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Article

Chrono-Nutrition, Chrono-Type, and the Prevalence of Type 2 Diabetes Mellitus in a Cross-Sectional Study from the European Prospective Investigation into Cancer and Nutrition (EPIC) Study

Running Title: Chrono-nutrition and T2DM in Caucasian Subjects

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Abstract: Background: It has shown that meal timing, poor sleep quality and chronotype could play a relevant role in the development of type 2 diabetes mellitus (T2DM). However, the relationship with macronutrients by eating occasions has not been explored deeply. **Objective:** Our aim was to estimate the association between chrono-nutrition, sleep quality, chronotype and the prevalence of T2DM. **Methods:** This cross-sectional study included a subset of 3465 middle-aged adults (2068 women) from the European Prospective Investigation into Cancer and Nutrition (EPIC) Spain cohort study. In the 2017-18 follow-up, we assessed chronotype, sleep quality, diet, and sociodemographic data by validated questionnaires. Further, we used blood samples to determinate serum levels of glucose. We defined a case of T2DM when serum glucose concentration was ≥126 mg/dl or when participants self-reported diabetes. **Results:** Higher prevalence of T2DM was associated with poor sleep quality ($OR_{poor vs good}$=2.90, 95%CI=1.30, 6.28). Carbohydrate intake at breakfast was inversely associated with the prevalence of T2DM (OR=0.75, 95%CI=0.66, 0.85). Finally, lipid intake at breakfast were associated with a 13% higher the prevalence of T2DM (OR=1.13, 95%CI=1.01, 1.26) for each 1 standard deviation (1-SD) increase. We observed no associations between macronutrient intake at lunch or dinner and T2DM. **Conclusions:** The study

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concludes that a breakfast with higher content in carbohydrate at breakfast is correlated with a reduced prevalence of T2DM. While higher lipids intake at breakfast was associated with higher prevalence of T2DM. Furthermore, poor sleep quality is as a potential factor associated with an elevated prevalence of T2DM. Our results emphasize the need for prospective studies to validate and strengthen these observed associations.

Keywords: chrono-nutrition; type 2 diabetes; meal timing; macronutrients; EPIC-Spain

1. Introduction

The prevalence of type 2 diabetes mellitus (T2DM) is rising worldwide; in 2019 a 9% of adult population was affected by this pathology (463 million) increasing to a 10.5% in 2021 with predictions of increase up to 12.2% (783.2 million) by 2045[1]. In Europe, estimated prevalence in 2021 was 9.2% and is expected to increase to 10.4% in 2045. Multiple risk factors including diet, central obesity, high-level serum uric acid, smoking, depression, cardiovascular disease, dyslipidemia, hypertension, aging, ethnicity, family history of diabetes and physical inactivity might impact glycemic control[2,3]. Understanding them is key towards achieving increased quality of life and reduced mortality rates.

In recent years, chronobiology has provided new information on risk factors for T2DM, as well as on obesity and metabolic syndrome[4–6]. Previous investigations have shown that modern society has misaligned sleep and eating patterns with biological cycles, term known as chrono-disruption, which could promote detrimental effects on health, such as the risk of suffering chronic diseases, like T2DM. Recent studies have shown that regularity, duration, and sleep quality seem to play an important role in glycemic control[2,7].

Emerging evidence has mentioned that factors affecting circadian rhythms, such as meal timing and nutrient components (chrono-nutrition), might lead to a higher risk of diabetes when the circadian clock system is desynchronized[8]. Chrono-nutrition is influenced by the individual's chronotype, and it has been observed that there is poorer glycemic control when intakes are made at night-dark hours, especially in T2DM adult patients[8,9]. Indeed, recent studies have suggested that reducing energy and carbohydrate (CHO) consumption in the evening hours and eating in synchrony with the circadian clock by shifting more energy and CHO to the morning hours enhances postprandial glycemia, and reduces appetite and craving in metabolic syndrome and T2DM[10]. In contrast, other pieces of research suggest that high protein meal (41% of energy from protein, 29% from carbohydrates) could have a modulating effect on postprandial glycemia in daily intakes, where it has been observed that it might be beneficial mainly in people who are late-night eaters, since they are more likely to have altered blood sugar levels[11].

