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Adolescent oligomenorrhea in a biracial schoolgirl cohort: a simple clinical parameter predicting impaired fasting glucose plus type 2 diabetes mellitus, insulin, glucose, insulin resistance, and centripetal obesity from age 19 to 25 years

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ABSTRACT

We hypothesized that adolescent oligomenorrhea (ages 14-19) would independently predict impaired fasting glucose (IFG; ≥110 to <126 mg/dL) plus type 2 diabetes mellitus (T2DM; ≥126 mg/dL), insulin and glucose levels, and insulin resistance (IR) in young adulthood (ages 19-25). A prospective 15-year follow-up of 370 schoolgirls starting at age 10 was performed. Age 14 waist circumference was the most important explanatory variable for IFG + T2DM during ages 19 to 24 ($P = .002$; odds ratio, 1.06; 95% confidence interval, 1.02-1.10), along with oligomenorrhea category from ages 14 to 19 (0, 1, 2, ≥3 reports over 6 years; $P = .032$; odds ratio, 1.82; 95% confidence interval, 1.05-3.14). Impaired fasting glucose + T2DM at ages 19 to 24 were more common in girls having 1 (6%), 2 (11%), and ≥3 (38%) oligomenorrhea reports from ages 14 to 19 than in girls without oligomenorrhea (3%; $P = .0003$). Positive explanatory variables (all $Ps \leq .05$) for homeostasis model assessment of IR at ages 19 to 24 included age 14 waist (partial R^2 = 30.1%), oligomenorrhea with hyperandrogenism (polycystic ovary syndrome; partial R^2 = 4.1%), black race (3.8%), and oligomenorrhea frequency during ages 14 to 19 (0.8%); sex hormone binding globulin was a negative explanatory variable (0.7%). This is the first prospective study to report an independent association of adolescent oligomenorrhea with young adult IFG + T2DM, with insulin and glucose levels, and with IR. Age 14 waist circumference, oligomenorrhea with hyperandrogenism (polycystic ovary syndrome), black race, oligomenorrhea frequency at ages 14 to 19, and age 14 sex hormone binding globulin were independently associated with IR at ages 19 to 24, potentially facilitating primary prevention of IFG, T2DM, and hyperinsulinemia.

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1. Introduction

Women with a history of irregular cycles have increased risk of coronary heart disease (CHD), type 2 diabetes mellitus (T2DM), and gestational diabetes mellitus compared with women with regular cycles (variously defined as 27-29 or 26-31 days) [1-3]. The increased risk of T2DM was not completely explained by obesity [1]. Determining the degree of menstrual cycle irregularity in adult women appears to be a valuable instrument to estimate the degree of metabolic and endocrine disorders [2,3]. Postmenopausal women with a history of irregular menses and elevated androgen measurements have been reported to be at high risk for worsening cardiovascular event-free survival [4] and increased risk of coronary artery calcification [5].

Within the frame of reference that infrequent, irregular menses are associated with increased risk of T2DM and CHD in adult women [6], we hypothesized that adolescent oligomenorrhea would predict impaired fasting glucose (IFG) plus T2DM, homeostatic model assessment (HOMA) of insulin resistance (IR) from ages 19 to 24, and insulin levels from ages 19 to 25.

2. Methods

2.1. The study population

The National Heart, Lung, and Blood Institute Growth and Health Study (NGHS), a 10-year (1987-1997) multicenter collaborative study of the development of obesity in adolescent black and white girls and its environmental, psychosocial, and cardiovascular disease risk factor correlates, has been previously described [7]. Briefly, 9- and 10-year-old schoolgirls were recruited and seen annually for 10 years. Participant eligibility was limited by the National Heart, Lung, and Blood Institute design [7] to girls who declared themselves as black or white and lived in racially concordant households. After the completion of NGHS, the Cincinnati Clinic carried out investigator-initiated studies for 5 more years, measuring fasting insulin at ages 20 to 25 and fasting glucose at ages 20 to 24, thus providing up to 15 years of follow-up.

All clinical assessments were conducted using a standard protocol by centrally trained staff. In ancillary projects, the Cincinnati Clinic measured fasting insulin at study entry (mean age, 10) and at mean ages 16 and 19; sex steroid hormones; and sex hormone binding globulin (SHBG) at mean ages 10, 12, and 14 [8], in addition to NGHS variables—lipid profiles, systolic and diastolic blood pressure, body mass index (BMI) (in kilograms per square meter), and (starting at mean age 11) waist circumference.

Trained registered pediatric nurses assessed sexual maturation, onset of menarche [9], the number of days since the previous menstrual cycle, and cigarette smoking by direct interview and examination, without parents present. Oligomenorrhea at age 14 and ages 14 through 19 was defined by menstrual cyclicity greater than or equal to 42 days based on studies by van Hooff et al [10,11] and Chiazze et al [12].

