from the inclusion date within HELIUS and subdivided in the following categories: "spring" (March 21 to May 20), "summer" (June 21 to August 20), "autumn" (September 21 to November 20), and "winter" (December 21 to February 20).

Socioeconomic status was based on highest reported education and categorized into "never been to school or elementary schooling only," "lower vocational schooling or lower secondary schooling," "intermediate vocational schooling or intermediate/higher schooling (general)," or "higher vocational schooling or university."

Fasting plasma glucose was determined from fasting blood samples by spectrophotometry in plasma (hexokinase primary enzyme; Roche Diagnostics, Tokyo, Japan).

Information on physical activity was determined from the questionnaire. The physical activity score was derived by the Short Questionnaire to Assess Health enhancing physical activity and classified as meeting or not meeting the Dutch Healthy Physical Activity norm of 30 minutes of moderate-intensity physical activity daily (29).

Statistical analyses

First, baseline characteristics of the participants were presented for complete cases of each variable by means and SD for continuous normally distributed variables, by medians and interquartile ranges for continuous not-normally distributed variables, and by numbers of observations and percentages for categorical variables.

The prevalence of included behavioral circadian disruptors (skipping breakfast, eating erratically, timing of the hot [largest] meal, timing of the last snack, and sleep duration) was estimated for each of the disruptors, and distributions by ethnicity, sex, and age were examined. Ethnic differences were studied by multinomial logistic regression.

Cox regression was used to study the association of disruptors with incident T2D. To test whether the association between disruptors and T2D differed by ethnicity, a multiplicative interaction term between disruptors and ethnicity with T2D as the outcome was added. If an association between disruptors and incident T2D was observed, we studied whether disruptors accounted for the association between ethnicity and incident T2D. This was done by estimating the association between ethnicity and incident T2D and comparing hazard ratios (HRs) before and after adjustment for circadian disruptors in each of the models. All analyses

were adjusted for the *a priori* determined confounders' ethnicity, sex, age, season, and socioeconomic status.

As sensitivity analyses, we repeated the analyses without the adjustment for socioeconomic status; the variable was included in the models to account for residual confounding but may cause overadjustment regarding the ethnicity variable. In addition, we explored confounding by physical activity and BMI. *A priori*, we intended to explore confounding by energy intake as well, but because this variable was only available for a subcohort of the population, no valid estimates could be made.

Missing covariates were imputed by single stochastic regression, as less than 5% of the data were missing. Analyses with missing independent variables were analyzed based on complete case analyses. Additionally, we repeated all analyses after exclusion of people with cardiovascular disease at baseline. All analyses were conducted in RStudio version 0.99.903 (RStudio, Inc., Boston, Massachusetts (30)). $P < 0.05$ was considered statistically significant.

Results

More women than men were included, ranging from 56.4% women among Dutch and 66.2% among Moroccans (Table 1). The mean age ranged from 38.7 years old among Moroccans to 46.1 among Dutch. Socioeconomic status was highest among Dutch participants and lowest among Ghanaian participants; for example, 61.8% of Dutch participants obtained a higher vocational or university degree, while 6.5% of Ghanaian obtained such a degree. The median self-reported energy intake ranged from 7,974 kJ among South Asian Surinamese participants to 9,092 kJ among Turkish participants (Ghanaians not measured). Turkish participants were the least physically active (1,917 metabolic equivalent of task [MET]/week), while Dutch participants were the most active (2,730 MET/week).

Dutch skipped breakfast less often than other ethnic groups; approximately 20% of the Dutch skipped breakfast often or regularly, while a third of Turkish and Moroccan participants and half of South Asian Surinamese, African Surinamese, and Ghanaian participants skipped breakfast often or regularly (Table 2). Moreover, Dutch also had the most regular eating patterns; while 5% to 10% of the Dutch ate somewhat or very erratically, approximately one-quarter of the other ethnic groups ate somewhat or very erratically. Most of the included participants had their hot meal between 18 hours and 20 hours, ranging from 46.2% among Ghanaian participants to 82.0% among Dutch participants, while a large part of Ghanaian participants (~14%) reported to eat their hot meal between 12 hours and 16 hours. Most participants had a last snack between 20 hours and 24 hours, or, alternatively, between 18 hours and 20 hours. Distributions were similar among most ethnic groups, except for Ghanaians, who reported having their last snack of the day somewhat earlier in the evening than the other ethnic groups. Short periods of fasting were most common among Dutch (24.5%), especially compared with Ghanaians (7.0%). Intermediate sleep duration (7-9 hours per night) ranged from 25.3% among African Surinamese to 39.0% among Dutch participants. Adjustment for confounders (sex, age, season, socioeconomic status, energy intake, physical activity, and BMI) did not alter our interpretation.