The reduction of glycemic peaks is an essential target in the treatment of T2DM, where meal timing exerts a critical influence on peripheral clocks involved in postprandial glycemia[10]. However, the timing of intake, distribution, and the type of macronutrients on glucose homeostasis remains slightly investigated. Hence, we aimed to cross-sectionally assess the association between chrono-nutrition, sleep quality, chronotype and the prevalence of T2DM. In addition, we also evaluated the interaction with relevant risk factors such as BMI, sex, and smoking status.

2. Materials & Methods

2.1. Study Design and Population

This cross-sectional study was established from a sample of the Spanish cohort of the European Prospective Investigation into Cancer and Nutrition (EPIC) study. The Spanish cohort included 41 437 subjects, ages 29-69 years, who were recruited between 1992 and 1996 from five Spanish regions (Asturias, Granada, Murcia, Navarra, and Gipuzkoa). Further details on study design and sample characteristics can be found elsewhere[12,13].

 doi:10.20944/preprints202407.2513.v1

The eligible participants for this analysis were described previously[6,14] and were younger than 67 years (in the case of men) and younger than 60 years (in the case of women) at December 2015 (N = 8000). Aged restriction was based on evidence showing that the effect of chronotype and social jetlag diminishes in older generations[15], while the different sex-specific cut-off points for ages allowed us to obtain a balanced sample by sex. From them 5600 were invited to participate and finally a total of 4224 (75.4%) accepted to take part of the study. Furthermore, a total of 4031 (95.4%) participants underwent a physical examination by a nurse and, 3772 (89.3%) agreed to a blood sampling procedure extraction.

The study was conducted according to the guidelines of the Declaration of Helsinki, and the study protocol was approved by the Medical Ethical Committee of the Bellvitge Hospital (Barcelona) and all the participants signed informed consent.

2.2. Data Collection

Data collection was previously described[6,14]. Briefly, between 2017-18, phone interviews were performed by trained professionals to collect information on socio-demographic, reproductive and lifestyle factors, as well as on medical history, meal timing, chronotype[16], and sleeping patterns (used to define chronotype). The chronotype questionnaire allowed us to calculate mid-sleep time corrected for sleeping on working and weekend days (MSFc), used to order participants into three chronotypes categories. The cut-off points of MSFc were at percentiles 10 (2:20 a.m.) and 90 (6:30 a.m.) and classify individuals' chronotypes as follows: early type, normal type, and late type; and to calculate the amount of social jetlag accrued by each participant. Social jetlag was determined by estimating the difference between average sleep duration on free days and sleep duration on working days. Sleep quality information was assessed through the Pittsburgh Sleep Quality Index (PSQI) questionnaire[17], a questionnaire of 19 items that gave us information on sleep quality over the previous month. The final score rage from 0- 21 points and poor sleep quality is considered when the punctuation is greater than five.

2.3. Biological Samples

Blood samples (n=3772) were collected to determine serum levels of specific biochemical parameters (i.e., glucose, insulin, triglycerides, and cholesterol) measured by standard laboratory techniques. The samples were obtained in a fasting state (10-12h to since last intake), fractioned, aliquoted and stored at -80°C following standard protocols[6].

2.4. Dietary Information

Comprehensive dietary data was collected using the validated diet history questionnaire from the Study on Nutrition and Cardiovascular Risk in Spain (DH-ENRICA® [DH-E])[18]. The DH-E questionnaire is based on a previous EPIC validated dietary questionnaire; but included larger numbers of items and traditional dishes and cooking methods of Spain. DH-E considered ten occasions of eating, including those occurring from immediately after waking up to during the night. Meals were classified according to frequency: less than 3, 4 to 5 and more than 5[6]. Additionally, DH-E uses food composition tables from Spain and other countries to convert the foods to nutrients. Nutrient intakes covering total and simple CHO, fiber, proteins (including animal and plant-based) and lipids (monounsaturated, polyunsaturated, and saturated) for the overall and specific daily intake. The percent of energy from CHO, proteins and fats consumed at breakfast, lunch and dinner were calculated. And so were the time-dependent energy percentages, relative to the daily total energy intake.

