Adult weight change and cardiometabolic disease: studies into underlying pathways

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CHAPTER 3

Abdominal adiposity in adolescence and early changes in atherogenic metabolites into young adulthood

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ABSTRACT

Introduction: Obesity in adolescence tends to track into adulthood and increases the risk of cardiovascular disease later in life. It is unclear whether excess abdominal adiposity in adolescence is associated with changes in circulating metabolites indicative of an emerging atherogenic profile into young adulthood.

Methods: In first-generation offspring of the Avon Longitudinal Study of Parents and Children (ALSPAC), total and trunk fat mass were measured using dual-energy X-ray absorptiometry scans at age 15y. Targeted nuclear magnetic resonance-based metabolomics was used to quantify 145 metabolites (mostly subclasses of lipoproteins) at age 15y, 18y and 24y. Using linear spline multilevel models, we examined sex-specific associations of total and trunk fat mass at 15y with trajectories of metabolites from 15y to 24y.

Results: Analyses included 3851 participants, 53% female. At age 15y, median (interquartile range) total fat mass was 13.7 (8.3-20.1) kg and 6.1 (3.6-9.4) kg for trunk fat mass. Higher trunk fat at 15y was associated with an increase in concentrations of multiple metabolites, including non-high-density lipoproteins, more so in males than in females. Specifically, each SD ln higher trunk fat mass (corresponding to 0.69 kg in males and 0.48 kg in females) was associated with increasing cholesterol in large very-low-density lipoprotein (2.05 [95% confidence interval 0.54–3.57] SD, total serum triglycerides (2.10 [0.77–3.44] SD and apolipoprotein B (1.90 [1.13–2.66] SD in males, but not in females (0.05 [-0.67–0.77] SD, 0.23 [-0.64-1.10] SD and 0.29 [-0.54–1.13] SD, respectively). Results were similar for total fat mass.

Conclusion: Excess abdominal fat in adolescence was associated with an increasingly atherogenic lipid profile in males only. Adolescence may therefore be a critical period for the early prevention of adiposity-induced atherosclerosis in males.

INTRODUCTION

The prevalence of childhood and adolescent obesity is increasing worldwide, contributing to obesity-related disease burdens and associated healthcare costs (1). Obesity in childhood and adolescence, which typically persists into adulthood (2), is associated with an increased risk of cardiometabolic diseases later in life, including type 2 diabetes and coronary heart disease (CHD) (3, 4), as well as increased mortality in middle age (5). A recent Mendelian randomization (MR) analysis further suggested that higher body size in childhood, via body size in adulthood, increases risk of CHD (16). In addition, children and adolescents with obesity already show insulin resistance, dyslipidaemia, and increased prevalence of metabolic risk factor clustering (6-8). The increased cardiometabolic risk conferred by total body fat is likely driven by an adverse fat distribution, particularly by fat stored in and around the abdomen (9-11), which was also demonstrated in children and adolescents (12).

Circulating metabolites may be important intermediates of adiposity and cardiometabolic disease. In a cross-sectional study of 12,664 adolescents, higher body mass index (BMI) was strongly associated with unfavourable concentrations of very low-density lipoproteins (VLDLs) and low-density lipoproteins (LDLs), and high-density lipoprotein (HDLs), which was supported by MR analyses in young adults (13). Additionally, higher BMI was associated with higher concentrations of monounsaturated fatty acids and saturated fatty acids, as well as of branched-chain amino acids (13, 14). In a study of 7821 children and adolescents, higher body fat percentage was associated with adverse total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides (15). MR analyses further support the potential for higher body size in childhood (via body size in adulthood) to alter concentrations of numerous metabolites including apolipoprotein B-containing lipoproteins, and inflammatory glycoprotein acetyls (16), all indicative of a more atherogenic profile.

