Trajectories of total and central adiposity throughout adolescence and cardiometabolic factors in early adulthood

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ABSTRACT

BACKGROUND/OBJECTIVES: We aimed to identify trajectories of total and central adiposity from 13 to 21 years, and to investigate how adiposity changes at different phases of adolescence relate to adulthood cardiovascular risk factors.

SUBJECTS/METHODS: We analysed data from a population-based cohort (EPITeen), Portugal. Body mass index (BMI) and waist circumference (WC) were measured at 13, 17 and 21y, and sex- and age-specific z-scores were calculated. Adiposity trajectories were identified using mixture growth models (BMI, n=2901; WC, n=2898). Cardiovascular risk factors were evaluated at 21 years (n=1763): systolic (SBP) and diastolic blood pressure (DBP), insulin resistance (HOMA-IR), triglycerides and cholesterol. Association of trajectory, and changes in adiposity z-scores with each cardiovascular risk factor was estimated by linear regression models.

RESULTS: 'Normal', 'high, declining' and 'high, increasing' trajectories were identified in both sexes. 'High, increasing' BMI trajectory was associated with less favourable cardiovascular risk profile at 21 years in both sexes, while 'high, declining' presented a more favourable profile, similar to 'normal' trajectory in females. Additionally, BMI increases between 13-17y and 17-21y were associated with increases in systolic and diastolic blood pressure, and insulin resistance, but more strongly for the later period. For every SD increase in BMI between 17-21y, mean SBP increased by 1.99 mmHg (95% CI: 1.01; 2.97) for females and 3.83 mmHg (2.67; 4.98) for males; the respective increase was 1.56 mmHg (0.72; 2.40) and 2.80 mmHg (1.97; 3.64) for DBP and 0.27 (0.21; 0.32) and 0.30 (0.24; 0.36) for HOMA-IR (log transformed). Similar results were found for WC.

CONCLUSIONS: Increases in adiposity, particularly from late adolescence-to-young adulthood, were associated with unfavourable cardiovascular profile in early adulthood. A benefit on the cardiovascular risk profile for participants in the declining adiposity trajectory was observed.

KEYWORDS: adiposity; adolescents; cardiovascular disease; longitudinal; trajectory

INTRODUCTION

The prevalence of obesity has risen rapidly in the recent decades in most western populations.[1] High adiposity is one of main determinants of cardiovascular disease and its role as a cardiovascular risk factor starts early in life. It has also been implicated in the development of other cardiovascular risk factors.[2] Therefore, the study of how changes in adiposity across the life span influence the unfavourable progression of the cardiovascular risk factors is important to understand their impact on the disease development.

The study of growth trajectories in pediatric age is recognized to be of great relevance for surveillance, etiology and clinical practice,[3] being useful for the identification of critical windows for intervention. A systematic review has shown a moderate tracking of childhood overweight status into adulthood.[4] There is also evidence indicating substantial variations in individual growth trajectories.[5-7] Some studies identified distinct groups of trajectories over the life course, which might impact differently on the risk of disease.[5, 8-11]

While growth characteristics from birth to adolescence and its later association with cardiovascular risk factors are well documented,[8, 9, 11, 12] the impact of changes in adiposity from adolescence to young adulthood is less well described. Yet this period is recognized as critical for weight gain[13, 14] and subject to important biological changes (e.g. puberty).[15]

Research to estimate the relative contribution of fatness and fat gain at different life stages on adult cardiovascular risk factors tends to focus mainly on increases in adiposity in childhood[16, 17] and adulthood.[18] Some studies have reported that changes in BMI early in life were of greater relevance for future atherosclerosis[19] or metabolic disturbances.[20, 21] Also, changes in weight or BMI during adolescence or later in life are strongly associated to adult blood pressure and metabolic abnormalities.[22-24] However, the periods assessed were different which may limit comparisons between studies, and limited evidence is available for the changes in other adiposity measures.

Therefore, this study aims: i) to identify distinct trajectories of total and central adiposity from adolescence (13 years) to early adulthood (21 years); ii) to investigate how adiposity changes at

particular age periods (13 to 17, or 17 to 21 years) are associated with cardiovascular risk factors at early adulthood.

SUBJECTS AND METHODS

Study sample

We used information from the Epidemiological Health Investigation of Teenagers (EPITeen) study, a population-based cohort that recruited 13-year-old adolescents born in 1990 and enrolled at schools of Porto, Portugal, during 2003-2004.[25] A second (2007-2008) and a third (2011-2013) evaluations took place when participants were on average 17 and 21 years.

