

ORIGINAL ARTICLE

Sleep Quality and Nocturnal Sleep Duration in Pregnancy and Risk of Gestational Diabetes Mellitus

Shirong Cai, PhD¹; Sara Tan, MD²; Peter D. Gluckman, FRS^{3,4}; Keith M. Godfrey, PhD⁵; Seang-Mei Saw, PhD⁶; Oon Hoe Teoh, MBBS⁷; Yap-Seng Chong, MD^{1,4}; Michael J. Meaney, PhD⁸; Michael S. Kramer, MD^{9,10}; Joshua J. Gooley, PhD^{2,11} on behalf of the GUSTO study group

¹Department of Obstetrics & Gynaecology, Yong Loo Lin School of Medicine, National University of Singapore, National University Health System, Singapore, Singapore; ²Program in Neuroscience and Behavioral Disorders, Duke-NUS Medical School, Singapore, Singapore; ³Liggins Institute, University of Auckland, Auckland, New Zealand; ⁴Singapore Institute for Clinical Sciences, Agency for Science, Technology and Research (A*STAR), Singapore, Singapore; ⁵MRC Lifecourse Epidemiology Unit & NIHR Southampton Biomedical Research Centre, University of Southampton & University Hospital Southampton NHS Foundation Trust Southampton, England; ⁶Saw Swee Hock School of Public Health, National University of Singapore, Singapore, Singapore; ⁷Department of Pediatrics, KK Women's and Children's Hospital, Singapore, Singapore; ⁸Department of Psychiatry, McGill University Faculty of Medicine, Montreal, Canada; ⁹Department of Epidemiology, Biostatistics and Occupational Health, McGill University Faculty of Medicine, Montreal, Canada; ¹⁰Department of Pediatrics, McGill University Faculty of Medicine, Montreal, Canada; ¹¹Department of Physiology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore

Study Objectives: To examine the influence of maternal sleep quality and nocturnal sleep duration on risk of gestational diabetes mellitus (GDM) in a multiethnic Asian population.

Methods: A cohort of 686 women (376 Chinese, 186 Malay, and 124 Indian) with a singleton pregnancy attended a clinic visit at 26–28 weeks of gestation as part of the Growing Up in Singapore Towards healthy Outcomes mother–offspring cohort study. Self-reported sleep quality and sleep duration were assessed using the Pittsburgh Sleep Quality Index (PSQI). GDM was diagnosed based on a 75-g oral glucose tolerance test administered after an overnight fast (1999 WHO criteria). Multiple logistic regression was used to model separately the associations of poor sleep quality (PSQI score > 5) and short nocturnal sleep duration (<6 h) with GDM, adjusting for age, ethnicity, maternal education, body mass index, previous history of GDM, and anxiety (State-Trait Anxiety Inventory score).

Results: In the cohort 296 women (43.1%) had poor sleep quality and 77 women (11.2%) were categorized as short sleepers; 131 women (19.1%) were diagnosed with GDM. Poor sleep quality and short nocturnal sleep duration were independently associated with increased risk of GDM (poor sleep, adjusted odds ratio [OR] = 1.75, 95% confidence interval [CI] 1.11 to 2.76; short sleep, adjusted OR = 1.96, 95% CI 1.05 to 3.66).

Conclusions: During pregnancy, Asian women with poor sleep quality or short nocturnal sleep duration exhibited abnormal glucose regulation. Treating sleep problems and improving sleep behavior in pregnancy could potentially reduce the risk and burden of GDM.

Keywords: sleep duration, sleep quality, gestational diabetes mellitus, Asian women.

Statement of Significance

Diabetes is a global health burden that is growing rapidly in Asia. To reduce and manage the burden of diabetes, it is imperative to identify modifiable risk factors that contribute to glucose dysregulation. Sleep deficiency results in impaired glucose metabolism and is thought to be a contributing factor to the development of type 2 diabetes. However, few studies have examined the potential role of sleep deficiency in the etiology of gestational diabetes mellitus (GDM), which itself is a risk factor for type 2 diabetes. In a multiethnic Asian population, we show that poor sleep quality and short sleep (<6 h per night) were independently associated with increased risk of GDM. These findings suggest that sleep is important for normal energy metabolism in pregnancy. Managing sleep problems and encouraging good sleep habits in pregnancy could reduce the likelihood of developing hyperglycemia and GDM.

INTRODUCTION

Sleep disturbances and short sleep duration are common in pregnancy as a consequence of hormonal changes, physical discomfort, sleep disorders, and anxiety associated with childbearing.^{1–4} Chronic exposure to short nocturnal sleep duration is a risk factor for type 2 diabetes,^{5–7} but less is known about the role of insufficient sleep in the etiology of gestational diabetes mellitus (GDM). Women with GDM are at increased risk of preeclampsia and cesarean delivery, and their newborns are at increased risk of macrosomia and birth-related injuries, hypoglycemia, and jaundice.^{8,9} Furthermore, women with GDM are more likely to develop type 2 diabetes after giving birth,¹⁰ and offspring of diabetic mothers are at increased risk of obesity, type 2 diabetes, and metabolic syndrome.^{11,12} To reduce the burden of GDM and its complications, it is important to identify behavioral risk factors that are treatable or preventable.

Growing evidence suggests that sleep insufficiency during pregnancy might contribute to the development of hyperglycemia and GDM.^{13,14} Short sleep duration has been associated

with increased risk of GDM in samples that were predominantly Caucasian and African American,^{15–17} but these studies included a small number of GDM cases (≤ 26 cases per study). It is unclear whether these findings are generalizable to other populations, including Asian women, in whom the prevalence of GDM is higher than among non-Hispanic whites and African Americans living in the same communities.^{18–23} The greater risk of GDM in Asians can potentially be explained by ethnic differences in body composition (e.g., accumulation of visceral fat) and sensitivity to adiposity,^{24,25} or by differences in dietary and lifestyle factors that affect glucose metabolism.²⁶ Adults residing in urbanized Asian countries (e.g., Japan, Korea, and Singapore) sleep substantially less than their counterparts in Western countries;^{27–30} hence, raising the possibility that short sleep duration may contribute to the risk profile for GDM in Asian women. We therefore studied a multiethnic Asian population in Singapore to examine the relationship between sleep behavior and glucose tolerance. We hypothesized that exposure to poor sleep quality or short sleep duration (<6 h per night) would associate with increased risk of GDM.

