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Eating jetlag based on meal timing discrepancies and risk of cardiovascular disease using the prospective cohort NutriNet-Santé

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Abstract

Background Eating jetlag is an emerging concept defined as meal timing regularity between free and work days. We evaluated the association between eating jetlag and the risk of cardiovascular disease in a French cohort.

Methods Data of 104,806 participants (79% women, mean age=42.7 years (SD 14.6)) were collected from the NutriNet-Santé prospective cohort (2009-2023). Cardiovascular disease was self-reported and validated against medical records. Eating jetlag intensity was calculated using times of first and last caloric intakes in repeated 24-hour dietary records (5.8 (SD 3.2) records on average)), as the absolute difference between weekends and weekdays, and its associations with cardiovascular disease risk were assessed through multi-adjusted Cox models. Eating jetlag direction was assessed using 3 categories: "Advance", "Maintenance", "Delay", in weekends compared to weekdays.

Results During a median follow-up of 8.1 years, eating jetlag was associated, in male participants, with higher cardiovascular disease (HR = 1.14 [1.05-1.23]) and coronary heart disease (HR = 1.21 [1.11-1.33]) risks. In males, participants in the "Advance" group had higher risks of cardiovascular and coronary heart diseases (HR = 1.44 [1.08-1.93], and HR = 1.68 [1.19-2.39], respectively) compared to those in the "Maintenance" group; while those in the "Delay" group had a higher coronary heart disease risk (HR = 1.36 [1.05-1.77]).

Conclusion Our results suggest a role for meal timing regularity between weekends and weekdays in CVD etiology, independently of sleep duration and diet quality, specifically in males. If confirmed in other studies, meal timing regularity could be a strategy to mitigate cardiovascular disease risk.

Trial registration NCT03335644.

Plain language summary

Fixed work schedules often force individuals to adapt their eating rhythms throughout the week, creating a weekdays-weekends discrepancy qualified as "eating jetlag". This phenomenon can disrupt biological clocks and circadian rhythms. Since circadian disruption was shown to entail cardiometabolic complications, the study aimed to investigate the links between eating jetlag and cardiovascular disease risk. Adapted statistical models were built, leveraging data from the NutriNet-Santé cohort (104,806 participants), where volunteers reported their detailed dietary intakes on weekdays and weekends through repeated questionnaires, and were followed between 2009 and 2023. Eating jetlag intensity was associated with a higher cardiovascular disease risk, especially among males. This study suggests the importance of regular meal-timing patterns, beyond sleep and diet quality, in cardiovascular disease prevention.

In many industrialised societies, irregular eating patterns, such as skipping breakfast and late-night eating, are becoming more frequent[1]. People often adapt their daily routines around fixed work schedules[2]. While workday schedules are largely organised around professional, educational, or household commitments[3,4], rest days (usually Saturday and Sunday) generally allow individuals to align their sleep and meal patterns more closely with their biological clock (chronotype)[3,5], consequently marking a discrepancy between workdays and days off, even though days off may also often involve childcare, social obligations, and leisure. This inconsistency in sleep and food intake timing may disrupt circadian rhythms—the internal

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clocks that coordinate homeostasis and metabolism and run on an ~24-h cycle (the circadian clock)[5,6]. The discrepancy in sleep–wake timing between workdays and free days is termed social jetlag (SJL)[7]. SJL is more emphasised (1) in late chronotypes—i.e., individuals who prefer to time their sleep and activity late in the day—having to begin their professional activities in the morning[8], (2) and among night shift workers[9]. Several epidemiological studies have shown that SJL is associated with adverse metabolic risk factors, such as higher body mass index (BMI), systolic blood pressure and levels of glycated haemoglobin HbA1c[10], in the general population[11], as well as less healthy eating patterns[12].

In a similar way to the concept of SJL, eating jetlag (EJL) corresponds to the discrepancy of the timing of the eating period during rest days and work days[13], which may or may not be subsequent to SJL. Studies on EJL remain scarce, and its association with health outcomes are still unclear. A cross-sectional study revealed that EJL was associated with higher BMI amongst participants aged 18–25 in Mexico and Spain, independently of SJL and chronotype[13]. A 1-year prospective study held between 2018 and 2019 amongst women from a specific American Heart Association cohort found that EJL was associated with higher blood pressure and impaired glycaemic control[14].

Meal timing interacts with circadian rhythms to regulate metabolic health[15,16]. Food intake can act as a primary synchroniser for the internal clocks, and thus, aligning eating patterns with circadian rhythms bolsters metabolic homeostasis[17]. A meta-analysis of 29 randomised controlled trials suggested that time-restricted eating (TRE), reduced meal frequency, and earlier distribution of caloric intake throughout the day may contribute to weight reduction when compared to standard care and/or conventional nutritional guidance. However, the observed effect sizes were modest, and their clinical significance remains uncertain, given the high heterogeneity[18]. In the French e-cohort NutriNet-santé, later first and last meals during the day were associated with a higher risk of CVD[19], and a later time of first meal was associated with a higher incidence of type 2 diabetes[20].

Despite the aforementioned research investigating meal timing, the links between EJL—reflecting meal timing regularity—and the risk of cardiovascular disease events have never been reported, to the best of our knowledge.

Assuming that EJL could increase the risk of CVD through circadian disruption, we conducted a prospective study aiming to explore the association of EJL with the risk of developing CVD among adults of the NutriNet-Santé e-cohort.

This study highlights that EJL intensity is associated with the risk of CVD and CHD, specifically among male participants, regardless of the direction of eating timing discrepancies. These associations are independent of diet quality and remain significant after adjustment for bedtime, total sleep time, and social jetlag.

Methods

Study population

This study was based on data from the ongoing NutriNet-santé e-cohort, which aims to study the relationship between nutrition and health. Since its launch in 2009, participants aged 18 years and above have been continuously enrolled through multimedia campaigns. They regularly fill multiple online questionnaires, including repeated 24-h dietary records and physical activity questionnaires. Participants are also invited to fill in questionnaires regarding their health, medical history, sociodemographics, anthropometry, and lifestyle. The study protocol has been previously published[21]. All participants provided an electronic informed consent at enrolment. The NutriNet-santé is conducted in compliance with the Declaration of Helsinki guidelines and is registered at clinicaltrials.gov (NCT03335644). The study was approved by the Institutional Review Board of the French Institute for Health and Medical Research (IRB Inserm no 0000388FWA00005831) and the "Commission Nationale de l'Informatique et des Libertés" (CNIL n°908450/n°909216). Confidentiality and security of the data are assured at all times.