During a median follow-up duration of 3 years (interquartile range, 2-4 years), 13 Dutch, 22 Ghanaian, 26 South Asian Surinamese, 30 Moroccan, 40 Turkish, and 46 South Asian Surinamese participants

TABLE 1 Baseline characteristics per ethnic group

	Total population	Dutch	South Asian Surinamese	African Surinamese	Ghanaian	Turkish	Moroccan
<i>n</i>	12,774	3,077	1,575	2,174	1,347	2,237	2,364
Male, %	61.8 (4,882)	43.6 (1,341)	38.2 (602)	36.7 (798)	34.5 (465)	39.2 (878)	33.8 (798)
Mean age, y	42.8 (13.2)	46.1 (13.8)	42.5 (13.4)	46.0 (12.7)	43.4 (11.1)	39.1 (12.0)	38.7 (12.6)
Season, %							
Autumn	28.6 (3,652)	27.5 (845)	24.0 (378)	33.2 (721)	24.4 (329)	30.1 (674)	29.8 (705)
Winter	21.3 (2,717)	21.5 (663)	21.5 (339)	18.3 (398)	27.8 (375)	15.2 (340)	25.5 (602)
Spring	24.0 (3,063)	25.0 (769)	26.5 (418)	19.5 (425)	23.4 (315)	27.3 (610)	22.3 (526)
Summer	26.2 (3,342)	26.0 (800)	27.9 (440)	29.0 (630)	24.4 (328)	27.4 (613)	22.5 (498)
Socioeconomic status, %							
Never been to school or elementary schooling only	16.9 (2,148)	3.2 (97)	11.8 (186)	4.6 (100)	30.1 (406)	30.1 (673)	29.0 (686)
Lower vocational schooling or lower secondary schooling	23.8 (3,022)	13.3 (410)	27.9 (440)	31.7 (690)	39.2 (528)	24.1 (540)	17.5 (414)
Intermediate vocational schooling or intermediate/higher secondary schooling	29.7 (3,776)	21.3 (656)	32.5 (512)	37.1 (806)	23.2 (312)	29.4 (657)	35.2 (833)
Higher vocational schooling or university	29.6 (3,754)	61.8 (1,902)	27.3 (430)	26.0 (565)	6.5 (88)	15.9 (355)	17.5 (414)
Median energy intake, kJ	8,628 (6,707-10,945)	8,830 (7,29-10,772)	7,974 (6,172-10,230)	8,757 (6,357-11,103)	-	9,092 (6,795-11,843)	8,448 (6,392-11,128)
Achieving norm for physical activity, %	56.0 (7,092)	75.0 (2,307)	49.4 (777)	58.5 (1,271)	51.7 (697)	42.2 (941)	46.6 (1,099)
Mean fasting plasma glucose	5.18 (0.50)	5.20 (0.50)	5.28 (0.51)	5.14 (0.50)	5.08 (0.49)	5.20 (0.49)	5.17 (0.50)
Incidence density T2D per 1,000 person-years	4.2 (177)	1.3 (13)	8.3 (46)	3.4 (26)	4.4 (22)	5.7 (40)	4.6 (30)
Prevalence of CVD	12.0 (1,524)	4.1 (126)	13.5 (212)	11.3 (246)	11.2 (149)	19.8 (441)	14.8 (350)

Data are mean (SD), median (interquartile range), or % (*n*).

developed T2D. No evidence for associations between skipping breakfast, eating erratically, timing of hot meal, or the period of fasting and incident T2D were observed (Figure 1). Both short and long sleep were significantly associated with a higher risk for T2D (HR 1.48, 95% CI: 1.03-2.12; and HR 3.09, 95% CI: 1.54-6.22, respectively). Night snacking (last reported snack of the day between 4 hours and 6 hours) was associated with a higher risk for T2D (HR 5.82, 95% CI: 1.42-23.91). There was no evidence of a multiplicative interaction between behavioral disruptors and ethnicity (data not shown). Ethnic minority participants were at elevated risk for T2D compared with the Dutch (HR 2.65-6.98). Timing of last snack (HR 2.52-6.49) and sleep duration (HR 2.52-6.44) did not account for the elevated risk for T2D among ethnic minority participants (Table 3). Sensitivity analyses did not alter the interpretations of our results (data not shown).