Taken together, there may be an early opportunity to reduce the atherogenic consequences of adiposity during childhood and adolescence, as adiposity often persists into adulthood (2). However, longitudinal studies in the field of metabolomics are lacking and it is unknown how directly measured body fat distribution during adolescence is associated with early subsequent changes in circulating metabolites. Given that men tend to store more fat in and around the abdomen, whereas women tend to store more fat subcutaneously in the hips and legs, we might also expect sex differences in effects of adiposity on metabolites (17).

In this study, we used a British birth cohort data to investigate the sex-specific associations of directly measured total and abdominal fat in adolescence with subsequent changes over time in a comprehensive set of circulating metabolites. This enabled us to capture early atherogenic changes occurring into young adulthood in response to adolescent adiposity and provide new evidence on when the first indications of cardiometabolic disease begin to develop in young males and females.

METHODS

Study design and study population

The Avon Longitudinal Study of Parents and Children (ALSPAC) is a population-based birth cohort study in which 14,541 pregnant women expected to deliver between 1 April and 31 of December 1991 were recruited from the former county of Avon in southwest England. Offspring (G1) alive at 1 year of age (n=13,988) have been followed since with multiple assessments, with an additional 913 children enrolled over the course of the study (18-20). Follow-up has included parent- and child-completed questionnaires, clinic attendances, and links to routine data. Research clinics were held when the G1 participants were approximately 7 years (y), 9y, 10y, 11y, 13y, 15y, and 18y. Study data among G1 cohort participants after age 22y were collected and managed using REDCap electronic data capture tools hosted at University of Bristol (21, 22). The present analyses were conducted using all eligible participants with data on total body fat mass or trunk fat at age 15y, sex, age, and at least one of the metabolomic measures at any age. This resulted in 3851 eligible participants (1810 men, 2041 women) contributing to our analyses.

Ethical approval as obtained from the ALSPAC Law and Ethics and Local Research Ethics Committee. Informed consent for the use of data collected via questionnaires and clinics was obtained from participants following the recommendations of the ALSPAC Ethics and Law Committee at the time. The study website contains details of all the data that is available through a fully searchable data dictionary and variable search tool (http://www.bristol.ac.uk/alspac/researchers/our-data/).

Assessment of total and abdominal fat mass

Dual-energy X-ray absorptiometry (DXA)-determined total fat mass and trunk fat mass were measured at mean age 15y using a GE Lunar Prodigy (Madison, WI, USA) narrow fan beam densitometer. Total body fat mass (in kg, less head) was derived from whole body DXA scans. Trunk fat mass was estimated using the automatic region of interest that included chest, abdomen, and pelvis. The scans were visually inspected and realigned where necessary.

Assessment of metabolites

Blood samples were drawn at clinic attendance of the offspring at mean ages 15y, 18y and 24y, after a minimum of a 6-hour fast. Proton nuclear magnetic resonance (^{1}H-NMR) spectroscopy from a targeted metabolomics platform (23) was performed on EDTA-plasma samples from each of these three occasions to quantify 145 traits.

The NMR spectroscopy was conducted at the Medical Research Council Integrative Epidemiology Unit (MRC IEU) at the University of Bristol, Bristol, United Kingdom, and processed by Nightingale's biomarker quantification algorithms (version 2014). This method provides quantification of lipoprotein subclass profiling with lipid concentrations within 14 lipoprotein subclasses. The 14 subclass sizes were defined as follows: extremely large VLDL with particle diameters from 75 nm upwards and a possible contribution of chylomicrons, five VLDL subclasses (average particle diameters of 64.0 nm, 53.6 nm, 44.5 nm, 36.8 nm, and 31.3 nm), intermediate-density lipoprotein (IDL, 28.6 nm), three LDL subclasses (25.5 nm, 23.0 nm, and 18.7 nm), and four HDL subclasses (14.3 nm, 12.1 nm, 10.9 nm, and 8.7 nm).

