**Associations of predominant night-eating with plasma glycemic status and continuous glucose monitoring measures among pregnant women**

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### Abstract

**Background & Aims**

To examine whether predominant night-eating, defined as more than 50% of total daily energy intake consumed between 1900-0659 hours, is associated with glycemic outcomes in pregnancy.

**Methods**

This was a prospective cohort study of 277 healthy pregnant women with complete 4-day dietary intake records at 18-24 weeks gestation, recruited from KK Women’s and Children’s Hospital, Singapore. Primary outcomes were fasting, 1-hour, and 2-hour plasma glucose after a 75-g oral glucose tolerance test at 24-28 weeks gestation. Secondary outcomes were gestational diabetes mellitus (GDM), fasting insulin, homeostasis model assessment of insulin resistance (HOMA2-IR), β-cell function (HOMA2-%B), and continuous glucose monitoring (CGM) measures. Glucose variables in continuous form were loge-transformed before analyses.

**Results**

Predominant night-eating (11.6%) was associated with higher fasting glucose (geometric mean ratio (95% confidence interval) 1.05 (1.01, 1.08)) and 1-hour glucose (1.11 (1.01, 1.21)), but not with 2-hour glucose or GDM risk. Predominant night-eating women had lower fasting insulin (0.77 (0.63, 0.95)), lower HOMA2-IR (0.78 (0.64, 0.97)), and lower HOMA2-%B (0.77 (0.67, 0.89)) than their predominant day-eating counterparts. For CGM measures, predominant night-eating was associated with higher mean glucose (1.07 (1.00, 1.15)), higher glucose management indicator (1.05 (1.00, 1.10)), and higher overall glucose levels throughout 24 hours (1.10 (1.02, 1.19)). All these associations were adjusted for socio-demographic, lifestyle factors, and diet composition.

**Conclusion**

Predominant night-eating was mainly associated with less desirable glycemic outcomes during pregnancy. Future studies should explore dietary interventions aimed at reducing consumption of relatively more calories at night than day during pregnancy.

**Keywords**

Night-eating, chrononutrition, pregnancy, continuous glucose monitoring, diabetes

**Introduction**

Optimizing diet during pregnancy can improve both maternal and offspring health outcomes (1, 2). In recent years, the field of chrononutrition, the study of nutritional impact on metabolism through the circadian system, has brought to fore the importance of understanding appropriate dietary intake based on 24-hour clock time (3). During pregnancy, higher energy intake in the late evening or at nighthas been associated with poorer dietary quality (4), higher plasma glucose levels, higher gestational weight gain, higher risk of postpartum obesity, and multiple adverse obstetric outcomes in several studies (5, 6). These findings are highly relevant as night-eatinghas become an increasingly prevalent phenomenon (7). Furthermore, pregnancy has the potential to induce night-eating due to the effect of physiological changes and disturbed sleep patterns (8-10).

Understanding the glycemic response according to meal timing is especially crucial for pregnant women, as pregnancy itself is already associated with altered circadian patterns and increased insulin resistance (11, 12).Higher maternal glucose concentrations, even below diagnostic levels of diabetes, are associated with adverse birth outcomes, such as fetal overgrowth and adiposity, as shown by the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study (13). However, it remains not clear to what extent night-eating alters glucose metabolism during pregnancy, as reported in a recent systematic review (14). Previous studies were mainly cross-sectional, employed single day diet assessment for examining meal timing, or evaluated glycemic measures without considering 24-hour glucose levels (8-10).

To address these gaps, we conducted a prospective cohort study that was specifically designed to examine the association between maternal night-eating and gestational glycemic status, using a comprehensive set of dietary assessment tools and glucose measures. We hypothesized that consuming energy predominantly at night, assessed by 4-day dietary intakes based on a combination of a paper-based food diary and a mobile phone food picture app, was associated with higher plasma glucose levels after oral glucose tolerance test (OGTT) and insulin dysregulation. We also hypothesized that these women with predominant night-eating (PNE) would have poorer glycemic control and larger glycemic variability, based on their ambulatory glucose profile compared to women with predominant day-eating (PDE)*.*

### Materials and Methods

Data were drawn from a prospective cohort study that was designed to examine nocturnal eating pattern and glucose metabolism among pregnant women (NCT03803345) (15). The study was conducted at KK Women’s and Children’s Hospital (KKH), Singapore, and recruitment took place between March 2019 and October 2021. We performed the study according to the Declaration of Helsinki and the research was granted ethics approval by the Centralized Institutional Review Board of SingHealth (Reference 2018/2529). This study was reported using the Strengthening the Report of Observational Studies in Epidemiology (STROBE) guidelines (16). The study was approved by the Centralized Institutional Review Board of SingHealth (Reference 2018/2529). All participants provided written informed consent.