Discussion

Our study shows that ethnic minority populations living in Amsterdam, the Netherlands, skip breakfast more often, eat more erratically, and have more short/long sleep durations than the Dutch, while more Dutch

participants tend to have a shorter period of fasting. Meal timing also differs across ethnic groups. Importantly, our study suggests that both short as well as long sleep duration and night snacking (between 4 hours and 6 hours) are associated with incident T2D. We did not find evidence for an association between skipping breakfast, eating erratically, timing of hot (largest) meal, or period of fasting and incident T2D. Circadian disruptors did not account for the higher T2D risk among ethnic minority populations compared with Dutch.

We were not able to show expected associations between other behavioral circadian disruptors than those related to the last snack of the day or sleep duration and T2D. While associations might not exist in a free-living population, we cannot exclude that the limitations of our data (discussed further below) restrained us from finding these associations. This may also explain the lack of multiplicative interaction by ethnicity. On the contrary, the lack of interaction may imply that associations between behavioral circadian disruptors and T2D show robustness independent of differing patterns of behavior between ethnic groups.

As expected, prevalence of behavioral circadian disruptors differed across ethnic groups. A previous analysis of HELIUS data already

TABLE 2 Prevalence of behavioral circadian disruptors per ethnic group

	Total population	Dutch	South Asian Surinamese	African Surinamese	Ghanaian	Turkish	Moroccan
Skipping breakfast							
	<i>n</i> =12,719	<i>n</i> =3,071	<i>n</i> =1,567	<i>n</i> =2,170	<i>n</i> =1,338	<i>n</i> =2,223	<i>n</i> =2,350
Never or almost never	65.0 (8,273)	82.2 (2,524)	58.1 (910)*	55.9 (1,212)*	48.1 (643)*	62.9 (1,398)*	67.5 (1,586)*
Regularly	17.3 (2,196)	9.6 (295)	19.4 (304)*	21.6 (469)*	25.6 (343)*	18.4 (408)*	16.0 (377)*
Often	17.7 (2,250)	8.2 (252)	22.5 (353)*	22.5 (489)*	26.3 (352)*	18.8 (417)*	18.8 (387)*
Eating erratically							
	<i>n</i> =12,774	<i>n</i> =3,077	<i>n</i> =1,575	<i>n</i> =2,174	<i>n</i> =1,347	<i>n</i> =2,237	<i>n</i> =2,364
Not erratically	79.4 (10,101)	92.6 (2,845)	78.9 (1,237)*	71.0 (1,538)*	76.9 (921)*	76.9 (1,713)*	78.7 (1,847)*
Somewhat erratically	10.4 (1,322)	3.2 (98)	11.4 (178)*	13.6 (294)*	15.6 (208)*	13.4 (298)*	10.5 (246)*
Very erratically	10.2 (1,295)	4.3 (131)	9.8 (153)*	15.5 (335)*	15.4 (206)*	9.7 (217)*	10.8 (253)*
Hot meal							
	<i>n</i> =12,652	<i>n</i> =3,069	<i>n</i> =1,556	<i>n</i> =2,151	<i>n</i> =1,317	<i>n</i> =2,210	<i>n</i> =2,349
12-14 h	1.6 (206)	0.7 (22)	0.8 (12)	1.6 (34)*	6.1 (80)*	1.9 (41)*	0.7 (17)
14-16 h	1.8 (232)	0.2 (5)	1.2 (19)*	1.9 (40)*	7.7 (101)	0.9 (20)*	2.0 (47)*