Dietary data and meal timing

Diet was assessed online through 24-h dietary records for 3 non-consecutive days, including one weekend day (i.e., Saturday or Sunday), repeated every 6 months. Participants were asked to report every food and beverage consumed during the day, and the corresponding times. Portion sizes of each food and drink were assessed using comparisons with validated photographs[22], or entered directly in grams or litres. The NutriNet-santé web-based self-administered 24-h dietary records have shown acceptable accuracy and reliability when tested against an interview by a trained dietitian[23] and good validity against blood and urinary biomarkers[24,25]. Additional details for dietary data collection and energy under/over-reporting can be found in Supplemental Method 1. When needed, average dietary intakes and meal timing variables throughout the week, from 24-h records collected during the first 2 years of follow-up, were weighted according to a 5:2 weekday/weekend ratio. For this study, an eating episode was defined as any dietary intake with energy content greater than 0 kcal[19].

Exposure variables

We assumed that non-working days corresponded to weekends in France (i.e. Saturdays and Sundays), while working days corresponded to Monday through Friday. This is the most common working schedule in France[26], and was taken as a proxy for non-working and working days, as this information was not reported by participants.

To compute EJL, we followed the method proposed by Zerón-Rugerio et al.[13], inspired by SJL. First, we computed the eating midpoint for non-working and working days separately, which is defined as the middle time point between the first and the last eating episodes of the day. We used the following formula:

$$\text{Eating Midpoint} = (\text{Time of last intake} - \text{Time of first intake})/2 + \text{Time of first intake}$$

Times of intake were based on the average intake times reported during the first 2 years of follow-up. Then, EJL was computed through the following formula:

$$\text{EJL} = \text{Eating Midpoint (non-working days)} - \text{Eating Midpoint (working days)}.$$

Two concepts were studied as variables of interest:

1) EJL intensity (EJLI), calculated as the absolute value of EJL and used as a continuous variable, was investigated in association with CVD risk, to explore the role of EJL regardless of its direction.
2) EJL categories were modelled, using the original signed EJL variable (i.e., not EJLI) as follows: "Advance" if the Eating Midpoint is more than 1 h earlier on non-working days, than on working days ($\text{EJL} < -1$ h), "Maintenance" if the Eating Midpoint is less than 1 h earlier or later on non-working days, than on working days ($-1\text{ h} \leq \text{EJL} \leq 1$ h), and "Delay" if the Eating Midpoint is 1 h later on non-working days, than on working days ($\text{EJL} > 1$ h).

Graphical representations displayed in Fig. 1 facilitate a clearer visualisation and more intuitive assessment of the derived exposure variables.

Health data and ascertainment of CVD cases

Participants' health status was registered at baseline. Incident health events, including CVD, were self-declared by participants via a biannual follow-up questionnaire or through a dedicated platform permanently available on the NutriNet-santé website. All medical data were reviewed by the research team's physicians, and CVD events were then validated against medical records sent by participants. If needed, the participant's personal physician was contacted. NutriNet-santé is also linked to data from the medico-administrative databases of the National Health Insurance, which includes information about prescribed and reimbursed medications, consultations, hospitalisations and disease leaves. A linkage to the databases from the French National cause-specific mortality registry was available to ascertain date and cause of death.

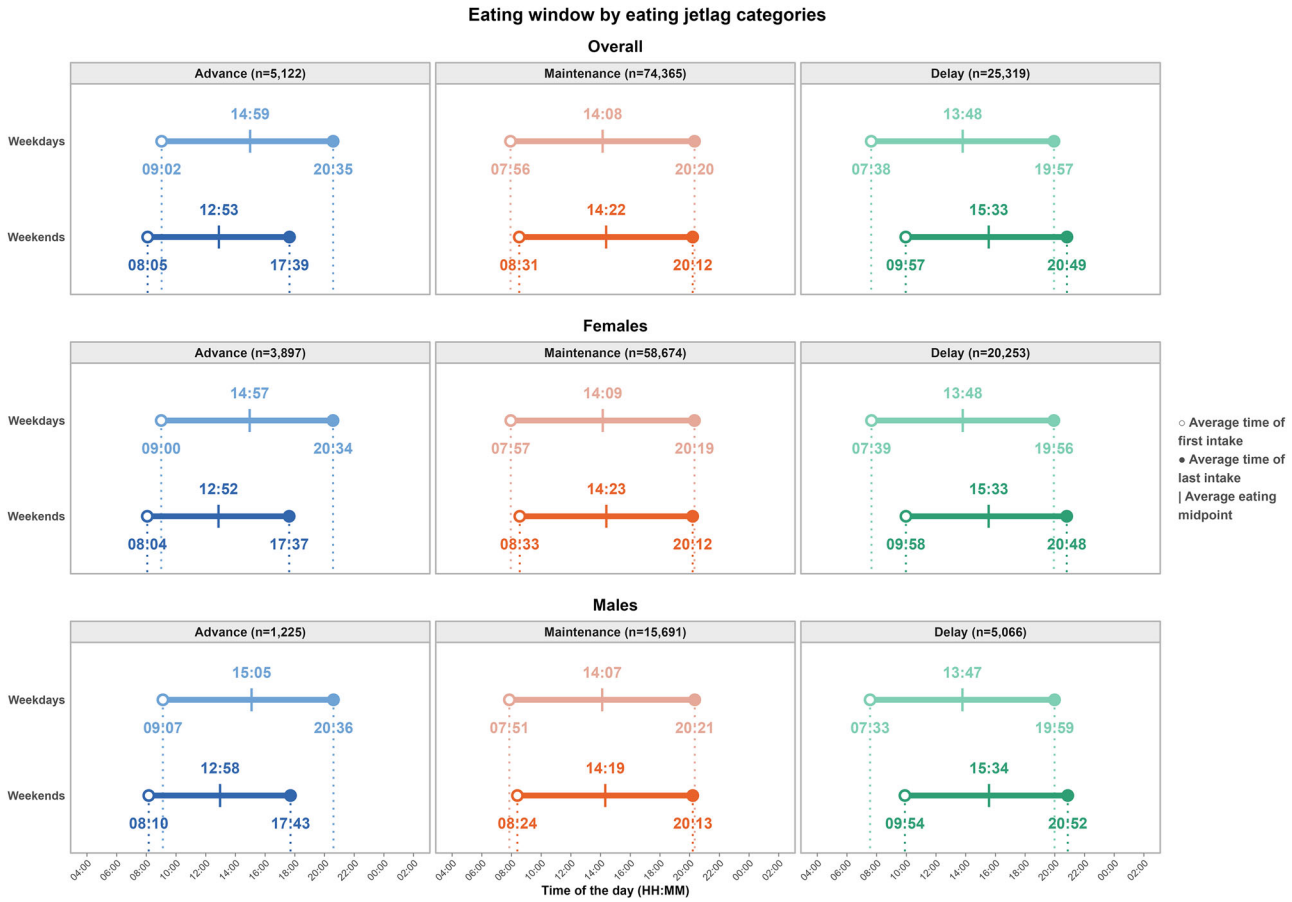


Fig. 1 | Visual representation of EJL by EJL category and sex, NutriNet-Santé cohort, France 2009–2023 ($N = 104,806$). Representation of the timing of the first and last eating occasions on weekdays and weekends according to eating jetlag (EJL) category (Advance, Maintenance, and Delay) in the overall population and among female and male participants. Participants in the Advance category exhibit earlier meal timing on weekends compared with weekdays, whereas those in the Delay category exhibit later meal timing on weekends. Participants in the Maintenance category show rather similar meal timing patterns across weekdays and weekends. Source Data are available in Supplementary Data 1.