METHODS

Study Population

Pregnant women aged 18 years and older were recruited in their first trimester (<14 weeks of pregnancy) to participate in the Growing Up in Singapore Towards healthy Outcomes (GUSTO) mother-offspring cohort study. The overall aim of the GUSTO study is to identify maternal and early life factors that affect metabolic health outcomes of children raised in Singapore.³¹ A total of 1247 women who were seeking obstetric services from KK Women's and Children's Hospital or the National University Hospital were enrolled in the GUSTO study from June 2009 to September 2010. Demographic data including maternal age, ethnicity, and education were collected using an interviewer-administered questionnaire at the time of enrollment. Height and weight were measured by trained clinical staff to calculate body mass index (BMI, in kilograms per square meter). Women were eligible if they were Chinese, Malay, or Indian with a homogeneous parental ethnic background. Informed written consent was obtained from each participant, with procedures approved by the National Healthcare Group Institutional Review Board (IRB) and the SingHealth Centralized IRB.

Measurements at 26–28 Weeks of Gestation

At 26–28 weeks of pregnancy, 1214 study participants attended a clinic visit that included questionnaire-based behavioral assessments and an oral glucose tolerance test (OGTT). Women with multiple pregnancies ($n = 5$) or prior diagnosis of type 2 diabetes ($n = 10$) were excluded. During the clinic visit, participants completed the Edinburgh Postnatal Depression Scale (EPDS) and the State-Trait Anxiety Inventory (STAI). To evaluate sleep quality in the previous month, a subset of 917 women were asked to complete the Pittsburgh Sleep Quality Index (PSQI), with a PSQI score >5 defined as poor sleep.³² A total of 745 women responded to all questions on the PSQI, allowing a valid PSQI global score to be calculated. Previous studies have shown that the PSQI has similar psychometric properties in pregnant women and in non-pregnant populations.^{33,34} The PSQI global score (range 0–21) represents the sum of component scores for subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, use of sleep medications, and daytime dysfunction. Self-reported nocturnal sleep duration was taken from the following question of the PSQI: “During the past month, how many hours of actual sleep did you get at night? (This may be different than the number of hours you spend in bed).”

Short nocturnal sleep duration was defined as <6 h based on epidemiological and laboratory studies demonstrating that short sleep by this definition is associated with abnormal glucose regulation. Specifically, meta-analyses of prospective studies have shown that short sleep duration (defined as ≤ 5 h or <6 h in most studies) is associated with increased risk of developing type 2 diabetes.^{5–7} These studies included men and women across a broad range of ages and from several geographic regions,^{6,35–42} suggesting that results for short sleep and diabetes risk are generalizable. Our definition of short sleep is also consistent with laboratory studies in which experimentally induced sleep restriction (ranging from 4 to 5.5 h of time in bed each night)

resulted in decreased glucose tolerance, decreased insulin sensitivity, and increased insulin resistance.^{43–48} Additionally, our cutoff for short sleep duration is consistent with recent recommendations by the National Sleep Foundation, USA, in which <6 h of sleep was categorized as “not recommended” in adults aged 18–64 years.⁴⁹

Oral Glucose Tolerance Test

Of the 745 pregnant women with a valid PSQI score, 686 participants completed a 75-g OGTT after overnight fasting (8–10 h). Blood glucose levels were measured before and 2 h after administration of oral glucose. GDM was defined using the 1999 WHO diagnostic criteria: ≥ 7.0 mmol/L (126 mg/dL) for fasting glucose and/or ≥ 7.8 mmol/L (140 mg/dL) for 2-h OGTT glucose.⁵⁰ These criteria were chosen because they represent the standard clinical guidelines for diagnosing GDM in Singapore.⁵¹ Results of the OGTT were conveyed to participants 1–2 weeks after the clinic visit.

Statistical Methods

Independent Student *t*-tests and chi-squared tests were used to compare continuous and categorical maternal characteristics between groups of women with normal glucose levels versus women with GDM. Because prior studies have shown an inverse correlation between sleep duration and glucose levels in pregnant women,^{52,53} bivariate analyses (Pearson's correlation analysis) were used to examine the strength of the linear relationship between each sleep measure (PSQI score or nocturnal sleep duration) and glucose levels (fasting glucose or 2-h OGTT glucose levels). Separate multivariable linear regression analyses were used to model associations of (1) sleep quality (i.e., PSQI scores) with fasting glucose levels, (2) sleep quality with 2-h OGTT glucose levels, (3) nocturnal sleep duration with fasting glucose levels, and (4) nocturnal sleep duration with 2-h OGTT glucose levels. In each analysis, only 1 sleep variable (PSQI score or sleep duration) was entered into the model simultaneously (i.e., in 1 step) with the following independent variables: maternal age, ethnicity, maternal education, history of GDM, BMI at the time of enrollment (<14 weeks of pregnancy), and maternal anxiety (STAI total score).

Separate multivariable logistic regression models were used to estimate (1) the association of poor sleep quality (PSQI score >5) on GDM risk and (2) the association of short nocturnal sleep duration (<6 h) on GDM risk. Those regression models were adjusted for maternal age, ethnicity, maternal education, history of GDM, BMI at <14 weeks of pregnancy, and maternal anxiety score. Data were missing for maternal education in 1.2% of women ($n = 8$), for history of GDM in 2.3% of women ($n = 16$), and for antenatal STAI scores in 5.2% of women ($n = 36$). Case-wise exclusion was used to handle missing data in the adjusted models. All analyses were carried out using SPSS software, version 22.0 (IBM, Armonk, NY, USA).

RESULTS

Participant Characteristics

Of the 1214 women who attended the clinic visit at 26–28 weeks of gestation, 686 women completed the PSQI and underwent the

OGTT. Women who did not have PSQI and/or OGTT data were similar to participants who were included in the present analysis with respect to maternal age, ethnicity, BMI, EPDS score, alcohol consumption, and smoking, but had significantly lower educational attainment (28.6% vs. 38.2% with university and above, $p < .001$), lower household income (19.9% vs. 36.9% with household income $> \$6000$ Singapore dollars, $p < .001$), and higher STAI scores (72.9 ± 16.6 vs. 69.9 ± 18.5 , $p = .004$).

