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Original article

Associations of meal timing, number of eating occasions and night-time fasting duration with incidence of type 2 diabetes in the NutriNet-Santé cohort

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Abstract

Background: Food intake plays a pivotal role in regulating circadian rhythms, which modulate glucose and lipid homeostasis. However, studies investigating the association of meal timing and type 2 diabetes (T2D) incidence are lacking. The objective of this study was to investigate the longitudinal associations of meal timing, number of eating occasions and night-time fasting duration with incidence of T2D.

Methods: In total, 103 312 adults [79% women, mean age at baseline = 42.7 (SD = 14.6)] from the NutriNet-Santé cohort (2009–21) were included. Participants' meal timings and frequency were assessed using repeated 24-h dietary records and averaged from the first 2 years of follow-up (5.7 records/participant). Associations of meal timing, number of eating occasions and night-time fasting duration with incidence of T2D were assessed by using multivariable Cox proportional hazard models adjusted for known risk factors.

Results: During a median follow-up of 7.3 years, 963 new cases of T2D were ascertained. Compared with participants habitually having a first meal before 8AM, those eating after 9AM had a higher incidence of T2D (HR = 1.59, 95% CI 1.30–1.94). Time of last meal was

not associated with T2D incidence. Each additional eating episode was associated with a lower incidence of T2D (HR = 0.95, 95% CI 0.90–0.99). Night-time fasting duration was not associated with T2D incidence, except in participants having breakfast before 8AM and fasting for >13 h overnight (HR = 0.47, 95% CI 0.27–0.82).

Conclusions: In this large prospective study, a later first meal was associated with a higher incidence of T2D. If confirmed in other large-scale studies, an early breakfast should be considered in preventing T2D.

Key words: Meal timing, type 2 diabetes mellitus, circadian rhythms, cohort, breakfast, fasting

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Key Messages

- Although meal timing plays a key role in the regulation of circadian rhythms and glucose and lipid homeostasis, it remains unclear which are the optimal daily timings for eating and fasting to prevent type 2 diabetes (T2D).
- In this large prospective study with data from 103 312 participants, habitually having a first meal later in the day (after 8AM) was associated with a higher incidence of T2D.
- These results show that beyond the nutritional quality of the diet, having an early first meal may be associated with a lower incidence of T2D and, if confirmed, could lead to promising lifestyle interventions, using chrononutrition to prevent T2D.

Introduction

In 2019, 463 million individuals were living worldwide with diabetes—a number expected to double by 2045.[1] The development of type 2 diabetes (T2D) is mostly determined by modifiable risk factors including an unhealthy diet, physical inactivity or smoking.[2] Recently, meal timing has been added to the list.

Chrononutrition is an emerging field studying the interplay between the timing of food intake, circadian rhythms and health.[3] Circadian rhythms are involved in virtually all functions of the body and are regulated by the circadian clock, which is mainly synchronized by light but also by food.[4] The correct functioning of this system is crucial to ensure an optimal metabolism.[5] Glucose tolerance and insulin sensitivity follow a circadian rhythmicity reaching its maximum in the morning.[6] Circadian misalignment induced by night shift work or later eating times has been associated with cancer,[7,8] obesity[9] and diabetes.[10]

It has been shown that beta-cell responsiveness and insulin sensitivity are better at breakfast than dinner.[11] Data from randomized–controlled trials (RCTs) suggest a link between late dinner and nocturnal glucose intolerance[12] and insulin resistance,[13] which are predictors in the development of T2D.[14] Skipping breakfast has been associated in observational studies with worse glycaemic control,[15] increased low-density lipoprotein (LDL) cholesterol and serum insulin levels[16] in healthy individuals. Results from

a randomized study showed as well an increased daily average blood glucose.[17] Skipping breakfast has been also linked to obesity in a meta-analysis of observational studies.[18] In 2018, a meta-analysis of prospective cohort studies reported an association between breakfast omission and risk of T2D, partly mediated by body mass index (BMI).[19]

Similarly, a reduced number of daily meals has been inconsistently associated with an increased T2D risk in cohort studies.[20,21] Only one study has explored the association between breakfast timing and risk of T2D, showing a lower risk of T2D for those participants having breakfast after 9AM.[22] However, this study was conducted in adults aged ≥65 years and assessed meal timing using a questionnaire at baseline. Multiple RCTs have linked time-restricted eating (TRE), implying an elongated night-time fasting duration, with a reduction in body weight and fat, an improved glycaemic profile and insulin sensitivity.[23]

In this prospective study, we aim to evaluate the association of meal timing, number of eating occasions and night-time fasting duration, assessed using comprehensive and repeated daily food records, with incidence of T2D.

Methods

Study population

The NutriNet-Santé study (https://etude-nutrinet-sante.fr/) is an ongoing web-based cohort established in 2009 in

France to investigate the relationship between nutrition and health.[24] Recruitment targets volunteers aged ≥18 years with access to the internet through vast multimedia campaigns. The study protocol is registered at https://clinicaltrials.gov/: NCT03335644.