Within the lipoprotein subclasses the following components were quantified: total cholesterol, total lipids, phospholipids, free cholesterol, cholesteryl esters, and triglycerides. The mean sizes for VLDL, LDL and HDL particles were calculated by weighting the corresponding subclass diameters with their particle concentrations. Furthermore, 58 metabolites were determined, including cholesterol, triglyceride, and other lipid content in lipoprotein subclass particles, apolipoproteins, fatty acids, amino acids, and inflammatory glycoprotein acetyls.

In the present study, we excluded metabolites representing ratios between two measures. We additionally excluded diacylglycerol, fatty acid length, conjugated linoleic acid and pyruvate, which were not measured at age 24y, resulting in an outcome set of 145 metabolites.

Assessment of confounding factors

We considered the following as potential confounders of the association between fat mass at age 15y and metabolite trajectories from 15y to 24y: ethnicity (white or non-white), age at puberty onset, maternal educational level, smoking status at age 15y, alcohol intake at age 15y, medication use (hormonal contraceptives, glucocorticoids, antipsychotics/antidepressants), height at age 15y and height at age 15y squared (height^2). Age at puberty onset was estimated by the age at peak height velocity based on the SuperImposition by Translation And Rotation (SITAR) growth curve modelling of repeated height measures from age 5y to 20y (detailed previously) (24). Highest educational attainment of the participant's mother (Certificate of Secondary Education [CSE], vocational, O-level, A-level or degree) was used to indicate socioeconomic position at birth. Smoking status (ever smoked a whole cigarette yes/no) at age 15ywas recorded via questionnaire, as well as alcohol intake (ever had a whole drink yes/no) and medication use. Height was measured in light clothing without shoes to the nearest 0.1 cm using a Harpenden stadiometer.

Statistical analyses

Linear spline multilevel models were used to model trajectories from 7y to 24y, as described previously (25). For the present analysis, we included these trajectories from 15y only and used linear spline multilevel models to examine associations of total and trunk fat mass at age 15y and trajectories from 15y to 24y. Multilevel models estimate mean trajectories of the outcome while accounting for the non-independence or clustering of repeated measurements within individuals, change in scale and variance of measures over time, and differences in the number and timing of measurements between individuals (using all available data from all eligible participants under a missing-at-random assumption (26, 27). Linear splines allow knot points to be fit at different ages to derive periods in which change is approximately linear. All linear spline multilevel models included here had two linear spline periods from 15y to 18y and 18y to 24 (two levels: measurement occasion and individual). Further details for each model for the 145 metabolites included in our analysis are included in the Supplementary material. All models included robust standard errors to accommodate skewed outcome distributions.

Participants were included in the present analyses if they had data on total or trunk fat mass at age 15y, sex, age, at least one of the metabolites at 15y, 18y or 24y and data on all potential confounders. This resulted in 3851 eligible participants (1810 males, 2041 females contributing to our analyses. All analyses were performed separately for males and females

and adjusted for all potential confounders as listed previously, further information on the inclusion of confounders in models is included in the supplementary material.

We transformed total body fat mass and trunk fat using the natural logarithm due to skewed distributions and subsequently standardised these measures into SD units by generating z-scores (with a mean of zero and SD of 1). We assessed linearity of our models by using likelihood ratio tests with total and trunk fat mass treated as continuous variables and as categorical variables in quartiles in relation to all metabolites for males and females separately. We did not find evidence for non-linearity for most metabolites across time points and therefore treated both fat measures as continuous exposures. We assessed and removed outliers in the metabolites by using a cut-off of the mean and ±4 SD across the three included assessment rounds.

In addition, we centred the continuous confounding factors based on their mean values, and created dummy/binary variables for all categorical variables. We fitted a spline interaction term and sex interaction term with all confounding factors to allow confounding structures to differ y sex during the two time periods (i.e. between 15y and 18y, and between 18y and 24y).