Health events were classified according to the International Classification of Diseases (Clinical Modification (ICD-CM, 10th revision)). Incident CVD included incident cases of stroke (I64), transient ischaemic attack (G45.8, G45.9), myocardial infarction (I21), angina (I20.1, I20.8, I20.9), acute coronary syndrome (I20.0, I12.4), and angioplasty (Z95.8). We classified stroke and transient ischaemic attack as cerebrovascular diseases (CVA) and myocardial infarction, angina, acute coronary syndrome, and angioplasty as coronary heart diseases (CHD). In this study, we considered as cases all primary CVD events diagnosed between the inclusion date and December 31, 2023.

Covariates

We used data from baseline questionnaires dedicated to socio-demographic, anthropometric, medical, and physical activity characteristics. We selected the following covariates: age (in years), sex (female, male), socio-professional status (employed, self-employed/farmer, student, unemployed, retired), high-school degrees (no, yes ≤3 years after high-school, yes >3 years after high-school), marital status (single, divorced/separated/widower, married/in couple), level of physical activity according to IPAQ in its short form[27] (low, moderate, high), family history of CVD (yes, no), average daily alcohol intake derived from 24-h records (g/day), smoking status (former smoker, current smoker, never), intensity of smoking (number of pack-years), number of daily eating episodes, number of children aged below 13 years-old living in the household, number of children aged between 14 and 17 living in the household, BMI (kg/m^2), average daily energy intake without alcohol (kcal/day), average time of first eating/drinking episode over the entire week, average time of last eating episode over the entire week, as well as a posteriori dietary profiles (determined by Principal Component Analysis (PCA) on 20 food groups) retaining a western and a healthy pattern (Supplemental method 2). A sleep questionnaire was available for a subsample of 57,098 volunteers of the cohort in 2014, and was used to calculate weighted bedtime over the entire week, weighted total sleep time over the entire week, and SJL.

Statistics and reproducibility

Participants who had completed at least two valid 24-h dietary records during their first 2 years of follow-up, and who had available health follow-up data, were included. We excluded under-reporters for energy intake based on the method proposed by Black[28], using the Goldberg cut-off methodology[29]. Then, we excluded participants having valid dietary 24-h dietary records during only weekdays or only weekends, as the calculation of EJL was not possible. Participants with a history of CVD at cohort inclusion were also excluded. The selection details are presented in the flowchart (Fig. 2). A total of 104,806 participants were included. The characteristics of the study population according to their EJL category (Maintenance, Advance, Delay) were described.

Models

In order to assess associations between EJLI and risk of incident CVD, Cox proportional hazards models were built, and hazard ratios (HR) and

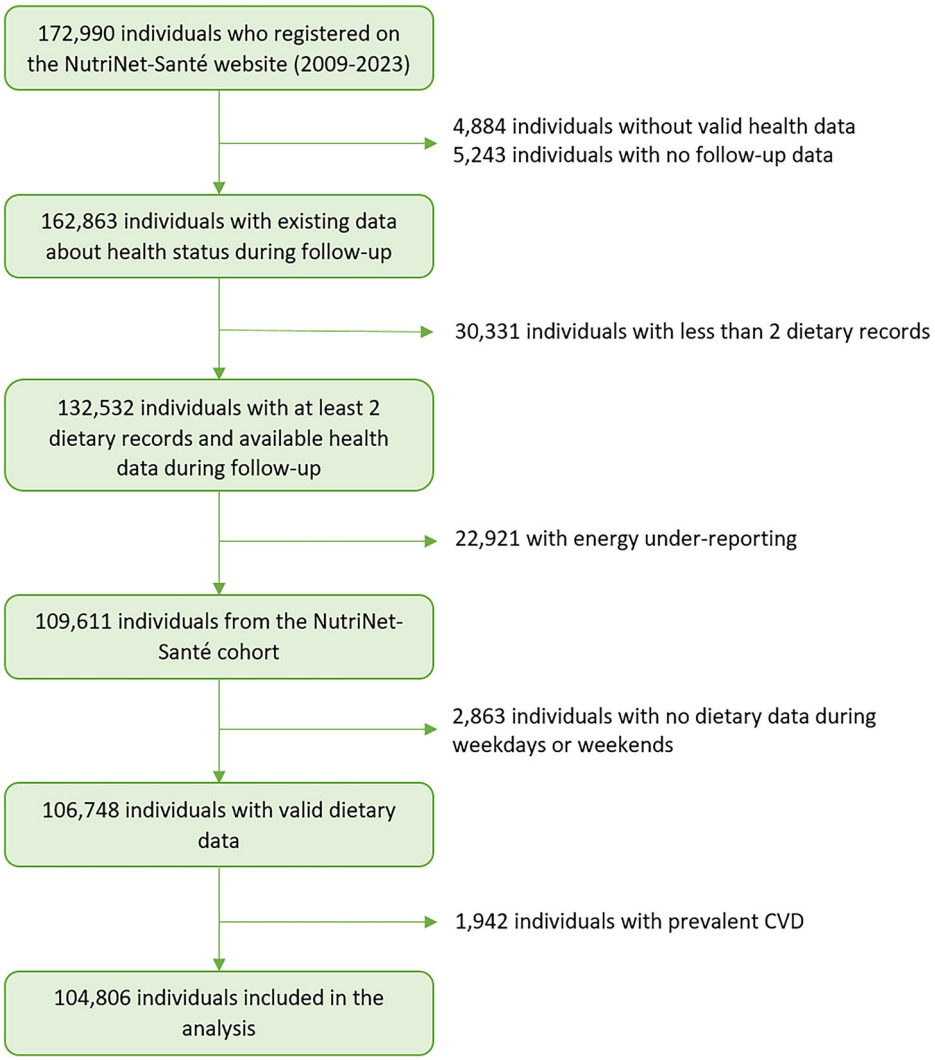


Fig. 2 | Flowchart of participants included from the NutriNet-Santé cohort ($N = 104,806$). Selection process showing initial enrollment, detailed exclusion steps, and the final sample size analyzed.

