

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

Corresponding Author: Ms Xuân Le Folcalvez

This file contains all reviewer reports in order by version, followed by all author rebuttals in order by version.

Version 0:

Reviewer comments:

Reviewer #1

(Remarks to the Author)

Le Folcalvez et al. investigated the long-term association between “Eating Jetlag” (weekday–weekend variability in meal timing) and cardiovascular disease risk within the large prospective cohort NutriNet-Santé. The topic is of significant public health relevance. However, several aspects of the study could be further strengthened to enhance its overall quality:

Major: the writing in the Introduction

The first paragraph line 91-100 is too length, recommended to summarize in 1-2 sentences, could start from the different eating behaviors mentioned in the first sentence of the third paragraph.

The importance of eating rhythms needs to be strengthened.

Recommend showing a Figure for the created eating jetlag, which may enhance visualization.

Did you assess the interaction between EIJL and sex on the risk of CVDs??

The quality control procedures for the 24-hour dietary record are not sufficiently detailed. Please provide specific information regarding completion rates, data integrity checks, and methods for handling extreme energy intake values.

The performed sensitivity analyses excluded the unemployed and proxies for shift workers, but no assessment has been conducted for retired participants (16.5% at baseline). Retirees lack a typical workday, and their inclusion may dilute or confound the true association.

Though the manuscript incorporated social jetlag as an adjustment variable in sensitivity analyses, I wonder what the correlation between EIJL is and SJL, nor did it validate their independent contributions to CVD risk through interaction or stratified analyses. Therefore, we cannot rule out the possibility that the observed association between EIJL and CVD risk is actually driven by SJL. Better to supplement the results of the EIJL-SJL correlation analysis and add an interaction analysis.

Reviewer #2

(Remarks to the Author)

Leveraging data from the NutriNet-Santé cohort, this study reported that irregular eating timing between weekdays and weekends is associated with a higher cardiovascular risk, regardless of the direction of whether the difference reflects earlier or later timing on weekends. The topic is important, and the manuscript is well written. The study has several advantages including prospective cohort design, repeated dietary recall measurements, and comprehensive covariate adjustment. I only have a few minor comments.

1. CVD events were identified through biannual follow-up questionnaires. It remains unclear how December 31, 2023 was used to define person-time. Typically, the end of follow-up should be defined as the earliest of the date of CVD event, date of death, or date of last follow-up.

2. Figs 2-4 present related results and could be merged into a single figure to improve readability and reduce redundancy.

Reviewer #3

(Remarks to the Author)

Thank you for inviting me to review this manuscript. Please see my comments below.

1. Line 38: please make it explicit that the mean of 5.8 (SD 3.2) refers to the number of dietary recalls.

2. Please provide model estimates adjusted only for sociodemographic variables to allow clearer insights into the effects of lifestyle factors. In addition, please justify the adjustment for the average timing of the first and last eating episodes across the week in Model 3.
3. Are there any indications of effect modification by age, socioeconomic status, and family history of CVD?
4. It is interesting that adjustment for commonly considered confounders has little impact on the observed associations. This may suggest that the association between EJLI and cardiovascular outcomes may be largely independent of these factors, potentially reflecting distinct etiological pathways. Please expand the discussion on this point.
5. Please briefly explain the observation (Line 320) that the associations between EJLI and the risks of CVD were observed only among participants with later first meals.
6. Please further elaborate on the observed non-linear associations with possible explanations and implications.
7. Are there any other ways to define EJLI. What are the limitations of using this definition.
8. Please comment on the potential influence of attrition as approximately 70,000 participants were excluded from the analysis.

Version 1:

Reviewer comments:

Reviewer #1

(Remarks to the Author)

All major concerns have been adequately addressed. I have no further comments.

Reviewer #2

(Remarks to the Author)

The authors have sufficiently addressed my concerns, and I don't have further comments.