For each sex, models directly estimate mean predicted difference in level of each metabolite at 15y (the intercept) and mean predicted difference in slopes in original units per 1-SD higher total or trunk fat mass, with sloped interpreted as change per year in each metabolite in the respective spline period. Following analyses, these estimates were then combined to provide other estimates of interest including mean predicted difference in absolute change in each metabolite level from 15y to 24y per 1-SD higher total or trunk fat mass using the sloped given by each model. The mean predicted difference in the level of each metabolite at 24y per 1-SD higher total or trunk mass was also estimated. All of the above estimates were then converted to SD units by dividing by the sex-combined standard deviation (SD) of the observed metabolite at 15y, in order to aid comparison of results between metabolites. Note that all analyses were performed in original units and converted SD units post analysis to aid comparison between results. All results in original units, including slopes for linear spline periods, are presented in the **Supplementary Material**.

The results can be interpreted as the association between 1-SD higher ln total fat mass (corresponding to 0.63 kg in men and 0.41 kg in women) or trunk fat (corresponding to 0.69 kg in men and 0.48 kg in women) with SD-unit change in a specific metabolite between 15y and 24y, i.e. over a 9 year period. The standardized mean differences between 15y and 24y of all metabolites associated with exposure to total fat mass at 15y were plotted in a circle plot to illustrate the illustrate the results.

Additional and sensitivity analyses

To reduce potential for residual confounding by hormonal factors related to puberty that we were not able to account for, we additionally examined the association between total and trunk fat mass at age 18y (log-transformed and z-scored) and changes in the metabolites between ages 18y and 24y. We calculated the absolute difference between metabolite concentrations between 18y and 24y and then standardized these differences. Because there were only two time points, we used a (non-mixed) linear regression model adjusted for

ethnicity, exact age at 18y, height at 18y, age at puberty onset and maternal educational attainment, stratified by sex.

To account for changes in total and trunk fat mass occurring after 15y, which might differentially influence changes in the concentrations of metabolites, we additionally divided participants into four groups, based on their fat mass at 15y and at 24y. The cut-offs were based on the 50th percentile of total fat mass at 15y and at 24y, calculated separately for men and women. We then established four categories: 1) individuals who stayed in the 'low fat' category between age 15y and 24y, 2) individuals who went from the 'low fat' to the 'high fat' category, 3) individuals who went from the 'high fat' to the 'low fat' category, and 4) individuals who stayed in the 'high fat' category between age 15y and 24y. We then repeated our primary analyses separately in the two categories remaining at a stable level of fat mass (category 1 and 4). Of note, the population included in this sensitivity analysis is slightly different than the population we included in our main analyses, as participants needed to have data on both total fat mass at age 15y and at 24y.

Analyses were conducted using Stata 14.0 (StataCorp, College Station, Texas, USA) and data visualisation was performed in Python and R (version 4.0.3).

RESULTS

Participant characteristics

3851 participants with measures of total or trunk fat mass at age 15y and at least one metabolomics measurement were included in analyses (**Table 1**). Of these, 53% of the participants were female, and 91% were of self-reported white ethnicity. The mean age (SD) at puberty onset was 11.7y (0.8) for females and 13.6y (0.9) for males. In females, mean body mass index at age 15y was 21.7 (3.5) kg/m^2 with a median (interquartile range) total fat of 17.2 (13.3 – 22.3) kg and median trunk fat of 7.8 (5.8 – 10.7) kg. In males, mean BMI at 15y was 20.9 (3.1) kg/m^2, with a lower median total fat (8.4 [5.8 – 13.1] kg) and trunk fat (3.7 [2.5 – 6.1] kg) than females.

