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## **Prospective association between late evening food consumption and risk of prediabetes and diabetes: the Whitehall II cohort study**

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### What's new?

- Eating within a specific time window each day, i.e. time-restricted eating, reduces cardiometabolic risk in rodents.
- In humans, timing of meal intake has acute effects on glucose regulation, but the long-term effects of meal timing on diabetes risk are less clear.
- In more than 3500 men and women from the Whitehall II study, we found no associations between timing of last eating episode and 5-year development of prediabetes or diabetes.
- However, explorative analyses suggested that late evening food consumption was associated with increased 5-year risk of developing prediabetes or diabetes among women with good glycaemic control.
- Whether restricting late evening food consumption is effective and feasible for the prevention of Type 2 diabetes needs testing in randomized controlled trials.

### Abstract

**Aims** We examined whether late evening food consumption was prospectively associated with the risk of developing prediabetes or diabetes in a large observational study of individuals with normoglycaemia.

**Methods** Participants were 2642 men and women with normoglycaemia ( $\text{HbA}_{1c} < 39 \text{ mmol/mol}$ ;  $< 5.7\%$ ) from Whitehall II. Time of last eating episode (TLEE) before the examination day was assessed at baseline. We studied the associations of TLEE with 5-year

changes in HbA<sub>1c</sub> and risk of developing prediabetes or diabetes (HbA<sub>1c</sub> ≥ 39 mmol/mol; ≥ 5.7%). Potential heterogeneity in the association between TLEE and prediabetes or diabetes was examined using recursive partitioning modelling for time-to-event outcomes.

**Results** There was a tendency of an overall association of TLEE with change in HbA<sub>1c</sub> but with little effect size [ $\beta$  per 1-h increase in TLEE = 0.2 mmol/mol, 95% CI -0.0 to 0.3 (0.01%, -0.00 to 0.03);  $P = 0.055$ ] and no association with the risk of developing prediabetes/diabetes (risk ratio per 1-h increase in TLEE = 1.03, 95% CI 0.94 to 1.13;  $P = 0.511$ ). According to the recursive partitioning modelling, women with HbA<sub>1c</sub> ≤ 36 mmol/mol and TLEE after 21:00 had a 1.51 times (95% CI 1.16 to 1.93) higher 5-year risk of developing prediabetes or diabetes than those having their TLEE between 16:00 and 21:00 (35.4% vs. 23.5%;  $P = 0.003$ ).

**Conclusions** There was no overall association of TLEE with the development of prediabetes or diabetes in the Whitehall II population. However, explorative analyses suggested that eating late in the evening was associated with increased risk of developing prediabetes/diabetes among women with good glycaemic control. Whether restricting late evening food consumption is effective and feasible for the prevention of Type 2 diabetes needs testing in randomized controlled trials.

## <H1>Introduction

Current prevention strategies and treatment of obesity and Type 2 diabetes focus on energy-restricted diets, increased physical activity or medication [1,2], but adherence to such strategies is challenging for most individuals. Timing of food intake and fasting periods affects the circadian rhythms of metabolic organs, and experimental data from animal studies suggest promising effects of timing of dietary intake on metabolic functions [3]. Also, in

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smaller human studies, restricting late evening food consumption seems to have beneficial effects on body weight and metabolism [4]. Whether timing of food intake is related to long-term changes in glucose metabolism is not known. In the current analysis, we examined whether late evening food consumption is prospectively associated with the risk of prediabetes and diabetes in a large observational study of individuals with normoglycaemia.

## **<H1>Methods**

Data were from the Whitehall II study including 2642 men and women from the British civil service (no shift workers) who were free of diabetes or prediabetes in 2002–2004 and who participated in a 5-year follow-up examination in 2007–2009. At both visits, all participants attended a clinical examination after an overnight fast of at least 8 h and their ‘time of last eating episode’ (TLEE) prior to the examination was requested. The examinations were distributed equally across weekdays (21.0% Monday, 17.2% Tuesday, 21.3% Wednesday, 18.4% Thursday and 22.2% Friday).

HbA<sub>1c</sub> was measured in whole blood using high-performance liquid chromatography. Prediabetes (HbA<sub>1c</sub> 39–47 mmol/mol) and diabetes (HbA<sub>1c</sub> ≥ 48 mmol/mol) were classified according to the American Diabetes Association definition [5]. Diabetes could also be diagnosed by a doctor outside the study between the visits. Information on ethnicity, employment, smoking, sleep, physical activity, alcohol, family history of diabetes, medication and energy intake was obtained from questionnaires.

Using linear regression, we studied the association of TLEE (16:00–04:00) with 5-year changes in HbA<sub>1c</sub>. The analysis was adjusted for baseline HbA<sub>1c</sub>, age, sex, ethnicity, employment, family history of diabetes, anti-hypertensive treatment, lipid-lowering treatment, BMI, average sleep duration, smoking status, physical activity, alcohol intake, energy intake, waist circumference, triglycerides, total-, HDL- and LDL cholesterol, systolic and diastolic BP.

