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**Normal weight obesity and cardio-metabolic risk:
A 7 year longitudinal study in girls from pre-puberty to early adulthood**

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Abstract

Background

Normal weight obesity, defined as the combination of normal body mass index (BMI) and high body fat content appears to be highly prevalent in children and adolescents, but the long-term consequences for health are still unclear.

Methods

This was an 8 year longitudinal study of 236 girls followed from pre-puberty to early adulthood. Body composition was assessed by DXA and cardiometabolic risk by calculating continuous clustered risk score using abdominal fat mass, glucose, triacylglycerols, HDL-cholesterol and blood pressure. Growth chart was obtained from birth to 18 years. Subjects were categorized based on body weight status at the age 18 as overweight or obese (BMI >25 with fat% >30), Normal Weight Obese (BMI; 18.5-24.9 with fat% >30) and Normal Weight lean (BMI; 18.5-24.9 with fat% <30). The association of body composition and cardiometabolic risk was examined retrospectively for these groups.

Results

Continuous cardio-metabolic risk was higher already at the age of 11 years in subjects who were overweight or obese at the age of 18 compared with normal weight subjects ($p < 0.001$ for all). The cardio-metabolic risk score was also higher in the normal weight obese subjects compared with their normal weight lean peers in childhood and this difference persisted into early adulthood ($p < 0.001$ for all).

Conclusion

children and adolescent with normal BMI and elevated body fat percentage may be at increased risk for cardiometabolic morbidity in adulthood. Screening for adiposity in children and adolescent with a normal BMI could better identify those at higher risk for cardiometabolic morbidities.

Introduction

Obesity in childhood is associated with increased risk for coronary heart disease later in life¹. Timely recognition of excess adiposity in childhood is therefore highly important for prevention of the adverse health consequences. Clinical guidelines for diagnosis of childhood overweight and obesity recommend measuring height and weight, calculate the body mass index (BMI) and determine the weight status of children with based on national reference data².

Although BMI has many advantages as a surrogate of body fatness such as simplicity and reproducibility³, its diagnostic performance is not optimal to identify excessive adiposity because it cannot distinguish between fat mass and fat-free mass⁴, both of which contribute to BMI. Indeed, recent studies suggest that over a quarter of children and adolescent with high percent body fat may be misclassified as normal weight when using only BMI to diagnose obesity⁵. However, whether children with normal body weight but high percent body fat are at increased risk for cardio-metabolic disease in adulthood is not known. The purpose of this study was to assess the relationship between adiposity and cardio-metabolic risk among peripubertal girls with different body weight status using a longitudinal study design from childhood to early adulthood.

Methods

Study population

A total of 396 girls (mean age 11.2 years at baseline) participated in a longitudinal study for an average of 7.5 years. Detailed information regarding the participants and study design has been reported previously⁶⁻⁸. Briefly, the subjects were first contacted via class teachers teaching grades 4 to 6 (age 9 to 13 years old) in 61 schools in the city of Jyväskylä and its surroundings in Central Finland (96% of all the schools in these areas). Of the eligible samples, a subgroup (n=236) had total body composition assessments and serum metabolomics analysis at the age of 18 years and were included in this report. The participants provided their written consent in accordance with the guidelines laid down by the ethical committees.

Growth chart and define relative weight groups

Growth charts of each participant were obtained from Finnish School Health Care System from birth to 17-20 years of age (10-41 tests per subjects) in 61 schools from the city of Jyväskylä and its surroundings in Central Finland (96% of the total schools in these areas). To be able to compare the growth at the certain time points, the Weight % and height z-score was extrapolated from the growth chart using the form which was created by the Finnish Paediatric Research Association and accepted by Finnish National Health Administration (Form No 7466:92). On the basis of their growth chart data, participants were classified into under weight (relative weight to height from growth chart under -10%), normal weight (relative weight between -10 to +20%), and overweight+obese (relative weight between > +20%).

In addition, on the basis of their body composition assessment by dual X-ray densitometry (DXA) of fat mass % (above or below 30% as obese or normal weight)⁹ and combined with growth chart definition, the subjects are classified into 3 groups: 1) underweight (UW, relative weight to height from growth chart under -10% and fat <30% ,n=22), 2) normal weight (NW, relative weight between -10 to +20% and fat % <30%, n=87), 3) normal weight obese (NWO, relative weight between -10 to +20% and fat % >30%, n=92), and over weight+obese (OWOB, relative weight between > +20% and fat % >30%, n=35). The study protocol was approved by the ethical committee of the University of Jyväskylä and the Central Hospital of Central Finland (memo 22/8/2008).