95% confidence intervals (CIs) were estimated. The same method was then applied to evaluate specifically the association between EJLI and the risk of coronary heart disease and cerebrovascular disease. The proportional hazards assumption was tested using Schoenfeld residuals (30). EJLI was introduced in the model as a continuous variable, and dose–response curves were plotted to assess potential non-linearity. *P* values for non-linearity were calculated. Age was used as the timescale in all models. Participants contributed person-time to the models until the date of CVD diagnosis, the date of death, the date of last completed questionnaire, or December 31, 2023 (date of our administrative censoring for follow-up through medico-administrative databases), whichever occurred first. December 31, 2023 was fixed as our administrative right-censoring date, given the time required by the medical and operational teams to clean the data and validate health events. Cause-specific hazard ratios were computed so that non-CVD death and CVD events other than the one studied (for coronary heart disease and cerebrovascular disease analyses) occurring during follow-up were handled as competing risks, and thus censored. Four nested models were built and tested. The first model was adjusted for potential confounders related to sociodemographic and lifestyle factors, i.e., age (as timescale), sex, socio-professional status, educational level, marital status, physical activity level, family history of CVD, average daily alcohol intake, smoking status, intensity of smoking, average number of daily eating episodes, number of 24-h dietary records, number of children aged less than 13 years old living in the household, as well as number of children aged between 14 and 17 years old living in the household. Model 2 was further adjusted for baseline BMI and the average daily energy intake without alcohol. In order to account for usual food intake timing and diet quality, model 3 was further adjusted for the average times of first and last eating episode of the day throughout the week (as our previous findings suggested associations between later timings and a higher risk of CVD[19]), as well as diet quality, using two dietary pattern variables: the Western diet and the healthy diet patterns, computed using a principal component analysis (detailed in the supplemental material). Finally, to account for confounding by sleep timing, we adjusted model 4 for the weighted bedtime and the total sleep time over the week, on a subsample of the cohort.

To investigate whether EJL direction plays a role, beyond EJLI, we modelled the association between EJL categories (Maintenance [reference], Advance, Delay) and CVD risk using the same adjustment strategy. Despite the absence of a significant interaction between sex and EJLI (*P*-interaction = 0.3), we still investigated sex-specific associations, given the sexual dimorphism in the circadian clock[30] and CVD[31], and the different health and dietary behaviours across genders[32] (childcare responsibilities, lifestyle, occupation). All models in female participants were further adjusted for menopausal condition.

Missing data did not exceed the threshold of 2% for covariates, except for physical activity level (14% of missing data). We performed multiple imputation by chained equations (MICE) on missing values[33], and combined the results for 10 generated databases.

Table 1 | Associations of eating jetlag intensity (EJLI) with the risk of cardiovascular disease, coronary heart disease, cerebrovascular disease, NutriNet-Santé cohort, France 2009–2023 (*N* = 104,806)

	Population	Overall	Females[†]	Males
Cardiovascular disease	No. of cases/non-cases	2368/102,438	1271/81,553	1097/20,885
	Model 1[‡]	1.08 (1.02–1.14)*	1.03 (0.95– 1.12)	1.14 (1.05– 1.23)*
	Model 2[§]	1.08 (1.02–1.14)*	1.03 (0.95– 1.12)	1.14 (1.05– 1.23)*
	Model 3[**]	1.08 (1.02–1.15)*	1.04 (0.96–1.13)	1.13 (1.04–1.23)*
	No. of cases/non-cases	1781/43,997	930/34,865	851/9132
	Model 4[††]	1.07 (0.99–1.15)	0.98 (0.88–1.09)	1.15 (1.04–1.28)*
Coronary heart disease	No. of cases/non-cases	1270/103,536	581/82,243	689/21,293
	Model 1	1.11 (1.0 – 1.19)*	0.98 (0.87– 1.11)	1.21 (1.11– 1.33)*
	Model 2	1.10 (1.02–1.19)*	0.98 (0.86– 1.10)	1.21 (1.11– 1.32)*
	Model 3	1.09 (1.01– 1.18)*	0.98 (0.86– 1.11)	1.18 (1.07– 1.30)*
	No. of cases/non-cases	952/44,826	416/35,379	536/9447
	Model 4	1.11 (1.00– 1.22)*	0.95 (0.81– 1.13)	1.20 (1.07– 1.35)*
Cerebrovascular disease	No. of cases/non-cases	1098/103,708	690/82,134	408/21,574
	Model 1	1.04 (0.96 – 1.14)	1.08 (0.97– 1.20)	0.97 (0.83– 1.13)
	Model 2	1.04 (0.95 – 1.14)	1.08 (0.97–1.20)	0.97 (0.83–1.14)
	Model 3	1.06 (0.97– 1.16)	1.09 (0.98– 1.22)	1.00 (0.85– 1.17)
	No. of cases/non-cases	829/44,949	514/35,281	315/9668
	Model 4	1.01 (0.90 – 1.14)	0.99 (0.86– 1.15)	1.02 (0.85– 1.24)

The results shown in this table were derived from Cox proportional hazards models, with statistical significance assessed using two-sided Wald tests.
*$P < 0.05$.
[†]All the models were further adjusted for menopausal status at enrolment.
[‡]Adjusted for age, sex, socio-professional status, high-school degree, marital status, level of physical activity, family history of CVD, average daily alcohol intake, smoking status, intensity of smoking, average number of daily eating episodes, number of 24-h dietary recalls, number of children aged less than 13 years old, and those aged between 14 and 17 years old living with the participant.
[§]Same as [‡] but with additional adjustments for BMI and average daily energy intake without alcohol.
[**]Same as [§] but with additional adjustments for times of first and last eating episodes of the day, Western diet and healthy diet patterns.
[††]Same as [**] but with additional adjustments for weighted bedtime and total sleep time.

Stratified and sensitivity analyses

As the objective is to estimate the association of EJL with the risk of CVD, assuming the most common working scheme in France, we performed two sensitivity analyses excluding (1) participants reporting a first meal after 3 pm or a last meal before 3 pm, as a proxy for night-work, and (2) unemployed participants at baseline.

As later first and last eating occasions were associated with CVD risk in NutriNet-santé[19], and first intake was an effect modifier of the associations between nighttime fasting duration and type-2 diabetes[20], we investigated if the link between EJLI and CVD risk is different according to time of first intake, through stratified analyses on the median time of first intake.

To disentangle EJL from SJL, we additionally adjusted our models for SJL, and we also tested interactions by SJL. Lastly, we also performed an analysis for a minimally adjusted model for age, sex and sociodemographic variables to isolate the confounding magnitude linked to lifestyle factors alone.

The data management and the descriptive analyses were performed on SAS Enterprise Guide (8.3 version). All the statistical analyses were conducted using R-4.3.2 (The R Project for Statistical Computing, Vienna, Austria), using the survival package. All tests were two-sided Wald tests, and a P value < 0.05 was considered significant. No specific adjustments were made for multiple comparisons. Code book and analytic code will be made available upon request, pending application and approval, by sending an email to collaboration@etude-nutrinet-sante.fr.

Results

A total of 104,806 participants (79.0% females) with a mean age at baseline of 42.7 ± 14.6 years were included (flowchart in Fig. 2). The baseline characteristics of the study population according to their EJL category are presented in Table S2.