**Participants**

Women were eligible for the study if they were between 18 and 24 weeks gestation, aged 18 years and above, had Singapore citizenship or Singapore permanent residence status. We excluded women who were diagnosed with gestational diabetes mellitus (GDM) at recruitment, had pre-existing Type 1 or 2 diabetes, were on routine night-shift work, used anticonvulsant medications or oral steroids in the past month, had known or suspected allergy to medical grade adhesives. We also excluded women who were diagnosed with chronic kidney disease, preeclampsia, or had multiple pregnancies.

**Study procedures and data collection**

Women completed a baseline assessment at 18-24 weeks gestation in the clinic. The baseline assessment assessed demographic characteristics (age, ethnicity), indicators of socioeconomic status (years of education, employment status) (17), meal regularity (frequency of skipped and/or delayed meal timing a week), physical activity (assessed using the International Physical Activity Questionnaire-Short Form (18), allowing the derivation of the metabolic equivalent of task score [MET-min]), and bedtime (asked by question ‘when do you usually go to bed?’). Pre-pregnancy body mass index (BMI) was calculated from self-reported weight (kg) divided by height squared (m2 [measured by the SECA 213 stadiometer, Germany]). Women were asked to record their 4-day dietary intake using a paper-based food diary (three weekdays and one weekend day) and the mobile phone food picture app (MealLogger, Wellness Foundry) on the same days. Food images captured before and after eating were automatically time-stamped and uploaded by the app to the subscribed website, which could only be accessed by the research staff. At the end of the baseline visit, a continuous glucose monitoring (CGM) sensor (Freestyle Libre Pro, Abbott, Germany) measuring interstitial glucose every 15 minutes was applied on the back of woman’s upper arm and required to be worn for 10 continuous days. No calibration was needed for the CGM sensor during the wearing period. Women were blinded from the CGM readings to avoid any dietary modification. By 24-28 weeks gestation, women returned to the follow-up visit which was aligned with their OGTT clinical appointment. Women underwent a 3-point (0, 1- and 2-hour) 75-g OGTT in the morning after an overnight fast of 8-10 hours, following standardized clinical procedures. Plasma glucose (assessed by the Abbott Alinity c glucose enzymatic [Hexokinase] assay, Germany) and fasting insulin (assessed by the Abbott Alinity i insulin immunochemiluminometric assay, Germany) were analyzed in the KKH laboratory within one hour after blood was drawn, following standardized clinical protocols.

**Night-time eating assessment**

Research staff verified the information in the food diaries by checking against food images from the food app. Discrepancies between both sources were clarified with the women. We used the Dietplan software containing the Singapore food composition database (Forestfield, UK) to analyze and subsequently compute the average calorie and nutrient intakes of women based on the recorded dietary data and/ or images. We applied the same definitions to define day-night eating as previously reported (10, 19-21), considering its practical application in clinical practice. PNE was defined as consuming more than 50% of total daily energy intake between 1900 h and 0659 h; PDE, which served as the reference group, was defined as consuming equal to or more than 50% of total daily energy intake between 0700 h and 1859 h. Given that daylight is a strong environmental signal for the human circadian clock which regulates metabolism (22, 23), we determined day- and night-time periods based on local sunrise (~0700 h) and sunset times (~1900 h), which remain nearly constant throughout the year in Singapore.

**Glycemic outcomes**

We have pre-specified the glycemic outcomes. Primary outcomes were fasting, 1-hour, and/or 2-hour plasma glucose levels after 75-g OGTT at 24-28 weeks gestation. Secondary outcomes were GDM (defined by the International Association of Diabetes and Pregnancy Study Groups criteria (24)); fasting insulin level; updated homeostasis model assessment of insulin resistance (HOMA2-IR, a surrogate measure of insulin sensitivity (25); a higher HOMA2-IR suggests increased insulin resistance, or reduced insulin sensitivity); updated homeostasis model assessment of β-cell function (HOMA2-%B, a surrogate marker for fasting insulin secretion (25); a lower HOMA2-%B suggests decreased fasting insulin secretion); CGM-derived glycemic control and glycemic variability indices. HOMA2-IR and HOMA2-%B were calculated using the HOMA2 calculator (https://www.dtu.ox.ac.uk/homacalculator/). The glycemic control indices included mean glucose, glucose management indicator (GMI) (26), J-index (27), percentage of time in range 3.5 – 7.8 mmol/L (TIR) (28), percentage of time above the target range 7.8 mmol/L (TAR) (28), and percentage of time below the target range 3.5 mmol/L (TBR) during pregnancy (28). The glycemic variability indices included standard deviation (SD), coefficient of variation (CV), and mean amplitude of glucose excursions (MAGE), derived from the EasyGV software (29). These indices provide estimates of daily glycemic control and fluctuations. Since most sensors were worn at the end of the first day, we excluded the first two days of CGM readings to mitigate the potential for inaccurate measurements in the initial 24 hours (30). Consequently, we only included women with a minimum of three complete consecutive days of 24-hour data in the main analysis for CGM measures.