Of the 686 pregnant women included in our analysis, 131 (19.1%) were diagnosed with GDM. All of these women met the diagnostic criterion for GDM based on their 2-h OGTT result (i.e., plasma glucose ≥ 7.8 mmol/L), while 2 of the women also met the diagnostic criterion for fasting glucose levels (i.e., plasma glucose ≥ 7.0 mmol/L). Ethnic distribution differed for groups with normal glucose levels versus GDM (Table 1), with a higher percentage of GDM cases observed in Indian and Chinese participants (25.0% and 20.5%) than in Malay participants (12.4%). Women with GDM were older (32.1 ± 4.8 years vs. 30.3 ± 5.1 years), had a higher BMI at < 14 weeks of pregnancy (24.6 ± 4.6 kg/m² vs. 23.6 ± 4.9 kg/m²), and had lower anxiety scores (66.5 ± 17.5 vs. 70.6 ± 18.7), whereas maternal education, household income, nulliparous pregnancy, alcohol consumption, and smoking were similar between groups (Table 1). In univariable analyses, women with GDM tended to have poorer sleep quality than participants without GDM (PSQI score, 5.89 ± 3.07 vs. 5.36 ± 2.76), but the difference in PSQI global scores did not reach statistical significance ($p = .054$). Based on PSQI component scores, women with GDM rated their sleep quality as significantly worse than women without GDM (1.15 ± 0.70 vs. 1.02 ± 0.60 ; $p = .045$), whereas the other PSQI component scores did not differ between groups (Supplementary Table 1). Nocturnal sleep duration and the proportion of short sleepers (< 6 h per night) did not differ significantly in women with GDM vs. women with normal glucose levels (Table 1).

Influence of Sleep Quality and Sleep Duration on Blood Glucose Levels and Risk of GDM

The absolute frequency of GDM was higher in women with poor sleep quality (PSQI > 5 ; 22.0%) compared with women with better sleep quality (PSQI ≤ 5 ; 16.9%). A significant bivariate correlation was observed between fasting glucose levels and PSQI scores (Pearson's $r = 0.094$, $p = .014$), but not for 2-h glucose levels and PSQI scores (Pearson's $r = -0.003$, $p = .94$). In the multivariable linear regression model, pregnant women with poorer sleep quality (i.e., higher PSQI scores) exhibited higher fasting glucose levels but not 2-h OGTT glucose levels, adjusting for ethnicity, maternal age, education, BMI, history of GDM, and anxiety score (fasting glucose: unstandardized regression coefficient, $B = 0.016$, 95% confidence interval [CI] 0.003 to 0.029; 2-h glucose: $B = 0.030$, 95% CI -0.013 to 0.073).

Based on OGTT results across different sleep duration subgroups (< 6 h, 6–6.99 h, 7–7.99 h, 8–8.99 h, ≥ 9 h), the absolute frequency of GDM was highest in women who reported sleeping < 6 h per night (27.3%) and lowest in women with 7–7.99 h of sleep per night (16.8%) (Figure 1A). Fasting glucose levels, but not 2-h glucose levels, decreased linearly with increasing

sleep duration (Fasting glucose: Pearson's $r = -0.099$, $p < .01$; 2-h glucose: Pearson's $r = -0.048$, $p = .21$) (Figure 1B and C). In multivariable linear regression models, however, nocturnal sleep duration was not associated with either fasting glucose levels or 2-h OGTT glucose levels, after adjusting for covariates (Fasting glucose: $B = -0.017$, 95% CI -0.041 to 0.007; 2-h glucose: $B = -0.009$, 95% CI -0.088 to 0.069).

Next, we used multivariable logistic regression analysis to model the association between poor sleep quality and GDM risk and the association between short nocturnal sleep duration and GDM risk (Table 2). In our sample, 296 women (43.1%) were categorized as having poor sleep quality (PSQI global score > 5). These women had a higher risk of GDM relative to women with better sleep quality, after adjusting for ethnicity, maternal age, education, BMI, history of GDM, and anxiety scores (adjusted OR = 1.75, 95% CI 1.11 to 2.76). There were 77 women (11.2%) in our study who reported sleeping < 6 h per night. These women had an increased risk of GDM compared to women with longer sleep duration (≥ 6 h), after adjusting for covariates (adjusted OR = 1.96, 95% CI 1.05 to 3.66).

DISCUSSION

Poor sleep quality and short nocturnal sleep duration during pregnancy were independently associated with increased risk of GDM. Our results are consistent with previous studies that used the PSQI to assess sleep quality in non-pregnant populations with type 2 diabetes. For example, poorer sleep quality in diabetic patients has been associated with higher levels of hemoglobin A1c,^{54,55} a marker reflecting increased blood glucose levels, after adjusting for age, sex, and BMI. Recent studies suggest that poor sleep quality (PSQI > 5) is associated with increased risk of metabolic syndrome,⁵⁶ which is defined in part by impaired glucose tolerance. PSQI-defined poor sleep quality has also been associated with increased homeostatic model assessment-insulin resistance in Chinese patients with type 2 diabetes.⁵⁷ Our results therefore extend previous findings in non-pregnant adults to show that poor sleep quality in pregnancy is associated with hyperglycemia. Additionally, our findings are consistent with a recent study performed in pregnant Chinese women, in which it was reported that risk of GDM was greater in subjects who rated their sleep quality as 'poor' compared with subjects who rated their sleep quality as 'good'.⁵⁸

Similar to previous studies that included predominantly Caucasian and African American populations,^{15–17} we found short sleep duration to be associated with increased risk of GDM in Asian women. The small sample sizes and moderate participant diversity in prior studies limited the generalizability of the results, and estimates of relative risk were imprecise with large CIs. Hence, important strengths of our study were inclusion of women from 3 major Asian ethnic groups not studied previously, and a larger number of GDM cases that allowed for a more precise estimate of risk. Prior studies in non-pregnant populations have demonstrated a U-shape relationship between sleep duration and relative risk for type 2 diabetes,⁷ in which either short sleep duration or long sleep duration was associated with greater risk. Also, a recent study that included a large sample of pregnant Chinese women ($n = 12\,506$; including 919 GDM cases) found

Table 1—Characteristics of Women With Normal Glucose Levels (NGL) and Gestational Diabetes Mellitus (GDM).