At age 14, a subset of the girls with oligomenorrhea who also had biochemical hyperandrogenism was identified as probable polycystic ovary syndrome (PCOS) by Consensus Criteria [13]. Biochemical *hyperandrogenism* was defined by dehydroepiandrosterone sulfate (DHEAS) greater than 280 μg/dL, race-specific bottom decile sex hormone binding globulin (SHBG) ($\leq$6 nmol/L for black, $\leq$7 nmol/L for white), or race-specific top decile free testosterone (FT) ($\geq$2.13 pg/mL for black and white). Pelvic ultrasound to identify polycystic ovaries, one of the 3 diagnostic Consensus Criteria [13] (polycystic ovaries, oligomenorrhea, clinical or biochemical hyperandrogenism), was not done. No attempt was made in the oligomenorrheic girls to identify those with energy-deficient hypothalamic amenorrhea associated with energy deficits [14] or other causes of adolescent oligomenorrhea. No information was collected on family history of menstrual irregularities or cardiovascular risk factors.

In the study cohort, 493 girls had measures of sex hormones at age 14, 424 of them also had reports on menstrual status at age 14, and 370 of them had at least 5 menstrual status reports during the 6 annual reports from ages 14 to 19. In the current report, we prospectively assessed relationships of oligomenorrhea and sex hormones at age 14, and oligomenorrhea from age 14 to 19, to insulin and glucose levels and HOMA IR at ages 19 to 24/25.

In the NGHS and in the 5-year extension study [9], procedures followed were in accordance with the ethical standards of the Institutional Review Boards of the Centers, which approved the study. Signed informed consent was obtained from the girls' parents or guardians; assent, from the girls in NGHS; and signed consent, from the girls (now adult women) in the extension study.

2.2. Laboratory and clinical measurements

Blood was drawn after an overnight fast with participants in the seated position. Methods for measurement of SHBG, estradiol (E2), DHEAS, FT, lipids, apolipoprotein A1, fasting serum insulin and glucose levels, height, weight, waist circumference, and systolic and diastolic blood pressure have been previously described [7]. Blood drawing was not scheduled by menstrual status or day of menstrual period. The NGHS used annual measurements of BMI and waist circumference as an indicator of fat patterning [16-18].

The NGHS subjects having fasting blood glucose of at least 126 mg/dL [15] at study entry at mean age 10 and/or type 1 DM (T1DM) at any time from mean age 10 through mean age 25 were excluded (n = 7) from the analysis sample for this and other reports [16]. Diagnosis of T1DM was based on World Health Organization criteria, fasting glucose of at least 126 mg/dL, and self-reported diabetes with treatment by a physician [15]. We did not have measurement of C-peptides as well as diabetes autoantibody levels, criterion standard methods [17] to optimally distinguish T1DM from T2DM. There were no other exclusion criteria.

Impaired fasting glucose was defined as plasma glucose of at least 110 but less than 126 mg/dL using the 1997 American Diabetes Association definition [18]. In these analyses, having excluded T1DM, we defined *T2DM* as a fasting glucose of at least 126 mg/dL [15]. To increase the number of cases for

logistic regression analyses where maximum glucose from age 19 to 24 was the dependent variable, we combined 4 T2DM cases with 12 IFG cases.

Insulin levels were measured in Cincinnati girls at age 10 by the Michigan Diabetes Research and Training Center (Ann Arbor) and at age 16 and thereafter by the Endocrine Laboratory (Children's Hospital Medical Center) by competitive protein-binding radioimmunoassays. Because results of statistical analyses were virtually the same whether insulin levels were transformed into Z scores (data not shown), only insulin data are displayed. We denoted the first insulin measure from mean age 10 (n = 281) and age 16 (n = 87) as "childhood insulin." We assessed both fasting insulin [19,20] and HOMA IR [21].

2.3. *Metabolic syndrome at age 14*

We defined metabolic syndrome at mean age 14 using previously reported pediatric standards [22], that is, at least 3 of the following 5 components: triglycerides (TG) greater than 110 mg/dL, BMI at least the age-specific 90th percentile on the basis of Communicable Disease Center 2000 growth charts, blood pressure at least the age- and height-specific 90th percentile, high-density lipoprotein cholesterol (HDLC) not more than 50 mg/dL, and glucose at least 110 mg/dL.

2.4. *Statistical methods*

In 424 girls who had information on frequency of menses and measurements of sex hormones at age 14, 389 with menstrual cycle length less than 42 days were compared with 35 with oligomenorrhea (cycle length ≥42 days) and with a subset of the oligomenorrheic girls who also had hyperandrogenism (n = 14). Comparisons were made by Wilcoxon tests for continuous variables and by χ^2 or Fisher exact tests for categorical variables at age 14 (Table 1).

We focused on 370 girls having measurements of sex hormones at age 14 and having at least 5 annual reports on menstrual status over a 6-year period (ages 14-19) (Tables 2-5, Figs. 1-3). Oligomenorrhea categories were based on the number of oligomenorrhea reports (≥42 days since last menses cycle) [10]. Oligomenorrhea categories were 0 (no delay found), 1 (1 delay found), 2 (2 delays), 3 (≥3 delays found). A subset of oligomenorrheic girls who also had hyperandrogenism was classified as PCOS group (n = 28) (Table 2).