Our study complies with the Declaration of Helsinki and the Ethic Committee of Hospital S. João and the Ethics Committee of the Institute of Public Health from the University of Porto approved the research protocol. Written informed consent was obtained from parents and adolescents in the first and second study waves, and from participants in the third study wave.

At the recruitment, 2159 eligible adolescents agreed to participate (77.5% participation). In the second wave, we re-evaluated 1716 participants (79.5%), and a further 783 adolescents who moved to the schools in Porto joined the cohort. In the third study wave, 1764 participants (60.0%) were reevaluated.

Measures

Anthropometrics

At the study site, weight and height were measured with the subject in light indoor clothes and no shoes, according to standardized procedures. Waist circumference (to the nearest 0.1 cm) was measured midway between the lower limit of the rib cage and the iliac crest, at the end of gentle expiration, with a flexible and non-distensible tape.

BMI and WC z-scores were calculated by sex and age for each study wave, using the mean and standard deviation of the study sample.

Cardiovascular risk factors

For this analysis we considered cardiovascular risk factors assessed at 21 years.

An overnight fast intravenous blood sample was taken from an antecubital vein. Glucose, triglycerides, total cholesterol and high-density lipoprotein cholesterol (HDL) were measured using conventional methods with an Olympus AU5400® automated clinical chemistry analyzer (Beckman-Coulter®). Insulin was measured by electro chemiluminescent immunoassay using a Cobas® e411 automated analyzer (Roche®). All determinations took place in the Department of Clinical Pathology, Centro Hospitalar São João, Porto, Portugal.

Low-density lipoprotein cholesterol (LDL-C) was calculated according to the Friedewald equation.[26]

Insulin resistance was assessed by the homeostatic model assessment (HOMA-IR) method: HOMA-IR= insulin (µU/ml) * glucose (mg/dl) /405.[27]

Blood pressure was measured according to the guidelines from the American and International Societies of Hypertension,[28] using the oscillometric method (OMRON Blood Pressure Monitor, M6 Comfort). After 10 minutes of rest, two blood pressure measurements were taken, separately by at least five minutes. A third measure was taken when the difference between the first two was higher than 5 mmHg. The average of the two closest measurements was used in this analysis.

Covariates

Perinatal information was obtained at the baseline evaluation of the cohort using questionnaires administered to the mothers. When available, birth weight was extracted from child health book records (n=716); otherwise was based on mother's report. Maternal smoking was classified as: non-smoker; smoker, but not during pregnancy; smoker during pregnancy.

Parental educational level was defined according to the parent with the highest education level. Parental occupational position was categorized as "high" (professional and managerial occupations), "medium" (non-manual and manual skilled occupations) and "low" (semi-skilled and unskilled occupations). Parental BMI was calculated using self-reported weight and height, and converted to standard deviation (SD) scores separately for mother, father, and in each study wave. Parental BMI was defined using BMI z-score from the mother in study wave I, and if not available data from wave II (24.1%); or when mother's BMI was missing in both waves, from the father (2.9%).

Family history of diabetes, dyslipidemia and hypertension was asked separately to the mother and the father, and for each of the diseases classified as: positive, when at least one of the adolescent's parents had the diagnosis; negative, when both parents reported no diagnosis; or non-classifiable, when the available information showed no diagnosis for one of the parents, but missing regarding the other. The participant's practice of sports was defined as any planned, regular exercise, regardless of intensity, and excluding obligatory curricular activities.

Statistical analysis

In order to identify trajectories of BMI and of WC from adolescence into adulthood (aim 1), we applied mixture growth models, using the PROC TRAJ procedure in SAS (v9.3, SAS Institute Inc., Cary, NC).[29] The models were stratified by sex, and included a random intercept, a random linear and a quadratic age term. We tested models up to six trajectory groups, and the final number of trajectories was chosen based on the lowest Bayesian Information Criteria, and also by the interpretability of the results. For each individual, the mixture growth model generated the probability of belonging to each trajectory. Individuals were classified in the trajectory to which they had the highest probability of belonging.

Analysis of the growth trajectories was based on participants with adiposity measures at one or more ages (n=2901 for BMI; n=2898 for WC).