**Statistical analysis**

We compared the characteristics of pregnant women in the PDE and PNE groups using descriptive statistics. We applied multiple linear regression and modified Poisson regression models with covariate adjustment to examine the associations of PNE with glycemic outcomes in continuous and binary forms, respectively. Plasma glycemic outcomes were natural log-transformed (loge) to achieve approximately normal distributions before using these values for analyses. Covariates were identified *a priori* from the literature review (8, 10, 31, 32) and based on the disjunctive cause criteria (33), guided by the directed acyclic graph. We controlled for covariates recognized as either potential confounders or known to influence the exposure or outcomes (to increase the precision of estimates), but not those in the potential causal pathway linking exposure to outcomes. Minimum models were adjusted for age (continuous), ethnicity (Chinese, non-Chinese), years of education (continuous), employment status (unemployed, employed), pre-pregnancy BMI (continuous), and total daily energy intake (continuous). Main models were additionally adjusted for physical activity (<600, ≥600 MET-min/week) (18), irregular meal practice (no <3 times, yes ≥3 times skipped or delayed meal timing a week) (34), and bedtime (continuous; treated in 24-h clock such that 11:00 pm was treated as 2300 h and 1:00 am was treated as 2500 h). The extended models were further adjusted for the percentages of energy contributed by night-time dietary macronutrient intake to account for the possible influence of diet composition on the associations between PNE and glycemic outcomes. This was done by using substitution models, which examine the relative change of one dietary macronutrient to another under isocaloric conditions (i.e., keeping the total daily energy intake constant) (35).In view of the shortcomings and pitfalls of HOMA indices (36), we additionally adjusted for fasting glucose or fasting insulin in models of HOMA2-IR and HOMA2-%B (37) to determine whether the outcomes were driven by fasting insulin, fasting glucose, or both.

In addition, we used generalized estimating equations (GEE) with exchangeable covariance structure and an identity link to investigate and illustrate the associations between PNE and hourly median CGM glucose levels of each participant; GEE accounts for non-independence of multiple glucose measurements based on CGM. Through GEE, we obtained predicted estimates of mean glucose levels (adjusted for all covariates in the extended model and with an interaction term between PDE/PNE status and time) throughout the 24 hours and according to PDE/PNE status.

Given that maternal glucose response to night-time eating may be weight-dependent (38), we tested interaction between day-night eating and pre-pregnancy weight status on glycemic outcomes. We performed tests by introducing the cross-product term of PNE (vs. PDE) and BMI (<23 vs. ≥23 kg/m2) (39) into the extended models. For the CGM measures, we performed a sensitivity analysis including only women with a complete 10-day 24-hour ambulatory glucose profile, meeting the recommended 70% of CGM data coverage from a 14-day period (40). In view of the low response rate for CGM sensor wearing (57% with complete at least three days CGM data) which could potentially introduce self-selection bias, we performed a Heckman selection regression model.

Effect estimates are presented as geometric mean ratios (GMRs) for loge-transformed continuous outcomes and risk ratios (RRs) for binary outcomes, with respective 95% confidence intervals (CIs). Analyses of exposure and outcomes were based on all available data without imputation (we only considered imputation for covariates with missing values, but all the included covariates in the present study showed complete data). We used a two-sided significance level of 5% for pre-specified primary and secondary outcomes without adjustment for multiple comparisons. All statistical analyses were conducted with Stata version 16.

**Sample size**

With a sample size of 32 women with PNE and 245 women with PDE, the study had 80% statistical power with a two-sided 5% type 1 error rate that allowed the detection of a mean difference of 0.2 mmol/L in fasting glucose, a mean difference of 0.9 mmol/L in 1-hour glucose, and a mean difference of 0.8 mmol/L in 2-hour glucose between the groups.

**Patient and public involvement**

No patients were specifically involved in defining the research hypothesis or the outcome measures, nor were they involved in the design and implementation of the study. We plan to disseminate these findings to the general public in a press release.

**Data and Resource Availability**

The datasets generated during and/or analyzed in the current study are available from the corresponding author upon reasonable request.

### Results

**Participant characteristics**

Of the 300 enrolled women, 277 completed 4-day food diaries at 18-24 weeks gestation and OGTT at 24-28 weeks gestation. None of them reported an implausible total daily energy intake of <500 kcal/day or >3500 kcal/day. Of these women, 11.6% (n=32) practiced PNE, determined by calculating the average night calorie intake per day relative to the average total calorie intake per day. Most baseline characteristics were similar between women with PDE and PNE, except that the PNE group had a later bedtime (00:14 h vs. 23:20 h), were more likely to be unemployed (28.1% vs. 13.5%) and to report irregular meals (46.9% vs. 22.4%). **(Table 1)**. When comparing characteristics of included (n=277) and excluded women (n=23), included women were older (31.3 vs. 28.2 years), had longer years of education (14.5 vs. 12.2 years), and were more likely to have a lower level of physical activity (<600 MET-min/week 27.8% vs. 8.7%) **(Supplementary Table 1)**.