2.5. Outcome Variable - Type 2 Diabetes

The prevalence of T2DM was estimated based on laboratory and self-reported data. Fasting blood serum samples were used to determine levels of glucose, and self-reported diabetes was

 doi:10.20944/preprints202407.2513.v1

assessed during the telephone-based interview. Prevalent case of T2DM was considered when one of the following criteria was present: serum glucose concentration ≥126 mg/dl or self-reported diabetes.

2.6. Statistical Analyses

For continuous variables, descriptive statistics are presented as N (%) or median and percentiles 25 (p25) and 75 (p75). Adjusted means by diabetes status for dietary intake variables adjusted for center, sex, age at recruitment (years), educational level (none, primary, technical school, secondary, university or higher), smoking history (never, former, and current), non-laboral physical activity (MET-h/week), BMI (<25, 25- <30, ≥30), fat percentage, and hypertension (yes, no).

To estimate the odds ratio (OR) and their confidence intervals (CI), logistic regression was used to determine the associations between different exposure variables (sleep quality, chronotype, chrono-nutrition variables, and macronutrients) and the prevalence of T2DM. Macronutrients were evaluated both as categorical variables, expressed in grams/day (quintiles), and as continuous variables (1-SD increment of controls). For the assessment of the trend test, the categorical variable was used as a continuous one. All models were adjusted by age at recruitment, sex, center, educational level, smoking history, non-laboral physical activity, BMI, fat percentage, and hypertension. Moreover, the macronutrients, for the main groups, model was mutually adjusted and controlled by alcohol intake (yes/no) and quantity (grams/d), total energy intake (kcal/day), and sleep quality (poor/bad). Additional variables, including vigorous physical activity, chronotype, social jetlag, number of eating occasions, breakfast time, lunch time, and dinner time, were initially evaluated but were not included in the models since results do not change.

Multiplicative interactions were modeled separately by sex, BMI (<25, 25- <30, ≥30), smoking status (never, former, and current), and sleep quality (poor, good) with T2DM and evaluated using the log-likelihood ratio test. All statistical analyses were two-sided and evaluated at the significance level of 5%. Statistical analyses were performed using R 3.6.2 and SAS v 9.4.

3. Results

3.1. Descriptive Statistics

This study was based on data from 3465 participants (2068 women, 60%), with a median age of 65 (61-68) years. The prevalence of T2DM was 20% (689 cases; 368 males and 321 females) when we conducted the study. The prevalence of T2DM was higher when the sleep quality was poor (28.7%) compare with good sleep quality (19.6%), in late-type chronotype (24.2%) compare with in normal-type chronotype (19%), when social jet-lag was less than 30 minutes (21.5%) compare with more than 1:30h (14%), and the time of breakfast and dinner were later than 9 a.m. and late than 9 p.m. respectively compare with earlier hours. Furthermore, prevalent T2DM cases were one year older on average and had a higher body mass index than subjects without T2DM (Table 1).