Reviewer #3

(Remarks to the Author)

The authors have sufficiently addressed my comments. I have no further comments.

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Reviewers' comments:

Reviewer #1 (Remarks to the Author):

Le Folcalvez et al. investigated the long-term association between “Eating Jetlag” (weekday–weekend variability in meal timing) and cardiovascular disease risk within the large prospective cohort NutriNet-Santé. The topic is of significant public health relevance. However, several aspects of the study could be further strengthened to enhance its overall quality:

We thank Reviewer 1 for this careful review of our manuscript.

1. Major: the writing in the Introduction

The first paragraph line 91-100 is too length, recommended to summarize in 1-2 sentences, could start from the different eating behaviors mentioned in the first sentence of the third paragraph. The importance of eating rhythms needs to be strengthened.

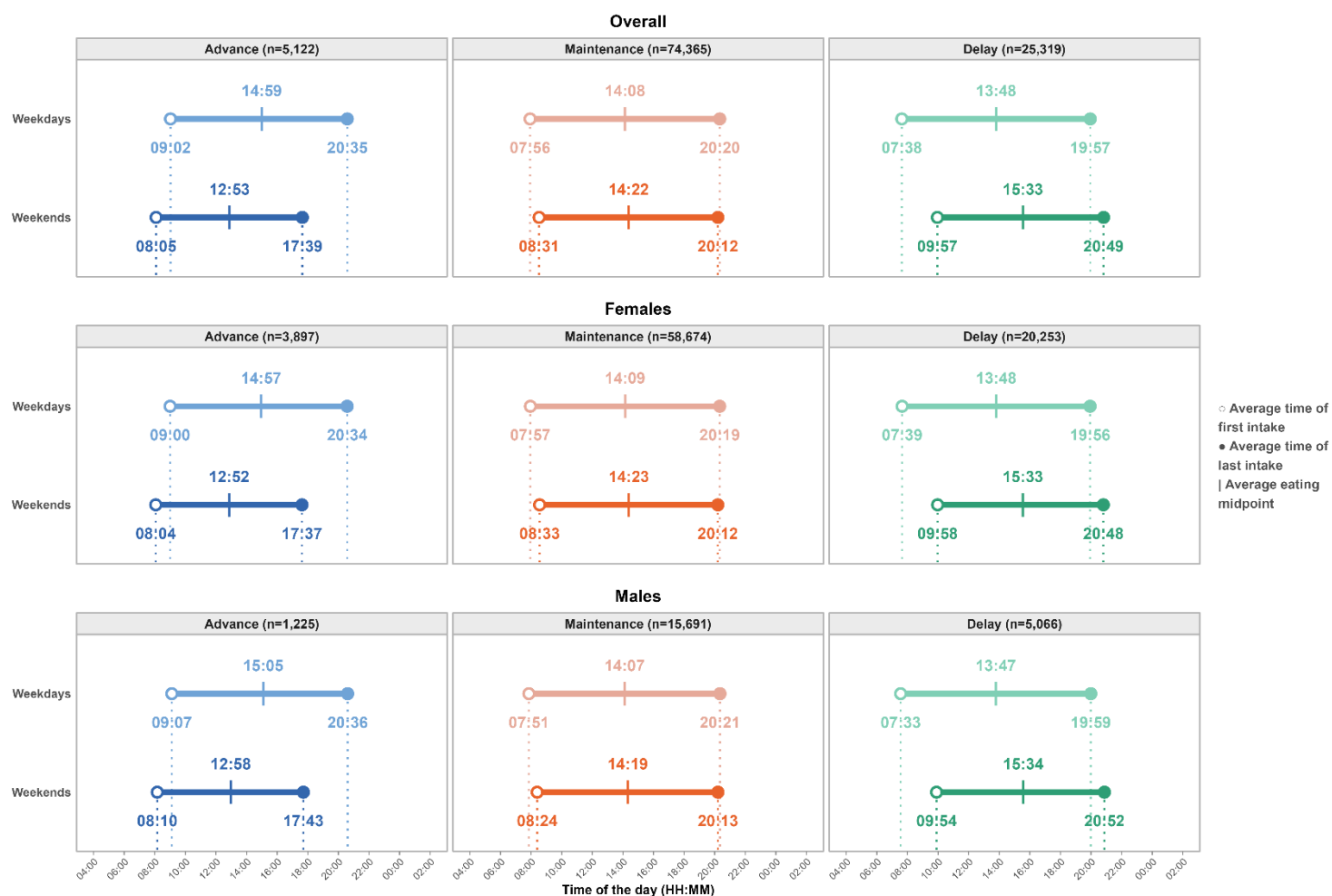
To comply with Reviewer 1 recommendations, we have shortened the first paragraph of the introduction. We now present eating behaviours from the very beginning, and we have expanded on the importance of eating rhythms. It now reads:

“In many industrialized societies, irregular eating patterns, such as skipping breakfast and late-night eating, are becoming more frequent¹. People often adapt their daily routines around fixed work schedules². While workday schedules are largely organized 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. [...] Meal timing interacts with circadian rhythms to regulate metabolic health^{15,16}. Food intake can act as a primary synchronizer for the internal clocks, and thus, aligning eating patterns with circadian rhythms bolsters metabolic homeostasis¹⁷.”

2. Recommend showing a Figure for the created eating jetlag, which may enhance visualization.

We thank Reviewer 1 for this comment. We have now added a figure (Figure 1) representing the created eating jetlag for each category of eating jetlag (“Advance”, “Maintenance”, “Delay). The figure summarizes the key meal-timing related variables used in the study to assess eating jetlag (Time of first intake on weekdays and weekends, eating midpoint on weekdays and weekends), in the full sample, and among males and females, separately.

Eating window by eating jetlag categories



3. Did you assess the interaction between EIJ and sex on the risk of CVDs??

We thank Reviewer 1 for this remark. We formerly tested the interaction between EIJ and sex and have now added the p-value for interaction in the “Statistical analysis” paragraph. Even though the p-value for interaction was not significant (p-value = 0.319), we still investigated sex-specific associations given the sexual dimorphism of the circadian clock¹, and cardiovascular disease². Beyond the sexual dimorphism, differences in behaviours, occupation and lifestyles do exist between genders (e.g. childcare responsibilities, occupation) and can therefore influence their meal-timing patterns³. Besides, stratified analyses allowed us to also account for the absolute difference in CVD risk between males and females. Our choice was justified in the methods paragraph (line 179-183).

4. The quality control procedures for the 24-hour dietary record are not sufficiently detailed. Please provide specific information regarding completion rates, data integrity checks, and methods for handling extreme energy intake values.

We have now added the detailed procedure regarding dietary data collection and identification of over/under-reporters of energy in the NutriNet-Santé in the Supplemental material (Supplemental method 1).

5. The performed sensitivity analyses excluded the unemployed and proxies for shift workers, but no assessment has been conducted for retired participants (16.5% at baseline). Retirees lack a typical workday, and their inclusion may dilute or confound the true association.

We thank Reviewer 1 for raising this point. Reviewer 1 is right noting that, among retirees, eating and sleeping 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 (even though we did not collect data on lifetime exposure to EJL in participants retired at baseline). 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. We have now developed this point in the Discussion section of the manuscript (lines 355-365).

6. Though the manuscript incorporated social jetlag as an adjustment variable in sensitivity analyses, I wonder what the correlation between EJL is and SJL, nor did it validate their independent contributions to CVD risk through interaction or stratified analyses. Therefore, we cannot rule out the possibility that the observed association between EJL and CVD risk is actually driven by SJL. Better to supplement the results of the EJL-SJL correlation analysis and add an interaction analysis.

