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Prolonged Juvenile States and Delay of Cardiovascular and Metabolic Risk Factors:

The Fels Longitudinal Study

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Abstract

Objectives—To ascertain the influence of such a prolonged juvenile state on delaying the onset of the metabolic syndrome, cardiovascular disease (CVD), and type 2 diabetes mellitus (T2DM) later in life.

Study design—We define prolongation of a juvenile state as a retarded tempo of growth, determined by the timing of peak height velocity in each subject and relate the retarded tempo of growth to metabolic syndrome, cardiovascular disease (CVD), and type 2 diabetes mellitus (T2DM) later in life using serial data of 237 study participants (119 men and 118 women) participants enrolled in the Fels Longitudinal study.

Results—Children who matured early tended to have greater BMI, waist circumference, percent of body fat and were more likely to have adverse cardiovascular risk profiles than children who matured late. The differences in these risk factors between early and late maturers were significant for percent body fat, fasting plasma triglycerides, and fasting plasma insulin.

Conclusions—The analyses disclosed a clear separation between early and late maturers in the appearance of these risk factors in young adulthood.

It is not currently known whether a prolonged juvenile state prevents unhealthy metabolic and cardiovascular aspects of aging, as would be indicated by a delayed appearance of positive risk factors for metabolic and cardiovascular disease in adulthood. The availability of long-term and frequently measured serial data of growth and body composition from the Fels Longitudinal Study (FLS) presents opportunities to link these common but unhealthy features of aging to childhood tempo of physiological development.

The timing of pubertal growth spurt in height is a clear marker of the tempo of physiological development. The pubertal growth spurt begins in girls at about 9 or 10 years and in boys at about 10 or 11 years, and the peak height velocity (PHV) is reached at about 12 years in girls

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and 14 years in boys (Malina et al, 2004; Buckler, 1990; Guo et al, 1991; Ramsay et al, 1995). The mean age of attaining the peak height velocity in the FLS population is 13.7 ± 1.0 years for boys and 11.6 ± 0.9 years for girls (Guo et al, 1991; Roche, 1992; Roche and Sun, 2003).

Recently, we derived age- and sex-specific childhood BMI, waist circumference, and blood pressures that predict obesity, central obesity, hypertension and the metabolic syndrome in adulthood using a random effects model in a discovery sample of the FLS. We validated these criterion values in a larger sample of the FLS using logistic regression. (Sun et al., 2003; Sun et al., 2007^{a, b}). In these studies we demonstrated that modestly elevated BP in childhood functions as a remarkably powerful predictor of the metabolic syndrome in adulthood. Until now there has been no published study of accelerated or retarded tempo of growth in relation to disease risk factors. This paper investigates the effect of a prolonged juvenile state, i.e., a delayed attainment of physiological milestones, on the appearance of positive risk factors for metabolic syndrome, CVD, and T2DM later in life. We use FLS data to elucidate these relationships because no other study has long-term, closely-spaced measurements of anthropometry, body composition, and risk factors for metabolic and cardiovascular disease throughout the lifespan.

Specifically, we address the hypothesis that boys and girls with prolonged juvenile states are less likely to be obese, insulin resistant, and dyslipidemic as adults than boys and girls with a curtailed juvenile state.

Methods

The study sample consists of 511 adults (265 men and 246 women) enrolled in the FLS. Of the 511, 237 study participants (119 men and 118 women) have sufficient childhood height data to capture the physiological milestones which mark the tempo of growth as well as sufficient serial risk factor data collected in the same subjects between 18 and 35 years of age. Measurements used to assess metabolic and cardiovascular risk include BMI, waist circumference, lipids and lipoproteins, systolic and diastolic blood pressure, and plasma glucose and insulin. The FLS began in 1929, and participants were examined at birth, 1, 3, 6, 9, and 12 months, then every 6 months for 18 years and biennially thereafter. Anthropometric variables and BP were measured and family health history recorded for participants 2 years and older since 1929. Beginning in 1976, body composition, fasting plasma lipids and lipoproteins were measured, and lifestyle variables such as cigarette smoking, and physical activity as well as family health history were recorded for participants 8 years and older. Approximately 8% of the Fels participants have been lost to follow-up, but their body composition data at last visit did not differ from the 92% who remain in the study. Reliability in the Fels Study is excellent, and reliability coefficients for most of the variables are well above 90%.