Background information assessment

Medical history were collected via validated self-administered questionnaire. Subjects under 15 years of age filled in the questionnaire with their guardians' assistance, and all the questionnaires were checked by a study nurse. Body weight was measured using an electronic scale and height using stadiometer with subjects wearing light clothes and without shoes. Body mass index was calculated by dividing body weight in kilograms by the square of the body height in meters. Blood pressure (BP) in the right arm was recorded using automated oscillometric device in a sitting position in the morning after 10 minute rest. Two consecutive measurements were performed, and the mean of the measurements were used. Waist circumference was measured on bare skin with a tape measure, midway between the top of the iliac crest and the bottom of the rib cage. Two independent measurements were performed and

the mean value was used. The menarche age of girls (the first onset of menstrual bleeding) were collected by questionnaire and retrospective by phone call as well as during follow-up visits.

Body Composition Assessments

Lean tissue mass (LM), and fat mass (FM) of the whole body, android and gynoid region were assessed using DXA (Prodigy GE Lunar Corp., Madison, WI USA). The precision of the results of the repeated measurements in this study were expressed by the percentage coefficient of variation (CV%) which was on average, 1.0% for LM, and 2.2% for FM.

Biochemical analyses

Blood samples were collected in the morning between 7:00 and 9:00 am after overnight fasting. The samples were collected on 2 to 5 days after menstruation among those girls with regular menses. Plasma glucose, high-density lipoprotein cholesterol (HDL-C) and triglycerides was assessed by KONELAB 20XTi analyzer (Thermo Fischer Scientific inc. Waltham, MA, USA).

Cardiometabolic risk assessment

To assess cardiometabolic risk we constructed a standardised, continuously distributed variable for clustered metabolic risk similarly to previously published scores^{10,11}. The risk score was calculated by standardising and then summing the following continuously distributed metabolic traits to create a z score: mean arterial pressure ($[(2 \times \text{diastolic blood pressure}) + \text{systolic blood pressure}] / 3$); abdominal fat mass; fasting plasma glucose; serum HDL cholesterol $\times -1$; and fasting serum

triglyceride z score. A higher score indicates a less favorable cardiometabolic risk profile. The purpose of using such continuously distributed risk score was to maximise statistical power¹² because average differences in metabolic traits are relatively small in children and adolescents.

Statistical analyses

Continuous data were checked for normality by Shapiro-Wilk's test before each analysis in the SPSS for Windows statistical software package version 18 (SPSS Inc., Chicago, IL, USA). If data were not normally distributed, natural logarithm transformations were used. ANOVA with the Least Significant Difference post hoc test was used to compare differences between OWOB, NWO, NW and UW groups. Statistical significance was set at $p < 0.05$.

Results

Longitudinal change of body weight

Longitudinal change of body weight collected from growth charts from birth to age of 20 are shown in **Figure 1**. It can be seen that the relative body weight was higher already at the age of four years in subjects who were OWOB at the age of 18 compared with those who were NWO, NW, or UW. However, the differences in relative body weight between the NWO and NW were not significant during growth.

Insert Figure 1 here

Longitudinal change in body composition:

Total and regional adiposity increased throughout growth in all groups from age of 11 to the age of 18 (**Figure 2**). At the age of 11, there was about 10kg difference in total FM between the OWOB and NW group ($p<0.001$) and about 7kg between the NWO and NW group ($p<0.001$), respectively. The most rapid gain in FM was between the age of 11 and 14 in all groups. The average increase of total FM was 13kg in the OWOB group, whereas the average increase in NWO and NW groups was about 6kg from prepubertal to early adulthood. In terms of FM distribution, the increase of FM was greatest in gynoid (lower body) region in all groups. Noticeably, in the OWOB group FM in the android region (abdominal area) increased significantly compared to the other weight groups ($p<0.001$ for all). The increase in LM was also greatest between the age of 11 and 14, the relative accrual being similar in all groups (**Figure 2**).