We thank Reviewer 1 for this comment. Reviewer 1 is right and we agree that EJL and SJL are correlated. We already mentioned the conceptual correlation between these two variables in the discussion (lines 289-295), and had already discussed it in the limitations (“Despite our adjustment for sleep timing and duration, the effect of SJL could not be entirely disentangled from EJL.”). To comply with this comment, we have now calculated the Spearman correlation coefficient between EJL and SJL (0.23). We added this figure in line 292. In our study, EJL and SJL were positively correlated but the magnitude of the correlation was very mild.

We have now performed an interaction analysis as suggested by Reviewer 1, limited to the 45,784 participants with SJL data. The p-value for interaction between EJLI and SJLI was 0.182 for CVD risk, 0.216 for CHD risk and 0.560 for CVA risk. We have added these results to the Results section (lines 252-253).

Reviewer #2 (Remarks to the Author):

Leveraging data from the NutriNet-Santé cohort, this study reported that irregular eating timing between weekdays and weekends is associated with a higher cardiovascular risk, regardless of the direction of whether the difference reflects earlier or later timing on weekends. The topic is important, and the manuscript is well written. The study has several advantages including prospective cohort design, repeated dietary recall measurements, and comprehensive covariate adjustment. I only have a few minor comments.

We thank Reviewer 2 for this overall positive comment.

1. CVD events were identified through biannual follow-up questionnaires. It remains unclear how December 31, 2023 was used to define person-time. Typically, the end of follow-up should be defined as the earliest of the date of CVD event, date of death, or date of last follow-up.

We thank Reviewer 2 for highlighting this point. In this study, the end of follow-up was indeed defined as the earliest of the date of CVD event, date of death, or date of loss to follow-up. In the NutriNet-Santé cohort, in addition to active follow-up via questionnaires, we also have a “passive” continuous follow-up through medico-administrative databases, therefore, we needed an administrative right-censoring date. Given the time required by our operational and medical teams to clean the data, validate health events coming from different sources, etc., our databases were fixed to the date of December 31st 2023, by administrative censoring, which was our cut-off date. We have now clarified this point in the Methods section.

2. Figs 2-4 present related results and could be merged into a single figure to improve readability and reduce redundancy.

We thank Reviewer 2 for this suggestion. Figures 2 to 4 were merged into one single figure (Figure 3).

Reviewer #3 (Remarks to the Author):

Thank you for inviting me to review this manuscript. Please see my comments below.

We thank Reviewer 3 for the helpful and constructive comments.

1. Line 38: please make it explicit that the mean of 5.8 (SD 3.2) refers to the number of dietary recalls.

We clarified this point at the corresponding line in the abstract.

2. Please provide model estimates adjusted only for sociodemographic variables to allow clearer insights into the effects of lifestyle factors. In addition, please justify the adjustment for the average timing of the first and last eating episodes across the week in Model 3.

We thank Reviewer 3 for this suggestion. A minimally adjusted model, only adjusted for sociodemographic variables (age, sex, socio-professional status, high-school degree, marital status, number of 24h-dietary recalls (as an estimation for the accuracy of the exposure), number of children aged less than 13 years old, and those aged between 14 and 17 years old living with the participant) was further performed and results are displayed in the supplemental material (Tables S1 and S2). Lifestyle factors seemed to have minor effects on the risk of CVD in relation to EJM, since the results in the minimally adjusted model show very similar estimates as those in model 1. The methods section was completed (lines 198-199) and the related observations were added to the results section (lines 233-234).

We adjusted for the average timing of first and last eating episodes across the week in model 3 as a previous study of our team suggested that having a later first and last eating occasion of the day was associated with a higher risk of cardiovascular diseases, especially among women⁴. In addition, table 1 suggests that times of the first and last eating episodes were different across EJM categories; therefore, these variables might be confounders of the association between EJM and CVD. We have clarified this in the methods section lines 172-173.