**Table 1** Baseline characteristics of women with the practice of PDE and PNE at 18-24 weeks gestation

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Characteristics** | **Total (n=277)** | **PDE (n=245)** | **PNE (n=32)** | ***p-value*** |
| Gestation, weeks | 20.33 (0.46) | 20.32 (0.45) | 20.46 (0.57) | 0.167 |
| Age, years | 31.33 (4.15) | 31.33 (4.16) | 31.37 (4.09) | 0.635 |
| Pre-pregnancy BMI, kg/m2 | 22.89 (4.19) | 22.80 (4.11) | 23.58 (4.80) | 0.312 |
| Education, years | 14.48 (2.32) | 14.56 (2.23) | 13.81 (2.91) | 0.208 |
| Employment status |  |  |  | 0.048 |
| Unemployed | 42 (15.2) | 33 (13.5) | 9 (28.1) |  |
| Employed | 235 (84.8) | 212 (86.5) | 23 (71.9) |  |
| Ethnicity, n (%) |  |  |  | 0.768 |
| Chinese | 230 (83.0) | 203 (82.9) | 27 (84.4) |  |
| Non-Chinese | 47 (17.0) | 42 (17.1) | 5 (15.6) |  |
| Physical activity, n (%) |  |  |  | 0.684 |
| <600 (MET-min/week) | 77 (27.8) | 69 (28.2) | 8 (25.0) |  |
| ≥600 (MET-min/week) | 200 (72.2) | 176 (71.8) | 24 (75.0) |  |
| Bedtime, 24-h clock | 23:26 (1:18) | 23:20 (1:12) | 00:14 (1:43) | 0.007 |
| Irregular meal, n (%) |  |  |  | 0.004 |
| No | 207 (74.7) | 190 (77.6) | 17 (53.1) |  |
| Yes | 70 (25.3) | 55 (22.4) | 15 (46.9) |  |
| Total daily energy intake, kcal/day | 1679 (405) | 1686 (408) | 1621 (379) | 0.283 |
| Total fat intake, % energy | 34.0 (4.8) | 34.0 (4.8) | 33.9 (5.1) | 0.946 |
| Total carbohydrate intake, % energy | 48.2 (5.7) | 48.2 (5.6) | 47.8 (6.3) | 0.733 |
| Total protein intake, % energy | 16.9 (2.9) | 16.9 (2.8) | 17.4 (3.4) | 0.340 |
| Night-time energy intake, kcal/night | 590 (256) | 550 (235) | 891 (211) | <0.001 |
| Night-time energy intake, % energy\* | 35.1 (13.1) | 32.4 (11.2) | 55.6 (7.2) | <0.001 |
| Night-time fat intake, % energy† | 33.0 (7.7) | 32.8 (7.8) | 35.1 (6.3) | 0.129 |
| Night-time carbohydrate intake, % energy† | 46.9 (10.0) | 47.0 (10.3) | 45.7 (8.1) | 0.453 |
| Night-time protein intake, % energy† | 18.5 (5.5) | 18.5 (5.7) | 18.3 (4.3) | 0.738 |

Data are presented as mean (standard deviation) unless indicated otherwise. PDE, predominantly day-eating; PNE, predominantly night-eating; BMI, body mass index; MET, metabolic equivalent of task. *P*-values derived from independent t-test or Pearson’s Chi-squared test.

\*Computed from night-time energy intake (kilocalories)/total daily energy intake (kilocalories) x 100.

†Computed from energy from night-time macronutrient intake (kilocalories)/night-time energy intake (kilocalories) x 100

**PNE and glycemic status as assessed by OGTT**

The adjusted associations between PNE and plasma glycemic status at 24-28 weeks of gestation are presented in **Table 2**. In the extended model with an additional adjustment made for diet composition (Model 3), PNE was associated with 5% higher fasting glucose (GMR 1.05 (95% CI 1.01, 1.08); equivalent to 0.19 mmol/L glucose) and 11% higher 1-hour glycemia (1.11 (1.01, 1.21); equivalent to 0.57 mmol/L glucose) but was not associated with 2-hour glycemia or GDM risk. PNE was also associated with a lower fasting insulin (0.77 (0.63, 0.95)). Before adjusting for fasting insulin or fasting glucose, PNE was associated with a lower HOMA2-IR (0.78 (0.64, 0.97)) and a lower HOMA2-%B (0.77 (0.67, 0.89)), respectively. After adjusting for fasting glucose, the association between PNE and a lower HOMA2-IR (0.73 (0.60, 0.89)), and HOMA2-%B (0.80 (0.70, 0.92)) persisted. However, upon adjusting for fasting insulin, PNE was associated with a higher HOMA2-IR (1.02 (1.00, 1.03)) and a lower HOMA2-%B (0.90 (0.84, 0.96)).

