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Weight-neutral approach and later sleep midpoint in adolescents with "emerging polycystic ovary syndrome phenotype" as vehicles for sustainable weight loss

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Objective: Incorporate sleep into a novel lifestyle intervention strategy in adolescents with Emerging symptoms of polycystic ovary syndrome (E-PCOS).
Design: A single-center cohort study.
Setting: University hospital-based clinic for adolescents with PCOS.
Patients: Forty-three girls at an age between 10 and 18 years presenting with E-PCOS between March 2015 and September 2017 with clinical signs of androgen excess and/or accelerated weight gain, acanthosis nigricans, irregular periods, or delayed menarche and followed every 6 months for a minimum of 4 visits, to October 2020.
Interventions: All patients received nutritional counseling, with a goal of "zero weight gain," daily moderate physical activity goals of 45 minutes per day, and education regarding age-appropriate sleep duration. Three treatment strategies for E-PCOS symptoms were applied depending on the chief clinical complaint: anti-insulin approach with metformin; antiandrogen approach with oral contraceptive and spironolactone; and surveillance.
Main Outcome Measures: Body mass index (BMI) Z-score over time. Alanine Transaminase (ALT) levels as a risk factor for nonalcoholic fatty liver.
Results: Average number of return visits was 4 with 58% having >4 return visits. Testosterone levels were correlated with ALT ($r = 0.68$). Weeknight sleep duration was less than age-appropriate recommendations for 63% of participants. Sleep midpoint correlated with ALT levels ($r = 0.48$). Despite the weight-neutral approach, regression models all demonstrated significant weight loss regardless of menarche status, metformin use, number of visits, and high vs. low ALT groups. Those with the latest sleep midpoint at baseline benefited the most, with BMI Z-score dropping significantly (interaction of time and baseline sleep midpoint from the first visit on school night).
Conclusion: A novel approach for adolescent girls with E-PCOS that focuses on metabolic endpoints and includes sleep duration and timing as specific targets, led to significant weight loss irrespective of treatment group. (F S Rep® 2024;5:402–10. ©2024 by American Society for Reproductive Medicine.)
Key Words: Obesity, puberty, sleep

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Exaggerated pubertal weight gain, hirsutism and irregular periods persisting beyond 2 years after menarche are early symptoms of polycystic ovary syndrome (PCOS) (1, 2). As the most frequent cause of infertility in adult women, PCOS is associated with insulin resistance (3, 4), hypertension (5), type 2 diabetes (6), increased risk of heart disease (7), nonalcoholic fatty liver disease (NAFLD) (8), and gynecological cancers (9, 10). Because of the heterogeneity of the disorder, building a consensus on the diagnosis of adult PCOS has been a challenge, revisited several times over the last few decades (3, 11, 12). There is growing awareness that early recognition and management are likely to have the most impact on adverse long-term health outcomes of PCOS, many of them metabolic in nature (13). Obstacles to the timely recognition and management of early PCOS are plentiful (14, 15). First, normative data on progression from menarche to a fully established cycle in adolescents are lacking; second, the morphology of maturing ovaries is in flux at this young age; third, accurate imaging with intravaginal ultrasonic imaging of ovaries is objectionable in adolescent girls; fourth, the cause of irregular periods may be obscured by the early institution of contraceptives; and fifth, hormonal causes of acne, acanthosis nigricans, hirsutism or hair loss are not systematically investigated. One of the most significant advances in understanding the pathogenesis of PCOS over the last 30 years was the demonstration of insulin resistance and altered glucose homeostasis in women affected with PCOS across the weight spectrum (16, 17). Yet none of the various iterations of multidisciplinary consensus about PCOS have included these adverse metabolic characteristics, in part because they are difficult to ascertain in routine clinical care. In addition to prediabetes risk associated with PCOS, NAFLD is also emerging as a potential metabolic complication (8, 18, 19). In recent years the hemoglobin A1C (HbA1C) has gained recognition as readily available metabolic marker of altered glucose homeostasis (20, 21) and alanine transaminase (ALT) threshold has been linked to early evidence of fatty liver disease (22, 23).