Weight, stature, and abdominal circumference were measured using standardized procedures similar to recommendations of the Airlie Consensus Conference (Lohman et al., 1988). Weight and stature were used to calculate BMI. Weight is measured to the nearest 10 grams and stature is measured to the nearest millimeter. The waist circumference measurement is recorded to the nearest millimeter. Percent body fat in subjects 8 years of age and older was ascertained by hydrodensitometry and by dual energy x-rays absorptiometry. Systolic blood pressure measurements were measured by trained technicians with the participant seated, using a standard mercury sphygmomanometer with the procedure recommended by the American Heart Association (NHLBI, 1974). Serial fasting plasma lipids and lipoprotein cholesterol were measured annually near the time of the participants' birthdays from 8 years and older. These measurements, including fasting plasma levels of triglycerides, HDL-cholesterol and total

cholesterol, were measured at the Medical Research Laboratory in Cincinnati. The Friedewald equation was used for indirect calculation of LDL-cholesterol, i.e., LDL=total cholesterol – HDL cholesterol – VLDL, where VLDL=0.2 × triglycerides. The intra-assay and inter-assay coefficients of variation were 3.6% and 9.3% for low and 1.8% and 9.3% for high serum concentrations, respectively. Fasting plasma levels of glucose, insulin, leptin were also measured. All procedures were approved by the Institutional Review Boards of Virginia Commonwealth University and Wright State University.

Statistical Analysis

Serial data for height collected at six-month intervals during childhood in the FLS allow accurate estimation of ages at peak height velocity during the growth spurt. The tempo of physiological development was determined in each subject by documenting his or her age at peak height velocity. A triple logistical model was applied to individual semi-annual data for height from 2 to 18 years of age to derive the timing of the onset of the pubertal growth spurt and the age at PHV (Guo et al 1991; Bock et al 1994):

$$h(t) = \frac{a_1 q}{1 + e^{-b_1(t-c_1)}} + \frac{a_1 p}{1 + e^{-b_2(t-c_2)}} + \frac{f - a_1}{1 + e^{-b_3(t-c_3)}}$$

where $h(t)$ =height at time t , a_1 =contribution of prepubertal growth to mature height, b_1 =slope of the early childhood component at maximum velocity, c_1 =age at maximum velocity of the early-childhood component; b_2 =slope of the middle-childhood component at maximum velocity, c_2 =age at maximum velocity of the middle-childhood component, p =proportion of prepubertal growth due to the middle-childhood component, $q=1-p$, $f-a_1$ =contribution of the adolescent component to mature stature, b_3 =slope of the adolescent component at maximum velocity, c_3 =age at maximum velocity of the adolescent component.

Rate of Maturation—We define those boys and girls whose age of attainment of PHV is above the median (50th percentile) of the study population as having a prolonged juvenile state. Conversely, we define those boys and girls whose age of attainment of PHV is below the median of the study population as having a curtailed juvenile state.

Results

The pubertal growth spurt

Among 292 boys and the 268 girls in the FLS, the onset of the pubertal growth spurt was 10.7 ± 0.8 for boys and 8.7 ± 0.8 for girls. In our study sample of 119 male and 118 female Fels participants, PHV was attained at 13.7 ± 0.9 years for boys and 11.6 ± 0.8 years for girls. Figure 1 demonstrates an example of fitting triple logistic models to the individual serial height data collected from 2 to 18 years of age for a boy. The left panel presents the individual boy with observed serial data and predicted values for height. The right panel presents individual incremental data and the corresponding velocity curves on the same boy. The individual fitted growth curve allows the estimation of the onset of the pubertal growth spurt and the age at peak height velocity. This boy started the pubertal spurt at age 9.9 years and reached his peak velocity at age 12.5 years.