Table 2 provides a comprehensive overview of dietary information by T2DM status, accounting for potential confounders. In terms of carbohydrates, T2DM cases showed lower adjusted means of % energy from CHO (non-cases: 41.61% *vs* cases: 40.90%), total carbohydrates (non-cases: 256.62 *vs* cases: 250.00), and simple carbohydrates (non-cases: 96.62 *vs* cases: 90.10). Conversely, higher means were observed for percentage energy from proteins (non-cases:18.50% *vs* cases: 18.90%) and animal protein (non-cases: 69.34 *vs* cases: 71.43). When we explored by meal-specific occasion we observed that, at breakfast, non-cases were characterized by a higher energy intake (non-cases: 378.42 *vs* cases: 357.97) and energy contribution (non-cases: 15.46% *vs* cases: 14.78%). Non-cases also had a higher percentage of CHO (non-cases: 20.53% *vs* cases: 19.09%), simple CHO (non-cases: 27.52% vs cases: 24.56%), proteins (non-cases: 11.70% *vs* cases: 11.20%) and plant-based proteins (non-cases: 14.25% *vs* cases: 13.45%) from the total. Same differences were observed when the macronutrients were evaluated as grams/breakfast. Additionally, prevalent T2DM cases showed a higher percentage of lipids at breakfast (non-cases: 28.08% *vs* cases: 29.45%). At lunch, prevalent cases had a higher percentage of simple CHO from the total (non-cases: 30.20% *vs* cases: 31.29%) and percentage from proteins (non-cases: 20.74% *vs* cases: 21.10%). However, simple CHO measured in grams/lunch were

 doi:10.20944/preprints202407.2513.v1

higher in no-cases. Finally, at dinner, prevalent T2DM cases showed a higher percentage of CHO (non-cases: 21.28% *vs* cases: 22.24%), simple CHO (non-cases: 20.44% *vs* cases: 22.14%), plant-based proteins (non-cases: 20.62 *vs* cases: 21.53) and fiber (non-cases: 19.48 *vs* cases: 20.86) than the total. When macronutrients are measured in grams/dinner higher intakes were observed in T2DM cases for total and animal proteins, and fiber.

In the multivariable logistic analysis, as shown in Table 3, higher prevalence of T2DM was associated with a poor sleep quality ($OR_{poor vs good}$= 2.90, 95% CI = 1.30, 6.28). We observed no difference in T2DM prevalence in relation to time of sleep, chronotype, social jetlag, and chrono-nutrition variables.

Regarding associations between macronutrients by eating occasions, prevalence of T2DM (Table 4), was near 60% lower for participants in the highest quintile of carbohydrate intake at breakfast ($OR_{Q5 vs Q1}$= 0.40, 95% CI = 0.27, 0.59; p-trend=0.01). Increasing 1-SD from carbohydrates at breakfast was inversely associated with the prevalence of T2DM by 25% (OR = 0.75, 95% CI = 0.66, 0.85; p-trend = <0.01). On the contrary, the OR for lipids at breakfast, was 1.13 (95% CI = 1.01, 1.26) per 1-SD increase. No statistical significance was found for associations of macronutrients at lunch and dinner with T2DM.

Estimation of the OR was not modified by sex, smoking status, BMI, or sleep quality (table S1).

4. Discussion

To the best of our knowledge, this is the first population-based study using a large sample that analyzes the influence of macronutrients, the timing of intake, sleep quality and the type of chronotype to T2DM, especially in a middle-aged to elderly population in Spain.

4.1. Sleeping Patterns

Our findings showed a positive association between poor sleep quality and T2DM prevalence (OR = 2.90, 95%CI= 1.30, 6.28), which is in line with the results of a large cross-sectional study from China[19] and with a cohort study from Korea[20], both of which reported that poor sleep quality was associated with higher odds of being diagnosed with T2DM. Further, the US NHANES linked the poor sleep quality and the prevalence of clinically identified prediabetes[21]. Briefly, this positive association could be attributed to disruptions in the circadian rhythm influencing insulin sensitivity, and consequently leading to an increased risk of T2DM[2]. Another possible explanation is that people who sleep poorly are generally more likely to have an unbalanced diet and eat more foods that raise blood sugar, which correlates with obesity, a risk factor for T2DM[22].

4.2. Chronotype

In relation to chronotype, it has been seen that chronotype changes with the age becoming more stable and earlier with increasing age[23]. In that line, we observed that 79.7% of our participants had similar chronotype (normal type); then, we were not able to find a statistically significant association with the prevalence of T2DM.