	Total (<i>n</i> = 686)	NGL (<i>n</i> = 555)	GDM (<i>n</i> = 131)	<i>p</i> -value
Demographic and lifestyle factors				
Maternal age (years)	30.7 ± 5.1	30.3 ± 5.1	32.1 ± 4.8	<.001
Ethnicity, <i>n</i> (%)				
Chinese	376 (54.8)	299 (53.9)	77 (58.8)	.013
Malay	186 (27.1)	163 (29.4)	23 (17.6)	
Indian	124 (18.1)	93 (16.8)	31 (23.7)	
Maternal education, <i>n</i> (%)				
Primary and below	28 (4.1)	25 (4.5)	3 (2.3)	.283
Secondary	143 (20.8)	120 (21.6)	23 (17.6)	
Diploma/technical	248 (36.2)	202 (36.4)	46 (35.1)	
University and above	259 (37.8)	200 (36.0)	59 (45.0)	
Missing/ refused	8 (1.2)	8 (1.4)	0 (0.0)	
Monthly household income (SGD), <i>n</i> (%)				
0–1999	80 (11.7)	69 (12.4)	11 (8.4)	.226
2000–3999	171 (24.9)	143 (25.8)	28 (21.4)	
4000–5999	155 (22.6)	119 (21.4)	36 (27.5)	
≥6000	237 (34.5)	188 (33.9)	49 (37.4)	
Missing or refused	43 (6.3)	36 (6.5)	7 (5.3)	
Nulliparous, <i>n</i> (%)	333 (48.5)	275 (49.5)	58 (44.3)	.269
BMI at <14 weeks (kg/m ²)	23.8 ± 4.8	23.6 ± 4.9	24.6 ± 4.6	.034
Previous history of GDM	23 (3.4)	11 (2.0)	12 (9.2)	<.001
Alcohol consumption, <i>n</i> (%)	6 (0.9)	4 (0.7)	2 (1.5)	.538
Smoking, <i>n</i> (%)	22 (3.2)	20 (3.6)	2 (1.5)	.229
Sleep and mood				
EPDS score	7.41 ± 4.47	7.53 ± 4.55	6.93 ± 4.09	.176
STAI total score	69.9 ± 18.5	70.6 ± 18.7	66.5 ± 17.5	.027
PSQI global score	5.47 ± 2.83	5.36 ± 2.76	5.89 ± 3.07	.054
Poor sleepers (PSQI >5), <i>n</i> (%)	296 (43.1)	231 (41.6)	65 (49.6)	.096
Nocturnal sleep duration (h)	7.21 ± 1.48	7.25 ± 1.48	7.03 ± 1.47	.124
Short sleepers (<6 h), <i>n</i> (%)	77 (11.2)	56 (10.1)	21 (16.0)	.053
Blood glucose at 26–28 weeks				
Fasting glucose (mmol/L)	4.35 ± 0.49	4.28 ± 0.37	4.65 ± 0.75	<.001
2-h glucose (mmol/L)	6.54 ± 1.52	6.00 ± 1.00	8.84 ± 1.19	<.001

EPDS, Edinburgh Postnatal Depression Scale; PSQI, Pittsburgh Sleep Quality Index; SGD, Singapore Dollars; STAI, State-Trait Anxiety Inventory. Data are presented as mean ± SD unless otherwise stated.

that sleep duration ≥9 h per day associated with increased risk of GDM relative to women who reported sleeping ≥7 h to <9 h per day.⁵⁸ In the present study, we did not observe a U-shape relationship between sleep duration and frequency of GDM, fasting glucose levels, or 2-h OGTT glucose levels (Figure 1), however our sample included a small number of women with long sleep duration (only 32 women reported sleeping >9 h per night).

We used the 1999 WHO diagnostic criteria for GDM, but many countries and organizations have now adopted the diagnostic criteria recommended by the International Association of Diabetes and Pregnancy Study Groups (IADPSG): fasting glucose ≥5.1 mmol/L and/or 1-h OGTT glucose ≥10.0 mmol/L and/or 2-h OGTT glucose ≥8.5 mmol/L.⁵⁹ The IADPSG recommendations are largely based on results of the Hyperglycemia

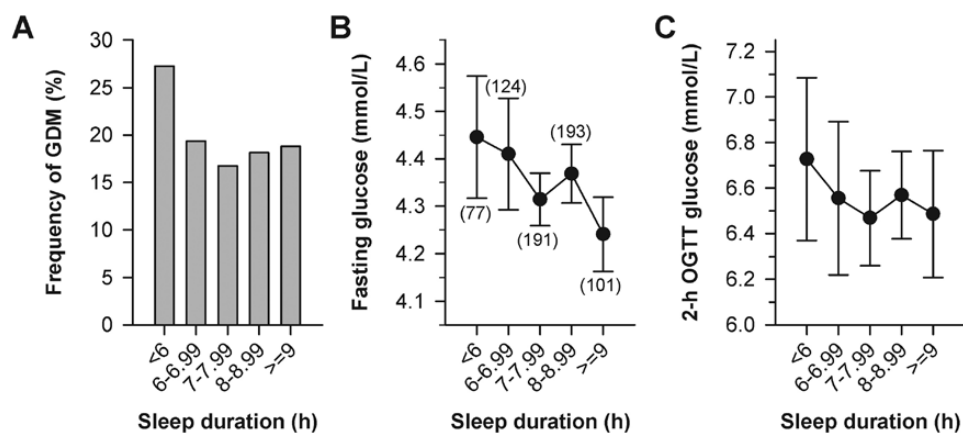


Figure 1—Relationships between blood glucose and sleep duration in pregnant women. Participants completed a 75-g oral glucose tolerance test (OGTT) and reported their nocturnal sleep duration by questionnaire. **(A)** The frequency of gestational diabetes mellitus (GDM), **(B)** fasting glucose levels, and **(C)** 2-h OGTT glucose levels are shown across different sleep duration categories. The number of subjects in each sleep duration bin is indicated in parentheses in panel **B**. The mean and 95% CIs are shown in panels **B** and **C**.

Table 2—Associations Between Poor Sleep Quality and Short Sleep Duration With Risk of Gestational Diabetes Mellitus.