In the 370 girls with at least 5 annual menstrual status reports, adjusting for race, analysis of variance (ANOVA) was used to determine differences between oligomenorrhea categories 1, 2, and 3 vs category 0 and between PCOS group vs category 0 (Table 2). Hochberg-Benjamini [23] correction for multiple comparisons was used to control the false discovery rate (<.05) for 4 comparisons of 3 oligomenorrhea groups and PCOS group vs no oligomenorrhea group (category 0) for each variable (Table 2).

Separated by oligomenorrhea category groups, unadjusted mean BMI and waist circumference at each annual visit from age 14 to 25 are displayed in Fig. 1, with *P* values taken from ANOVA after covariance adjustment for race. Unadjusted mean insulin, glucose, and HOMA IR values at each annual visit from ages 19 to 24/25 are displayed in Fig. 2, with *P* values taken from ANOVA after covariance adjustment for race and BMI at each follow-up year. The Mantel-Haenszel χ^2 test was used to assess the percentage of girls having IFG + T2DM at ages 19 to 24 in girls categorized by at least 3, 2, 1, and 0 oligomenorrhea reports from ages 14 to 19 (Fig. 3).

After we first determined that patterns of significant explanatory variables in regression models for insulin and glucose levels and HOMA IR were the same for the average of years 19 to 24/25 as for individual years, average insulin (from mean ages 19-25), glucose, and HOMA IR (from mean ages 19-24) were used as dependent variables. Regression models were constructed by stepwise selection from candidate explanatory variables: race, age 14 variables (BMI, waist circumference, metabolic syndrome, FT, E2, DHEAS, and SHBG), and age 14 to 19 variables (cigarette smoking, the number of oligomenorrhea reports [range, 0-6] found in 6 annual reports from age 14 to age 19, and PCOS [yes, no]) (Table 3).

Table 1 – Mean (SD) BMI, waist circumference, sex hormones, lipids, race, cigarette smoking, and metabolic syndrome status at age 14, categorized by age 14 oligomenorrhea status in 424 Cincinnati schoolgirls

	Menstrual cycle <42 d		Oligomenorrhea (menstrual cycle ≥42 d)		Oligomenorrhea and hyperandrogenism [a]	
Measures	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD
BMI (kg/m^2)	389	22.4 ± 4.9	35	24.9 ± 6.6	14	28.0 ± 5.9‡
Waist circumference (cm)	389	71 ± 9	35	76 ± 13*	14	83 ± 11§
FT (pg/mL)	389	1.19 ± 0.69	35	1.61 ± 0.90†	14	2.19 ± 1.01 ‡
E2 (pg/mL)	389	137 ± 121	34	123 ± 158	14	108 ± 44
DHEAS (μg/dL)	389	185 ± 97	35	202 ± 128	14	278 ± 155*
SHBG (nmol/L)	389	18.7 ± 10.1	35	17.2 ± 12.1	14	10.3 ± 7.3†
TG (mg/dL)	356	78 ± 38	31	100 ± 66†	13	120 ± 93*
HDLC (mg/dL)	356	56 ± 11	31	51 ± 10†	13	47 ± 10†
LDLC (mg/dL)	356	91 ± 25	31	97 ± 29	13	102 ± 26
Race	389	170 W, 219 B (56%)	35	14 W, 21 B (60%)	14	6 W, 8 B (57%)
Cigarette smoking	389	149 Y (38%)	35	13 Y (37%)	14	5 Y (36%)
Metabolic syndrome	389	17 Y (4%)	35	3 Y (9%)	14	1 Y (7%)

Compared with normal menses group: *P<.05, †P<.01, ‡P<.001, and §P<.0001. LDLC indicates low-density lipoprotein cholesterol.
[a] Subset of oligomenorrheic girls with hyperandrogenism/PCOS.

Table 2 – Mean (SD) BMI, waist circumference, sex hormones, lipids, cigarette smoking, and metabolic syndrome status at age 14 in 370 girls who had at least 5 reports on menstrual frequency from ages 14 to 19, categorized by oligomenorrhea status