Table 1. Characteristics of the first offspring generation of the Avon Longitudinal Study of Parents and Children (ALSPAC) participants included in the analyses, stratified by sex

	Women (53%)	Men (46%)
White ethnicity (%)	91	91
Height at age 15 (cm)	164.8 (6.0)	174.7 (7.6)
BMI at age 15 (kg/m^2)	21.7 (3.5)	20.9 (3.1)
Fat mass at age 15 (kg)	17.2 (13.3; 22.3)	8.4 (5.8 - 13.1)
Trunk fat at age 15 (kg)	7.8 (5.8; 10.7)	3.7 (2.5 - 6.1)
BMI at age 18 (kg/m^2)	22.8 (4.0)	22.4 (3.6)
Fat mass at age 18 (kg)	19.3 (15.0 – 25.0)	10.6 (6.8 - 16.8)
Trunk fat at age 18 (kg)	9.4 (7.1 – 12.6)	5.5 (3.4 – 8.8)
BMI at age 24 (kg/m^2)	24.8 (5.2)	24.7 (4.2)
Fat mass at age 24 (kg)	21.7 (17.2 – 28.9)	18.2 (13.8 – 24.8)
Trunk fat at age 24 (kg)	9.8 (7.2 – 14.0)	9.0 (6.4 – 12.8)
Age at puberty onset (years)	11.7 (0.8)	13.6 (0.9)
Age at puberty onset ≥15.5y (%)	5	7
Maternal education (%)		
CSE	10	9
Vocational	6	7
O Level	34	31
A Level	29	32
Degree	20	21
Ever smoked by age 15 (%)	71	58
Ever drank alcohol by age 15 (%)	87	85
Use of hormonal contraceptives (%)	14	-
Use of glucocorticoids (%)	0.3	0
Use of antipsychotics or antidepressants (%)	0.6	0.4

This table includes participants with data on sex, fat mass at age 15y and trunk fat at age 15y, and at least one metabolomic measure at any age. Abbreviations: BMI, body mass index; CSE, certificate of secondary education; O level, ordinary level; A level, advanced level. Data are presented as mean (SD or range), median (25th–75th percentile) or percentage.

Associations of total and trunk fat mass at age 15y with subsequent changes in metabolites
Patterns of associations of total and trunk fat mass at age 15y with the average rate of change in metabolites between age 15y and 24y differed substantially for males and females (see **Supplementary Table 1** and **Supplementary Table 2**).

In males, higher trunk fat at 15y was associated with an increase in almost all VLDL measures, whereas in females these associations were slightly negative or null. For example, in

males, each SD ln higher trunk fat mass at age 15y (corresponding to 0.69 kg and 0.48 kg in women), was associated with a 2.05 SD (95% CI 0.54 – 3.57) increase in cholesterol in large VLDL, and in women with a 0.05 SD (95% CI -0.67 – 0.77) change. We observed similar patterns for LDL measures.

In contrast, we found no strong evidence that higher trunk fat mass at 15y was associated with changes in total cholesterol in high-density lipoprotein (HDL) in males and females. Higher trunk fat mass at age 15y was associated with an increase in total serum triglycerides in men (2.10 SD, 95% CI 0.77 – 3.44), and but evidence of this change was weak in females. In males, higher trunk fat mass at 15y was associated with an increase in apolipoprotein B (1.90 SD, 95% CI 1.13 – 2.66), whereas in females there was no strong evidence of this change (0.29 SD (-0.54 – 1.13).

The results were similar for total fat mass (see **Figure 1** and **Supplementary table 2**). We observed comparable patterns of association for VLDL measures, as well as for LDL and HDL measures. For instance, a 1 SD ln (corresponding to 0.63 kg in males and 0.41 kg in females) higher total fat at 15y was associated with 2.06 SD (95% CI 0.54 – 3.58) change in cholesterol in large VLDL in males, and a 0.03 SD (95% CI -0.68 – 0.75) change in cholesterol in large VLDL in females. In addition, total fat at 15y was associated with an increase in total serum triglycerides in males (2.11 SD, 95% CI 0.77 – 3.45), but not in females. In males, total fat at 15y was associated with an increase in apolipoprotein B (1.88 SD, 95% CI 1.11 – 2.65), whereas in females there was weak evidence of this (0.27 SD (-0.56 – 1.10).