	Unadjusted	Adjusted*
	OR (95% CI)	OR (95% CI)
Poor sleep quality (PSQI > 5)	1.38 (0.94 to 2.02)	1.75 (1.11 to 2.76)
Short sleep duration (<6 h)	1.70 (0.99 to 2.93)	1.96 (1.05 to 3.66)

*Adjusted for maternal age, ethnicity, education, BMI at <14 weeks of gestation, history of gestational diabetes, and State-Trait Anxiety Inventory total score. OR, odds ratio; CI, confidence interval; PSQI, Pittsburgh Sleep Quality Index.

and Adverse Pregnancy Outcome (HAPO) study, which examined associations between maternal glucose and risk of several adverse pregnancy outcomes.^{9,26,59} Compared with the 1999 WHO diagnostic criteria, the IADPSG recommends a lower fasting glucose threshold and a higher 2-h OGTT glucose threshold for diagnosing GDM. Consequently, if we had used the IADPSG diagnostic criteria in our study, more women would have met the diagnostic threshold for fasting glucose (33 women, 4.8% of the sample), whereas fewer women would have met the diagnostic threshold for 2-h OGTT glucose (68 women, 9.9% of the sample). Because our OGTT did not include a 1-h blood sample, we could not retroactively apply the IADPSG criteria to diagnose women with GDM. In supplementary analyses, however, we found that the percentage of women whose fasting glucose or 2-h OGTT glucose levels met the IADPSG diagnostic thresholds was the highest in the subgroup exposed to <6 h of sleep per night (fasting glucose, 9.1%; 2-h OGTT glucose, 14.3%) and the lowest in the subgroup that reported 7–7.99 h of sleep per night (fasting glucose, 2.6%; 2-h OGTT glucose, 7.9%) (Supplementary Figure S1). These findings suggest that our results based on the 1999 WHO diagnostic criteria

are likely to apply to other screening guidelines, including the IADPSG criteria, for diagnosing GDM.

The high frequency of GDM in our study is consistent with prior findings in the HAPO study, in which the prevalence of GDM in Singapore was 25.1% based on the IADPSG diagnostic criteria.⁶⁰ In addition, the 2010 National Health Survey in Singapore found a prevalence of diabetes in non-pregnant adults aged 18–69 years of 11.3% (2-h OGTT glucose levels ≥ 11.1 mmol/L).⁶¹ The high prevalence of GDM and type 2 diabetes in Singapore may be explained by ethnic differences in body composition and lifestyle factors.^{24,62} For example, Chinese and South Indian populations tend to accumulate more abdominal fat compared with Europeans at the same BMI, which could contribute to increased insulin resistance in these Asian ethnic groups.⁶¹ Lifestyle factors such as increased sedentary behavior, decreased physical labor, voluntary sleep curtailment, and easy access to energy-dense foods might also be contributors to the rise in obesity and diabetes in Singapore. Additional studies are needed to assess the relative contribution of these lifestyle factors to GDM risk and to determine why risk of GDM varies across ethnic groups.²¹

Interestingly, diagnosis of GDM in our sample was established almost exclusively by 2-h OGTT glucose levels, rather than fasting glucose levels. The reason for this finding is unclear but has also been noted in our prior work examining the frequency of GDM in participants of the GUSTO study.⁶² Although few women met the diagnostic criterion for GDM based on their fasting glucose levels (using either the 1999 WHO criteria or the IADPSG criteria), a significant bivariate correlation was observed between sleep quality/duration and fasting glucose values. The effect size of PSQI scores on fasting glucose was very small, however, and the negative association between sleep duration and fasting glucose was not significant after adjusting for covariates in the multivariable regression model. The sleep variables we examined did not associate linearly with 2-h OGTT glucose levels, but a higher proportion of women with poor sleep quality and short sleep duration met the 2-h diagnostic criterion for GDM. Taken together, our results suggest

that exposure to poor sleep quality and short sleep duration can affect fasting glucose levels and glucose tolerance in pregnant women. However, additional studies are needed to establish whether fasting and 2-h glucose levels are differentially affected by individual differences in sleep quality or duration.

In this study, sleep quality in the previous month was assessed by questionnaire near the end of the second trimester, coincident with the OGTT. However, because we did not evaluate sleep behavior earlier in pregnancy or prior to conception, we do not know if poor sleep quality was preexisting or a consequence of pregnancy. Additionally, we did not collect information on the frequency or duration of daytime naps, which could potentially ameliorate effects of nocturnal sleep disturbances on glucose metabolism. It is possible that the association between PSQI-assessed sleep quality and risk of GDM can be explained by the occurrence of sleep disorders during pregnancy. Some but not all studies have found that symptoms of sleep-disordered breathing, including self-reported habitual snoring, high risk of obstructive sleep apnea (OSA) using the Berlin Questionnaire, or polysomnographically assessed OSA, are associated with an increased risk of GDM.^{63,64} In non-pregnant women, OSA has been reported to be associated with decreased insulin sensitivity after adjusting for age and waist-hip ratio,⁶⁵ but a recent meta-analysis did not find a significant difference in the prevalence of GDM between pregnant women with OSA vs. those without OSA.⁶⁶ Because we did not screen for sleep disorders polysomnographically or collect information on risk of OSA, these factors could not be included in our analyses. Although the PSQI includes a question on the frequency of snoring/coughing (with the highest frequency listed as “3 or more times a week”), it does not capture specific information on habitual snoring, which is usually defined as every night or almost every night.⁶⁷ Therefore, habitual snoring could not be examined as a risk factor for GDM in our study.

Another limitation of our study is that sleep quality and sleep duration were assessed by self-report, rather than using objective measures of sleep behavior. A recent study that used actigraphy to estimate nocturnal sleep duration found that shorter sleep was associated with increased risk of hyperglycemia (defined as non-fasting 1-h OGTT glucose ≥ 130 mg/dL), but the sample included only 7 women who were classified as having hyperglycemia.⁵² Nonetheless, nocturnal sleep duration was shown to correlate inversely with 1-h OGTT glucose levels in the full sample ($r = -0.28$, $n = 63$), and similar results were obtained in a study that used actigraphy to assess nocturnal sleep duration in women diagnosed with GDM ($n = 37$), in which each hour of additional sleep was associated with a ~ 2 mg/dL decrease in fasting glucose levels.⁵³ In contrast to these findings, a study that assessed sleep in the first trimester using polysomnography found that nocturnal sleep duration was not associated with hyperglycemia later in pregnancy (defined as non-fasting 1-h OGTT glucose ≥ 135 mg/dL), but only 11 participants were classified as having hyperglycemia, including 6 women diagnosed with GDM.⁶⁸ These studies help to establish the feasibility of using objectively determined sleep measurements to examine the impact of sleep duration on glucose metabolism in pregnancy. In future studies, objective measures of sleep behavior

should be collected at multiple time points across pregnancy in larger samples to assess whether pregnancy-induced changes in sleep quality and sleep duration alter glucose regulation and risk of GDM.