**Table 2** Associations between maternal PNE and plasma glycemic status at 24-28 weeks gestation (n=277)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Geometric mean (95% CI)** | |  | **Geometric mean ratio (95% CI)** | | |
| **Plasma glycemic outcomes** | **PDE (n=245)** | **PNE (n=32)** |  | **Model 1**\* | **Model 2**† | **Model 3**‡ |
| Fasting glucose, mmol/L | 4.23 (4.19, 4.27) | 4.45 (4.23, 4.69) |  | 1.05 (1.01, 1.08) | 1.04 (1.01, 1.08) | 1.05 (1.01, 1.08) |
| 1-h glucose, mmol/L | 7.49 (7.27, 7.72) | 8.30 (7.69, 8.96) |  | 1.09 (1.00, 1.19) | 1.10 (1.01, 1.21) | 1.11 (1.01, 1.21) |
| 2-h glucose, mmol/L | 6.34 (6.17, 6.51) | 6.37 (5.82, 6.97) |  | 1.00 (0.92, 1.08) | 1.01 (0.93, 1.10) | 1.02 (0.94, 1.11) |
| Fasting insulin, μIU/ml | 7.71 (7.15, 8.33) | 6.54 (5.64, 7.60) |  | 0.76 (0.62, 0.93) | 0.77 (0.63, 0.94) | 0.77 (0.63, 0.95) |
| HOMA2-IR | 0.96 (0.89, 1.03) | 0.83 (0.71, 0.96) |  | 0.77 (0.63, 0.94) | 0.78 (0.64, 0.96) | 0.78 (0.64, 0.97) |
| HOMA2-%B | 133.49 (127.21, 140.07) | 107.45 (96.33, 119.86) |  | 0.76 (0.67, 0.87) | 0.77 (0.67, 0.88) | 0.77 (0.67, 0.89) |
|  |  |  |  |  |  |  |
| Models with fasting glucose adjustment |  |  |  |  |  |  |
| HOMA2-IR | - | - |  | 0.71 (0.59, 0.86) | 0.72 (0.59, 0.88) | 0.73 (0.60, 0.89) |
| HOMA2-%B | - | - |  | 0.79 (0.70, 0.90) | 0.80 (0.70, 0.92) | 0.80 (0.70, 0.92) |
| Models with fasting insulin adjustment |  |  |  |  |  |  |
| HOMA2-IR | - | - |  | 1.01 (1.00, 1.03) | 1.01 (1.00, 1.03) | 1.02 (1.00, 1.03) |
| HOMA2-%B | - | - |  | 0.89 (0.83, 0.95) | 0.90 (0.84, 0.96) | 0.90 (0.84, 0.96) |
|  |  |  |  |  |  |  |
|  | **n (%)** | |  | **Risk Ratio (95% CI)** | | |
| Gestational diabetes mellitus | 38 (15.5) | 5 (15.6) |  | 1.00 (0.43, 2.30) | 1.07 (0.46, 2.45) | 1.02 (0.44, 2.39) |

Data were analyzed using multiple linear regression models for loge-transformed continuous glycemic outcomes and modified Poisson regression models for gestational diabetes mellitus. CI, confidence interval; PDE, predominantly day-eating; PNE, predominantly night-eating; HOMA2-IR, updated homeostasis model assessment of insulin resistance; HOMA2-%B, updated homeostasis model assessment of β-cell function.

\*Model 1: adjusted for age, ethnicity, education, employment status, pre-pregnancy body mass index, and total daily energy intake.

†Model 2: adjusted for Model 1 + bedtime, irregular meal, and physical activity.

‡Model 3: adjusted for Model 2 + percentage of energy from night-time protein intake and percentage of energy from night-time fat intake.

**PNE and CGM measures**

Adjusted associations between PNE and CGM measures are presented in **Table 3**. Fifty-seven percent (n=157) of women had a complete 24-hour ambulatory glucose profile spanning at least three days, with a mean of 862 readings and a median of 895 readings, ranging from 319 (3 days) to 1217 (13 days) readings. For glycemic control indices, PNE was associated with higher mean glucose (1.07; (1.00, 1.15)) and GMI values (1.05 (1.00, 1.10)). The regression models with sample selection revealed similar findings with the correlation between error terms (ρ) shown to be non-significant **(Supplementary Table 2** and **Supplementary Table 3)**. We observed no associations between PNE and glycemic variability indices.