Data collection

Dietary data

Dietary intakes were assessed every 6 months through online 24-h dietary records for 3 non-consecutive days (including 1 non-working day). In these records, participants were asked to report any food or beverage taken during that day and the times of the meals. The validity of these dietary records has been previously tested against an interview by a dietician[25] and biomarkers.[26,27] Then, we used food composition tables to estimate daily energy intake, alcohol and macronutrients.[28] We calculated these values as an individual daily average. We identified energy under-reporters with the method proposed by Black.[29] Participants were not considered as under-reporters if they reported practising a weight-loss restrictive diet, ate less than usual on the day of the dietary record or had a recent weight variation (Supplementary Method S1, available as Supplementary data at *IJE* online).

Exposure variables

To estimate the time of the first meal, the time of the last meal and the number of eating occasions, we computed averages across all available food records from the first 2 years of follow-up. We considered an eating episode any food or beverage intake of ≥1 kcal (to exclude water). We calculated night-time fasting duration as the difference between the last and the first eating episodes, assuming that daily behaviours remain similar. We then explored different categorizations for the most consistently reported fasting/eating schemes,[23] as a night-time fasting duration of ≤12 h, 12–13 h and >13 h.

Covariates

At inclusion and on a yearly basis, participants filled in a set of questionnaires on diet, socio-demographics and lifestyle,[30] anthropometrics,[31,32] physical activity (validated International Physical Activity Questionnaire questionnaire)[33] and health status (with information on personal and family medical history and medication use). In 2014, 44 591 participants responded to a sleep questionnaire.[34]

Case ascertainment

Participants' health status was reported at enrolment and reassessed biannually by using a check-up questionnaire. At any time, participants could also declare a health event,

a new treatment or a medical exam via a secured online platform. In addition, data were linked to SNIIRAM medico-administrative databases, providing detailed information about medication reimbursement and medical consultations (Supplementary Method S2, available as Supplementary data at *IJE* online). Mortality cases were identified using linkage to CépiDC, the French national mortality registry.

Statistical analyses

We included participants who completed at least three 24-h dietary records during their first 2 years of follow-up; we excluded under-reporters, those with prevalent diabetes and those having reported a first meal after 3PM or a last meal before 3PM (as a proxy of night shift) (Figure 1).

Time of first meal, time of last meal and number of eating occasions were modelled as continuous variables (per-hour and per-meal increase). We explored their correlation by using Spearman's rank correlation (Supplementary Figure S1, available as Supplementary data at *IJE* online). We categorized these variables as an approximation of the sample tertiles for readability purposes. To examine the association between these behaviours and the incidence of T2D, we built cause-specific Cox proportional hazards models and estimated hazard ratios (HRs) and 95% CIs. Death and incident cases of type 1 diabetes were considered as competing events. Participants contributed person-time until date of T2D diagnosis, competing event, last connection or 30 September 2021, whichever occurred first.

Models were adjusted for age (timescale), sex, educational level (<high-school degree, <2 years after high-school degree, ≥2 years after high-school degree), baseline BMI (continuous, kg/m^2), family history of T2D (no, yes), alcohol intake (continuous, g/day), daily energy intake excluding alcohol (continuous, kcal/day), smoking (current, former, never), physical activity (low, moderated, elevated, as defined by IPAQ[33]), number of dietary records (continuous) and number of meals (continuous). We also adjusted for healthy and Western dietary patterns (continuous) obtained from principal component analysis based on 20 pre-defined food groups (Supplementary Method S3, available as Supplementary data at *IJE* online) (Model a). We did a second model (Model b) mutually adjusting time of first meal, time of last meal and number of eating occasions. We verified the assumptions of proportional hazards using Shoenfeld Residuals and of linearity using spline terms.