16-18 h	15.1 (1,907)	6.3 (192)	19.9 (309)*	16.9 (363)*	21.0 (277)*	17.3 (383)*	16.3 (383)*
18-20 h	67.7 (8,568)	82.0 (2,518)	64.0 (996)*	66.2 (1,425)*	46.2 (609)*	68.8 (1,520)	63.9 (1,500)*
20-22 h	8.7 (1,107)	8.1 (249)	9.1 (141)*	7.8 (167)*	10.6 (140)*	7.0 (154)	10.9 (256)*
22-24 h	0.5 (59)	0.0 (1)	0.8 (13)*	0.6 (13)*	0.1 (3)*	0.1 (3)	0.8 (18)*
Last snack							
	<i>n</i> =12,130	<i>n</i> =2,971	<i>n</i> =1,469	<i>n</i> =2,084	<i>n</i> =1,209	<i>n</i> =2,136	<i>n</i> =2,261
16-18 h	1.3 (163)	0.5 (14)	1.2 (17)	1.1 (23)*	4.9 (59)*	1.1 (24)	1.1 (26)
18-20 h	11.7 (1,414)	11.6 (344)	14.0 (206)*	9.2 (191)	20.5 (248)*	10.3 (219)	9.1 (206)
20-22 h	46.1 (5,594)	48.5 (1,440)	46.1 (677)	43.7 (910)*	45.6 (551)	44.9 (959)	46.7 (1,057)
22-24 h	30.0 (3,638)	30.6 (908)	28.7 (422)	33.4 (697)*	19.3 (233)*	32.5 (694)	30.3 (684)
0-2 h	4.1 (493)	3.0 (89)	3.8 (56)	4.8 (99)*	3.1 (38)	4.8 (103)	4.8 (108)
2-4 h	1.2 (149)	1.3 (38)	1.0 (15)	1.3 (28)	1.0 (12)	1.3 (27)	1.3 (29)
4-6 h	0.2 (28)	0.3 (8)	0.3 (5)	0.2 (4)	0.4 (5)	0.1 (2)	0.2 (4)
Period of fasting							
	<i>n</i> =2,467	<i>n</i> =771	<i>n</i> =241	<i>n</i> =384	<i>n</i> =134	<i>n</i> =458	<i>n</i> =479
Long	1.4 (176)	0.5 (16)	1.8 (28)*	1.7 (37)*	3.0 (40)*	1.1 (24)	1.3 (31)*
Short	17.9 (2,291)	24.5 (755)	13.5 (213)*	16.0 (347)*	7.0 (94)*	19.4 (434)	19.0 (448)*
Sleep							
	<i>n</i> =12,625	<i>n</i> =3,064	<i>n</i> =1,560	<i>n</i> =2,149	<i>n</i> =1,306	<i>n</i> =2,210	<i>n</i> =2,336
Intermediate	33.7 (4,251)	39.0 (1,201)	28.3 (445)*	25.3 (551)*	29.0 (39.0)*	36.0 (806)*	36.3 (858)*
Short	63.8 (8,049)	60.0 (1,847)	69.7 (1,097)*	73.3 (1,593)*	67.9 (915)*	59.9 (1,341)*	59.4 (1,405)*
Long	2.6 (325)	0.9 (29)	2.1 (33)*	1.4 (30)	3.1 (42)*	4.0 (7)*	4.3 (101)*

Data are % (*n*). Prevalence of circadian disruptors by ethnic group tested for differences in distribution by multinomial logistic regression with the Dutch as the reference population. Model was adjusted for age, sex, season, and socioeconomic status.

*Prevalence of circadian disruptors differed significantly ($P < 0.05$) from the Dutch.

showed that the prevalence of short and long sleep is higher among ethnic minority populations than among the Dutch (18). The limited research available has further indicated that breakfast consumption was lower among South Asian and African Surinamese than the Dutch (19); we have now extended the evidence to those of Ghanaian, Turkish, and Moroccan background. Furthermore, we now added that eating erratically was more prevalent among ethnic minority populations than among Dutch participants, while short periods of fasting were relatively common among the latter group. The distribution of timing of meals differed across ethnic populations; Ghanaians, in particular, reported

having their largest hot meal and latest snack earlier in the day than other ethnic groups.