4.3. Chrono-Nutrition

Our findings regarding macronutrients intake and prevalence of T2DM showed that a higher intake of lipids at breakfast had a positive association with the prevalence of T2DM; particularly we observed that for each 1-SD lipid increase the prevalence of T2DM was up to 13% higher (OR = 1.13, 95% CI = 1.01, 1.26). We observed comparable results with higher intakes of protein, although the association was not statistically significant. On the contrary, T2DM prevalence was 60% lower in participants that had a higher intake of carbohydrates at breakfast (OR_{Q5vsQ1}= 0.40, 95% CI = 0.27, 0.59; p-trend = 0.01). The investigation into the influence of these macronutrients (lipids and carbohydrates) distribution throughout the day on T2DM remains relatively underexplored. The China Health and Nutrition Survey (CHNS), an ongoing cohort study, observed that higher intake of lipids at dinner than at breakfast increased the risk of T2DM. In addition, increasing energy from

 doi:10.20944/preprints202407.2513.v1

carbohydrates at breakfast (5%) by reducing energy from lipids at dinner was associated with a reduced risk of T2DM[24]. In a British cohort was shown that eating more carbohydrates at morning while the consumption of lipids was reduced was related with lower of T2DM[25], and in general with metabolic syndrome and its components[26]. A recent comprehensive literature review tried to figure out this aspect, concluding that an earlier consumption of carbohydrates may mitigate the risk of obesity, which is of the main risk factors of T2DM. Moreover, the timing of carbohydrates intake significantly impacts glycometabolic control, with a higher proportion of carbohydrates consumed in the evening potentially negatively influence on it[27]. These findings underscore the direct association between patterns of carbohydrate consumption and the susceptibility to the development of T2DM.

4.4. Strengths and Limitations

The main limitation of our study was that the cross-sectional design does not allow to infer causality. Information on antidiabetic medication use was not available, so prevalence of T2DM could have been underestimated. Participants for the study were recruited from a convenience sample, so selection and participation bias may be present in our study. Finally, our study included participants from a Mediterranean cohort, which might hamper extrapolation of our findings to other populations. However, we obtained information on diet using a validated diet history, including timing of intake and the specific time of day that foods were consumed at to gather accurate dietary data.

The strengths in this study are, firstly this study is the first one to examine the relationship between chrono-nutrition and chronotype with T2DM prevalence in a Spanish study. Second, we assessed chronotype and sleep quality using a validated method. Third, we adjusted for potential confounding factors in the analyses making the association reported robust.

5. Conclusions

Our results suggest that a higher intake of carbohydrates (CHO) and lower consumption of lipids at breakfast are associated with a lower prevalence of Type 2 Diabetes. Additionally, poor sleep quality appears to be linked to an increased prevalence of T2DM. However, it is crucial to note that these findings warrant confirmation through prospective studies to establish a more robust and conclusive understanding of the relationships.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org. Table S1: Estimation of the modification of the OR by sex, smoking status, BMI, sleep quality and chronotype.

Authors' contribution: The authors' responsibilities were as follows: P.J. and J.R.Q: designed research; L.L.-B. and H.J.M.-E performed the statistical analysis; L.L.-B., H.J.M.-E wrote the original draft; P.J. had primary responsibility for final content. All authors read and approved the final manuscript.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data availability statement: The data of this study is preserved by the EPIC-Spain research group. Data are subject to data sharing agreements and are not publicly available.

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Conflicts of interest: The authors declare no conflicts of interest to disclose.

Abbreviations

CHNS, China Health and Nutrition Survey, CHO, carbohydrate; CI, confidence interval; DH-E, diet history questionnaire – ENRICA; EPIC, European Prospective Investigation into Cancer and Nutrition; h, hour; g, grams; MSFc, mid-sleep time corrected for sleeping on working and weekend days; OR, odds ratio; PA, physical activity; PSQI, Pittsburgh Sleep Quality Index; Q, quartile; T2DM, type 2 diabetes mellitus

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