In our experience, rapid weight gain in childhood and the peripubertal years is a common characteristic of adolescents presenting with symptoms of PCOS (24). This is often the motivation to seek care, even though lifestyle interventions – traditionally composed of diet and exercise recommendations – are challenging to implement in adolescents and difficult to sustain (2).

In the past decade, suboptimal sleep has emerged as a robust predictor of weight gain and adverse metabolic outcomes (25, 26). During adolescence, there is a natural shift in the circadian biological clock, as the sleep–wake cycle and other circadian-regulated biological processes become more delayed with the onset of puberty (27, 28). Although insufficient sleep duration in youth is associated with weight gain (29, 30) circadian misalignment has also emerged as being associated with obesity and altered glucose in adolescents (31–33) Moreover, female adolescents may be more vulnerable to the obesogenic effects of circadian misalignment (34). We therefore sought to incorporate sleep into a novel lifestyle intervention strategy that was weight-neutral, with a target to stabilize weight trajectory thereby improving metabolic health.

METHODS

This study was approved by the Michigan Medicine Institutional Review Board.

Sleep was characterized in girls 9–18 years of age who were referred to the Michigan Medicine Polycystic Ovary Syndrome Program for Girls and Adolescents between July 2015 and September 2017 and clinically followed upto July 2020. This program evaluates adolescent girls with Emerging symptoms of PCOS (E-PCOS) and offers a lifestyle intervention program aiming at improving metabolic health in their daily lives. Patients were referred to the clinic for concerns of E-PCOS on the basis of clinical signs of androgen excess and/or accelerated weight gain, acanthosis nigricans, and irregular periods.

Clinical data

A physical examination was performed and data from the clinical evaluation collected included body mass index (BMI) Z-score, HbA1c, estradiol, testosterone, liver enzymes ALT, and aspartate aminotransferase (AST). Age and sex-standardized BMI Z-score is a standard deviation score and is calculated on the basis of the Centers for Disease Control and World Health Organization data. It is the preferred measure for research purposes (35). ALT values $\geq$22 IU/L are associated with nonalcoholic steatohepatitis, a metabolic complication of obesity (36). The precision of the assays is provided in the Online Appendix.

Sleep data

Information about the participant's sleep duration, sleep time, and wake time were obtained for weekdays and weekends. The midpoint of sleep was also calculated. The sleep midpoint was estimated as the clock time halfway between sleep onset and wake times and is a marker of chronotype (37).

Lifestyle recommendations: stop-the-freight-train

At each nutrition encounter, all patients received counseling that emphasized a weight-neutral, euglycemic approach discouraging starvation strategies and emphasizing food as fuel throughout the day. In addition, all patients were given instructions about sleep hygiene, namely optimal targets for age-appropriate sleep duration on the basis of recommendations from the American Academy of Sleep Medicine (38), as well as daily moderate physical activity of 45 minutes per day. At the first endocrine encounter, the lifestyle instructions were reviewed at the end of the clinic and an interactive discussion occurred to ensure that the recommendations were feasible and realistic within the household structure. At each subsequent encounter the lifestyle goals, including optimal sleep, were rereviewed to ensure patients were meeting identified goals. Controlling a pattern of rapidly increasing weight gain was emphasized with a recommended target of "zero weight gain" over the following 6

months, using the analogy of "stopping the advance of a freight train" in a realistic fashion. This counseling was provided inclusively to all patients, regardless of weight status, and the zero weight gain strategy also applied to those with a normal BMI.