In summary, we found that poor sleep quality and <6 h of sleep per night during pregnancy were associated with increased risk of GDM in a multiethnic Asian population. Future studies should examine the pathways by which sleep disturbances in pregnancy contribute to hyperglycemia and other adverse maternal health outcomes. Early screening and interventions for sleep problems in pregnancy could potentially reduce the risk of developing maternal hyperglycemia and GDM. The importance of healthy sleep habits and obtaining sufficient sleep should also be emphasized by prenatal care providers, with the aim of improving pregnancy outcomes.

REFERENCES

1. Hall WA, Hauck YL, Carty EM, Hutton EK, Fenwick J, Stoll K. Childbirth fear, anxiety, fatigue, and sleep deprivation in pregnant women. *J Obstet Gynecol Neonatal Nurs*. 2009; 38(5): 567–576.
2. Lee KA, Zaffke ME, McEnany G. Parity and sleep patterns during and after pregnancy. *Obstet Gynecol*. 2000; 95(1): 14–18.
3. Sahota PK, Jain SS, Dhand R. Sleep disorders in pregnancy. *Curr Opin Pulm Med*. 2003; 9(6): 477–483.
4. Pien GW, Schwab RJ. Sleep disorders during pregnancy. *Sleep*. 2004; 27(7): 1405–1417.
5. Cappuccio FP, D’Elia L, Strazzullo P, Miller MA. Quantity and quality of sleep and incidence of type 2 diabetes: a systematic review and meta-analysis. *Diabetes Care*. 2010; 33(2): 414–420.
6. Holliday EG, Magee CA, Kritharides L, Banks E, Attia J. Short sleep duration is associated with risk of future diabetes but not cardiovascular disease: a prospective study and meta-analysis. *PLoS One*. 2013; 8(11): e82305.
7. Shan Z, Ma H, Xie M, et al. Sleep duration and risk of type 2 diabetes: a meta-analysis of prospective studies. *Diabetes Care*. 2015; 38(3): 529–537.
8. Catalano PM, McIntyre HD, Cruickshank JK, et al.; HAPO Study Cooperative Research Group. The hyperglycemia and adverse pregnancy outcome study: associations of GDM and obesity with pregnancy outcomes. *Diabetes Care*. 2012; 35(4): 780–786.
9. Metzger BE, Lowe LP, Dyer AR, et al. Hyperglycemia and adverse pregnancy outcomes. *N Engl J Med*. 2008; 358(19): 1991–2002.
10. Kim C, Newton KM, Knopp RH. Gestational diabetes and the incidence of type 2 diabetes: a systematic review. *Diabetes Care*. 2002; 25(10): 1862–1868.
11. Philipps LH, Santhakumaran S, Gale C, et al. The diabetic pregnancy and offspring BMI in childhood: a systematic review and meta-analysis. *Diabetologia*. 2011; 54(8): 1957–1966.
12. Clausen TD, Mathiesen ER, Hansen T, et al. High prevalence of type 2 diabetes and pre-diabetes in adult offspring of women with gestational diabetes mellitus or type 1 diabetes: the role of intrauterine hyperglycemia. *Diabetes Care*. 2008; 31(2): 340–346.
13. Reutrakul S, Van Cauter E. Interactions between sleep, circadian function, and glucose metabolism: implications for risk and severity of diabetes. *Ann NY Acad Sci*. 2014; 1311: 151–173.
14. Izi-Balserak B, Pien GW. The relationship and potential mechanistic pathways between sleep disturbances and maternal hyperglycemia. *Curr Diab Rep*. 2014; 14(2): 459.
15. Facco FL, Grobman WA, Kramer J, Ho KH, Zee PC. Self-reported short sleep duration and frequent snoring in pregnancy: impact on glucose metabolism. *Am J Obstet Gynecol*. 2010; 203(2): 142.e1–142.e5.
16. Qiu C, Enquobahrie D, Frederick IO, Abetew D, Williams MA. Glucose intolerance and gestational diabetes risk in relation to sleep duration and snoring during pregnancy: a pilot study. *BMC Womens Health*. 2010; 10: 17.