Metabolic and CVD Risk Factors

Table I illustrates the means and standard deviations of BMI, waist circumference, percent body fat, systolic and diastolic blood pressure, glucose and insulin concentrations, and triglycerides and HDL-cholesterol. There was no significant difference in BMI and waist

circumference between men and women, but women have a significantly higher mean percent body fat than men. Men had significantly higher levels of systolic and diastolic blood pressure, fasting plasma glucose, insulin, and triglycerides and significantly lower levels of HDL-cholesterol than women (all $p < 0.05$) and, are at significantly higher risk for metabolic and cardiovascular disease than women.

Effects of Rate of Maturation on Risk Factors

We examined data collected the same individuals between the ages 18 and 35 years for differences between early and late maturers in BMI, waist circumference percent body fat, systolic and diastolic blood pressures, fasting plasma triglycerides, HDL-cholesterol, fasting plasma glucose and insulin (Table II). Children who matured early tended to have greater BMI, waist circumference, percent of body fat and were more likely to have adverse cardiovascular risk profiles than children who matured late. The differences in these risk factors between early and late maturers were significant for percent body fat, fasting plasma triglycerides, and fasting plasma insulin. The analyses disclosed a clear separation between early and late maturers in the appearance of these risk factors in young adulthood.

Figure 2 illustrates the means and standard deviations on individual serial data for percent body fat, triglycerides, and insulin levels and found a clear separation in percent body fat between early maturers and late maturers from age 18 to 35 years.

Discussion

The present study is innovative in several ways. This is the first report that directly links childhood tempo of physiological development to BMI, waist circumference, and the metabolic syndrome ascertained in the same subjects decades later. The effects of rate of maturation on subsequent metabolic variables and risk factors for cardiovascular disease in the same individuals over 40 years of the lifespan has never been investigated. The use of long-term serial height data in conjunction with mathematical growth models allows us to describe the pattern of growth in height with great accuracy and to capture within-individual variations in tempo of pubertal growth. Despite the high correlations between BMI and percent body fat, BMI is also correlated with fat-free mass, and the correlations are complicated by varying growth rates and maturity levels in both boys and girls (Maynard et al., 2001; Guo et al., 1997). The present study involves direct measurements of body composition in addition to BMI.

We previously characterized human growth in height from 2 to 18 years (Guo et al., 1991; Bock et al., 2005). In these earlier studies, the onset of the pubertal growth spurt was 11.2 ± 0.8 for boys and 9.2 ± 0.8 for girls (Guo et al., 1991). These data also show that peak height velocities were reached at 13.7 ± 0.9 years for boys and 11.6 ± 0.8 years for girls.

Rapidly maturing children tend to have larger BMI values than those who are maturing slowly (Morrison et al., 1994; Miller et al., 1972; Simmons & Greulich, 1943; Lindgren, 1978). Previous studies have shown the predictive accuracy of childhood BMI for adult obesity (Guo et al., 1994; Whitaker, et al., 1997). As age-specific BMI increases above the 75th percentile during childhood, the probability of obesity in adulthood increases (Guo et al., 1994). Children whose weight and/or BMI fall within high age-specific percentiles, are at increased risk for overweight and obesity in adulthood. Some of these children are early maturers. The parallel changes in BMI and rates of maturation that we observed may reflect changes in hormone levels, particularly leptin (Saenger, 1998), which might affect both BMI and the timing of pubescence

It should be noted that none of the earlier studies examined the effects of rate of maturation on direct measure of body fatness. The present study shows that children who mature early have significantly higher level of percent body fat later in life. Elevated levels of fat mass and centripetal fat distribution persist from childhood into adulthood. Therefore, the tempo of physiological development contributes to the established tracking in obesity from childhood into adulthood. The impact of the effect of earlier maturation on subsequent development of body fat and fat distribution, metabolic and cardiovascular risk factors has significant health implications. Obesity is an important risk factor for cardiovascular morbidity and mortality and type 2 diabetes. This is especially true for males, and our study indicates that boys who mature early are more likely to develop insulin resistance and dyslipidemia than boys who mature late as adults.