Less than 1% of participants had missing data on the covariates, except for physical activity (14% of missing data). We applied mean and mode imputation for
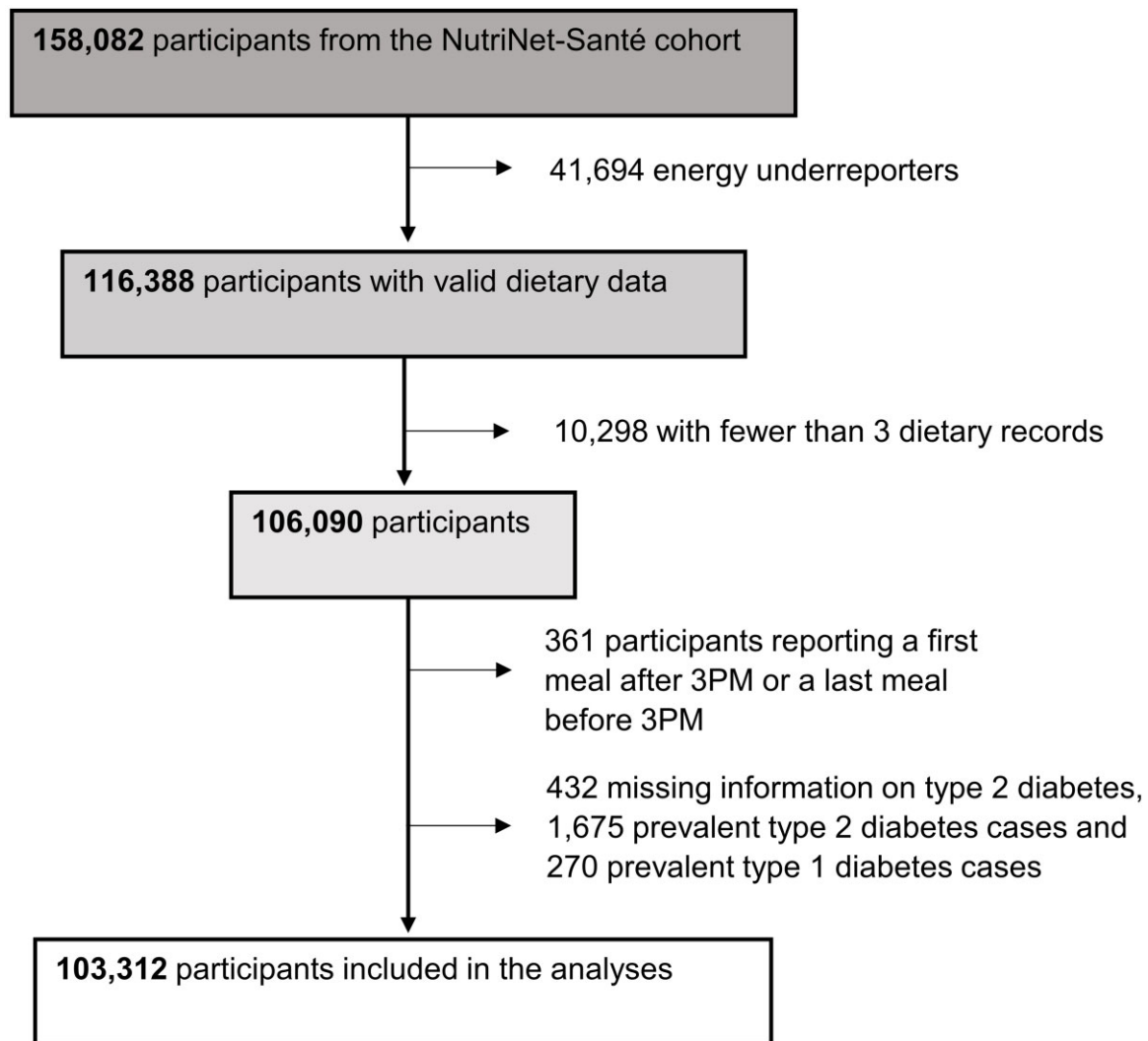
Figure 1 Flowchart of study population in the NutriNet-Santé cohort, 2009–21 ($N = 103\,312$ participants)

continuous and categorical variables, respectively. We also explored multiple imputation using the multivariate imputation by chained equations method (Supplementary Table S1, available as Supplementary data at *IJE* online).

Then, we tested whether night-time fasting duration was associated with T2D. We built Cox models with the continuous and categorical variable of night-time fasting duration. Models were adjusted for the same confounders as before.

We tested for effect modification by time of first meal by introducing an interaction term between night-time fasting duration and time of first meal, using a likelihood ratio test. Finally, we calculated the specific estimates for those breaking the night-time fasting at 8AM or before, i.e. early time-restricted eating (eTRE), and those breaking it after 8AM, i.e. late time-restricted eating (lTRE). This threshold was chosen as it was the most frequently used time in studies on eTRE.[23]

Sensitivity analyses

We explored further adjustment for intake of saturated fatty acids, sodium, sugar and fibre during the first meal. We also explored adjusting for daily consumption of red and processed meat, sugary drinks, fruits and vegetables, nuts, whole grain, yoghurt, caffeine, ultra-processed food, region of residence and profession. We also tested a model without baseline BMI and total energy intake to explore their confounding effect and a model with weight change during follow-up to account for its potential mediator role.

We investigated excluding T2D cases diagnosed during the first 2 years of follow-up (to limit reverse causality). Among the subset who responded to the sleep questionnaire, we selected individuals who reported going to bed at any time between 6 PM and 8 AM ($N = 37\,042$) to exclude potential night shift workers. We also explored including bedtime and total sleep duration (min/24 h). We explored

further categorization of our main exposure variables, after adjustment for Model b covariates: for time of first meal as: <7AM, between 7AM and 8AM, between 8AM and 9AM, between 9AM and 10AM, and ≥10AM; for time of last meal as: <7PM, between 7PM and 8PM, between 8PM and 9PM, between 9PM and 10PM, and ≥10PM.

Finally, we tested for effect modification of the association between meal timing and number of eating occasions and the incidence of T2D by: obesity, sex, chronotype (morning, intermediate, evening) and physical activity. Analyses were conducted using the statistical package R-4.2.1 (The R Project for Statistical Computing, Vienna, Austria).