Measures	Oligomenorrhea categories Mean ± SD, P				Oligomenorrhea and hyperandrogenism (n = 28)[a]
	0 (n = 269)	1 (n = 74)	2 (n = 19)	3 (n = 8)	
BMI (kg/m^2)	22.2 ± 5.1	22.8 ± 5.6	22.3 ± 4.3	29.4 ± 7.2 .0060[b]	26.6 ± 5.3 <.0001[b]
Waist circumference (cm)	70 ± 10	71 ± 11	71 ± 10	84 ± 14 .0048[b]	79 ± 11 <.0001[b]
FT (pg/mL)	1.18 ± 0.65	1.26 ± 0.66	1.16 ± 1.01	1.94 ± 1.20 .0012[b]	2.11 ± 0.87 <.0001[b]
E2 (pg/mL)	131 ± 108	125 ± 135	94 ± 52	69 ± 49	139 ± 90
DHEAS (μg/dL)	177 ± 83	203 ± 138 .0054[b]	135 ± 65	275 ± 135 .0032[b]	340 ± 153 <.0001[b]
SHBG (nmol/L)	18.3 ± 10.4	17.7 ± 8.9	21.4 ± 13.3	16.8 ± 16.9	11.6 ± 7.0 .0010[b]
TG (mg/dL)	79 ± 38	92 ± 59 .013[b]	81 ± 25	75 ± 18	104 ± 82 .0018[b]
HDLC (mg/dL)	55 ± 12	56 ± 11	57 ± 9	53 ± 6	51 ± 8 .038
LDLC (mg/dL)	92 ± 26	91 ± 25	79 ± 27	95 ± 13	89 ± 21
No. of oligomenorrheic and hyperandrogenic (PCOS) by age 19	0	21/74 (28%)	2/19 (11%)	5/8 (63%)	
Race	W 134 B 135 (50%) Mantel-Haenszel χ^2 = 6.7, P = .0097	W 11 B 17 (61%)	W 3 B 16 (84%)	W 2 B 6 (75%)	W 11 B 17 (61%) χ^2 = 1.13, P = .29
Metabolic syndrome at age 14	12 (5%) Yes 257 No Mantel-Haenszel χ^2 = 1.51 P = .22	6 (8%) Yes 68 No	1 (5%) Yes 18 No	1 (13%) Yes 7 No	4 (14%) Yes 24 No Fisher P = .052

P adjusted for race; compared with category 0.

[a] Subset of oligomenorrheic girls with hyperandrogenism/PCOS.

[b] Significant using Hochberg-Benjamini method controlling for false discovery rate (<.05) for 4 comparisons of oligomenorrhea groups vs no-oligomenorrhea group (category 0) for each variable.

Impaired fasting glucose + T2DM were determined as exclusive, nonoverlapping groups by maximum glucose during ages 19 to 24. Stepwise logistic regression was done with the dependent variable being IFG + T2DM vs normal glucose, and explanatory variables including age 14 measures (race, BMI, waist circumference, FT, E2, DHEAS, and SHBG), childhood insulin, and age 14 to 19 variables (cigarette smoking, oligomenorrhea category [age 14-19 reports], and PCOS [yes, no]) (Table 4).

As per the analyses of De Pergola et al [24], to examine the association between oligomenorrhea during ages 14 to 19 and age 14 variables (race, age, BMI, waist circumference, sex hormones, cigarette smoking), childhood insulin, and HOMA IR, stepwise logistic regression models were fit with the oligomenorrhea category (4 levels or 3 levels) as dependent variable. A similar logistic stepwise regression was run with the same dependent variable, oligomenorrhea during ages 14 to 19; and candidate explanatory variables

Table 3 – Regression models for averaged insulin, glucose, and IR during ages 19 to 24/25 in 370 girls who had at least 5 reports on menstrual status over 6 years from ages 14 to 19

Dependent variables	Explanatory variables	Sign, P	Partial R^2
Averaged insulin during age 19-25	Waist circumference	+, <.0001	29.7%
356 observations (169 W, 187 B) used	Black race	+, <.0001	5.5%
	Oligomenorrhea and hyperandrogenic (PCOS) by age 19	+, .0002	2.6%
Averaged glucose during age 19-24	Waist circumference	+, <.0001	6.6%
358 observations (168 W, 190 B) used	Oligomenorrhea and hyperandrogenic (PCOS) by age 19	+, .0001	3.8%
Averaged IR during age 19-24	Waist circumference	+, <.0001	30.1%
354 observations (168 W, 186 B) used	Oligomenorrhea and hyperandrogenic (PCOS) by age 19	+, .0027	4.1%
	Black race	+, <.0001	3.8%
	Oligomenorrhea frequency age 14 to 19	+, .023	0.8%
	SHBG at age 14	–, .050	0.7%

Stepwise selection from age 14 variables (race, BMI, waist circumference, metabolic syndrome, FT, E2, DHEAS, SHBG) and age 14 to 19 variables (cigarette smoking, oligomenorrhea frequency [0-6] in 6 annual reports, and PCOS [yes = 1, no = 0]).

Table 4 – Stepwise logistic regression: significant explanatory variables for IFG and T2DM (age 19-24 maximum glucose ≥110 mg/dL) in 370 NGHS girls

Dependent variable	Significant explanatory variables	P	Odds ratio, (95% CI)
Maximum glucose from age 19 to 24 ≥110 & <126 mg/dL (IFG, n = 12) and ≥126 mg/dL (T2DM, n = 4) vs <110 mg/dL (n = 312) 328 observations used AUC = 0.834	Waist circumference at age 14 (cm) Oligomenorrhea category: 0 (no oligomenorrhea), 1 (1 report), 2 (2 reports), 3 (≥3 reports)	+, .002 +, .032	1.06 (1.02-1.10) 1.82 (1.05-3.14)

Candidate explanatory variables: race (W = 1, B = 2), age 14 variables (BMI, waist circumference, FT, E2, DHEAS, SHBG), childhood insulin,[a] and age 14 to 19 variables (cigarette smoking, oligomenorrhea category [0-3] in 6 annual reports, and PCOS [yes = 1, no = 0]).