Overall, participants who maintained their eating rhythms similar on weekends and on weekdays (i.e., the Maintenance category) accounted for 71.0% of our population and were more likely to be older, married or partnered, retired, and to have children aged less than 13 years old living in their household than other participants. Almost 5% of our participants were assigned to the "Advance" category (having earlier eating rhythms on the weekend compared to the weekdays). They were more inclined to be males, to have a lower education level, and to be unemployed. Participants in the "Delay" category (having later eating rhythms on the weekend compared to the weekdays) represented 24.2% of our population and tended to be younger and single. A higher proportion of students and employed people belonged to this category. Daily smoking was more prevalent in both the "Advance" and "Delay" categories.

EJL intensity and risk of total CVD, coronary heart disease and cerebrovascular disease

During a median follow-up time of 8.1 years (814,338 person-years), 2368 incident cases of CVD, including 1270 CHD and 1098 CVA were identified. The associations between EJLI and CVD, CHD and CVA risk are presented in Table 1. The proportional hazard assumption was met (Fig. S1). EJLI was associated with a higher CVD risk (HR per 1-h increase = 1.08 [95% CI: 1.02–1.14], $P = 0.008$ after adjustment for model 1 covariates). Adjusting for models 2 and 3 covariates did not have an impact on the estimates. After adjustment for sleep data in model 4 (sub-sample), the associations were slightly attenuated (HR = 1.07 [95% CI: 0.99–1.15], $P = 0.09$). Associations were specific to male participants (HR = 1.14 [95% CI: 1.05–1.23], $P = 0.002$ in model 1 and 1.15 [95% CI: 1.04–1.28], $P = 0.005$ in model 4). No associations were detected in female participants in our study. Associations with CHD risk were also observed in the overall sample, but specific to male

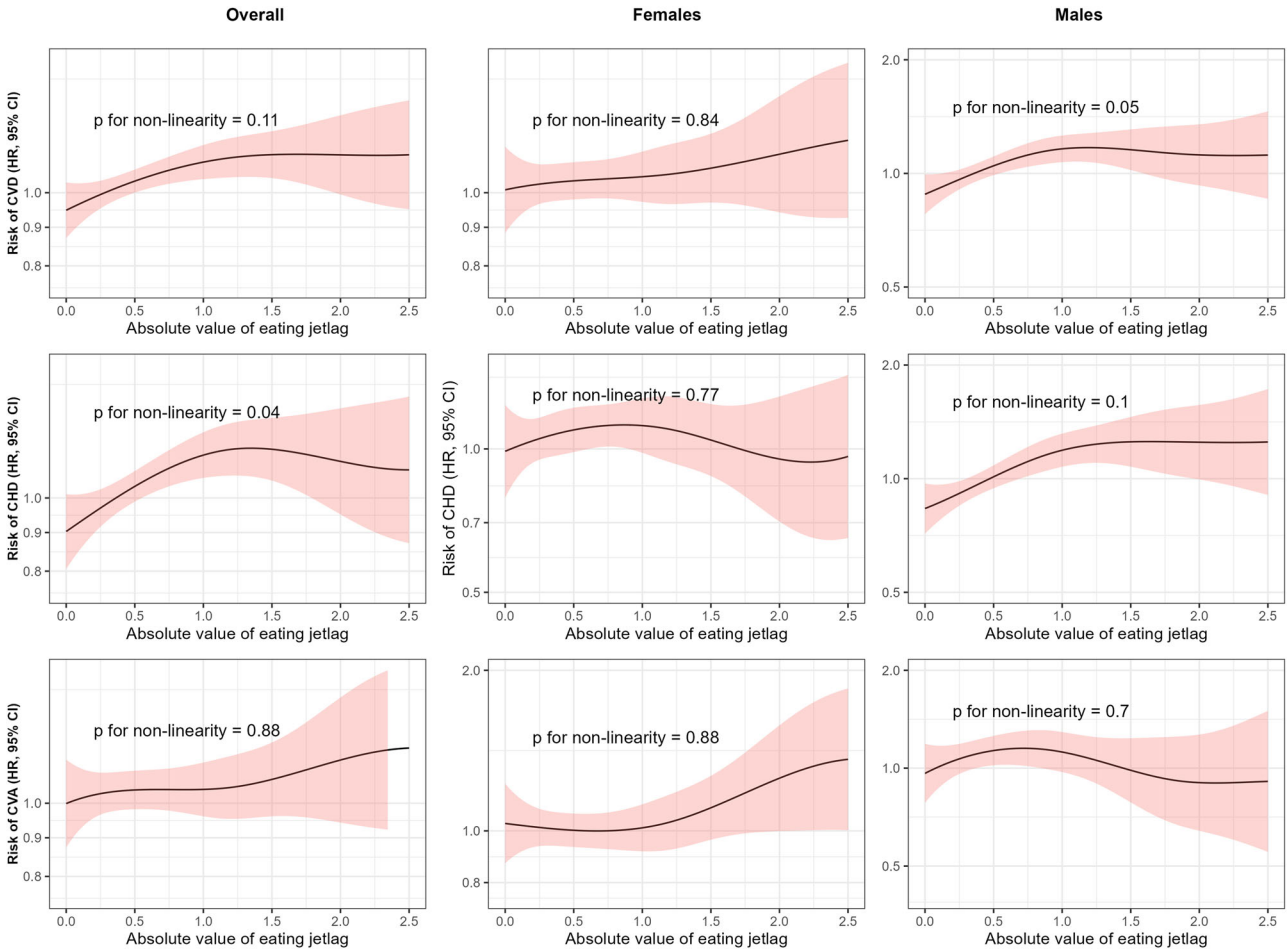


Fig. 3 | Dose–response curves of the relation between eating jetlag intensity and the risk of CVD, coronary heart disease and cerebrovascular disease adjusted for model 1 covariates ($N = 104,806$). Associations between eating jetlag intensity and risk of cardiovascular disease (CVD), coronary heart disease (CHD) and cerebrovascular disease (CVA), among the overall population, female participants and male participants. Hazard ratios (HRs) and 95% confidence intervals (shaded area) were estimated using a Cox proportional hazards model with a penalised spline term for eating jetlag intensity, with statistical significance assessed using two-sided Wald tests. Models were adjusted for age, sex, socio-professional status, high-school degree, marital status, level of physical activity, family history of CVD, average daily alcohol intake, smoking status, intensity of smoking, average number of daily eating episodes, number of 24h-dietary recalls, number of children aged less than 13 years old, and those aged between 14- and 17-years old living with the participant. Source Data are available in Supplementary Data 2.

participants (HR = 1.11 [95% CI: 1.00–1.22], $P = 0.04$ in model 4 for the overall sample, and 1.20 [95% CI: 1.07–1.35], $P = 0.002$ in model 4 among male participants). There was no evidence of an association between EJLI and CVA risk. Dose-response curves (Fig. 3) suggested a plateau effect for CVD and CHD starting around 1.5 h of EJLI. Models adjusted only for age, sex and sociodemographic factors showed very similar estimates to model 1, suggesting a very minor additional confounding by lifestyle factors, when added to sociodemographic factors (Tables S3 and 4).