Results

In these analyses, we included 103 312 participants (78.9% women) with a mean age at baseline of 42.7 ± 14.6 years. Up to 30 September 2021 [703 752.9 person-years; median follow-up time, 7.3 years; first quartile (Q1) to third quartile (Q3), 3.2 to 10.1 years], 963 cases of T2D were identified. During the first 2 years of follow-up, participants responded to a mean of 5.7 (SD 3.0, max 18.0) dietary records.

The baseline characteristics of the study population, according to the averaged time of first meal of the day, are shown in Table 1. Overall, participants reporting an habitual first meal before 8AM were older compared with participants having the first meal between 8AM and 9AM and those having it after 9AM. Compared with the other two groups, participants in the group with the earliest first meal were more likely to have lower physical activity levels, lower education levels and an earlier last meal of the day. Additionally, they were less likely to be current smokers and to have a family history of T2D.

Meal timing, number of eating occasions and incidence of T2D

Compared with participants reporting a first meal before 8AM, those reporting a first meal after 9AM had a higher incidence of T2D (HR = 1.62, 95% CI 1.33–1.97, *P* for trend < 0.001, Table 2). Similarly, participants reporting a late last meal (after 9PM) had a higher incidence of T2D compared with participants reporting a last meal before 8PM (HR = 1.28, 95% CI 1.06–1.54, *P* for trend 0.05).

When circadian behaviours were mutually adjusted, the association of time of first meal remained stable (HR = 1.59, 95% CI 1.30–1.94, *P* for trend < 0.001, for a

first meal after 9AM compared with a first meal before 8AM). However, the association between time of last meal did not persist.

In this model, eating on more than five occasions per day was associated with a lower incidence of T2D compared with four or fewer occasions (HR = 0.80, 95% CI 0.68–0.95, *P* for trend 0.02).

There was no clear evidence for non-linear associations (Figure 2).

Night-time fasting duration and incidence of T2D

Extending the night-time fasting duration was not associated with T2D incidence (Table 3). We found an effect modification of this association by time of first meal (*P*-value for interaction < 0.001). Our results suggest that a night-time fasting of >13 h would be inversely associated with T2D incidence only when fasting is broken at 8AM or before (HR = 0.47, 95% CI 0.27–0.82, compared with a fasting duration of ≤12 h, *P* for trend = 0.3).

Sensitivity analyses

The associations between meal timing and T2D incidence remained stable in sensitivity analyses (Supplementary Table S1, available as Supplementary data at *IJE* online). The association between daily number of eating occasions and incidence of T2D was no longer evident after adjusting for daily intake of caffeine, after considering sleep and excluding cases ascertained during the first 2 years of follow-up (Supplementary Table S1, available as Supplementary data at *IJE* online).

Overall, we observed that the association between a later first meal of the day and a higher incidence of T2D was similar for both women and men (*P*-interaction for sex = 0.2) (Supplementary Table S2, available as Supplementary data at *IJE* online). A positive association between having a later last meal of the day (after 9PM compared with before 8PM) and higher incidence of T2D was evident in men only (HR = 1.51, 95% CI 1.13–2.00, *P* for trend = 0.01; *P*-interaction for sex = 0.2) (Supplementary Table S2, available as Supplementary data at *IJE* online). Then, as regards stratification for BMI categories, we observed overall similar results for the association between meal timings and incidence of T2D (Supplementary Table S3, available as Supplementary data at *IJE* online) (*P*-interaction for time of first meal = 0.9, for time of last meal = 0.7). Results remained similar across different chronotypes (*P*-interaction for time of first meal = 0.7, for time of last meal = 0.9) (Supplementary Table S4, available as Supplementary data at *IJE* online). The association between a later last meal of the day and

Table 1 Baseline characteristics of study population, 103 312 participants in the NutriNet-Santé cohort (2009–21)