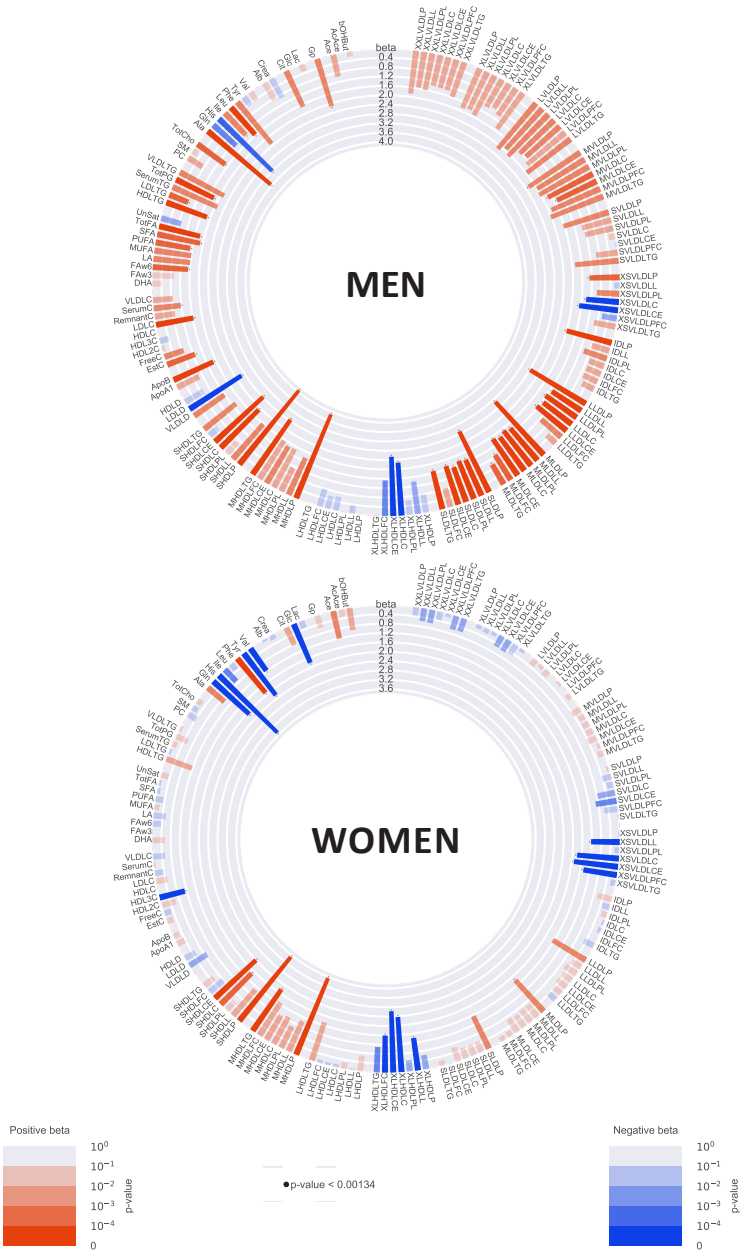

Figure 1. The circle plots show the associations between total fat mass at age 15y and the average rate of change in the individual metabolites from age 15y to age 24y in the ALSPAC. The metabolomic measures are indicated at the outer circle. A red bar indicates a positive rate of change, whereas a blue bar indicates a negative rate of change. The colour intensity and height of the bar indicate the magnitude of association. A black dot above a bar indicates association at the level of $p < 0.00134$.

Associations of total fat mass at 18y and change in metabolomic measures between 18y and 24y
The associations of total fat mass at age 18y and the changes in metabolites between age 18y and 24y were less pronounced than the results of our main analyses, which examined the change from age 15y onwards (see **Supplementary Table 3**). In males, we observed that higher fat mass at age 18y was associated with a decrease of 0.16 SD [95% CI -0.07; -0.25] in triglycerides in large LDL between age 18y and 24y. We also observed a decrease in triglycerides in large LDL in females (-0.44 SD, CI -0.25; -0.62). Furthermore, we observed strong decreases in several measures of XXL- to XL-VLDL in females related to fat mass at age 18y, in line with the findings of our main analyses.