Group allocation

The decision to start any of the following approaches was a result of the patient's expressed priority, and the clinician's recommendation on the basis of metabolic and androgenic indices as well as family history of type 2 diabetes or PCOS. Patients who had both metabolic and androgenic features were asked to prioritize the approach that suited their health goals. For patients who opted for the insulin-sensitizing approach, the possibility of progressing to combination therapy once metformin responsiveness was established was discussed. All patients received education about the impact of metabolism on the restoration of the menstrual cycle and potential links to fertility. Reasons to add oral contraceptives and sprinolactone could occur any time after the first or second visit (i.e., 6 or 12 months) and were decided concurrently with the patient. The decision was made taking into account the following factors: persistent and/or progressive hirsuitism and acne; need for contraception; and improved menstrual cyclicity to the satisfaction of the patient. See Figure 1.

Target-focused treatment strategies

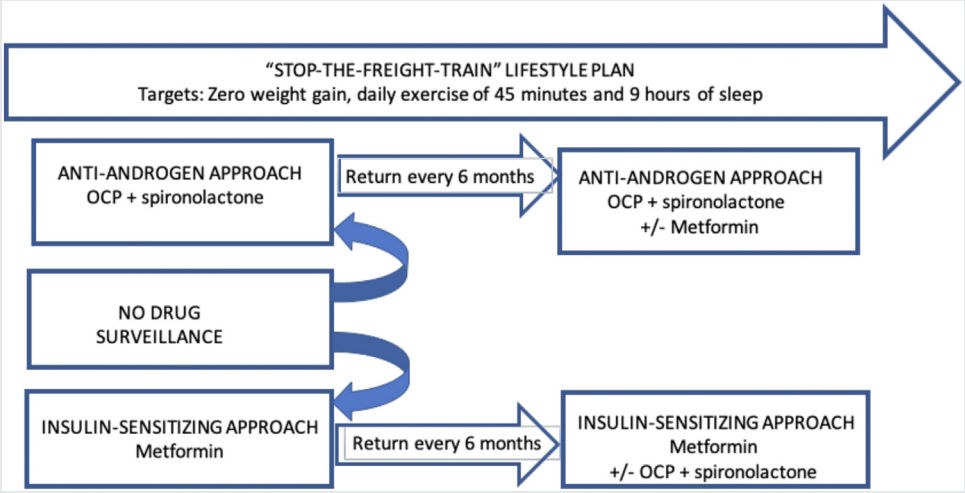
Insulin-sensitizing approach. Metformin was prescribed in patients with oligomenorrhea at the starting dose of 500 mg extended-release daily with a target of restoration of the menstrual cycle over time. The initial dose was purposely low to optimize adherence. The dose was titrated in increments every 6 months depending on response and tolerance of the drug, with most patients taking 750 mg extended-release twice a day after 2–4 visits (which spanned approximately 1–2 years).

Antiandrogen approach. Patients who prioritized the antiandrogen approach included those with severe hirsutism; longstanding history of acne resistant to standard dermatological approaches; and androgenic alopecia. Oral contraceptives (OC; combination of 0.15 mg desogestrel and 0.03 mg ethinyl estradiol) and spironolactone (SP; 50 mg twice per day) were initiated with a target of decreasing the frequency of grooming, stabilizing androgen-related hair thinning, decreasing acne and increasing patient satisfaction. Spironolactone was always prescribed in combination with an oral contraceptive and the patients were counseled on the teratogenic risk associated with spironolactone (39).

Combined approach. Over time, the combination of both antiandrogen and insulin-sensitizing approaches was considered on the basis of need, and preferably once the treatment target of the initial approach was reached. Patients starting with an antiandrogen approach would have metformin offered if the HbA1C increased above 6% at any follow-up visit. Patients starting with the insulin-sensitizing approach would have SP and OC added if there were progressive signs of androgen excess.

Surveillance/nonmedical approach. This option was available for patients who were either; within 2 years of menarche; preferred the lifestyle approach alone; or were initially reluctant to start drug therapy.