	All participants		First meal before 8AM		First meal between 8AM and 9AM		First meal after 9AM	
	No. (%)	Mean (SD)	No. (%)	Mean (SD)	No. (%)	Mean (SD)	No. (%)	Mean (SD)
Number of participants	103 312		46 256		36 964		20 092	
Age at baseline (years)	103 312	42.7 (14.6)	46 256	46.6 (13.1)	36 964	42.5 (14.8)	20 092	33.9 (13.4)
Sex	103 312		46 256		36 964		20 092	
Women	81 529 (78.9)		35 621 (77.0)		29 755 (80.5)		16 153 (80.4)	
Men	21 783 (21.1)		10 635 (23.0)		7209 (19.5)		3939 (19.6)	
BMI (kg/m^2)^a	102 167	23.7 (4.4)	45 754	23.8 (4.4)	36 562	23.6 (4.3)	19 851	23.4 (4.7)
Normal weight	72 004 (70.5)		31 619 (69.1)		25 868 (70.8)		14 517 (73.1)	
Overweight	21 602 (21.1)		10 274 (22.5)		7746 (21.2)		3582 (18.1)	
Obesity	167 (8.4)		3861 (8.4)		2948 (8.0)		1752 (8.8)	
Family history of T2D	101 871		45 619		36 536		19 716	
No	87 576 (86.0)		38 649 (84.7)		31 568 (86.4)		17 359 (88.0)	
Yes	14 295 (14.0)		6970 (15.3)		4968 (13.6)		2357 (12.0)	
Smoking status	103 271		46 242		36 951		20 078	
Current	17 893 (17.3)		6389 (13.8)		6267 (17.0)		5237 (26.1)	
Former	33 573 (32.5)		16 825 (36.4)		11 958 (32.4)		4790 (23.9)	
Never	51 805 (50.2)		23 028 (49.8)		18 726 (50.7)		10 051 (50.1)	
Physical activity	89 121		40 059		32 075		16 987	
Low	29 235 (32.8)		14 806 (37.0)		9892 (30.8)		4537 (26.7)	
Moderated	21 551 (24.2)		8831 (22.0)		7843 (24.5)		4877 (28.7)	
Elevated	38 335 (43.0)		16 422 (41.0)		14 340 (44.7)		7573 (44.6)	
Daily alcohol intake (g)	103 312	7.86 (11.9)	46 256	7.64 (11.4)	36 964	8.10 (11.8)	20 092	7.94 (13.0)
Daily energy intake (kcal)	103 312	1847 (451)	46 256	1856 (448)	36 964	1856 (440)	20 092	1809 (473)
High-school degree	103 244		46 229		36 944		20 071	
No	17 812 (17.2)		9446 (20.4)		5833 (15.7)		2533 (12.6)	
Yes (<2 years after high school)	16 291 (15.8)		7142 (15.4)		5453 (14.8)		3696 (18.4)	
Yes (≥2 years after high school)	69 141 (67)		29 641 (64.1)		25 658 (69.5)		13 842 (69.0)	
Time of first meal (AM)	103 312	8.14 (1.1)	46 256	7.22 (0.5)	36 964	8.24 (0.3)	20 092	9.57 (1.0)
Time of last meal (PM)	103 312	8.24 (1.1)	46 256	8.06 (1.0)	36 964	8.24 (1.0)	20 092	8.48 (1.3)
Night-time fasting duration (h)	103 312	11.9 (1.4)	46 256	11.2 (1.0)	36 964	12.0 (1.0)	20 092	13.2 (1.5)
Number of eating occasions	103 312	4.89 (1.7)	46 256	5.00 (1.8)	36 964	4.89 (1.6)	20 092	4.63 (1.7)

BMI, body mass index; T2D, type 2 diabetes.

^{a}Normal weight: BMI <25 kg/m^2; overweight: BMI = 25–29.9 kg/m^2; obesity ≥30 kg/m^2.

a higher incidence of T2D was slightly stronger in participants having medium levels of physical activity (HR per-hour increase = 1.10, 95% CI 1.01–1.21, $P = 0.03$; P-interaction = 0.06), although results for the categorical exposure variables were similar across the three groups (Supplementary Table S5, available as Supplementary data at *IJE* online).

Finally, when exploring further categorization of the main exposure variables, we observed that participants having a last meal of the day after 10PM had a higher incidence of T2D compared with participants eating before 7PM (HR = 1.44, 95% CI 1.00–2.09, P-value

for trend = 0.1), which is suggestive of a threshold effect also consistent with the shape of the association in Figure 2.

Discussion

To our knowledge, this is the first prospective study to investigate the associations of, comprehensively assessed, meal timings, number of eating occasions and night-time fasting duration with incident T2D. Our results suggest that having a late first meal could be associated with a higher incidence of T2D.

Table 2 Associations of meal timing and number of eating occasions with incidence of T2D in 103 312 participants from the NutriNet-Santé cohort (2009–21)

	No. of cases/non-cases	Model a		Model b	
		HR (95% CI)[a]	P	HR (95% CI)[b]	P[c]
Time of first meal					
Continuous (per hour)	963/102 349	1.16 (1.08–1.24)	<0.001	1.14 (1.07–1.22)	<0.001
Before 8AM[d]	462/45 794	Ref.	<0.001	Ref.	<0.001
Between 8AM and 9AM	361/36 603	1.26 (1.09–1.45)		1.26 (1.09–1.45)	
After 9AM	140/19 952	1.62 (1.33–1.97)		1.59 (1.30–1.94)	
Time of last meal					
Continuous	963/102 349	1.08 (1.02–1.15)	0.01	1.05 (0.98–1.11)	0.2
Before 8PM	373/34 365	Ref.	0.05	Ref.	0.4
Between 8PM and 9PM	378/45 181	0.93 (0.80–1.08)		0.88 (0.76–1.02)	
After 9PM	212/22 803	1.28 (1.06–1.54)		1.11 (0.92–1.34)	
Number of eating occasions					
Continuous (per meal)	963/102 349	0.96 (0.92–0.99)	0.04	0.95 (0.90–0.99)	0.01
≤4	397/39 202	Ref.	0.03	Ref.	0.02
5	284/29 006	0.92 (0.79–1.08)		0.92 (0.79–1.08)	
>5	282/34 141	0.83 (0.71–0.98)		0.80 (0.68–0.95)	

T2D, type 2 diabetes; HR, hazard ratio.