Associations of stable amounts of total and trunk fat mass with metabolites
At age 15y, the median total fat mass for males was 8.5 kg, whereas for females it was 17.3 kg. In males, the median increased to 18.3 kg at age 24y, in females this was 22.2 kg. In total, of the 1127 males and 1683 females eligible for the sensitivity analysis, 771 males remained in the same category of fat mass (either 'low' or 'high') between age 15y and 24y, and 1252 females remained at a stable total fat mass.

Overall, we observed similar patterns in the associations of fat mass at age 15y and the rate of change of metabolites in individuals who remained in the same category of fat mass, as compared with the complete population (see **Supplementary Table 4**). We observed an association between total fat mass at age 15y and increased rate of change in total cholesterol in HDL in males (0.76 SD [95% CI 0.08 – 1.45] per log total fat mass in kg). In females, we observed 0.96 SD decrease in triglycerides in LDL (95% CI -1.68; -0.24) per SD ln fat mass at age 15y. Lastly, we observed that total fat mass at age 15y was associated with a decreased rate of change in glucose levels in males (-1.80 SD, 95% CI -2.61; -0.98).

DISCUSSION

In this population-based birth cohort of adolescents, we examined the sex-specific associations of total and trunk fat mass with early changes over time in atherogenic metabolites. Overall, our results suggest that higher total and trunk fat at adolescence were associated with increasing concentrations of apolipoprotein-B-containing lipoprotein particles, indicative of a more atherogenic progression, but that these adverse changes are only apparent in males. In addition, our findings suggest that this result is consistent for individuals after puberty and individuals who remained at a stable amount of fat mass (either low or high) during adolescence and young adulthood. This indicates that our results are not driven by changes related to puberty or increases in fat mass.

Previous studies suggested that men are at a higher risk of cardiovascular disease than women until after age 75y (27). One potential explanation is that cardiovascular disease is understudied in women, and symptoms might present differently than in men (28), leading to underdiagnosis and undertreatment of cardiovascular disease in women (29). However, we observed that atherogenic changes are already apparent at a young age. Secondly, men tend to store body fat in the abdomen, where women are more likely to store fat at the hips and thighs (17). It is well-established that abdominal adiposity, and in particular visceral

adipose tissue located around the organs, is strongly related to insulin resistance (28) and risk of type 2 diabetes mellitus (9) raising cardiovascular disease risk (29).

One mechanism explaining the association between total fat mass at adolescence and young adulthood and a more atherogenic metabolic profile is adipocyte hypertrophy. As a result of hypertrophy, adipose tissue becomes dysfunctional, ultimately leading to insulin resistance and metabolic disturbances (30-32). Spalding et al. observed that the number of adipocytes is set before adulthood, and the expansion of adipocyte number ends around the age of 16.5y in individuals with obesity and 18.5y in lean individuals (33). Taken together, this suggests that adipocytes respond to increases in fat mass by expansion during young adulthood, and thereby contribute to adipocyte hypertrophy, ultimately leading to metabolic disturbances as we observed in our study.

Childhood BMI and adult BMI were shown to be strongly genetically correlated (34). This suggests that the associations between childhood BMI and cardiometabolic diseases in adulthood may be explained by persistence of BMI from childhood into adulthood, reflected by partial genetic overlap and a common onset. In line, a recent MR analysis showed that body size in childhood was associated with an increased risk of coronary artery disease (35). However, when childhood body size was analysed in a multivariable framework with adult body size, this effect attenuated. Further MR analyses showed body size in childhood to be associated with concentrations of 42 metabolomic measures, including VLDL cholesterol and triglycerides, amino acids, glycoprotein acetyls, and HDL cholesterol (16). Although these associations were indicative of a more atherogenic cardiometabolic profile, most associations also attenuated in multivariable MR models with adult body size, with exception of the amino acids leucine, isoleucine and tyrosine. Taken together, the results of these studies indicate that the effects of childhood adiposity are mainly mediated via body size during adulthood. In addition, this suggests that there is an opportunity to reduce the cardiometabolic consequences of body size during childhood, as childhood adiposity is often carried over into adulthood (2).