Insert Figure 2 here

Cardio-metabolic risk:

The OWOB group had higher MetS score compared with all other weight groups throughout growth ($p<0.001$ for all, **Figure 3**). The MetS score was also higher in the NWO group compared with the NW and UW groups at all time points ($p<0.001$ for all), but no difference was found between the NW and UW groups.

Insert Figure here 3

Discussion

This longitudinal study showed that subjects who were overweight or obese in adulthood had higher relative body weight to height already at the age of four compared with those who were normal weight. Moreover, overweight and obese subjects had a worse cardio-metabolic risk profile than normal weight subjects in childhood, and this difference persisted through puberty into early adulthood. We also showed that children with normal body weight but high body fat percent had significantly higher cardio-metabolic risk compared with normal weight children with low body fat percent, but no difference in relative body weight was observed throughout childhood and adolescence. These findings suggest that excess adiposity starts to develop early in life and it is a significant risk factor for cardio-metabolic disease in adulthood regardless of body weight status.

Higher BMI in childhood and adolescence is associated with an increased risk of cardiometabolic morbidity and mortality in adulthood¹³⁻¹⁶. Prevention remains the primary goal in the management of obesity, and therefore pediatricians are advised to measure BMI regularly and prescribe and support lifestyle modifications to the patient and their family^{17,18}. Although BMI is considered a useful tool in assessing the weight status¹⁹, recent evidence suggest that significant percentage of children might be at risk being misdiagnosed as lean if obesity is defined solely based on BMI⁵. Indeed, our study showed children who had normal body weight but high body fat percent are

virtually indistinguishable from their normal weight lean peers in terms of relative body weight in childhood and adolescence. Moreover, we showed that these normal weight but obese children have significantly higher cardio-metabolic risk compared with their normal weight lean or underweight subjects in childhood and this persisted into early adulthood. These results suggest that simply maintaining a normal body weight in childhood does not necessarily protect against cardio-metabolic abnormalities later in life.

Direct comparison of our results with earlier studies is difficult, because normal weight obesity has not been studied longitudinally before in children and adolescents. Overall, data on normal weight obesity children is sparse. There are few reports that describe cross-sectional data on children and adolescents with cardio-metabolic risk factors who are not obese according to BMI, but in these studies body composition was not assessed and thus it remains unclear whether these children had low or high body fat percent ²⁰. Moreover, most of the children with metabolic abnormalities in these studies had a family history of hypertension, atherogenic serum lipid profile or type II diabetes, suggesting that family history of cardio-metabolic disease is a significant cardiovascular risk factor in non-obese children. In our study, normal weight obese children did not have history of cardio-metabolic disease in their immediate family, therefore it seems likely that the increased cardio-metabolic risk in these children is attributable to their relatively high body fat content. In supporting our findings, studies in adults have shown that normal weight obesity is associated

with higher cardiovascular risk factors²¹, cardio-metabolic dysregulation²², coronary heart disease²³ and cardiovascular mortality^{24,25}. Taken together, our results suggest that the cumulative burden of excessive body fat begins at an early age and this is irrespective of body weight.

Our results provide an important message for clinicians and public health officers as well as the individual child and their families. Measurements of body composition should be included in the screening for cardiovascular risk because evidently BMI does not recognize a substantial number of children who are at increased risk for cardio-metabolic disease later in life. Failure to recognize excess adiposity in childhood may translate into missed opportunities to prescribe appropriate lifestyle modification to prevent future cardio-metabolic morbidity. These results should also encourage research in the field to identify and validate definition of normal weight obesity in children because currently there is no universally accepted definition of a normal value for percent body fat.

Our study is not without limitations. The sample size for obese and normal weight obese subjects was relatively small. Also, the study subjects included only females, so the results may not be applied to males. Strengths of this study include research-quality measures of body composition and cardiometabolic biomarkers, and the data obtained from growth charts.

Conclusion

The results of our study suggest that children and adolescent with normal BMI and elevated body fat percentage may be at increased risk for cardiometabolic morbidity in adulthood. Screening for adiposity in children and adolescent with a normal BMI could better identify those at higher risk for cardiometabolic morbidities.

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Figure Legends

Figure 1. Longitudinal changes of relative body weight from birth to age of 18 years. Bodyweight groups are defined by BMI and fat % at the age of 18 years and the comparison between groups were done retrospectively.