To investigate the association of adiposity levels and their changes at different ages with cardiovascular risk factors in early adulthood (aim 2), we used sex-specific SD scores of BMI and WC at each age so their associations with CV risk factors can be compared across ages. A logarithmic transformation was applied to triglycerides and HOMA-IR, since these variables were skewed.

First, we examined the simple associations of CV risk factors at 21 years with adiposity measures at each age separately. The regression coefficient represents the change in CV risk factor for a SD increase in the adiposity measure.

Second, the associations of changes in each adiposity measure (i.e. a change in the relative position in the distribution) between two ages (13 to 17, and 17 to 21 years), with adult CV risk factors were examined. Each model was conditioned on the adiposity measure at the previous age. For example, in order to estimate the change in BMI z-score between 13 and 17 years of age on SBP at 21 years, we applied the regression model: $SBP21 = a + b\ BMI13 + c\ BMI17$ which can be rewritten as $SBP21 = a + (b + c)\ BMI13 + c\ (BMI17 - BMI13)$. The coefficient c can be interpreted as the estimated change in SBP associated with a SD increase in BMI between 13 and 17 years, given the BMI at 13 years.

All models were stratified by sex and further adjusted for birth weight, mother's smoking during pregnancy, parental education, household occupational position, family history of disease, parental BMI z-score, and participant's practice of sports. Regarding practice of sports, for associations with changes in adiposity between 13-17y we used sports at 13y; for changes between 17-21y, sports at 17y.

We applied multiple imputation to the total cohort in order to use the maximum information available. The imputation model included factors predicting non-response (i.e. sex, maternal/paternal education and occupation), adiposity measures at all ages, CV risk factors at 21y and all covariates in the analysis models. We created 30 imputed datasets assuming missing was at random given observed values of other variables. The regression models and multiple imputation by chained equations were conducted using SPSS (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.). In the regression models we used imputed

171 covariates and adiposity measures, but not imputed outcomes, i.e. we restricted our analysis to
172 individuals with observed CV risk factors (1763 participants with valid information for at least one
173 cardiovascular risk factor at 21y). Parameters estimated were combined to obtain overall estimates
174 using Rubin's rule.
175
176
177 **RESULTS**

178 Descriptive data on BMI and WC at each study wave and cardiovascular risk factors at 21 years is
179 presented in Table 1.
180
181 **Trajectories of BMI/WC from adolescence into adulthood**
182 Three trajectory groups of BMI were identified for each sex (Figure 1): 'normal' (78.7% in females;
183 80.4% in males); 'high, increasing' (17.0% and 6.4%); and 'high, declining' (4.2% and 13.1%). 'Normal'
184 trajectory presented the lowest mean BMI values and low prevalence of overweight at any of the
185 three study-waves (Supplementary Table S1). At 13 years, subjects in trajectory 'high, increasing'
186 presented intermediate mean values of BMI, however they increased more rapidly with age, and
187 were the highest at 21 years (29.3% in females; 65.2% in males), compared to the other trajectories.
188 Trajectory 'high, declining' presented the highest mean values of BMI at 13 years, but they decreased
189 with age, being the prevalence of obesity at 21 years 7.5% and 11.2% for females and males,
190 respectively (Supplementary Table S1).
191 For waist circumference, 3 trajectories were also identified (Figure 2) and they were graphically and
192 in prevalence similar to those identified for BMI. The agreement between the trajectories identified
193 based on BMI and on WC was strong (observed agreement of 88.0% and 91.4%; kappa=0.657 and
194 0.745, respectively for females and males). 'Normal' WC trajectory was found in around 80% of the
195 subjects in both sexes; 'high, increasing' in 17.9% of females and 8.4% of males; and trajectory 'high,
196 declining' in 2.0% and 11.6% of females and males, respectively (Supplementary Table S2).

Table 2 relates cardiovascular risk factors at 21 years to the probability of belonging to each trajectory. Considering the 'normal' trajectory as the reference group, belonging to the 'high, increasing' trajectory was associated with higher SBP, HOMA-IR, triglycerides and LDL, and decreased HDL at 21y in both sexes, but stronger in males, except for HDL. For 'high, declining' trajectory, in females there were no statistically significant differences in cardiovascular risk factors, compared to the 'normal' trajectory, except for HDL. In males, higher probability of belonging to the 'high, declining' trajectory was associated with higher mean SBP, DBP, HOMA-IR and triglycerides, and lower HDL at 21 years, but the magnitude was lower than for subjects belonging to the 'high, increasing' trajectory.