Furthermore, our study showed that night snacking (between 4 AM and 6 AM) was associated with incident T2D. Previous research has shown diurnal variations in energy metabolism that may explain these observations (31). Mistimed food intake may lead to increased caloric intake, weight gain, and, thereby, T2D (32,33). For instance, prolonged high serum glucose concentrations probably lead to increased triglyceride storage in adipose tissue (34,35). On the contrary, we did not find an

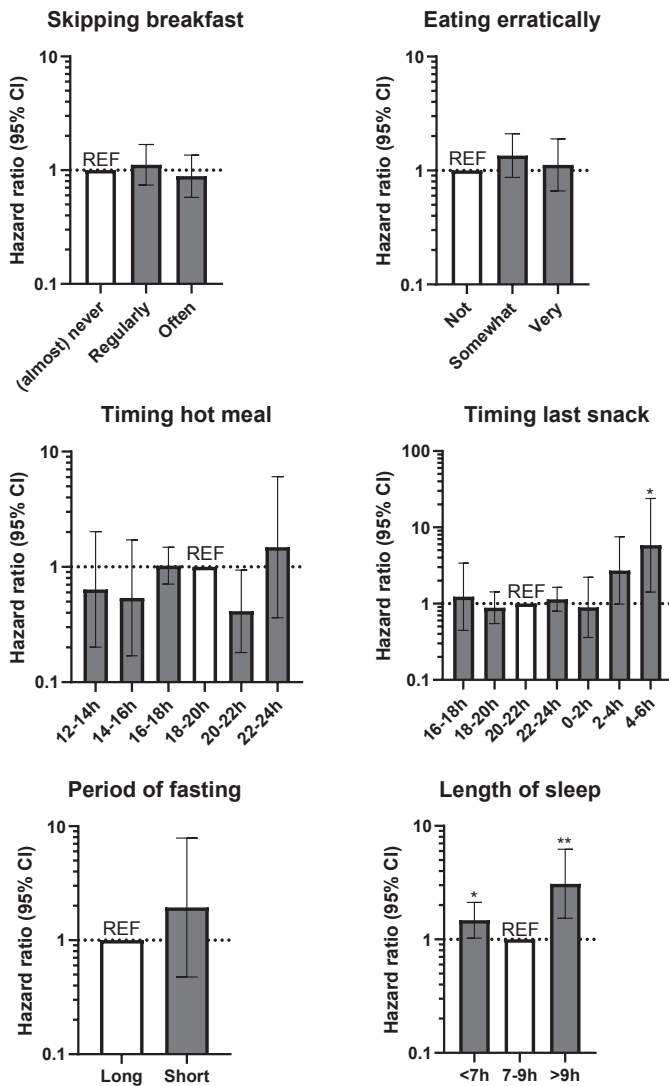


Figure 1 Association of behavioral circadian disruptors with incident T2D in the total population. The model was adjusted for ethnicity, sex, age, season, and socioeconomic status. * $P < 0.05$; ** $P = 0.001$. REF, reference group.

association between hot (largest) meal timing and incident T2D. This could imply that the exact timing of the hot meal might be less important than the timing of the last snack. We did also not find a significant association between length of eating period and T2D. This may be explained by the small number of participants that adhered to short eating periods. We did, however, find a (nonsignificant) tendency to a higher T2D risk with long eating periods. Previous studies have shown that reducing the daily time span of eating may lead to weight reduction and improved sleep; it may, therefore, be recommended to decrease T2D risk (32). We did not observe an association between skipping breakfast and T2D incidence in contrast to recent meta-analyses indicating that skipping breakfast is positively associated with T2D incidence (36,37). Former cohort studies investigating the effect of breakfast skipping have been conducted in the United States and Japan, where contextual factors may differ from those in Europe. The difference in study outcomes is perhaps explained by unmeasured correlates that explain or mask the

association between breakfast and T2D. None of the studies could, for instance, take the quality of the diet (e.g., low intake of whole grains or high intake of meat and sugar-sweetened beverages) into account. Diet quality may be correlated with consuming breakfast and, at the same time, with an increased risk of T2D (38) or increased body weight, which is the main risk factor for the development of T2D. We did not observe an association between erratic eating and T2D; no studies using comparable definitions were identified, but increased meal frequency may be important to reduce T2D risk (25).