Figure 2. Longitudinal change in body composition from age of 11 to age of 18. OWOB = overweight and obese (BMI>25 and fat % >30), NWO = normal weight obese (BMI 18.5 - 24.9 and fat % >30), NW = normal weight lean (BMI 18.5 - 25 and fat% <30), UW = underweight (BMI<18.5).

Figure 3. Longitudinal change in continuous cardio-metabolic risk (Mets) score from age of 11 to age of 18. Higher score indicates greater risk. OWOB = overweight and obese (BMI>25 and fat % >30), NWO = normal weight obese (BMI 18.5 - 24.9 and fat % >30), NW = normal weight lean (BMI 18.5 - 25 and fat% <30), UW = underweight (BMI<18.5).

Figure 1.

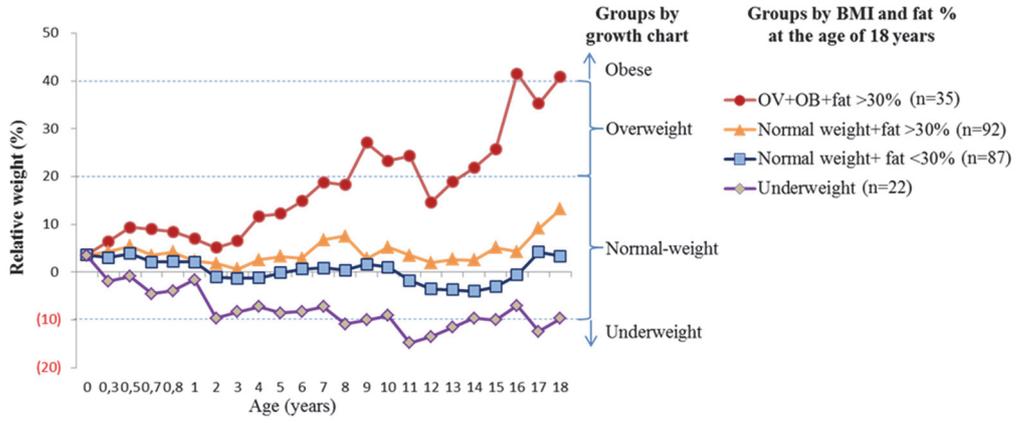


Figure 2.

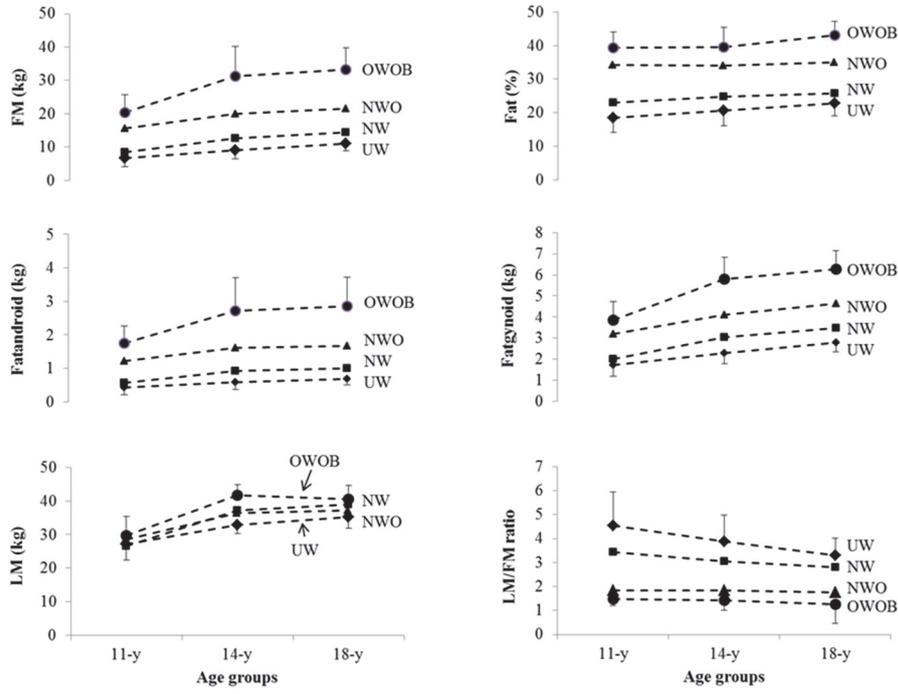


Figure 3.