EJL categories and risk of total CVD, coronary heart disease and cerebrovascular disease

To explore if the association between EJLI and CVD was driven by a specific direction, we investigated in Table 2 the associations between EJL categories (Advance, Maintenance, Delay) and CVD, CHD and CVA risk. The proportional hazard assumption was met (Fig. S2). In male participants, we observed associations with CVD and CHD both in the "Advance" and the "Delay" categories, *vs*. the "Maintenance" category, though the associations were stronger in the "Advance" category: for CVD, HR advance vs. maintenance = 1.44 [95% CI: 1.08–1.93], $P = 0.01$ in model 4; and HR delay vs. maintenance = 1.14 [95% CI: 0.92–1.42], $P = 0.2$ in model 4; for CHD, HR advance vs. maintenance = 1.68 [95% CI: 1.19–2.39], $P = 0.003$ in model 4; and HR delay vs. maintenance = 1.36 [95% CI: 1.05–1.77], $P = 0.02$ in model 4. The trends were similar, though not significant, in the overall sample. Consistent with analyses on EJLI, no associations were detected in females, nor with CVA (Table 2).

Sensitivity and stratified analyses

Excluding night-shift workers or unemployed participants had no major impact on the results (Tables S5–8). Results were also similar after adjusting for SJL (Tables S9 and 10). There was no interaction between EJLI and SJL intensity: *P*-interaction = 0.2 for CVD, 0.2 for CHD and 0.6 for CVA (data not tabulated).

We also stratified the analyses according to the median of time of first eating episode (i.e., 8:02 am) (Table S11). The association between EJLI and the risk of CVD, CHD and CVA was only observed in participants having later first meals.

Discussion

In this study, EJL intensity was associated with the risk of CVD and CHD, specifically in male participants. Our findings suggest higher risks in participants with either advanced or delayed meal timing patterns on weekends compared to weekdays, relative to those who maintained a consistent pattern. These associations were independent of diet quality and remained significant after adjusting for bedtime, total sleep time, and social jetlag.

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Table 2 | Associations of eating jetlag categories and the risk of cardiovascular disease, coronary heart disease, and cerebrovascular disease, NutriNet-Santé cohort, France 2009–2023 (*N* = 104,806)

	Population	Overall			Females[††]			Males		
		Advance ≤ 1 h	Maintenance Between ≥ −1h and ≤ 1 h (ref.)	Delay > 1 h	Advance ≤1 h	Maintenance Between ≥ -1h and ≤ 1 h (ref.)	Delay > 1 h	Advance ≤ 1 h	Maintenance Between ≥ −1h and ≤ 1 h (ref.)	Delay > 1 h
CVD	No. of cases/ non-cases	116/5006	1889/72,476	363/24,956	54/3843	1008/57,666	209/20,044	62/1163	881/14,810	154/4912
	Model 1[‡‡]	1.11 (0.92–1.34)	1.00	1.09 (0.97–1.23)	1.00 (0.76– 1.32)	1.00	1.03 (0.88 –1.21)	1.23 (0.95– 1.60)	1.00	1.18 (0.99–1.41)
	Model 2[§§]	1.10 (0.91– 1.33)	1.00	1.09 (0.97 –1.22)	1.00 (0.76– 1.32)	1.00	1.03 (0.88 –1.20)	1.21 (0.93– 1.57)	1.00	1.17 (0.98–1.40)
	Model 3***	1.10 (0.91– 1.33)	1.00	1.09 (0.97–1.23)	1.02 (0.77– 1.35)	1.00	1.04 (0.89 –1.21)	1.19 (0.91– 1.55)	1.00	1.16 (0.97–1.39)
	No. of cases/ non-cases	81/1526	1456/33,367	244/9104	30/1165	758/26,293	142/7407	51/361	698/7074	102/1697
	Model 4[†††]	1.15 (0.92– 1.45)	1.00	1.10 (0.96–1.27)	0.86 (0.59– 1.25)	1.00	1.07 (0.88 –1.29)	1.44 (1.08– 1.93)*	1.00	1.14 (0.92–1.42)
Coronary heart disease	No. of cases/ non-cases	70/5052	1000/73,365	200/25,119	24/3873	465/58,209	92/20,161	46/1179	535/15,156	108/4958
	Model 1	1.24 (0.97– 1.58)	1.00	1.15 (0.98 –1.35)	0.94 (0.62– 1.43)	1.00	0.94 (0.74 –1.19)	1.52 (1.12– 2.06)*	1.00	1.39 (1.12–1.73)*
	Model 2	1.23 (0.96– 1.57)	1.00	1.14 (0.97–1.33)	0.94 (0.62– 1.43)	1.00	0.93 (0.74 –1.18)	1.49 (1.10 – 2.02)*	1.00	1.38 (1.11–1.71)*
	Model 3	1.20 (0.94– 1.54)	1.00	1.13 (0.96–1.32)	0.95 (0.62– 1.44)	1.00	0.93 (0.74 –1.18)	1.43 (1.05– 1.95)	1.00	1.35 (1.09–1.68)*
	No. of cases/ non-cases	49/1558	768/34,055	135/9213	13/1182	340/26,711	63/7486	36/377	428/7344	72/1727
	Model 4	1.31 (0.98– 1.76)	1.00	1.19 (0.98–1.44)	0.83 (0.47– 1.46)	1.00	1.03 (0.78 –1.36)	1.68 (1.19– 2.39)*	1.00	1.36 (1.05–1.77)*
Cerebrovascular disease	No. of cases/ non-cases	46/5076	889/73,476	163/25,156	30/3867	543/58,131	117/20,136	16/1209	346/15,345	46/5020
	Model 1	0.95 (0.70– 1.28)	1.00	1.03 (0.87–1.23)	1.06 (0.73– 1.53)	1.00	1.12 (0.91–1.38)	0.79 (0.48– 1.31)	1.00	0.85 (0.62–1.17)
	Model 2	0.95 (0.70– 1.28)	1.00	1.03 (0.86 –1.22)	1.06 (0.73– 1.53)	1.00	1.12 (0.91 –1.37)	0.78 (0.47– 1.29)	1.00	0.85 (0.62–1.17)
	Model 3	0.97 (0.72– 1.31)	1.00	1.04 (0.87–1.24)	1.08 (0.74– 1.57)	1.00	1.13 (0.92–1.39)	0.80 (0.48– 1.33)	1.00	0.87 (0.63–1.20)
	No. of cases/ non-cases	32/1575	688/34,135	109/9239	17/1178	418/26,633	79/7470	15/397	270/7502	30/1769
	Model 4	0.97 (0.68– 1.40)	1.00	1.01 (0.82–1.24)	0.89 (0.54– 1.45)	1.00	1.09 (0.85 –1.41)	1.06 (0.63– 1.80)	1.00	0.82 (0.55 –1.22)

The results shown in this table were derived from Cox proportional hazards models, with statistical significance assessed using two-sided Wald tests.