**Table 3** Associations between maternal PNE and CGM measures at 18-24 weeks gestation (n=157)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Geometric mean (95% CI)** | |  | **Geometric mean ratio (95% CI)** | | |
| **CGM measures** | **PDE (n=140)** | **PNE (n=17)** |  | **Model 1\*** | **Model 2**† | **Model 3**‡ |
| **Glycemic control index** |  |  |  |  |  |  |
| Mean glucose, mmol/L | 4.45 (4.37, 4.54) | 4.65 (4.14, 5.22) |  | 1.04 (0.97, 1.11) | 1.06 (0.98, 1.13) | 1.07 (1.00, 1.15) |
| GMI, mmol/mol | 33.71 (33.31, 34.13) | 34.77 (32.07, 37.69) |  | 1.03 (0.98, 1.07) | 1.04 (0.99, 1.09) | 1.05 (1.00, 1.10) |
| J-index | 9.81 (9.38, 10.25) | 10.56 (8.33, 13.40) |  | 1.06 (0.91, 1.23) | 1.10 (0.94, 1.28) | 1.13 (0.97, 1.31) |
| TIR, % | 79.09 (76.04, 82.25) | 74.87 (59.90, 93.59) |  | 0.95 (0.83, 1.09) | 0.96 (0.84, 1.11) | 0.98 (0.85, 1.13) |
| TAR, % | 0.86 (0.67, 1.10) | 1.14 (0.22, 6.01) |  | 0.99 (0.69, 1.42) | 1.08 (0.75, 1.57) | 1.15 (0.80, 1.66) |
| TBR, % | 10.81 (8.85, 13.21) | 7.39 (3.54, 15.43) |  | 0.71 (0.40, 1.23) | 0.64 (0.36, 1.14) | 0.57 (0.32, 1.01) |
|  |  | |  |  | | |
| **Glycemic variability index** |  | |  |  | | |
| SD, mmol/L | 1.03 (0.99, 1.08) | 1.05 (0.90, 1.22) |  | 0.99 (0.87, 1.13) | 1.02 (0.89, 1.17) | 1.02 (0.90, 1.17) |
| CV, % | 23.17 (22.39, 23.98) | 22.55 (20.53, 24.77) |  | 0.96 (0.86, 1.06) | 0.96 (0.86, 1.08) | 0.96 (0.86, 1.07) |
| MAGE, mmol/L | 2.70 (2.59, 2.81) | 2.76 (2.38, 3.21) |  | 1.01 (0.88, 1.15) | 1.03 (0.90, 1.19) | 1.04 (0.90, 1.19) |

Data were analyzed using multiple linear regression models for loge-transformed CGM measures. CGM, continuous glucose monitoring; CI, confidence interval; PDE, predominantly day-eating; PNE, predominantly night-eating; GMI, glucose management indicator; TIR, percentage of time in range 3.5 – 7.8 mmol/L; TAR, percentage of time above target range 7.8 mmol/L; TBR, percentage of time below target range 3.5 mmol/L; SD, standard deviation; CV, coefficient of variation; MAGE, Mean amplitude of glycemic excursions.

\*Model 1: adjusted for age, ethnicity, education, employment status, pre-pregnancy body mass index, and total daily energy intake.

†Model 2: adjusted for Model 1 + bedtime, irregular meal, and physical activity.

‡Model 3: adjusted for Model 2 + percentage of energy from night-time protein intake and percentage of energy from night-time fat intake.

In the GEE analysis, the PNE women had a higher glucose level across 24 hours compared to the PDE women (1.10 (1.02, 1.19)). When the adjusted predicted mean glucose levels from GEE were plotted for the PNE and PDE groups (**Fig. 1**), it was evident that PNE women had consistently higher glucose levels compared to PDE women, especially around midnight from 23:00 to 03:00 h. When analysis was restricted to women with a complete 10 days 24-hour glucose ambulatory profile (n=108), the effect sizes became stronger **(Supplementary Table 4** and **Supplementary Figure 1)**.

We observed no interactions between PNE and pre-pregnancy BMI in relation to plasma glycemic and CGM measures (all *p*-interaction ≥0.100), except for fasting glycemia (*P*-interaction 0.027); the association between PNE and fasting glycemia was stronger in women with a pre-pregnancy BMI ≥23 kg/m2 (1.07 (1.00, 1.14)) than those with a pre-pregnancy BMI <23 kg/m2 (1.01 (0.97, 1.06)) **(Supplementary Table 5)**.

### Discussion

**Main findings**

In this prospective cohort study involving healthy pregnant women in the second trimester of pregnancy, we found that maternal consumption of relatively more calories at night than during the day was associated with higher fasting and 1-hour plasma glucose following the OGTT, poorer glycemic control, and consistently higher interstitial glucose levels across 24 hours based on their ambulatory glucose profile. Furthermore, PNE women were also found to have lower fasting insulin secretion and poorer β-cell function compared to PDE women. All these associations were independent of maternal sociodemographic characteristics, pre-pregnancy BMI, lifestyle factors, total daily energy intake, and diet composition.