[a]Adjusted for age (timescale), sex (women, men), educational level (less than high-school degree, <2 years after high-school degree, ≥2 years after high-school degree), body mass index at baseline (continuous, kg/m^2), family history of T2D (no, yes), alcohol intake (continuous, g/day), daily energy intake excluding alcohol (continuous, g/day), healthy dietary pattern (continuous), Western dietary pattern (continuous), smoking (current, former, never), physical activity (low, moderated, elevated), number of dietary records (continuous) and number of eating occasions (continuous). The model for number of eating occasions was adjusted for time of first meal.

[b]Same as [a] but time of first meal, time of last meal and number of eating occasions were mutually adjusted.

[c]P-value for continuous variables and P-trend for categorical variables.

[d]The exact tertiles were 5AM–7.7AM, 7.7AM–8.5AM and >8.5AM for time of first meal; 3PM–8PM, 8PM–8.7PM and >8.7PM for time of last meal; and 1.3–4, 4–5.3 and >5.3 for number of eating occasions.

In line with this, a meta-analysis of six cohort studies showed that skipping breakfast was associated with an increased risk of T2D [relative risk (RR) = 1.22, 95% CI 1.12–1.34].[19] In these studies, breakfast consumption was assessed as the frequency of breakfast consumption throughout the week (i.e. >3 days/week) and all the included cohort studies examined breakfast skipping from a single behavioural questionnaire without considering actual data based on the consumption. In our study, specific timing of food consumption and number of eating occasions were assessed using the same repeated and validated dietary records. Lack of time and appetite in the morning are the main reasons for skipping breakfast,[35] the latter one potentially being a consequence of a late dinner.[36] In a cross-sectional study, late-night-eating alone, but not breakfast skipping, was associated with hyperglycaemia.[36] However, in our analyses, time of first meal was adjusted for time of last meal.

Only one study has investigated the link between breakfast timing and risk of T2D, and showed, inconsistently with our results, an inverse association between a later timing of breakfast (after 9AM) and T2D risk.[22] However, the study population was older (aged ≥65 years) and

nutritional behaviours were assessed using one single questionnaire at baseline. Another study showed that the association between irregular breakfast and T2D was only observed among participants <65 years of age.[37] Taken together, these findings may suggest age-related heterogeneities in these associations.[22]

This association is biologically plausible considering the circadian rhythmicity in insulin sensitivity and glucose tolerance.[6] The optimal metabolic time is early in the morning. The omission of breakfast, and therefore the delay of this first meal, has been associated with worse glycaemic control.[15] It has also been associated with risk factors for T2D such as increased LDL cholesterol, decreased high-density lipoprotein cholesterol and elevated serum insulin.[16] Additionally, results from a randomized–controlled crossover trial suggest that skipping breakfast can increase the postprandial insulin concentrations and fat oxidation, potentially leading to low-grade inflammation and impaired glucose homeostasis.[38] Finally from a circadian perspective, the pivotal influence of the first meal of the day on circadian control, glucose and lipid homeostasis is now starting to be unravelled from evidence in mice[39,40] and humans.[41]

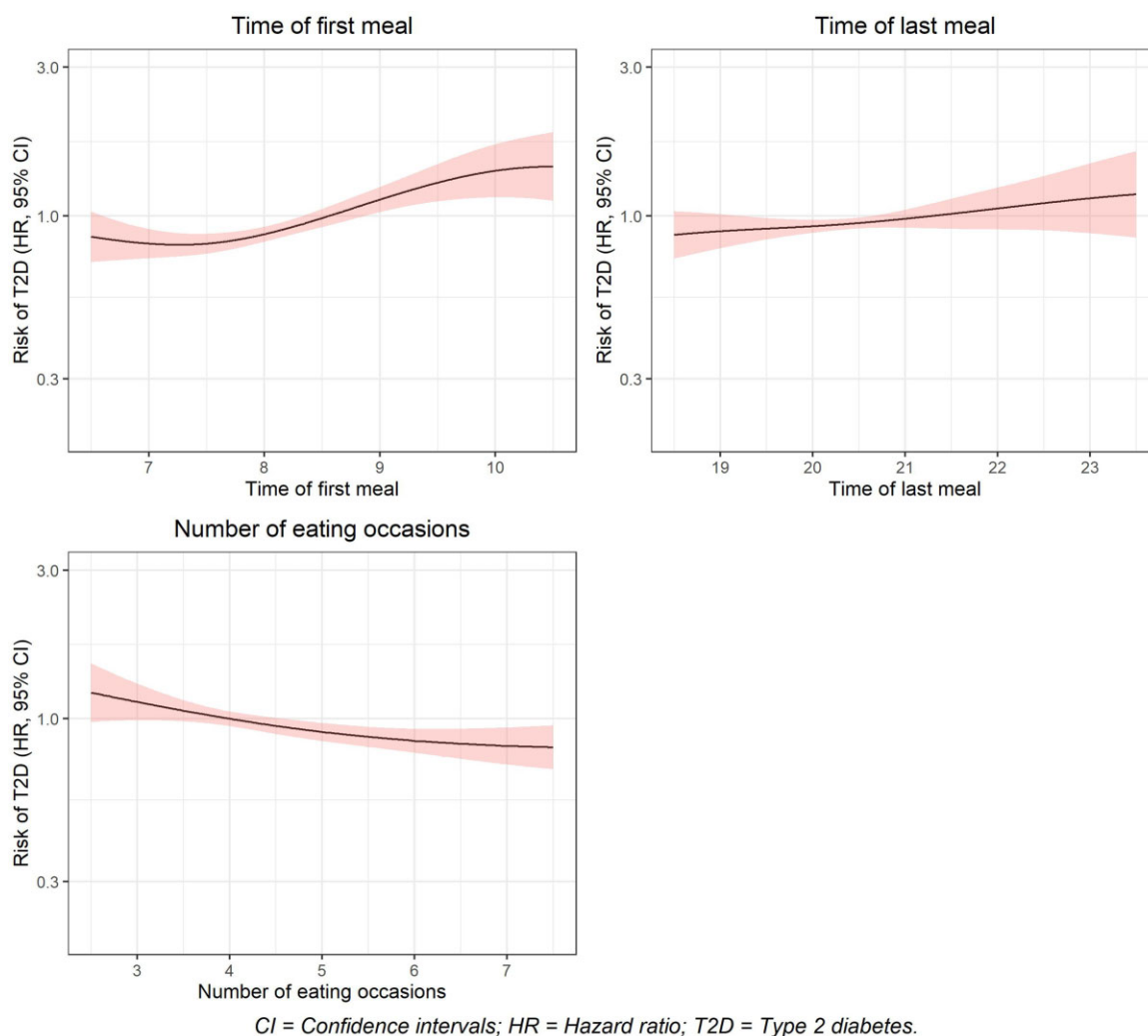CI = Confidence intervals; HR = Hazard ratio; T2D = Type 2 diabetes.