We are the first to report a longitudinal relationship between sleep and T2D in a multiethnic cohort. This indicates that the previously established cross-sectional associations (18,39) were probably not caused by selection bias or reverse causality, although well-designed experiments are needed to prove causality. Mechanisms proposed to be involved in the risk associated with short sleep are related to inflammatory responses (40), the activation of the sympathetic nervous system, and distortions in hormone balances of ghrelin and leptin, ultimately leading to an increase in food ingestion and obesity (41). On the contrary, participants who sleep long may be more sedentary and snack more than those with intermediate sleep (42). This suggests that in order to elucidate mechanisms behind the observed associations, it might be important to take behavioral patterns into account.

A first limitation of the study is the use of data obtained from a study not specifically designed to study circadian disruptors. Consequently, the questionnaires used were not specifically designed to investigate circadian disruptors. This especially hampered the definition of eating erratically, which is ideally derived from registered time points of eating during the week, while the HELIUS questionnaire only contained data on the regular timing of meals and how often participants usually consumed meals during the week. In addition, use of self-reported questionnaire data for the behavioral circadian disruptors may be subject to recall bias as well as socially desirable answers. Future studies should incorporate objective measures of behavioral circadian disruptors. Moreover, no power calculation was made beforehand, which means that the size of our population may have restrained us from finding existing associations. This especially limited us in comparing short and long periods of fasting. Only a few ($n = 176$) participants had their last snack of the day before 20 hours and had breakfast a maximum of once a week, whereas, ideally, we would have considered even longer periods of fasting to study the effects of intermittent fasting on T2D risk. In addition, a limited number of participants snacked during the night (e.g., $n = 28$ between 4 and 6 hours), which hampered the interpretation of time points at which night snacking may be associated with T2D.

Incident T2D was determined by record linkage with insurance data. Therefore, only those participants who received diabetes care were registered as T2D cases. We will have missed participants who, despite having developed T2D, were not diagnosed with it because, for instance, they did not visit their general practitioner during the period of follow-up or because of registration issues. Moreover, screening rates for T2D between ethnic groups may differ because of differences in awareness of T2D risk across ethnic groups, although awareness rates were previously shown to be higher among ethnic minority populations compared with the Dutch (5). The deterministic data linkage may also have been more accurate than the probabilistic data linkage, especially because partially identifying variables may be less distinctive among certain ethnic groups, such as date of birth in Moroccans. However, a more than 98% overlap was found in T2D statuses among participants who could be identified in both databases.

TABLE 3 Cox proportional hazard for T2D incidence compared with Dutch

	Dutch	South Asian Surinamese	African Surinamese	Ghanaian	Turkish	Moroccan
	HR	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Fully adjusted model	REF 1.00	6.98 (3.69-13.21)	2.65 (1.34-5.22)	3.64 (1.75-7.58)	5.62 (2.82-11.20)	4.76 (2.34-9.67)
Fully adjusted model + last snack	REF 1.00	6.49 (3.40-12.41)	2.52 (1.27-5.00)	3.42 (1.60-7.33)	5.47 (2.72-10.99)	4.77 (2.72-10.99)
Fully adjusted model + sleep	REF 1.00	6.44 (3.39-12.23)	2.52 (1.28-4.97)	3.42 (1.64-7.14)	5.08 (2.54-10.17)	4.13 (2.01-8.47)

Participants of Dutch ethnicity used as reference category. Analyses adjusted for age, sex, season, and socioeconomic status, then additionally adjusted for timing of last snack or sleep duration.
REF, reference.

Finally, the generalizability of the study may be limited because the included population is reflective of the population in Amsterdam, the Netherlands. Prevalence of circadian disruptors may be different among other Dutch and ethnic minority populations. Other populations may, for instance, differ in their timing of meals, dietary composition, and type of physical activity. Previous work has shown that, although absolute risks between people living in various countries may differ, relative differences in cardiovascular disease risk factors between ethnic groups are similar to other European countries, suggesting that our results may be generalizable to other European countries (43).

Conclusion

Our findings suggest that night snacking and both short and long sleep are associated with an increased risk for T2D in a free-living multiethnic cohort. Night snacking and sleep duration may represent potential targets to prevent T2D. However, to be able to make recommendations that are relevant to the clinic and for public health, our results need to be confirmed with objectively measured behavioral circadian disruptors. Finally, circadian disruptors do not account for ethnic differences in T2D risk, so other factors must be involved. **O**

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