*$P < 0.05$.

[††]All the models were further adjusted for menopausal status at enrolment.

[‡‡]Adjusted for age, sex, socio-professional status, high-school degree, marital status, level of physical activity, family history of CVD, average daily alcohol intake, smoking status, intensity of smoking, average number of daily eating episodes, number of 24-h dietary recalls, number of children aged less than 13 years old, and those aged between 14 and 17 years old living with the participant

[§§]Same as [‡‡] but with additional adjustments for BMI and average daily energy intake without alcohol.

***Same as [§§] but with additional adjustments for times of first and last eating episodes of the day, Western diet and healthy diet patterns.

[†††]Same as *** but with additional adjustments for weighted bedtime and total sleep time.

We investigated the long-term associations between EJL and the risk of developing CVD, in a large-scale sample of French adults. Our results in the whole sample align with evidence from a cross-sectional and a 1-year prospective analysis of a study conducted amongst women in the USA, on EJL and CVD risk factors[14]. This study suggested a significant cross-sectional association of meal timing irregularity between rest and working days with a higher BMI, and a longitudinal association after 1 year between EJL and both diastolic and systolic blood pressure. The associations we observed with CVD and CHD risk were specific to male participants. Even though the comparison between the 2 studies is not straightforward, as the outcome and the design were different, several factors are worth mentioning: the average EJL intensity in the study by Makarem et al.[14] was greater than that in our study (1.9 ± 1.8 *vs.* 0.8 ± 0.8 h, respectively), possibly due to different socio-professional profiles and cultural habits. Another reason could be the younger age, higher BMI, and lower educational levels in the American study. In a study amongst 1703 Japanese male students[34], the authors suggested an association between a higher EJL and a higher weekly frequency of post-dinner snacking. In our sample, 14.4% of the last eating episodes of the day in the "Maintenance" category were classified as snacks by the participants, i.e. eating episodes that were not reported as meals (breakfast, lunch, dinner) by participants, compared to 16.0% in the "Delay" category and 18.2% in the "Advance" category. Therefore, the nutritional quality of the last eating episode might partly explain our results, despite the adjustment for overall diet quality.

A cross-sectional study in Spanish and Mexican students found a positive link between EJL and BMI[13]. Our descriptive (unadjusted) analyses showed no clear trend between EJL and BMI. Age and cultural differences may explain these differences, as meal times in Spain and Mexico are usually later than in the French population[35]. Adjusting for baseline BMI in our models did not have a major effect on our estimates, suggesting that the mediating role of BMI in our population is minor.

As a more extensively studied phenomenon, SJL has a larger body of research than EJL[11,12], providing a solid foundation for comparison with our results, even if the link between EJL and SJL is not straightforward to elucidate. After additionally adjusting our models for SJL, minor variations of HRs were observed, implying a lesser confounding effect of SJL in the association between EJL and risk of CVD; even though we cannot entirely rule out the role of SJL in our associations[11,12], given the strong conceptual correlation between EJL and SJL (Spearman correlation coefficient = 0.23). Studying EJL specifically in large populations with a high exposure to SJL could offer insights into whether interventions targeting meal timing throughout the week might mitigate the negative health impacts of social jetlag.

Times of first and last intake were previously associated with CVD risk in our cohort[19]. However, adjusting for these factors (model 3) had no effect on our estimates. On the other hand, our findings suggested a slightly higher EJLI in individuals with a later first intake, and an effect modification by time of first intake, revealing a stronger association between EJL and CVD among those having a later first intake, which is somewhat consistent with previous findings suggesting that SJL can be more emphasised in participants with a late chronotype[8]. If our results are corroborated by other large-scale long-term studies, they would support recommending having both early first eating occasions and eating at regular times between weekdays and weekends.

We observed a plateau effect from an approximate threshold of 1.5 h of EJLI (Fig. 3). This might be explained by a restricted exposure range, as most participants in our study have only a modest jetlag intensity; therefore, there may be too few extreme values to show a stronger increase at higher levels. In addition, circadian disruption linked to EJL may reach a point where further delay or advance no longer produces much additional damage. This is consistent with previous studies exploring the link between SJL and other health outcomes, suggesting non-linear associations (e.g. social jetlag and BMI[36], social jetlag and risk of depression[37]).

Our associations were specific to male participants: several hypotheses can explain this finding. First, the higher absolute risk of cardiovascular events in men compared to women may partly account for these results. Second, lifestyle habits, rhythms and socio-professional activities could be different between men and women, as these behaviours are determinants of EJL. Furthermore, sexual dimorphism in energy metabolism linked to meal timing were highlighted in mice in a study where both male and females mice either underwent a 9-h time-restricted feeding (TRF) or were fed ad libitum[38]. The benefit of TRF on body weight gain was only detected amongst male mice. Sexual dimorphisms in the circadian liver transcriptome were also reported in murine models[39], leading to different metabolic responses in males and females, possibly explaining differences in energy metabolism. Circadian endocrine rhythms are also sensitive to sex dimorphisms[30], and the hormonal secretions are particularly different between premenopausal women and men of the same age. Women also tend to exhibit an earlier chronotype compared to men due to differences in anatomy, hormone secretion, such as cortisol, and distribution of gonadal hormone receptors[40,41]. Even though biological and molecular mechanisms underlying the links between EJL and CVD risk are not entirely clear, the role of clock genes and the importance of peripheral clocks in metabolic health is no longer in doubt[42–44], nor is the role of food intake in (de) regulating circadian rhythms. Indeed, food timing is a *zeitgeber* for peripheral clocks, and is therefore an environmental cue that entrains the peripheral clock, the same way light entrains the central clock[45,46]. On top of that, food entrainment on peripheral clocks is thought to be dominant over the entrainment by the central clock[47]. In the heart, TRF could improve mitochondrial structure, nitric oxide (NO) signalling, and glucose utilisation, and promote rhythmic activity in pathways associated with cytoskeletal organisation and muscle differentiation[48]. Circadian clocks regulate key physiological processes such as gene transcription[49–51], myocardial contractility[52], metabolic responses to various substrates[53,54], and mitochondrial function[55–58], that are all involved in the cardiovascular system. The possible alteration of mitochondrial dynamics caused by the disruption of the circadian rhythm or its clock components, whether through changes in the light/dark cycle or misaligned eating patterns, could promote cardiovascular disease[55,57]. If eating jetlag were to occur every week, it implies that in cases of severe EJL, there could be a chronic misalignment between behavioural rhythms and circadian rhythms.