**Comparison with other studies**

In the present study, 12% of women were found to practice PNE at a mean of 20 weeks gestation. Using the same definition, we previously observed a PNE incidence proportion of 15% among 985 pregnant women from Singapore at a mean of 26 weeks gestation (8-10). The slight difference in the incidence proportions of PNE between these two studies is in line with the findings from a prospective cohort study involving 100 Brazilian pregnant women, showing almost similar proportions of women who reported meals after dinner, which were at 36% and 38% in the second and third trimesters of pregnancy, respectively (41). This Brazilian study showed that there was no difference in maternal night-time energy intake throughout gestation trimesters (41), suggesting that our pregnant women could have engaged in PNE since early or even before pregnancy.

We confirmed and extended previous studies by showing that maternal night-eating was not only associated with increased fasting glucose (8-10), it was also associated with elevated 1-hour post-load glucose and 24-hour glucose levels, as well as reduced fasting insulin secretion during pregnancy. These findings are supported by a cross-sectional study involving 40 low-income African-American pregnant women, showing impaired glucose tolerance and early phase insulin action as assessed by 7-point OGTT in those with late-night eating at late pregnancy, in particular among women with obesity (8). Therefore, we posit that there are potential negative effects of night-eating on glucose regulation and β-cell function during pregnancy. Meanwhile, the weight-dependent effect of night-eating on glycemic status remained uncertain due to inconsistent findings across studies (8-10). Nevertheless, we acknowledge the possibility of reverse causation where pregnant women experiencing nocturnal hypoglycemia or impaired nocturnal fat oxidation might adopt night-eating as a compensatory mechanism for their symptoms or condition (42). However, our study showed that the percentage of TBR for the PNE group was low, and this group of women consistently demonstrated higher glucose levels across 24 hours compared to the PDE women. This is not in keeping with the hypothesis of low glucose triggering night-eating.

In the present study, the effect size for insulin resistance slightly increased after adjusting for fasting glucose levels, indicating the robustness of the association between nocturnal eating and insulin resistance. This suggests that the observed effect might not be solely driven by alterations in glucose metabolism but could involve other pathways such as lipid regulation (41, 43). Conversely, the adjustment of fasting insulin led to a change in the direction of the effect size for insulin resistance, which underscores the pivotal role of insulin. This highlights that night-eating may increase insulin resistance indirectly through its impact on insulin levels. However, further investigation of the underlying mechanisms explaining the relationship between night-eating and insulin resistance is required to confirm the present observations. Based on the findings of lower fasting insulin secretion and higher glucose levels in women with PNE than those with PDE, this suggests that the β-cells have evolved and progressed into the decompensation stage in PNE women, which is similar to prediabetes (44). Although we are unable to determine whether such an abnormal glucose metabolism was the result of PNE during pregnancy or if it was already present in women with PNE before conception, the coexistence of both increased glucose levels and reduced β-cell function as observed in PNE women is worrying as it might subject them to higher risk of developing type 2 diabetes during their postnatal phase (45).

Although PNE was not associated with glucose fluctuation, the higher mean 24-hour glucose and GMI in PNE women raise concerns that these women indeed have suboptimal glycemic control. The consistently higher 24-hour glucose levels as observed around 20 weeks gestation from the ambulatory glucose profile, especially after midnight among women with PNE, may help to explain the higher fasting glucose in the morning that was detected around 25 weeks gestation. Along with the higher 1-hour glucose, to some extent, these observations support the hypothesis that the concurrence of elevated melatonin concentrations (during dinner close to bedtime) and food intake decreases glucose tolerance (46). In a randomized crossover trial among 845 Spanish adults, the authors confirmed that late evening eating acutely impaired glucose tolerance through a defect in insulin secretion rather than a reduction in insulin sensitivity; this might be partly due to a higher melatonin concentration observed in late eaters than early eaters (47).

Even though PNE was not significantly associated with GDM risk, this may be largely attributable to a small sample size; any slight increment in glucose levels (i.e. every 0.12 mmol/L increase in fasting glucose or 0.45 mmol/L increase in 1-hour glucose) has the potential to adversely influence birth outcomes despite being below the GDM diagnostic threshold (13), highlighting the obstetric implications of PNE. A study investigating the role of maternal temporal glucose variation on birth size has shown that 0.50 mmol/L higher mean nocturnal glucose between 00:30 and 06:30 h as assessed by CGM was associated with large-for-gestational age in treated GDM (43).The observed 0.19 mmol/L higher fasting glucose, 0.57 mmol/L higher 1-hour glucose, and 0.52 mmol/L higher 24-hour glucose especially during post-midnight in women with PNE than those with PDE might have clinically appreciable effects on neonatal and long-term offspring health.