In a cross-sectional analysis in ALSPAC, it was previously observed that the absolute levels of lipids in VLDL are higher in men, whereas other cardiovascular traits, such as absolute levels of cholesterol in LDL particles, Apolipoprotein B and the inflammatory glycoprotein acetyls were higher in women throughout adolescence. These results in women are not in line with our findings: however, we assessed the sex-specific longitudinal changes in the metabolomic measures related to adiposity, taking into account the correlation between the repeated measures of the metabolomic measures.

The increased risk of cardiovascular disease related to adiposity is already reflected in the metabolic profile of young adults. For example, BMI in young adulthood has been associated with higher circulating VLDLs, monounsaturated fatty acids, saturated fatty acids and branched-chain amino acid levels, as well as lower plasma large HDL concentrations (13). Findings from another prospective study in ALSPAC suggested that the atherogenic consequences of adiposity on the metabolic profile were stronger and apparent at a younger age in men than in women (36). For example, LDL cholesterol, triglycerides in VLDL and Apolipoprotein B were all found to be strongly associated with adiposity in men throughout young adulthood, in line with the results of our study.

Previous studies have linked the identified adiposity-related metabolomic measures to cardiometabolic disease events occurring in adulthood. In an observational study, NMR-based measures of circulating cholesterol and triglycerides in VLDL and LDL particles, Apolipoprotein B and glucose are strongly and consistently associated with the risk of myocardial infarction (37). MR analyses showed that both LDL cholesterol and triglycerides play a causal role in the development of coronary heart disease (38, 39), as well as Apolipoprotein B (39).

Limitations that should be considered include missing data and loss to follow-up. However, by using multilevel modelling, we used all available data from all eligible participants under a missing-at-random assumption. In addition, earlier studies in ALSPAC using the metabolomic measures compared the characteristics of included and excluded participants and these were found to be highly similar (36, 40). Secondly, the exposure trunk fat does not differentiate between the location of the body fat in the trunk, for example body fat located in the chest, or subcutaneously or viscerally in the abdomen. Third, during adolescence and into young adulthood the participants are experiencing pubertal changes, such as changes in hormonal levels. Although we adjusted our analyses for age of puberty onset, residual confounding might still be present. Results from sensitivity analyses assessing the relation of total fat mass at age 18y and the change in metabolomic measures between age 18y and 24y, thereby largely ruling out changes related to puberty, were however similar as the main results. Lastly, most of the participants of ALSPAC were of white European ethnicity. Therefore, the results of our study need to be confirmed in other ethnic groups.

Strengths of our study are the use of measures of both overall as well as abdominal adiposity from DXA scans. Additionally, we included a wide range of atherogenic metabolomic measures as outcomes, measured at multiple occasions throughout adolescence and young adulthood. To the best of our knowledge, we are the first study to examine changes in levels of lipoprotein particles indicative of a more atherogenic risk profile in relation to adiposity in a cohort of adolescents and young adults. Lastly, results from several sensitivity analyses that accounted for changes in adiposity and metabolomic measures related to puberty and gains in total fat mass during young adulthood suggest that our results are robust.

In conclusion, the present study shows that there are already atherogenic changes visible in metabolomic measures related to total and trunk fat mass at a young age. Our results further indicate that there is a difference in risk for cardiometabolic disease for males and females, which is already apparent at a young age. Therefore, adolescence is a critical period for the prevention of adiposity-related changes in atherogenic risk factors in males.

COMPETING INTERESTS

None declared.

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SUPPLEMENTARY MATERIAL

The supplementary material can be found at
https://figshare.com/s/d516d56b49b16a7b87a3