17. Reutrakul S, Zaidi N, Wroblewski K, et al. Sleep disturbances and their relationship to glucose tolerance in pregnancy. *Diabetes Care*. 2011; 34(11): 2454–2457.
18. Dabelea D, Snell-Bergeon JK, Hartsfield CL, Bischoff KJ, Hamman RF, McDuffie RS; Kaiser Permanente of Colorado GDM Screening Program. Increasing prevalence of gestational diabetes mellitus (GDM) over time and by birth cohort: Kaiser Permanente of Colorado GDM Screening Program. *Diabetes Care*. 2005; 28(3): 579–584.
19. Ferrara A. Increasing prevalence of gestational diabetes mellitus: a public health perspective. *Diabetes Care*. 2007; 30 (Suppl. 2): S141–S146.
20. Thorpe LE, Berger D, Ellis JA, et al. Trends and racial/ethnic disparities in gestational diabetes among pregnant women in New York City, 1990–2001. *Am J Public Health*. 2005; 95(9): 1536–1539.
21. Pu J, Zhao B, Wang EJ, et al. Racial/ethnic differences in gestational diabetes prevalence and contribution of common risk factors. *Paediatr Perinat Epidemiol*. 2015; 29(5): 436–443.
22. Berkowitz GS, Lapinski RH, Wein R, Lee D. Race/ethnicity and other risk factors for gestational diabetes. *Am J Epidemiol*. 1992; 135(9): 965–973.
23. Caughey AB, Cheng YW, Stotland NE, Washington AE, Escobar GJ. Maternal and paternal race/ethnicity are both associated with gestational diabetes. *Am J Obstet Gynecol*. 2010; 202(6): 616.e1–616.e5.
24. Khoo CM, Sairazi S, Taslim S, et al. Ethnicity modifies the relationships of insulin resistance, inflammation, and adiponectin with obesity in a multiethnic Asian population. *Diabetes Care*. 2011; 34(5): 1120–1126.
25. Lear SA, Humphries KH, Kohli S, Chockalingam A, Frohlich JJ, Birmingham CL. Visceral adipose tissue accumulation differs according to ethnic background: results of the Multicultural Community Health Assessment Trial (M-CHAT). *Am J Clin Nutr*. 2007; 86(2): 353–359.
26. Zhu Y, Zhang C. Prevalence of gestational diabetes and risk of progression to type 2 diabetes: a global perspective. *Curr Diab Rep*. 2016; 16(1): 7.
27. Fisher K, Robinson J. Average weekly time spent in 30 basic activities across 17 countries. *Soc Indic Res*. 2009; 93: 249–254.
28. Lo JC, Leong RL, Loh KK, Dijk DJ, Chee MW. Young adults' sleep duration on work days: differences between east and west. *Front Neurol*. 2014; 5: 81.
29. Steptoe A, Peacey V, Wardle J. Sleep duration and health in young adults. *Arch Intern Med*. 2006; 166(16): 1689–1692.
30. Walch OJ, Cochran A, Forger DB. A global quantification of “normal” sleep schedules using smartphone data. *Sci Adv*. 2016; 2(5): e1501705.
31. Soh SE, Tint MT, Gluckman PD, et al.; GUSTO Study Group. Cohort profile: growing up in Singapore towards healthy outcomes (GUSTO) birth cohort study. *Int J Epidemiol*. 2014; 43(5): 1401–1409.
32. Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh sleep quality index: a new instrument for psychiatric practice and research. *Psychiatry Res*. 1989; 28(2): 193–213.
33. Zhong QY, Gelaye B, Sánchez SE, Williams MA. Psychometric properties of the Pittsburgh sleep quality index (PSQI) in a cohort of Peruvian pregnant women. *J Clin Sleep Med*. 2015; 11(8): 869–877.
34. Skouteris H, Wertheim EH, Germano C, Paxton SJ, Milgrom J. Assessing sleep during pregnancy: a study across two time points examining the Pittsburgh sleep quality index and associations with depressive symptoms. *Womens Health Issues*. 2009; 19(1): 45–51.
35. Ayas NT, White DP, Al-Delaimy WK, et al. A prospective study of self-reported sleep duration and incident diabetes in women. *Diabetes Care*. 2003; 26(2): 380–384.
36. Björkelund C, Bondyr-Carlsson D, Lapidus L, et al. Sleep disturbances in midlife unrelated to 32-year diabetes incidence: the prospective population study of women in Gothenburg. *Diabetes Care*. 2005; 28(11): 2739–2744.
37. Gangwisch JE, Heymsfield SB, Boden-Albala B, et al. Sleep duration as a risk factor for diabetes incidence in a large U.S. sample. *Diabetes Care*. 2007; 30(12): 1667–1673.
38. Hayashino Y, Fukuhara S, Suzukamo Y, Okamura T, Tanaka T, Ueshima H; HIPOP-OHP Research Group. Relation between sleep quality and quantity, quality of life, and risk of developing diabetes in healthy workers in Japan: the high-risk and population strategy for occupational health promotion (HIPOP-OHP) study. *BMC Public Health*. 2007; 7: 129.
39. Kita T, Yoshioka E, Satoh H, et al. Short sleep duration and poor sleep quality increase the risk of diabetes in Japanese workers with no family history of diabetes. *Diabetes Care*. 2012; 35(2): 313–318.
40. Mallon L, Broman JE, Hetta J. High incidence of diabetes in men with sleep complaints or short sleep duration: a 12-year follow-up study of a middle-aged population. *Diabetes Care*. 2005; 28(11): 2762–2767.
41. von Ruesten A, Weikert C, Fietze I, Boeing H. Association of sleep duration with chronic diseases in the European prospective investigation into cancer and nutrition (EPIC)-Potsdam study. *PLoS One*. 2012; 7(1): e30972.
42. Yaggi HK, Araujo AB, McKinlay JB. Sleep duration as a risk factor for the development of type 2 diabetes. *Diabetes Care*. 2006; 29(3): 657–661.
43. Spiegel K, Leproult R, Van Cauter E. Impact of sleep debt on metabolic and endocrine function. *Lancet*. 1999; 354(9188): 1435–1439.
44. Nedeltcheva AV, Kessler L, Imperial J, Penev PD. Exposure to recurrent sleep restriction in the setting of high caloric intake and physical inactivity results in increased insulin resistance and reduced glucose tolerance. *J Clin Endocrinol Metab*. 2009; 94(9): 3242–3250.
45. Buxton OM, Pavlova M, Reid EW, Wang W, Simonson DC, Adler GK. Sleep restriction for 1 week reduces insulin sensitivity in healthy men. *Diabetes*. 2010; 59(9): 2126–2133.
46. Rao MN, Neylan TC, Grunfeld C, Mulligan K, Schambelan M, Schwarz JM. Subchronic sleep restriction causes tissue-specific insulin resistance. *J Clin Endocrinol Metab*. 2015; 100(4): 1664–1671.
47. Broussard JL, Chapotot F, Abraham V, et al. Sleep restriction increases free fatty acids in healthy men. *Diabetologia*. 2015; 58(4): 791–798.
48. Eckel RH, Depner CM, Perreault L, et al. Morning circadian misalignment during short sleep duration impacts insulin sensitivity. *Curr Biol*. 2015; 25(22): 3004–3010.
49. Hirshkowitz M, Whiton K, Albert SM, et al. National Sleep Foundation's sleep time duration recommendations: methodology and results summary. *Sleep Health*. 2015; 1: 40–43.
50. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med*. 1998; 15(7): 539–553.
51. *Diabetes Mellitus: MOH Clinical Practice Guidelines 1/2014*. Singapore: Ministry of Health, Singapore; 2014.
52. Herring SJ, Nelson DB, Pien GW, et al. Objectively measured sleep duration and hyperglycemia in pregnancy. *Sleep Med*. 2014; 15(1): 51–55.
53. Twedt R, Bradley M, Deiseroth D, Althouse A, Facco F. Sleep duration and blood glucose control in women with gestational diabetes mellitus. *Obstet Gynecol*. 2015; 126(2): 326–331.
54. Tsai YW, Kann NH, Tung TH, et al. Impact of subjective sleep quality on glycemic control in type 2 diabetes mellitus. *Fam Pract*. 2012; 29(1): 30–35.
55. Knutson KL, Ryden AM, Mander BA, Van Cauter E. Role of sleep duration and quality in the risk and severity of type 2 diabetes mellitus. *Arch Intern Med*. 2006; 166(16): 1768–1774.
56. Okubo N, Matsuzaka M, Takahashi I, et al.; Hiroasaki University Graduate School of Medicine. Relationship between self-reported sleep quality and metabolic syndrome in general population. *BMC Public Health*. 2014; 14: 562.
57. Tang Y, Meng L, Li D, et al. Interaction of sleep quality and sleep duration on glycemic control in patients with type 2 diabetes mellitus. *Chin Med J (Engl)*. 2014; 127(20): 3543–3547.
58. Wang H, Leng J, Li W, et al. Sleep duration and quality, and risk of gestational diabetes mellitus in pregnant Chinese women. *Diabet Med*. 2016.
59. International Association of Diabetes and Pregnancy Study Groups Consensus Panel; Metzger BE, et al. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. *Diabetes Care*. 2010; 33(7): 676–682.
60. Sacks DA, Hadden DR, Maresh M, et al.; HAPO Study Cooperative Research Group. Frequency of gestational diabetes mellitus at collaborating centers based on IADPSG consensus panel-recommended criteria:

- the hyperglycemia and adverse pregnancy outcome (HAPO) study. *Diabetes Care*. 2012; 35(3): 526–528.
61. National Health Survey 2010. Singapore: Epidemiology & Disease Control Division; 2010.
 62. Chong YS, Cai S, Lin H, et al.; GUSTO study group. Ethnic differences translate to inadequacy of high-risk screening for gestational diabetes mellitus in an Asian population: a cohort study. *BMC Pregnancy Childbirth*. 2014; 14: 345.
 63. Luque-Fernandez MA, Bain PA, Gelaye B, Redline S, Williams MA. Sleep-disordered breathing and gestational diabetes mellitus: a meta-analysis of 9,795 participants enrolled in epidemiological observational studies. *Diabetes Care*. 2013; 36(10): 3353–3360.
 64. Pamidi S, Pinto LM, Marc I, Benedetti A, Schwartzman K, Kimoff RJ. Maternal sleep-disordered breathing and adverse pregnancy outcomes: a systematic review and metaanalysis. *Am J Obstet Gynecol*. 2014; 210(1): 52.e1–52.e14.
 65. Theorell-Haglöw J, Berne C, Janson C, Lindberg E. Obstructive sleep apnoea is associated with decreased insulin sensitivity in females. *Eur Respir J*. 2008; 31(5): 1054–1060.
 66. Xu T, Feng Y, Peng H, Guo D, Li T. Obstructive sleep apnea and the risk of perinatal outcomes: a meta-analysis of cohort studies. *Sci Rep*. 2014; 4: 6982.
 67. Partinen M, Hublin C. Epidemiology of sleep disorders. In: Kryger MH, Roth T, Dement WC, eds. *Principles and Practice of Sleep Medicine*. 5th ed. St. Louis: Elsevier; 2011: 694–715.
 68. Izci B, Baserak B, Jackson N, Ratcliffe SA, Pack AI, Pien GW. Sleep-disordered breathing and daytime napping are associated with maternal hyperglycemia. *Sleep Breath*. 2013; 17(3): 1093–1102.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *SLEEP* online.

FUNDING

This research was supported by the Singapore National Research Foundation under its Translational and Clinical Research (TCR) Flagship Program and administered by the Singapore Ministry of Health's National Medical Research Council (NMRC), Singapore (NMRC/TCR/004-NUS/2008; NMRC/

TCR/012-NUHS/2014). Additional funding was provided by the Singapore Institute for Clinical Sciences, Agency for Science, Technology and Research (A*STAR); and the Duke-National University of Singapore Signature Research Program, funded by A*STAR and the Ministry of Health, Singapore.

ACKNOWLEDGEMENTS

We thank participants and staff of the GUSTO study. The GUSTO study group includes Pratibha Agarwal, Arijit Biswas, Choon Looi Bong, Birit F.P. Broekman, Jerry Kok Yen Chan, Yiong Huak Chan, Cornelia Yin Ing Chee, Helen Chen, Yin Bun Cheung, Amutha Chinnadurai, Chai Kiat Chng, Mary Foong-Fong Chong, Shang Chee Chong, Mei Chien Chua, Doris Fok, Marielle V. Fortier, Anne Eng Neo Goh, Yam Thiam Daniel Goh, Wee Meng Han, Mark Hanson, Christiani Jeyakumar Henry, Joanna D. Holbrook, Chin-Ying Hsu, Hazel Inskip, Jeevesh Kapur, Ivy Yee-Man Lau, Bee Wah Lee, Yung Seng Lee, Ngee Lek, Sok Bee Lim, Iliana Magiati, Lourdes Mary Daniel, Cheryl Ngo, Krishnamoorthy Niduvaje, Wei Pang, Anqi Qiu, Boon Long Quah, Victor Samuel Rajadurai, Mary Rauff, Salome A. Rebello, Jenny L. Richmond, Anne Rifkin-Graboi, Lynette Pei-Chi Shek, Allan Sheppard, Borys Shuter, Leher Singh, Walter Stunkel, Lin Su, Kok-Hian Tan, Oon Hoe Teoh, Mya Thway Tint, Hugo P S van Bever, Rob M. van Dam, Inez Bik Yun Wong, P. C. Wong, Fabian Yap and George Seow Heong Yeo.

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication June, 2016

Submitted in final revised form October, 2016

Accepted for publication November, 2016

Address correspondence to: Joshua J. Gooley, PhD, Duke-NUS Medical School, Program in Neuroscience and Behavioral Disorders, 8 College Road, Singapore, Singapore 169857; Telephone: +65 6516 7430; Fax: +65 6221 8625; Email: joshua.gooley@duke-nus.edu.sg

DISCLOSURE STATEMENT

PDG, KMG, and YSC have received lecture fees from companies that sell nutritional products. They are part of an academic consortium that has received research funding from Abbott Nutrition, Nestec, and Danone. The other authors have nothing to disclose.