FIGURE 1



Treatment strategy. Patients were started with 1 of 2 treatment strategies selected and asked to return every 6 months. Patients who were not treated could over time start in of the 2 treatments. The target of antiandrogen treatment was a reduction of grooming frequency and or the stabilization of hair thinning. The target of insulin-sensitizing treatment was the restoration of menstrual cyclicity with titration of metformin dose every 6 months on the basis of patient tolerance and response. A lifestyle plan was presented and discussed at each visit. OCP = oral contraceptive.

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Statistical analysis

Data were entered into a database and double-checked for accuracy. Comparisons between continuous data were conducted with *t* tests and comparisons between dichotomous data were conducted with Chi-square analysis. We used mixed models, with random patient intercepts and slopes, to explore the effect that different measures of sleep midpoint had on the trajectory of BMI Z-score, ALT, and AST over time. Models included the time (years) since the first visit, the sleep midpoint, and the interaction of the 2 (this term indicates an impact of sleep midpoint on trajectory of BMI Z-score or liver enzyme). BMI Z-score models did not control for age, but ALT and AST models did. One set of models controlled for the 3-category treatment group; another set of models controlled for whether the subject was on metformin or not. When the *P* value for the interaction term was ≤ 10 we explored the nature of the interaction by graphing the predicted dependent variable values at the minimum, median, and maximum value of the sleep parameter.

RESULTS

Forty-three participants completed the sleep questionnaire at their initial visit.

Table 1 describes participant characteristics. In total, 10 (23%) received OC and SP, 21 (49%) received metformin, and 12 (28%) received surveillance only. Supplemental Table 1 (available online) describes the race and the chief complaints or reason for referral. The mean number of clinic visits was 4, with 58% of subjects having >4 visits.

Gestational history was available for 31 mothers with 5 (16%) recalling an abnormal oral glucose tolerance test during the index pregnancy. For participants with available family history, 10 out of 26 fathers (38%) and 8 out of 29 mothers (28%) had prediabetes or diabetes.

ALT measures ≥ 22 IU/L were present in 22/38 (58%) of participants. Although HbA1C was the same in the high vs. low ALT groups, testosterone was markedly higher in the high ALT group (Supplemental Table 2). Furthermore, total testosterone positively correlated with ALT values ($r = 0.68$, $P < .001$, Supplemental Fig. 1, available online).

Weeknight sleep duration fell short of age-appropriate AASM recommendations in almost two-thirds (63%) of participants. The mean midpoint on school nights was 02:19 AM and on weekends was 05:07 AM. Social jetlag (a difference in sleep midpoint of 2 hours or more) was present in 67% of girls. Sleep midpoint on school nights correlated significantly with ALT level after accounting for BMI Z-score and sleep duration ($r = 0.48$, $P = .006$), as shown in Figure 2.

Regression models all demonstrated significant weight loss over time regardless of menarche status, number of visits, and high vs. low ALT groups. Supplemental Table 3 demonstrates BMI Z-score progression over time depending on the baseline sleep midpoint on weekdays. In addition, regardless of treatment category, BMI Z-score significantly reduced over time. Modeling the predicted values for the minimum, median, and maximum sleep midpoint on school nights showed that the girls with the latest sleep midpoint on school nights benefited with the most improved BMI Z-scores over time (Fig. 3; *P* value for the interaction of time from the first visit and baseline sleep midpoint on school nights was $P = .04$). Similarly, Supplemental Figure 2 shows that modeling the predicted values for ALT, the interaction between social jetlag (a difference in sleep midpoint >2 hours between weekend and week nights) and time since first visit was significant ($P = .02$). The girls who had social jetlag at the initial clinic visit demonstrated improvement of ALT over time, compared with girls without social jetlag at the initial visit.

Supplemental Figure 3 shows representative BMI Z-score trajectories after the first "stop-the-freight-train" clinic encounter.

Our data demonstrated a decrease in BMI Z-score, with girls serving as their own controls as we compared BMI Z-score over time. The most conservative course is keeping the same BMI Z-score over time, which means an increase in BMI and represents the expected trajectory. For any

TABLE 1

Patient characteristics.