To our knowledge, this study is the first to investigate the prospective association between EJL and CVD risk. The large sample size as well as the repeated and detailed dietary questionnaires are among the strengths of the study. The format of the dietary questionnaires, i.e., repeated 24-h records, available during weekdays (3.8 ± 2.2) and weekends (2.0 ± 1.1) allowed us to compute EJL, without using an ad-hoc specific questionnaire on EJL that might influence the answers. The various questionnaires concerning socio-demographic, anthropometric, lifestyle, physical activity, and sleep characteristics updated regularly helped curb the effect of confounding factors. The prospective design of the study offers the possibility of studying the long-term association between EJL and the risk of developing CVD. We used validated CVD cases and multiple sources to achieve an accurate outcome ascertainment.

The main limitation of this study is that we assumed, as data on working schedule was not collected, that Monday to Friday corresponded to working days, and Saturday and Sunday to rest days. This is probably not the case for all our study participants; however, as our study included a major part of individuals with a higher educational level, we therefore assumed that these participants mainly follow professional cycles dictated by office hours, rather than irregular cycles that workers or farmers might follow. This might have underestimated the prevalence and intensity of EJL in our sample. Second, our sample included retired participants, who are generally less exposed to EJL, as their rhythms are less disrupted on weekends compared to weekdays. However, this population accounts for the most incident cases of CVD, as age is among the strongest risk factors for CVD. Consequently, excluding them would compromise the statistical power of our study, which would then become underpowered to detect associations. Moreover, CVDs are diseases with a long latency period. It is therefore unlikely that a low exposure to EJL after retirement could play a more significant role than

lifetime exposure to EJL prior to retirement. Similarly, we can also assume that even younger participants in our sample who are currently working and experiencing EJL will no longer (or at least to a lesser extent) experience it after retirement. Hence, it appears essential to consider trajectory data to estimate lifetime EJL, which is what we are currently investigating in the team with *ad hoc* questionnaires. Third, although multiple adjustments were made to limit confounding bias in our analyses, our study is an observational study, and no causal link can be established from this study alone. Indeed, our groups were not randomised, and despite our adjustment strategy, residual confounding cannot be excluded, due to unmeasured or mismeasured variables: Lifestyle factors seemed to have minor effects on the risk of CVD in relation to EJL in our study, since the results in the model adjusted only for age, sex and sociodemographic variables showed very similar estimates as those in model 1. This suggests that the association between EJLI and cardiovascular outcomes may be more explained by sociodemographic variables than by lifestyle factors, even though residual confounding by other factors cannot be entirely ruled out, for instance, exposure to light-at-night, stress at work, use of recreational drugs, as well as timing of physical activity and medication. However, our study provided a useful tool to assess circadian behaviours as a real-life exposure, coupled with a long follow-up, that would have been challenging to set up in a randomised controlled setting. With a higher proportion of women (79% of women in the study), besides having a higher socioeconomic status and health-oriented behaviours, our study population is not representative of the French population, and thus, this selection bias makes our results difficult to extrapolate to the general population[59]. Furthermore, a lower incidence of CVD was observed in this cohort, compared to the French population[60]. We considered 17.3% of the eligible participants as under-energy reporters and excluded them from the study. This proportion of under-reporters is common; for instance, in the nationally representative INCA 3 study conducted in 2016 by the French Food Safety Agency[61], 18% of adult participants were identified as under-reporters using the Black method[28]. Under-reporters in our study were older and were more inclined to be male and current smokers, to have a higher BMI and alcohol intake, and a lower educational level and monthly income[62]. Although their exclusion may limit the generalisability of the findings, it was necessary in order to avoid important exposure classification bias. Moreover, sleep variables are highly correlated with meal times. Despite our adjustment for sleep timing and duration, the effect of SJL could not be entirely disentangled from EJL. The data we had on sleep timing dated back to 2014, so we also assumed that sleeping behaviours remained the same during follow-up. Chronotype, and to another extent, the actual biological circadian rhythm of participants, which was not considered here, could have provided additional information on the real gap between biological rhythm and social rhythm. Still, measuring the actual biological circadian rhythm would be very difficult to implement within large cohorts such as ours, as it requires monitoring biomarkers for a large number of people. Lastly, EJL focuses on meal timing regularity in relation to social and professional obligations and constraints: it therefore covers a very specific aspect of meal timing regularity, and not the entire field. Other methods allowing for the study of intraindividual variability—by modelling the standard deviation of meal times throughout the whole week, or across a large number of repeated 24 h dietary records—in relation to cardiovascular health, could also be of great interest.

To conclude, this prospective study suggests a link between EJL and a higher risk of cardiovascular disease. Our findings indicate that irregular eating times between weekdays and weekends, both as later or earlier schemes, are associated with a higher cardiovascular risk, specifically in males and later chronotypes. If our results are confirmed in other studies, meal timing and regularity could be an important focus for interventions to reduce chronic disease risk and alleviate the associated public health burdens.

Data availability

Raw data described in the manuscript are protected and are not available due to data privacy laws, according to French regulations. Data can be made available upon request, pending application and approval. Researchers from public institutions can submit a collaboration request, including information on the institution and a brief description of the project, to collaboration@etude-nutrinet-sante.fr. All requests will be reviewed by the steering committee of the NutriNet-Santé study within 8–12 weeks. If the collaboration request is accepted, a data access agreement will be necessary, and appropriate authorisations from the competent administrative authorities may be needed. In accordance with existing regulations, no personal identification data will be accessible. The NutriNet-Santé food composition database is available in the book "Table de composition des aliments, Etude NutriNet-Santé, Editions Inserm— Economia", ISBN-10: 2717865373 ISBN-13: 978-2717865370. The source data for Figs. 1 and 3 are available in Supplementary Data 1 and 2, respectively.

Code availability

The R and SAS code used in this study is available upon request.

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Author contributions

X.L.F. and B.S.: designed the study; X.L.F., E.O., A.P.C. and B.S.: performed the data management for meal timing variables in the NutriNet-Santé database; X.L.F.: performed statistical analysis; B.S. supervised statistical analysis; X.L.F.: drafted the manuscript; BS: supervised the writing; X.L.F., E.O., A.P.C., L.K.F., L.B., A.B., S.P., V.D., M.D.T., M.T., S.H., C.J., E.K.G., V.A.A., C.L., A.M., H.G., D.J. and B.S. contributed to the data interpretation and revised each draft for important intellectual content. X.L.F., E.O., A.P.C., L.K.F., L.B., A.B., S.P., V.D., M.D.T., M.T., S.H., C.J., E.K.G., V.A.A., C.L., A.M., H.G., D.J. and B.S. read and approved the final manuscript. B.S. had full access to all the data in the study. B.S. takes responsibility for the integrity of the data and the accuracy of the data analysis; he is the guarantor. The corresponding authors (X.L.F. and B.S.) attest that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Competing interests

All authors have completed the ICMJE disclosure form at http://www.icmje.org/disclosure-of-interest/ and declare: no support from any for-profit organisation for the submitted work; no financial relationships with any organisation that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work. The authors declare no competing interests.

Additional information

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