**Strengths and limitations of the study**

The main strength of this study is the comprehensive evaluation of multiple maternal glycemic measures in response to night-eating during pregnancy, which included 24-hour glucose levels, glycemic control, and variability measures. This study also has one of the largest CGM datasets reported in apparently healthy pregnant women (non-GDM diagnosis). Last but not least, this study utilized both a food diary and a food picture mobile app to record maternal dietary intake up to four days, which improved the accuracy of dietary information captured.

While no significant difference was observed in total or night-time macronutrient distributions between PDE and PNE, it remains uncertain whether dietary quality at night, based on dietary fat types or glycemic index (4), could influence the association between PNE and glucose levels. In addition, despite the exclusion of pregnant women engaged in routine night-shift work, a study limitation we could not explore was the specific day-shift occupations or job types of the participants. Certain occupations can entail distinct stressors, physical demands and environmental factors that could potentially influence eating behavior and glycemic outcomes. Although employing years of education and employment status as indicators of socioeconomic status is a recognized approach (17), these indicators might not comprehensively capture the complexity of socioeconomic diversity and unmeasured variables related to socioeconomic status could impact the study’s findings.

Furthermore, there was no baseline measurement of glycemic variables at 20 weeks corresponding to the starting point of the assessment of eating behaviors. Such a measurement could have provided insights into the change in insulin resistance with increasing gestation. It is also possible that changes in eating habits, and consequently glycemic variables, occur between 20 weeks and 25 weeks. However, it has been reported that the temporal distribution of eating patterns, including meal timing and frequency, remains constant throughout the trimesters (41). Additionally, we observed a larger 95% CI in the predicted mean glucose levels over a 24-hour period for the PNE group as compared to the PDE group. This observation indicates a higher degree of variability in the predicted mean glucose levels among the PNE women, perhaps partly also reflecting the smaller sample size, in contrast to the PDE women. There may also be a self-selection bias in view of the high refusal and low compliance rates for CGM sensor wearing with only 57% of the women having complete CGM data for at least three days. However, a Heckman selection regression model similarly suggested that PNE was associated with poorer glycemic control. Finally, since this study was not population-based, the generalizability of the results may be compromised. Nonetheless, the PNE and GDM rates in this study are comparable with the prevalence reported in the largest pregnancy cohort in Singapore (48).

**Conclusion**

In conclusion, among healthy pregnant women at mid-gestation, consumption of relatively more calories at night compared to during the day was associated with dysregulated glycemic status, decompensated pancreatic β-cell function, and increased glucose levels throughout 24 hours. These findings suggest that misalignment of eating time with the day-night cycle may disrupt glucose homeostasis during pregnancy and highlights the crucial importance of mealtimes on antenatal glycemic control in addition to the conventional focus on dietary composition alone. Pregnant mothers, even with the absence of diabetes, are encouraged to refrain from developing or continuing PNE practice, which has potential to exacerbate the already increased risk of poor glucose control throughout their pregnancy. However, further studies are required to investigate the applicability of dietary intervention using chrononutrition approach in addressing PNE during pregnancy, and its clinical outcomes. In addition, the use of CGM monitoring to guide the control of maternal glycemic levels in patients demonstrating PNE remains to be elucidated.

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**Conflict of Interest**

KMG and FY received reimbursement for speaking at conferences sponsored by companies selling nutritional products. KMG is part of an academic consortium that received research funding from Abbott Nutrition, Nestle and Danone. All other authors declare no competing interests.

**Author Contributions**

SLL and CWK served as co-first authors and contributed equally to this work. SLL, YBC, JKYC and FY conceived and designed the study. CWK, KHT, NL, MFFC, JKYC and FY contributed to the study implementation. YBC advised on statistical analysis. RZT cleaned the data. SLL, RZT and LWC analyzed the data. SLL, CWK, CHFL and TYC wrote the first draft of the manuscript. All authors contributed to the interpretation of the results and critical revision of the manuscript for important intellectual content and approved the final version of the manuscript. The corresponding authors attest that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. SLL obtained funding and is the study guarantor and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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**Figure 1** The predicted 24-hour interstitial glucose levels from generalized estimating equations among predominantly day-eating and predominantly night-eating pregnant women, adjusted for age, ethnicity, education, pre-pregnancy body mass index, total daily energy intake, bedtime, irregular meal, physical activity, percentage of energy from night-time protein intake, and percentage of energy from night-time fat intake. The circle markers and capped vertical lines represent the predicted mean glucose levels and the respective 95% confidence intervals. Geometric mean ratio 1.10 (95% confidence interval 1.02, 1.19), equivalent to 0.52 mmol/L glucose.