Oligomenorrhea category	Odds ratio, 95% CI (vs category 0)	Odds ratio, 95% CI (vs category 1)	Odds ratio, 95% CI (vs category 2)
0			
1	1.82 (1.05-3.14)		
2	3.30 (1.11-9.85)	1.82 (1.05-3.14)	
3	6.54 (1.16-30.93)	3.30 (1.11-9.85)	1.82 (1.05-3.14)

AUC indicates area under receiver operating characteristic curve; CI, confidence interval.
[a]First childhood insulin: 281 girls had first insulin measure at age 10, and the other 87 girls had first insulin measure at age 16.

were measures at age 19: race, age, waist circumference, BMI, insulin, HOMA IR, and cigarette smoking during ages 14 to 19 (Table 5).

As per the analyses of Bhattacharya et al [25], we categorized girls by those with at least 2 and not more than 1 oligomenorrhea reports from ages 14 to 19 and again categorized them by insulin quintiles. Then we examined, by ANOVA, which age 14 variables (waist, BMI, sex hormone levels) differed between oligomenorrheic girls with top quintile insulin compared with oligomenorrheic girls with insulin in the lower 4 quintiles.

3. Results

Girls with oligomenorrhea at age 14 had greater waist circumference, higher TG, lower HDLC, and higher FT than girls with menstrual cycles less than 42 days (Table 1). Girls with oligomenorrhea and hyperandrogenism (PCOS) had higher BMI, greater waist circumference, higher TG, higher FT and DHEAS, and lower SHBG and HDLC than girls with menstrual cycles less than 42 days (Table 1). As displayed in Table 1, going from menses less than 42 days to

Table 5 – Stepwise logistic regression: significant explanatory variables for oligomenorrhea category in 370 NGHS girls

Dependent variable	Significant (age 14) explanatory variables	P	Odds ratio (95% CI)
Oligomenorrhea 4 categories: ≥3, (n = 7), 2 (n = 17), 1 (n = 69), and 0 (n = 245) 338 observations used AUC = 0.580	Childhood insulin (μU/mL)	+, .0081	1.02 (1.005-1.036)
Oligomenorrhea 3 categories: ≥2 (n = 24), 1 (n = 69), and 0 (n = 245) 338 observations used AUC = 0.579	Childhood insulin (μU/mL)	+, .0086	1.02 (1.005-1.036)

Candidate explanatory variables: race (W = 1, B = 2), age 14 variables (age, BMI, waist circumference, FT, E2, DHEAS, SHBG, cigarette smoking), and childhood insulin [a]

Dependent variable	Significant (age 19) explanatory variables	P	Odds ratio (95% CI)
Oligomenorrhea 4 categories ≥3 (n = 8), 2 (n = 19), 1 (n = 67), and 0 (n = 240) 334 observations used AUC = 0.596	Insulin (μ/mL)	+, .0009	1.04 (1.02-1.06)
Oligomenorrhea 3 categories ≥ 2, (n = 27); 1, (n = 67); 0, (n = 240) 334 observations used AUC = 0.595	Insulin (μU/mL)	+, .0010	1.04 (1.02-1.06)

Candidate explanatory variables: race (W = 1, B = 2), age 19 variables (age, BMI, waist circumference and insulin), cigarette smoking from age 14 to 19

[a] First childhood insulin: 281 girls had first insulin measure at age 10, and the other 87 girls had first insulin measure at age 16.