We further assessed the association between TLEE and the development of prediabetes or diabetes using Poisson regression with the same covariates and risk time as offset. Potential heterogeneity in the association between TLEE and prediabetes or diabetes was examined using recursive partitioning modelling for time-to-event outcomes (survival tree) [6] with the same explanatory variables as above.

## **<H1>Results**

Mean (SD) age of participants at baseline was 60.2 (5.8) years, BMI was 26.3 (4.1) kg/m<sup>2</sup> and 73.9% were men (Table 1). Median (range) TLEE at baseline was 21:00 (16:00–02:15) for men and 21:00 (16:00–02:20) for women (Fig. 1a). Median (IQR) population difference in TLEE between baseline and follow-up was 0.0 (–0.8; 1.5) h. At 5-year follow-up, 875 (33.1%) had developed prediabetes ( $n = 769$ , 29.1%) or diabetes ( $n = 106$ , 4.0%).

Results from the linear regression and Poisson regression analysis showed a tendency of an overall association of TLEE with change in HbA<sub>1c</sub> but with little effect size [ $\beta$  per 1-h increase in TLEE = 0.2 mmol/mol, 95% CI –0.0 to 0.3 (0.01%, –0.00 to 0.03);  $P = 0.055$ ]

and no association with the risk of developing prediabetes/diabetes (risk ratio per 1-h increase in TLEE = 1.03, 95% CI 0.94 to 1.13;  $P = 0.511$ ).

Interestingly, the recursive partitioning model showed heterogeneity in the association between TLEE and development of prediabetes or diabetes (Fig. 1b). The strongest predictor of development of prediabetes or diabetes was HbA<sub>1c</sub>. Around half of the participants with HbA<sub>1c</sub> concentrations of 36–38 mmol/mol (5.4–5.6%) developed prediabetes or diabetes during follow-up (47% of men and 61% of women; nodes 5 and 6), and these progression rates were independent of TLEE. For those with HbA<sub>1c</sub> concentrations  $\leq 36$  mmol/mol ( $< 5.4\%$ ), sex was a significant predictor of progression to prediabetes or diabetes. Men with HbA<sub>1c</sub>  $\leq 36$  mmol/mol ( $< 5.4\%$ ) had an estimated 7–18% 5-year risk of progressing to prediabetes or diabetes (nodes 1 and 2). The probability of progressing to prediabetes or diabetes in individuals with a good glycaemic control was higher among women and was related to TLEE. Women with HbA<sub>1c</sub>  $\leq 36$  mmol/mol ( $< 5.4\%$ ) and TLEE after 21:00 ( $n = 256$ ) had 1.51 times (95% CI 1.16 to 1.93) higher 5-year risk of developing prediabetes/diabetes than those having their TLEE between 16:00 and 21:00 (incidence 35.4% vs. 23.5%,  $P=0.003$ ; nodes 3 and 4). Changes in body weight from baseline to follow-up did not explain the differences in incidence rates. Women in node 3 on average gained 0.52 kg (95% CI  $-0.12$  to 1.16), whereas women in node 4 gained 0.38 kg ( $-0.18$  to 0.94) ( $P$  for difference = 0.753). At baseline, body weight was also similar among women in nodes 3 and 4 (66.5 vs. 67.2 kg,  $P = 0.570$ ).

In a sensitivity analysis, we used an HbA<sub>1c</sub> range of 42–47 mmol/mol (6.0–6.4%) for definition of prediabetes. In this analysis, TLEE after 21:00 was also associated with a higher risk of developing prediabetes/diabetes in women with a good glycaemic control ( $\leq 37$  mmol/mol) (Fig. S1).

## **<H1>Conclusions**

Our findings add to the evidence on late evening food consumption and cardiometabolic risk. Animal and smaller human studies have observed beneficial effects of timing of food intake on weight loss [3], but the effects on glucose regulation in the general population have not been known. One explanation for an increased diabetes risk associated with late evening food consumption could be circadian variation in hormones regulating glucose metabolism [7]. In healthy individuals, serum insulin concentration peaks between noon and 18:00 [8], whereas the appetite hormones leptin and ghrelin peak around midnight [9,10]. It has also been shown that the glucose response to identical meals is greater in the evening than in the morning [11]. Thus, it is possible that food intake late in the evening or during night-time is in misalignment with the circadian rhythm of the insulin response, which may result in a greater overall glycaemic exposure and thereby increased HbA<sub>1c</sub> levels over time.

We observed an association between TLEE and prediabetes/diabetes development among women with a good glycaemic control. Differences in food patterns between men and women are common [12], and we have previously observed sex-specific associations between lifestyle factors and glucose regulation in the Whitehall II cohort [13], supporting these findings. Whether late evening food consumption disturbs circadian rhythm differently in men and women needs further investigation.