Figure 2 Examining the linearity of the association between circadian nutritional behaviours and risk of type 2 diabetes in the NutriNet-Santé cohort, 2009–21 ($N = 103\,312$). HR, hazard ratio; T2D, type 2 diabetes

Breakfast omission has been associated with lower physical activity levels,[42] a higher consumption of alcohol and tobacco,[43] a worst diet quality[44] and a lower socio-economic status.[45] However, we considered all these factors in our analyses. It could also be that skipping breakfast is linked to a caloric compensation later in the day,[46] but we adjusted for daily energy intake. Although obesity could mediate this association,[18] we examined adjustment for weight change during follow-up, and also interaction with baseline BMI.

On the other hand, the association between time of last meal and incidence of T2D included the null after adjusting for time of first meal, indicating that this third variable was confounding the association. However, we observed that participants having a very late last meal of the day (after 10PM compared with before 7PM) had a higher risk of developing T2D. This could indicate that very late eating patterns could also have an impact of the development of

T2D, regardless of the time of first meal. A few clinical trials have reported similar results.[12,13] In a randomized crossover trial, a late dinner (10PM) induced nocturnal glucose intolerance compared with an earlier dinner (6PM).[12] In another study, compared with a late evening meal (10:30–11PM), an early evening meal (eating at 7–7:30PM) resulted in a reduction in a homeostasis model assessment of insulin resistance.[13] On the other hand, a cross-sectional observational study showed that night eating behaviour was not a predictor of T2D.[47] Overall, epidemiological data on this association are scarce and more studies are needed to explore this question, especially in participants or populations with very late behaviours.

Night shift work and sleep disruption have been also associated with a higher risk of T2D.[48,49] However, in our analyses, we excluded participants reporting very late nutritional behaviours as a proxy of night shift work. Moreover, when excluding participants reporting extreme

Table 3. Association between night-time fasting duration and incidence of T2D in 103 312 participants from the NutriNet-Santé cohort (2009–21)

Night-time fasting	No. of cases/non-cases	HR 95% CI[a]	P
Continuous (h)	963/102 349	0.96 (0.90–1.02)	0.2
≤12 h	537/57 403	Ref.	
12–13 h	289/28 652	1.08 (0.92–1.27)	0.4
>13 h	137/16 294	1.03 (0.80–1.33)	
In combination with an early breakfast (eTRE[b])			
Continuous (h)	462/45 794	0.93 (0.85–1.01)	0.07
≤12 h	362/36 991	Ref	0.3
12–13 h	85/7002	1.21 (0.95–1.54)	
>13 h	15/1801	0.47 (0.27–0.82)	
In combination with a late breakfast (lTRE[b])			
Continuous (h)	501/56 555	1.03 (0.95–1.11)	0.4
≤12 h	175/20 412	Ref	0.08
12–13 h	204/21 650	1.08 (0.88–1.33)	
>13 h	122/14 493	1.24 (0.98–1.58)	

T2D, type 2 diabetes; HR, hazard ratio; eTRE, early time-restricted eating; lTRE, late time-restricted eating.