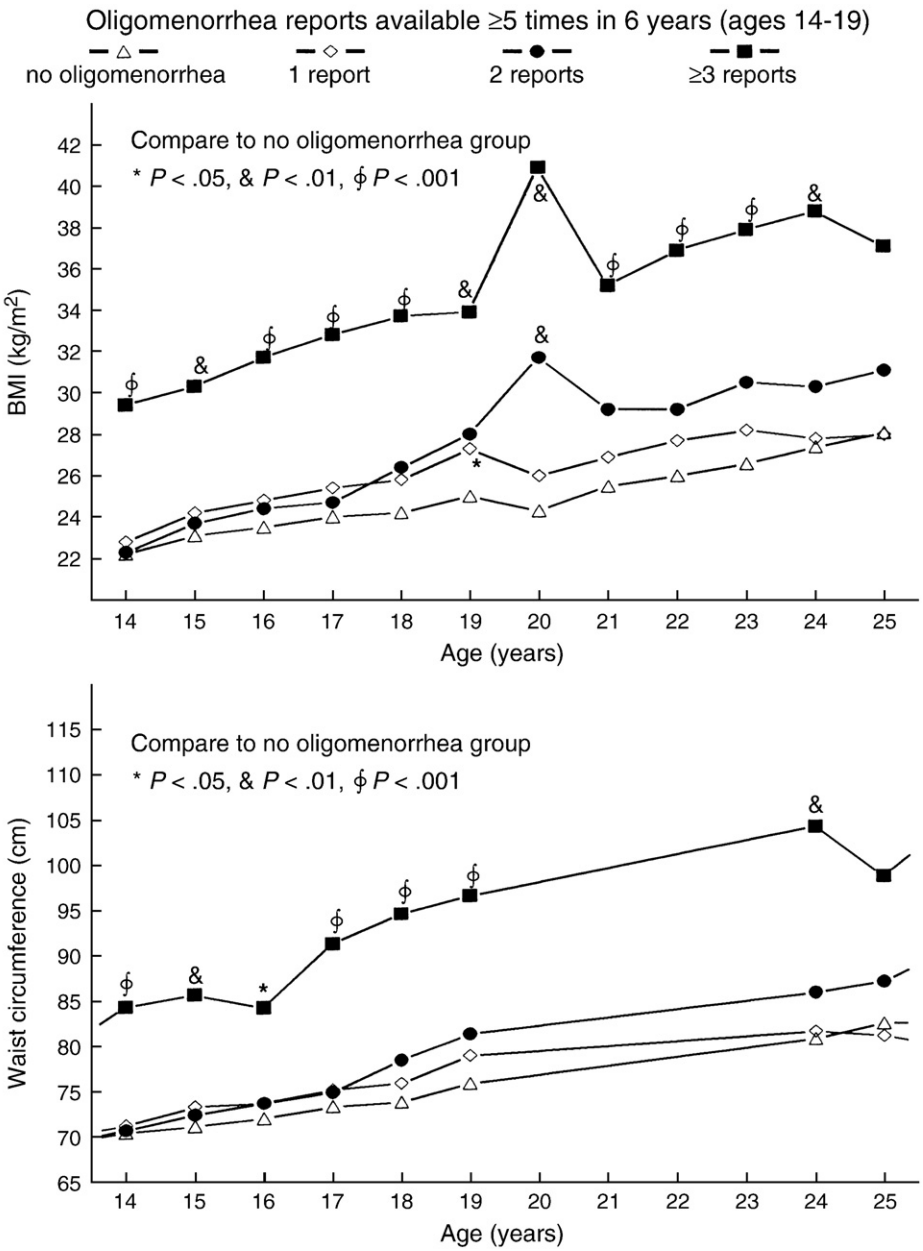

Fig. 1 – Body mass index (in kilograms per square meter) and waist circumference at ages 14 to 25 in 370 schoolgirls having at least 5 yearly reports on menstrual frequency from ages 14 to 19. Categorized by frequency of oligomenorrhea; unadjusted mean values displayed. *P* values are taken from ANOVA after covariance adjustment for race.

oligomenorrhea to oligomenorrhea-hyperandrogenism groups, with each progression, BMI, waist circumference, FT, DHEAS, and TG rose, whereas SHBG and HDLC fell.

Age 14 BMI, waist circumference, FT, and DHEAS were higher in girls who had at least 3 oligomenorrheic reports from ages 14 to 19 than in those with 0 report of oligomenorrhea (Table 2). Black girls were overrepresented in oligomenorrhea categories 2 and 3 (Table 2). The hyperandrogenic subset of oligomenorrheic girls had higher BMI, waist, FT, DHEAS, and TG and lower SHBG than those in the no-oligomenorrhea group (Table 2).

From ages 14 to 25, after covariance adjustment for race, girls with at least 3 positive oligomenorrhea reports over 6 years from ages 14 to 19 had consistently and significantly higher mean BMI (Fig. 1, upper panel) and waist circumference (Fig. 1, lower panel) than girls with no oligomenorrhea. After covariance adjustment for race, BMI was also higher at age 20 in girls with 2 oligomenorrhea reports than in girls with no oligomenorrhea (Fig. 1).

After covariance adjustment for BMI and race, girls in the at least 3 oligomenorrhea report category had higher fasting insulin and glucose levels and HOMA IR levels than girls having no oligomenorrhea (Fig. 2).