Characteristic	Minimum	Maximum	Mean/SD
Age (y)	9.6	18.2	15.4 ± 1.9
Maternal age at menarche (y)	9.0	16.0	12.3 ± 1.9
Birth weight (kg)	2.5	9.1	7.2 ± 1.3
HbA1C (%)	4.7	6.1	5.4 ± 0.3
Estradiol (mcg/mL)	26	204	74.4 ± 46.0
Testosterone (ng/mL)	23	164	59.3 ± 31.1
ALT (IU/L)	8	59	23.8 ± 10.9
AST (IU/L)	14	41	23.0 ± 6.7
Patient's age at menarche (y)	9	14	11.8 ± 1.3
Gynecological age (y)	0.6	9.6	4.0 ± 2.0
BMI Z-score	0.8	3.2	2.1 ± 0.5

ALT = alanine transaminase; AST = aspartate aminotransferase; BMI = body mass index; HbA1C = hemoglobin A1C; SD = standard deviation.

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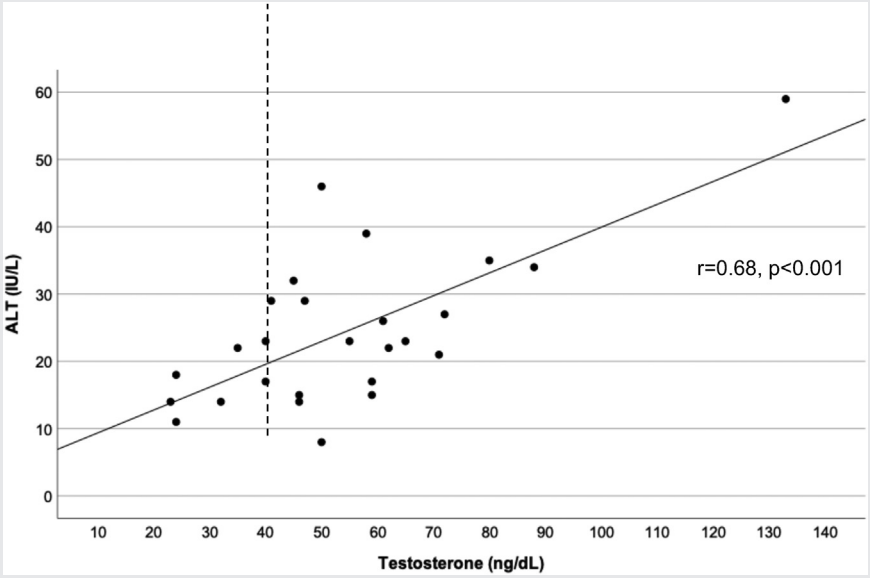
FIGURE 2



Correlation between sleep midpoint on a school night and ALT. ALT = alanine transaminase.

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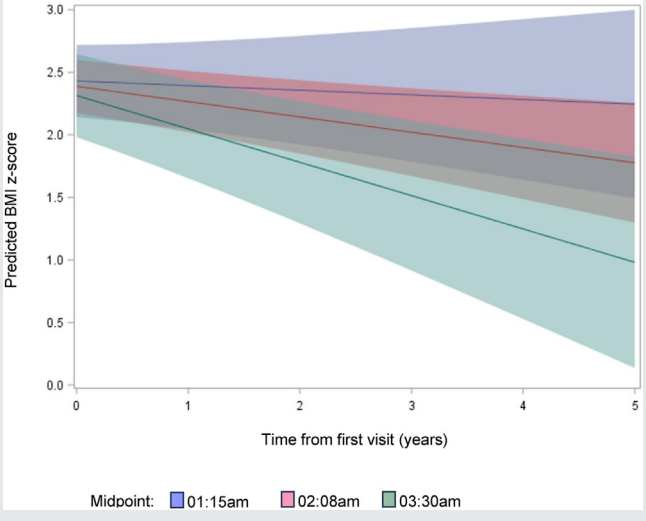
adolescent, keeping the same BMI over time means a reduction in the BMI Z-score. Supplemental Figure 4 illustrates a BMI-for-Age Centile chart (40) which shows a normal weight gain trajectory (blue), accelerated weight gain (orange), and a typical trajectory observed in the current study (green). Note that there is a positive incline of the BMI curve in late adolescence so a slightly higher BMI can correspond with a lower BMI Z-score as the child gets older. To put this into context, we will provide some examples:

Patient A aged 15 years and 5 months at the initial visit was 5′8″ in height and weighed 215 lbs (BMI 32.9) and had a BMI Z-score of 2.05. She had amenorrhea and menarche at the age of 10 years. She received metformin 500 mg two times per day at the first visit. Her BMI Z-score fell to 1.94

FIGURE 3



BMI Z-score progression over time depends on the baseline sleep midpoint on weekdays. BMI = body mass index.

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after 6 months, 1.6 after 12 months, and 1.24 after 18 months. At the 18-month visit, her weight was 179 lbs (no change in height) with a BMI of 27.0. This reduction in BMI Z-score from 2.05 to 1.24 corresponded to a weight loss of 36 lbs.

Patient B aged 12 years and 6 months at the initial visit was 5′7″ in height and weighed 191 lbs (BMI 29.8) and had a BMI Z-score of 2.08. She had menarche at the age of 11 years with 3 periods reported and had severe acanthosis. She received metformin 500 mg once per day initially. Her BMI Z-score fell to 1.99 at 6 months, 1.92 at 12 months, 1.8 at 18 months, and 1.55 at 24 months. She grew 0.5″. The change in BMI Z-score from 2.08 to 1.55 represented a weight loss of 16 lbs.

Patient C aged 17 years 5 months at the initial visit was 5′2″ in height and weighed 157 lbs (BMI 29.0) and had a BMI Z-score of 1.56. She had menarche at the age of 11 years and presented with concern for acne and irregular periods. She was prescribed spironolactone and birth control pills. Her BMI Z-score fell from 1.35 after 6 months to 0.79 after 12 months with no change in height. At 12 months her weight was 140 lbs. This change in BMI Z-score (from 1.56 to 0.79) represented a weight loss of 17 lbs. Notably, she was gaining weight before attending the clinic.

Patient D aged 16 years 11 months at the initial visit was 5′1.5″ in height and weighed 138 lbs (BMI 25.3) and had a BMI Z-score of 1.05. She had oligomenorrhea with only spotting and a primary concern of hirsutism. She received spironolactone and birth control pills. Her BMI Z-score fell to 0.65 after 6 months, stayed at 0.65 for the next 2 visits, and then fell to 0.62 by 24 months. Without any change in height, her weight fell to 127 lbs. This change in BMI Z-score from 1.05 to 0.62 represented a change in weight of 11 lbs.

DISCUSSION

These data demonstrate that poorly timed sleep is associated with elevated ALT measures in adolescent girls with emerging PCOS. Furthermore, despite the E-PCOS clinic having a "weight-neutral" approach, girls with the latest sleep midpoints on school nights at initial clinic visits showed the greatest improvement in BMI Z-score over time. These findings provide proof of concept and suggest that, in contrast to a focus on rapid weight loss and medical interventions, optimization of sleep may provide a cost-effective avenue to normalize ALT and stabilize or improve BMI in this population.