The associations for WC (Table 2) were in general similar to those for BMI, but weaker.

Associations between changes in BMI/WC and CV risk factors

Adjusted models using multiple imputation showed that BMI z-score at each age (13, 17 or 21y) was positively associated with SBP, DBP, HOMA-IR, triglycerides and LDL, and inversely associated with HDL, in both sexes, and appeared to be stronger in males (Table 3). Associations generally strengthened with increasing age. Results for WC z-score were similar, but associations were slightly weaker (Table 3).

Changes in BMI z-score from 13 to 17y and from 17 to 21y were positively associated with SBP, DBP and HOMA in both sexes (Table 4). For example, in females for every SD increase in BMI between 13-17y, SBP increased on average by 1.79 mmHg (95% CI 0.48; 3.10), while for every SD increase between 17-21y, SBP increased on average by 1.99 mmHg (1.01; 2.97); for males associations were stronger: 2.03 mmHg (0.47; 3.59) for BMI changes for 13-17y, and 3.83 mmHg (2.67; 4.98) for 17-21y. For triglycerides and LDL, the association was stronger for 17-21y than 13-17y. For HDL an inverse association was found for the period 13-17y in both sexes, and for 17-21y only in males.

Similar results were found for WC z-score (Table 4): positive associations between increases in WC and SBP, DBP, HOMA-IR, triglycerides and LDL and negative associations with HDL.

Either for BMI or WC, regression coefficients were in general stronger in males and for the period 17 to 21 years.

Analyses were repeated using complete cases and as conclusions were mostly unaltered, those results are presented only in supplementary information (Tables S3 and S4).

DISCUSSION

Main findings

Using our longitudinal population-based study we identified three trajectories of total and central adiposity from adolescence to adulthood. While the majority (>75%) of individuals were in the normal trajectory group, the 'high, increasing' trajectory (more frequently females) had a high BMI/WC in adolescence and gained BMI/WC more rapidly thereafter, presenting the highest prevalence of obesity and the worst profile of cardiovascular risk factors at 21 years of age, particularly in males. A small group (more frequently males) had a high BMI/WC in early adolescence but it declined from adolescence to early adulthood. Among 'high, declining' group, in females the CV risk factors at 21 years did not differ from normal group, while for males, although worse than those in the normal group, CV risk factors were more favorable than those in the 'high, increasing'. In addition to the identification of trajectories, we also found that adiposity changes from 13 to 21 years were associated with unfavorable values of the cardiovascular risk factors evaluated, and excessive increases between 17 and 21 years of age (moving up in relative position for BMI in the population) were particularly influential. These results were similar using either BMI or WC.

Strengths and limitations

Major strengths of this study include the use of both BMI and WC and applying innovative modelling techniques for the identification of trajectories, allowing the study of the effect of cumulative exposure to adiposity on CV risk factors, and not only the effect of the adiposity in a specific age. Additionally, in a period under characterized –transition from adolescence to adulthood, our study

adds information on the specific effect of adiposity changes at different ages. We used repeated measurements of adiposity objectively measured under standardized procedures, as well as repeated measurements of many confounders, from a population-based cohort, enabling the generalizability of the results.

Nonetheless, potential limitations of the study exist. Losses to follow-up and item non-response led to missing data. We conducted analyses using multiple imputation for BMI, WC and covariates including the main predictors of missing data, which would have reduced selection bias. However, our final models we fitted only to participants with measured outcomes in the third study wave. Attrition in the third wave was higher among participants with lower parental education, and among those obese at the recruitment age. The underrepresentation of obese participants may have led to an underestimation of the associations reported in our study.

Interpretation of findings

Information on growth trajectories in the period from adolescence to adulthood is limited. To our knowledge, five studies have identified BMI trajectories in this age period using similar methodology[11, 30-33] and found three to four distinct trajectories, with some groups being similar to the trajectories 'normal' and 'high, increasing' identified in our study. A declining trajectory was only identified in two of these studies.[11, 32] Ziyab and colleagues,[11] using data from infancy to 18 years, identified an 'early transient overweight' trajectory. However, this trajectory was characterized by a decline in BMI z-score from 1 to 10 years of age, and a stabilization from 10 to 18 years, while the declining trajectory in our study presented declining values of BMI more pronounced from 17 to 21 years of age, than from 13 to 17 years. In Canada's National Longitudinal Survey of Children and Youth[32] a decreasing trajectory was also identified from age 1 to 20 years and the decrease in BMI values was more evident in females, as we also found in our study, although it occurred at earlier ages in their study – from early to mid-adolescence. The small sample size of the group 'high,

declining' identified in our sample, particularly in females, limited our ability to explore in depth the characteristics of this group.