By stepwise regression, waist circumference at age 14 was the most significant explanatory variable for average insulin and glucose levels and HOMA IR from ages 19 to 24/25 (Table 3). Having oligomenorrhea and hyperandrogenism was a significant explanatory variable for average insulin and glucose levels and IR during ages 19 to 24 (Table 3). Black

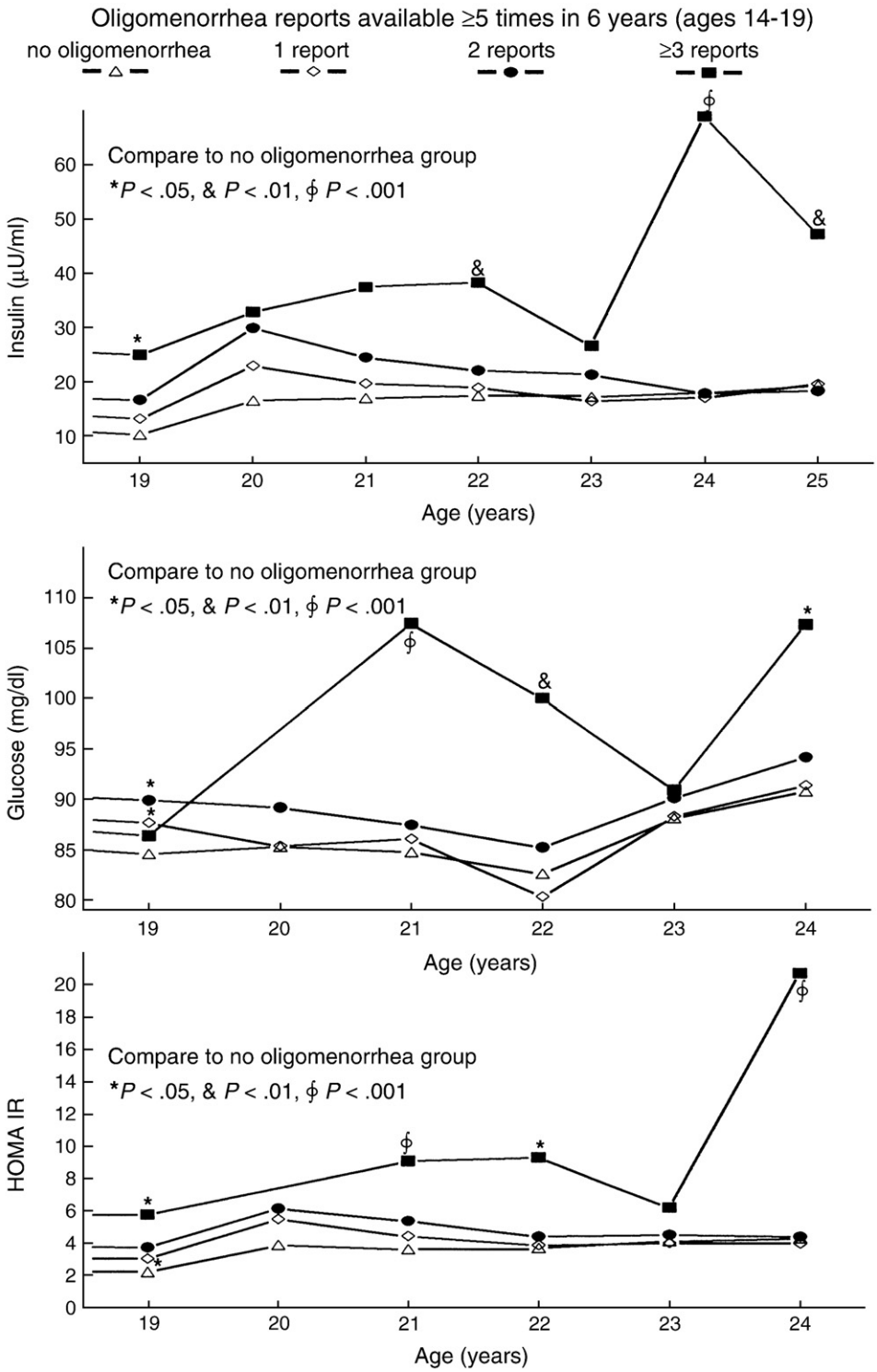

Fig. 2 – Fasting serum insulin (in microunits per milliliter) at ages 19 to 25 in 370 schoolgirls having at least 5 yearly reports on menstrual frequency from ages 14 to 19. Categorized by frequency of oligomenorrhea; unadjusted mean values displayed. *P* values are taken from ANOVA after covariance adjustment for race and BMI at each year of follow-up. Fasting plasma glucose (in milligrams per deciliter) at ages 19 to 24 years in 370 schoolgirls having at least 5 yearly reports on menstrual frequency from ages 14 to 19. Categorized by frequency of oligomenorrhea; unadjusted mean values displayed. *P* values are taken from ANOVA after covariance adjustment for race and BMI at each year of follow-up. Homeostatic model assessment of IR at ages 19 to 24 years in 370 schoolgirls having at least 5 yearly reports on menstrual frequency from ages 14 to 19. Categorized by frequency of oligomenorrhea; unadjusted mean values displayed. *P* values are taken from ANOVA after covariance adjustment for race and BMI at each year of follow-up.