3. Are there any indications of effect modification by age, socioeconomic status, and family history of CVD?

We tested interactions of the associations between EJLI and CVD by age, socioeconomic status and family history of CVD, and *P-interactions* were non-significant: 0.486, 0.13 and 0.85, respectively.

As stated in Question 5 to Reviewer 1, we could suspect that the associations would be different in retired participants, or after we exclude them from the sample. 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 EJI after retirement could play a more significant role than lifetime exposure to EJI prior to retirement (even though we did not collect data on lifetime exposure to EJI in participants retired at baseline). Similarly, we can also assume that even younger participants in our sample who are currently working and experiencing EJI, 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 EJI, which is what we are currently investigating in the team with adhoc questionnaires.

4. It is interesting that adjustment for commonly considered confounders has little impact on the observed associations. This may suggest that the association between EJLI and cardiovascular outcomes may be largely independent of these factors, potentially reflecting distinct etiological pathways. Please expand the discussion on this point.

As mentioned in the answer to Question 2, lifestyle factors seemed to have minor effects on the risk of CVD in relation to EJI, 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 independent of these lifestyle factors, and is mainly explained by sociodemographic variables, 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. We have now expanded the discussion on this point, lines 369-375.

5. Please briefly explain the observation (Line 320) that the associations between EJLI and the risks of CVD were observed only among participants with later first meals.

Our observations suggest that there might be a combined effect of a later first meal and high EJLI. We added this interpretation in the Discussion section. Having a later first meal might potentialize the effect of EJLI. These results support previous studies reporting that later first meals play a role in cardiometabolic health, but more generally that meal timing irregularity could be an independent risk factor for CVD. If our results were to be corroborated by other largescale long-term studies, they would support recommending having 1) early first meals, 2) and eating at regular times between weekdays and weekends.

6. Please further elaborate on the observed non-linear associations with possible explanations and implications.

We observed a plateau effect from a certain threshold of EJLI. 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 EJI 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 BMI⁵, social jetlag and risk of depression⁶). We have added these elements to the discussion page 13 lines 304-310.

7. Are there any other ways to define EJLI. What are the limitations of using this definition.

EJLI focuses on meal timing regularity in relation to social and professional obligations and constraints. EJLI is thus a specific aspect of meal timing regularity and does not cover the entire field, not to mention that EJLI only considers the times of first and last intake during weekends and weekdays. Other methods allow to study intra-individual variability by modelling the standard deviation of meal times throughout the whole week, or across a large number of repeated 24h records. Our team is currently working on these methods. This has been added to the discussion, page 15 (lines 396-400).

8. Please comment on the potential influence of attrition as approximately 70,000 participants were excluded from the analysis.

Individuals aged 18 years old and more and living in France can enrol in the NutriNet-Santé cohort by creating an account on the website. At this point, individuals are not considered as included in the cohort, as they have not filled the required data to be included yet. To be considered as an included participant in the cohort, the participant must have available valid data about health status, and at least 2 dietary records (n=132,532 participants). During the next step (as mentioned in the Flowchart, figure 2), 22,921 participants (corresponding to 17.29% of the subjects) were considered as under-energy reporters and were excluded 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 Agency⁷, 18% of adult participants were identified as under-reporters using the Black method⁸. 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 income⁹. Although their exclusion may limit the generalizability of the findings, it was necessary in order to avoid important exposure classification bias. We have made some amendments to the Flowchart to reflect these elements, and have added some discussion, to page 15 (lines 381-388).

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Reviewers' comments:

Reviewer #1 (Remarks to the Author):

All major concerns have been adequately addressed. I have no further comments.

We thank Reviewer 1 for their constructive feedback.

Reviewer #2 (Remarks to the Author):

The authors have sufficiently addressed my concerns, and I don't have further comments.

We thank Reviewer 2 for their constructive feedback.

Reviewer #3 (Remarks to the Author):

The authors have sufficiently addressed my comments. I have no further comments.

We thank Reviewer 3 for their constructive feedback.