Consensus criteria for established PCOS-hyperandrogenism, ovulatory dysfunction, and polycystic ovaries, have been proposed as the blueprint for the diagnosis of this condition but fall short for young patients who have not yet completed their pubertal maturation and are already exhibiting progressive symptoms concerning PCOS. Recognition of a heterogeneous disorder like PCOS in adolescents is a challenge because of the evolving nature of puberty progression and the time that needs to elapse to determine whether there are enough criteria to diagnose PCOS. It has been recently recognized that young patients may not yet fulfill the criteria for PCOS but still need to have their symptoms addressed and treated (41–43). We are introducing the concept of E-PCOS in which at least 2 of the following symptoms are present in a peripubertal girl: failure to establish a regular menstrual cycle 2 years or more postmenarche and clinical or biochemical evidence of hirsutism or androgen excess with or without rapidly progressive obesity. The lack of menarche in 8 of the participants illustrates the dilemma of the pediatrician as some adolescents experience the deleterious effect of androgen excess early enough at the outset of the puberty process that it may delay the onset of menarche (2). This becomes evident if there is absent menarche when the patient has reached final height as documented by a bone age or by evidence of final height attainment on the growth chart.

Weight-neutral strategy – "stop-the-freight-train"

Our metabolic approach was to focus on stopping the weight gain thus the "freight train" analogy. This concept emerged from the abundant published data (44) and our own clinical experience regarding the lack of sustainable results of weight loss strategies in youth and the inevitable rebound following restrictive diets or newer weight loss drugs (45). It was emphasized from the outset that the strategy's goal was weight-neutral to minimize the psychological pressure associated with weight loss in a vulnerable population of girls at risk for eating disorders. Despite being told that weight loss was not a priority, obese girls unexpectedly lost weight by the first follow-up visit at 6 months and this persisted over time. It is possible that removing the pressure of weight loss and shifting the focus to specific sleep targets relating to age-appropriate sleep duration and timing facilitated the implementation of nutritional and lifestyle counseling, but this hypothesis remains to be formally tested.

Insulin resistance as a target

The consensus about the diagnosis of PCOS omits the presence of well-demonstrated insulin resistance yet standard of care includes the use of metformin, an insulin sensitizer. We believe this omission has delayed the development of treatment paradigms that could be applied to adolescents. We chose to address insulin resistance by explaining its role in detail to all patients and by providing simple lifestyle interventions targeting sleep, exercise, and diet in ways easily applicable to a daily routine. The use of metformin was modest as the doses were initiated at a low level to address the high likelihood of undesirable gastrointestinal side effects, particularly in youth (46, 47). Adjustments were made every 6 months depending on tolerance.

Trials aimed at improving metabolic outcomes related to BMI in obese children and adolescents using a combination of medications and lifestyle interventions have shown little improvement in insulin or glucose measures after 6–12 months (48). A systematic evidence review for the US Preventive Services Task Force demonstrated a reduction in BMI Z-score of –0.1 from 6 pooled studies of metformin and lifestyle intervention (48), which is less than the reduction observed in our study. A recent trial of a standard diet and exercise intervention for prepubertal children with obesity has shown an

improvement in both markers of insulin resistance as well as ALT levels in children who lowered their BMI Z-score (49). ALT is a surrogate marker for NAFLD, which affects approximately 20% of adolescents aged 15–19 years (50). Those with increased ALT levels have a higher prevalence of prediabetes and type 2 diabetes mellitus compared with children with normal ALT levels (51). The presence of PCOS has been found to increase the risk for NAFLD, (19), particularly when type 2 diabetes is present (52). Thus, lowering of ALT levels may be an acceptable marker to assess the treatment response of interventions designed to reduce metabolic complications of obesity, particularly since fluctuations of ALT levels even within normal ranges appear to indicate a risk of cardiovascular disease (53). Of note, in the current study, later sleep midpoint was positively correlated with ALT level even after accounting for BMI Z-score and subjects with social jetlag at the initial clinic visit demonstrated improvement of ALT over time, compared with girls without social jetlag.

More recently the advent of glucagon-like peptide-1 agonists as weight loss-inducing tools available to the pediatric population has highlighted significant side effects, some severe, associated with long-term use (54, 55). In addition, concerns have been recently raised about the potential and unintended long-term consequences of their use in youth (56). There is also mounting evidence that discontinuation of glucagon-like peptide-1 agonists leads to weight regain within a short period (45, 57). The weight changes observed in our participants were unexpected and provided the possibility of sustainable weight loss in adolescents with a weight-neutral approach targeting lifestyle endpoints that may have been previously underestimated, such as sleep.