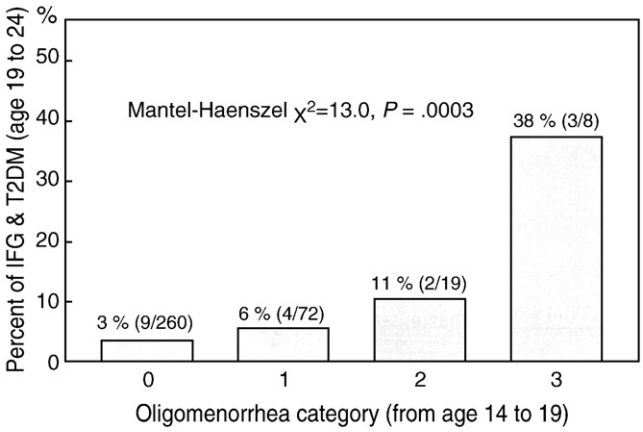

Fig. 3 – Percentage of IFG + T2DM at ages 19 to 24 in girls having at least 3, 2, 1, and 0 oligomenorrhea reports from ages 14 to 19.

race and the frequency of oligomenorrhea (ages 14-19) were significant positive explanatory variables for HOMA IR at ages 19 to 24, whereas SHBG was a significant negative explanatory variable (Table 3).

Significant explanatory variables for IFG + T2DM during ages 19 to 24 included waist circumference at age 14 and oligomenorrhea category during ages 14 to 19 (Table 4).

Impaired fasting glucose + T2DM during ages 19 to 24 were most common (38%) in girls having at least 3 oligomenorrhea reports during ages 14 to 19 and were also higher in girls having 2 (11%) or 1 (6%) oligomenorrhea reports than in those without oligomenorrhea (3%) (Fig. 3).

Irrespective of the oligomenorrhea category as 4 levels (0, 1, 2, ≥3) or 3 levels (0,1, ≥2) and irrespective whether the explanatory variables were at age 14 or 19, the significant explanatory variable associated with oligomenorrhea was HOMA IR in all models (data not shown). When HOMA IR was dropped from candidate explanatory variable list, then insulin was the significant explanatory variable in all models (Table 5).

At age 14, of the 35 girls with oligomenorrhea, 5 (14%) smoked. Free testosterone and insulin did not differ between the 5 oligomenorrheic girls who smoked and the 30 who did not smoke(P > .5), unlike the report by Cupisti et al [26] in women with oligomenorrhea where smoking was associated with increased FT and fasting insulin levels.

In 27 girls with at least 2 oligomenorrhea reports from ages 14 to 19, 12 (48%) had top quintile insulin; and in these 12 girls vs 13 without top quintile insulin, the differentiating factor was DHEAS (P = .033) at age 14, congruent with the conclusion of Bhattacharya and Ghosh [25] that girls with PCOS and IR have higher androgens. Age 14 FT, E2, and SHBG did not differ between oligomenorrheic girls with top and with bottom 4 insulin quintiles.

4. Discussion

Although menstrual cycle irregularity in adult women has been associated with IFG, gestational diabetes, and T2DM [1,6], this is the first prospective study to report an independent association of adolescent oligomenorrhea with young adult IFG + T2DM and with insulin and glucose levels and IR. In the current study, IFG + T2DM during ages 19 to 24 were most common (38%) in girls having at least 3 oligomenorrhea reports during ages 14 to 19 and were also higher in girls having 2 (11%) or 1 (6%) oligomenorrhea reports than in those without oligomenorrhea (3%).

Documentation of adolescent oligomenorrhea should lead to screening for IFG and T2DM and should prompt a workup for underlying PCOS [27]. Of 101 oligomenorrheic adolescent girls in the current study, 28% had concurrent hyperandrogenemia and were identified as having PCOS [13]. Because we did not have availability of pelvic ultrasound to more fully identify PCOS [13] in oligomenorrheic girls, we have probably underestimated the prevalence of PCOS. Recognition of PCOS in adolescence should facilitate therapeutic interventions [28-32], with an ultimate goal of primary prevention of T2DM, CHD [4, 5], and morbid obesity, all associated with PCOS in adolescents and adult women [27-30]. Polycystic ovary syndrome, in turn, is associated with IR, hyperinsulinemia, and T2DM [33]. Hyperandrogenic PCOS phenotypes have the greatest degree of IR and inflammation [33].

In the current study, oligomenorrhea during ages 14 to 19 was positively associated with FT and DHEAS, associations that parallel those in postmenopausal women, where women with a history of irregular menses and elevated androgens are at high risk for worsening cardiovascular event-free survival [6]. Age-adjusted risk for CHD mortality increases in women with irregular menstrual cycles [34].

In the current study, HOMA IR and insulin were the major significant explanatory variables for oligomenorrhea ages 14 to 19, unlike the finding of De Pergola et al [24] where waist circumference was the major correlate of oligomenorrhea. The association of insulin with oligomenorrhea is important because, in 24-year prospective follow-up, basal fasting insulin is the most important explanatory variable for the development of hyperglycemia [35]. Hence, by virtue of its independent and significant association with young adult IFG + T2DM, insulin and glucose levels, and HOMA IR, adolescent oligomenorrhea can be the diagnostic trigger for initiating primary prevention of T2DM by diet, exercise, weight loss or minimizing weight gain [36], and metformin [37].

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