[a]Adjusted for age (timescale), sex (women, men), educational level (less than high-school degree, <2 years after high-school degree, ≥2 years after high-school degree), body mass index at baseline (continuous, kg/m^2), family history of T2D (no, yes), alcohol intake (continuous, g/day), daily energy intake excluding alcohol (continuous, kcal/day), healthy dietary pattern (continuous), Western dietary pattern (continuous), smoking (current, former, never), physical activity (low, moderated, elevated), number of dietary records (continuous), number of eating occasions (continuous) and time of first meal (continuous).

[b]eTRE was defined as a first meal at or before 8AM. lTRE was defined as a first meal after 8AM. Effect modification of the association between night-time fasting and incidence of T2D by early (≤8AM) vs late time of first meal (P for interaction <0.001).

sleep times (also as a proxy of night shift), the estimates were weakened but remained evident, suggesting that night shift only partly explained the observed associations.

In this study, eating more frequently was inversely associated with T2D incidence. This could be explained by a reduction in serum insulin and lipids concentration between meals via a reduction in the hepatic synthesis of cholesterol.[50,51] In this line, a cross-sectional study within the EPIC-Norfolk cohort suggested that eating more frequently was associated with lower concentrations of total and LDL cholesterol.[52] Conversely, a clinical trial showed that having six meals a day resulted in higher glucose levels throughout the day compared with having three meals, with no changes in insulin.[53] Similarly, an observational study showed that additional snacks to the three main meals were associated with an increased risk of T2D.[20] On the other hand, a prospective cohort study suggested that a higher number of large and medium meals was linked to weight change, whereas having more small meals was inversely associated with weight gain.[54] In our study, this association included the null after excluding participants diagnosed during the first 2 years of follow-up, probably linked to modified behaviours in participants with early metabolic symptoms. In addition, this association was attenuated after adjustment for caffeine intake, which could be explained by the suggested inverse association with T2D.[55] Our findings on meal frequency and T2D highlight the need for further research.

Multiple RCTs have reported a link between TRE and a reduction in several risk factors for T2D including fasting glucose levels, insulin sensitivity, body weight and β-cell function.[23] In our secondary analyses, extending the duration of the night-time fasting appeared to be inversely associated with T2D incidence only if this window finished early in the morning (8AM) and after 13 h of fasting. These results were based on few participants and should be interpreted cautiously.

The main strengths of the study were the large sample size, its prospective design and the repeated dietary records including detailed assessments for nutritional intakes, meal timings and number of eating occasions. In addition, meal timing was assessed directly using comprehensive 24-h dietary records that could be less misleading and subject to misclassification bias than using ad-hoc questionnaires. As a first limitation, this is an observational study and residual confounding cannot be entirely ruled out, despite accounting for a large panel of confounders. Second, the participants are volunteers with a higher proportion of women from higher socio-economic status and with greater health conscious behaviours.[56] This limits the results extrapolation to the general population. Third, we had a limited number of T2D cases in stratified analyses, or in extreme circadian behaviour situations. Although we have considered sleep timing and duration, this was measured later during the follow-up, available for a part of the sample and could be affected by recall bias. Moreover, night shift

work was extrapolated from sleep variables; even though sleep duration could be a proxy for shift work, we had no information about the exposure to light-at-night, which could be another circadian disruptor.

Although dietary records in the NutriNet-Santé cohort have been previously validated, the assessment of meal timings and number of eating occasions have not been specifically validated. Yet, the large majority of our study sample (93%) reported last meal intakes (collected during the first 2 years of follow-up) that were anterior to their bedtime (assessed using an ad-hoc questionnaire administered in 2014), which served as a preliminary validation. However, further studies should address the validation of meal timings measured using questionnaires. Then, we used a multisource case ascertainment method to approach exhaustiveness. Nevertheless, cases might have been missed due to undiagnosed cases. About 20% of diabetes cases in France are estimated to be undiagnosed.[57] As NutriNet-Santé participants are younger than the general population and have better dietary behaviours and less prevalence of excess weight,[58] we could expect that the prevalence of undiagnosed diabetes would also be lower than in the general population. In any case, undiagnosed diabetes cases would have probably led to an underestimation of the associations. A final limitation, opening a research perspective, is that we did not examine the potential differences in meal timings between weekdays and weekends—something previously referred to as eating jet lag.[59]

To conclude, in this large prospective study, a late first meal was associated with a higher incidence of T2D. A circadian nutritional behaviour defined by an early first meal (before 8AM) and early last meal (before 7PM) might be beneficial to lower T2D incidence. If confirmed in other prospective studies and possibly clinical trials, these behaviours could be recommended as a preventive strategy for T2D.

Ethics approval

NutriNet-Santé is conducted according to the Declaration of Helsinki guidelines and was approved by the institutional review board of the French Institute for Health and Medical Research (IRB Inserm n 0000388FWA00005831) and the Commission Nationale de l'Informatique et des Libertés (CNIL n 908450/n 909216). Electronic informed consent was obtained from all participants included in this study and could be withdrawn at any point of the study.

Data availability

Data and code will be available upon request.

Supplementary data

Supplementary data are available at _IJE_ online.

Author contributions

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Conflict of interest

None declared.

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