Sleep as a lifestyle target

There is increasing evidence of a link between insufficient sleep and an increase in BMI in adolescents (58, 59), possibly due to an increase in poor dietary habits (60) via alterations in leptin and ghrelin (61). Sleep problems including insufficient sleep and shift work are known to contribute to metabolic diseases (62). Indeed, shift work is the extreme form of social jetlag, thus emerging evidence for metabolic consequences of circadian misalignment (63–65) is particularly pertinent to adolescents who have a biological circadian delay (27). Social jetlag quantifies the difference between circadian and social clocks which results in chronic sleep loss (66, 67). A large epidemiological study of >65,000 participants aged 10–65 years demonstrated that even beyond sleep duration, social jetlag is associated with increased BMI, particularly in young adults (68) The authors purported that living "against the clock" could contribute to the obesity epidemic.

Moreover, circadian misalignment has emerged as a strong predictor of metabolic problems (33, 34, 63, 69, 70). Adolescents with ≥1 hour below age-appropriate sleep duration recommendations or who had later sleep midpoints than their peers have been shown to have a 2.7 and 2.6 increased odds respectively of developing insulin resistance over the next 2 years (71). Moreover, in adolescents with circadian misalignment, including greater social jetlag, visceral adiposity has a larger impact on the metabolic syndrome than in adolescents without circadian misalignment, independent of other factors (31). Importantly, a sleep hygiene intervention in adolescents significantly reduced BMI Z-score despite no change in sleep duration (72), suggesting that addressing sleep health could help improve BMI. Furthermore, in obese adolescents with and without PCOS, those with PCOS had circadian misalignment – measured via melatonin – which was associated with higher free testosterone levels and worse insulin sensitivity (73). Given these data, it would seem pertinent to include sleep health when assessing obese adolescents with suspected PCOS with a goal of weight reduction and/or cardiometabolic improvement (24, 74). Nonetheless, the most recent (2023) guidelines for PCOS, while screening for sleep-disordered breathing is now recommended but there is no mention of other important measures of sleep (75).

The strengths of this study include a real-world analysis of girls with E-PCOS, with an extended follow-up. The weight-neutral approach that was emphasized provides a counterpoint to the current landscape of pharmacological weight-loss strategies and bears promise for sustainable intervention beyond weight-loss-inducing medications. This study also offers insights into additional endpoints, such as liver enzymes, as potential targets in the management of girls and young women with PCOS. Moreover, sleep characterization at baseline allowed for an additional opportunity in the management of their metabolic health.

This study is not without limitations. Sleep information was only obtained at the initial visit, thereby limiting our ability to assess longitudinal changes. In our clinic, the recommended follow-up is every 6 months, however, this was not universal due to expected variations in patient scheduling preferences.

CONCLUSION

A novel approach for adolescent girls with E-PCOS that focuses on metabolic endpoints and includes sleep duration and timing as specific targets, led to unexpected yet significant weight loss over time. We believe that the explicit addition of sleep duration and timing as a beneficial metabolic target likely contributed to the observed weight loss. Further studies are needed to tailor the management of adolescent girls with emerging symptoms of PCOS and identify motivational strategies to thwart adverse metabolic and reproductive consequences.

CRediT Authorship Contribution Statement

Josephine Z. Kasa-Vubu: Conceptualization, Methodology, Investigation, Resources, Writing – original draft, Writing – review editing. **Alexandra Waisanen:** Investigation, Writing – original draft, Writing – review & editing. **Julie Sturza:** Formal analysis, Writing – original draft, Writing – review editing. **Vasantha Padmanabhan:** Writing – original draft, Writing – review & editing. **Louise M. O'Brien:** Conceptualization, Methodology, Investigation, Formal analysis, Data curation, Writing – original draft, Writing – review & editing.

Declaration of Interests

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