This study has some limitations and needs confirmation in other studies with more detailed assessment of the time of dietary intake over several days. Information on time of dietary intake in Whitehall II was limited to 1 day at baseline and 1 day at follow-up. Although the TLEE measure was generally stable across the examinations conducted 5 years apart, there may still be misclassifications in participants' eating pattern. The participants were instructed to fast for 8 h prior to the health examinations, and therefore our data do not capture night-time eating. We used the HbA<sub>1c</sub> criteria for prediabetes/diabetes, because fasting and 2-h plasma glucose are affected by the time of day and fasting duration prior to blood sampling [14]. Accordingly, these measures would not be independent of the TLEE prior to the examination.

In conclusion, there was no overall association between TLEE and development of prediabetes/diabetes in the Whitehall II population. However, explorative analyses suggested that eating late in the evening was associated with increased risk of developing prediabetes/diabetes among women with good glycaemic control. Whether restricting late evening food consumption is effective and feasible for the prevention of Type 2 diabetes [3] needs testing in randomized controlled trials.

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### **Competing interests**

K.F and M.E.J. have received research grants from AstraZeneca (investigator-initiated research). S.P has published a book *The Circadian Code*. The other authors declare no competing interests.

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### **Author contributions**

K.F. and D.V. contributed to the study concept and design, planned the statistical analyses, and drafted the manuscript. D.V. conducted the statistical analysis. E.J.B., M.K. and A.G.T. provided data. All authors provided intellectual input and read and approved the final version of the manuscript. K.F. and D.V. are guarantors of the contents of the article and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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**FIGURE 1** Distribution of time of last meal among 1937 men and 705 women with normoglycaemia at baseline (a). Recursive partitioning model (survival tree) for progression from normoglycaemia to prediabetes or diabetes (b). The black boxes are the six terminal subgroups of the tree, each with the number of participants ( $n$ ) and their estimated 5-year probability of progressing to prediabetes or diabetes with 95% confidence intervals.

### <H1>Supporting information

Additional Supporting Information may be found in the online version of this article:

**Figure S1.** Recursive partitioning model (survival tree) for progression from normoglycaemia to prediabetes or diabetes.

**Table 1** Baseline characteristics of the study population by sex

	Men	Women
<i>N</i>	1937	705
White ethnicity (%)	96.6 (95.7; 97.4)	94.8 (92.8; 96.3)
Age (years)	59.9 (5.7)	59.7 (5.7)
BMI (kg/m <sup>2</sup> )	26.0 (3.5)	25.9 (4.8)
Waist circumference (cm)	94.3 (10.0)	85.0 (13.2)
HbA <sub>1c</sub> (mmol/mol)	35 (3)	35 (3)
HbA <sub>1c</sub> (%)	5.4 (0.3)	5.4 (0.3)
SBP (mmHg)	126.9 (15.5)	123.9 (18.0)
DBP (mmHg)	74.3 (10.3)	72.4 (10.8)
Total cholesterol (mmol/l)	5.7 (1.0)	5.9 (1.0)
LDL cholesterol (mmol/l)	3.6 (0.9)	3.5 (0.9)
HDL cholesterol (mmol/l)	1.5 (0.4)	1.9 (0.5)
Triglycerides (mmol/l)	1.1 (0.8; 1.6)	1.0 (0.7; 1.3)
Alcohol intake (units/week)*	12.0 (5.0; 21.0)	6.0 (2.0; 12.0)
Time of last meal intake	21:00 (20:00; 22:00)	21:00 (20:00; 22:00)
Nightly sleep < 7 h (%)	38.4 (36.2; 40.6)	43.7 (40.0; 47.4)
Daily energy intake (kcal·10 <sup>3</sup> )	2.25 (0.63)	1.97 (0.6)
Current smoker (%)	6.7 (5.6; 7.9)	7.1 (5.3; 9.2)
Employment (%)		
Administrative	53.8 (50.1; 57.5)	32.6 (27.1; 38.5)
Professional	41.3 (37.7; 44.9)	51.3 (45.2; 57.4)
Clerical	5.0 (3.5; 6.8)	16.1 (12.0; 21.0)
Physical activity ≥ 2.5 h/week	31.5 (29.4; 33.6)	25.6 (22.4; 29.1)
Family history of diabetes (%)	8.4 (7.2; 9.7)	8.7 (6.7; 11.0)
Antihypertensive treatment (%)	17.6 (15.9; 19.3)	18.7 (15.9; 21.8)
Lipid-lowering treatment (%)	7.4 (6.3; 8.7)	4.5 (3.1; 6.3)

Data are shown as mean (SD), median (IQR) or proportion (95% confidence intervals).

\*A unit alcohol: 8 g of pure alcohol.