The FLS provides a unique opportunity to characterize the rates and patterns of events during the pubertal growth spurt and to analyze their effects on changes in body fat, fat distribution, and fat-free mass. Preventing or reversing increases in levels of body fat and elevated levels of plasma insulin and triglycerides during adolescence and early adulthood are important goals for the prevention of cardiovascular disease and type 2 diabetes.

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Figure 1.
Height velocity curve for a boy in the FLS and physiological milestones

Figure 2.
Adult percent body fat values for early and late maturers.

Table 1

Means and standard deviations for values collected between 18 to 35 years of age for risk factors for cardiovascular disease and type 2 diabetes

	Males					Females					p ^a value
	N	Mean	Sd	Min	Max	N	Mean	Sd	Min	Max	
BMI (kg/m ²)	119	24.0	4.5	15.8	37.8	118	25.2	5.7	17.3	46.9	0.070
Waist Circumference (cm)	119	88.5	12.7	64.8	124.3	118	86.7	13.7	66.8	131.4	NS
Percent Body Fat (%)	119	18.8	8.0	2.3	40.2	118	32.9	9.0	12.0	51.3	<0.001
Systolic Blood Pressure (mmHg)	122	115.6	11.2	94.0	154.0	125	105.5	9.2	85.0	141.0	<0.001
Diastolic Blood Pressure (mmHg)	122	72.1	10.6	45.0	110.0	125	68.2	9.6	47.0	109.0	<0.001
Glucose (mg/dL)	83	91.9	9.1	70.0	118.0	88	85.9	6.5	71.0	100.0	<0.001
Insulin (mg/dL)	83	8.2	4.4	1.6	23.2	88	7.7	4.6	2.1	24.8	NS
Triglycerides (mg/dL)	111	143.3	132.7	36.0	1056.0	107	99.1	54.2	35.0	386.0	<0.001
HDL-cholesterol (mg/dL)	111	46.3	10.0	26.0	72.0	107	57.3	14.1	24.0	98.0	<0.001

^a p-value for sex-associated difference.

Table II

Means and standard deviations and standardized group differences between early late maturing boys and girls for values collected between 18 to 35 years of age for selected measurements of body size, body composition, and risk factors for cardiovascular disease and type 2 diabetes

Males	Early			Late			p value
	N	Mean	SD	N	Mean	SD	
BMI (kg/m ²)	64	24.4	4.5	55	23.5	4.5	
Waist Circumference (cm)	64	89.6	13.1	55	87.2	12.3	
Percent of Body Fat (%)	64	20.0	8.0	55	17.4	7.8	0.08
Systolic Blood Pressure (mmHg)	66	115.3	11.5	56	115.9	10.9	
Diastolic Blood Pressure (mmHg)	66	72.9	11.1	56	71.1	10.1	
Glucose (mg/dL)	48	92.7	9.3	35	90.7	9.0	
Insulin (mg/dL)	48	9.6	4.9	35	6.1	2.3	<0.001
Triglycerides (mg/dL)	60	169.8	169.4	51	112.2	55.3	0.02
HDL (mg/dL)	60	45.6	10.1	51	47.2	9.9	
Females							
Age (years)	70	26.3	5.8	48	26.9	6.4	
BMI (kg/m²)	70	26.1	5.3	48	23.8	6.1	0.03
Waist Circumference (cm)	70	88.0	12.9	48	84.8	14.7	
Percent of Body Fat (%)	70	34.8	8.6	48	30.2	9.0	<0.005
Systolic Blood Pressure (mmHg)	78	106.2	9.3	47	104.3	9.0	
Diastolic Blood Pressure (mmHg)	78	69.0	9.7	47	66.9	9.4	
Glucose (mg/dL)	61	85.5	6.3	27	86.9	7.0	
Insulin (mg/dL)	61	7.6	4.6	27	8.1	4.9	
Triglycerides (mg/dL)	66	102.2	57.0	41	94.1	49.5	
HDL (mg/dL)	66	57.2	13.7	41	57.3	15.0	