'High, increasing' trajectory presented the worst levels of cardiovascular risk factors at 21 years of age, while the levels in the 'high, declining' trajectory were closer to those in the 'normal' group. This finding is also in accordance to other study that found higher systolic and diastolic blood pressure at 18 years in the delayed overweight trajectory in comparison to the 'normal' trajectory, but still smaller than the values found for the early persistent obesity trajectory.[11] Regarding studies in other age ranges, in the Raine Study,[7] those in increasing trajectories from birth to 14 years presented the highest insulin resistance levels at 14 years, while the outcome in those from declining trajectories was similar to those in the reference trajectory ('Optimal growth'). Girls in the 'upward percentile crossing' trajectory from 5 to 15 years had highest metabolic risk factors at 15 years, while the 'delayed downward percentile crossing' presented similar levels in comparison to the '50th percentile tracking'.[9] These results and those from our study suggest that excessive gains in adiposity during the pediatric ages are associated with adverse cardiovascular risk factors, partly because it is likely to result in high current BMI. This is supported by the sex-differences in the association between 'high, declining' trajectory and the cardiovascular risk factors in our study. In females there was a marked decrease in BMI between 13 to 21 years in this trajectory, but the final BMI mean value was closer to the mean BMI value in the 'normal' trajectory and this resulted in no statistically significant differences in the outcomes between these two trajectories. In males, there was a small decline in BMI mean values, but the difference in BMI values at 21 years in comparison to the 'normal' trajectory was higher than in females, resulting in increased values of cardiovascular risk factors at 21 years, although of lower magnitude in comparison to the 'high, increasing' group.

To our knowledge, this is the first study addressing waist circumference trajectories in the period from adolescence to adulthood. Trajectories of WC were similar to the BMI trajectories, and associations of WC trajectories with cardiovascular risk factors at 21 years were of the same

magnitude to those found for BMI trajectories. Although WC is described as a measure of central or abdominal adiposity, it is highly correlated to BMI (correlations around 0.8 in females and 0.9 in males at each age, in our study). Other studies have found that BMI and WC perform similarly in the association with cardiovascular risk factors.[34-36]

We found that changes in adiposity, both from 13 to 17 years and from 17 to 21 years, were associated to unfavorable cardiovascular risk parameters at 21 years, but the magnitude was stronger for the later period. These results suggest that changes in adiposity in these specific ages (17 to 21 years) are more relevant for CV risk factors. During early and mid-adolescence the effect of adiposity changes in CV risk factors may be of lower magnitude, since other factors such as hormonal changes related to puberty may also influence lipid and insulin levels.[37, 38] The comparison of changes in the specific periods evaluated here with other studies is difficult due to the differences in the periods evaluated, but two studies using data from the 1958 British birth cohort, and evaluating similar periods (11-16 years and 16-23 years) also found stronger associations for the changes in BMI from 16 to 23 years with adult glycosylated hemoglobin[24] and blood pressure at 45 years.[39] However, this could be because the period is closer in time to the outcome, rather than an effect of this specific period (17-21 years) under study, as described in other studies.[22-24, 39]

In conclusion, our study identified three distinct trajectories of BMI and WC from adolescence to adulthood, and showed a benefit on the cardiovascular risk profile for those in the declining adiposity trajectory. The similar results for the two adiposity measures, support that both BMI and WC are surrogates of global adiposity. In addition, increases in BMI and WC, particularly recent changes from late adolescence-to-young adulthood, had a strong positive association with traditional cardiovascular risk factors. Our results highlight the importance of promote a healthy BMI at all ages to prevent unfavourable cardiovascular risk factors and future disease.

Supplementary information is available at International Journal of Obesity's website.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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443

444 **Figure legends**

445

446 **Figure 1.** Trajectories of body mass index from 13 to 21 years of age in females (left) and in males

447 (right), in the EPITeen cohort, Porto, Portugal

448

449 **Figure 2.** Trajectories of waist circumference from 13 to 21 years of age in females (left) and in males

450 (right), in the EPITeen cohort, Porto, Portugal