Metabolomic correlates of central adiposity and earlier-life body mass index

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Abstract  BMI is correlated with circulating metabolites, but few studies discuss other adiposity measures, and little is known about metabolomic correlates of BMI from early life. We investigated associations between different adiposity measures, BMI from childhood through adulthood, and metabolites quantified from serum using $^1$H NMR spectroscopy in 900 British men and women aged 60–64. We assessed BMI, waist-to-hip ratio (WHR), android-to-gynoid fat ratio (AGR), and BMI from childhood through adulthood. Linear regression with Bonferroni adjustment was performed to assess adiposity and metabolites. Of 233 metabolites, 168; 126; and 133 were associated with BMI, WHR, and AGR at age 60–64, respectively. Associations were strongest for HDL, particularly HDL particle size—e.g., there was 0.08 SD decrease in HDL diameter (95% CI: 0.07–0.10) with each unit increase in BMI. BMI-adjusted AGR or WHR were associated with 31 metabolites where there was no metabolome-wide association with BMI. We identified inverse associations between BMI at age 7 and glucose or glycoprotein at age 60–64 and relatively large LDL cholesterol ester with post-adolescent BMI gains. In summary, we identified metabolomic correlates of central adiposity and earlier-life BMI. These findings support opportunities to leverage metabolomics in early prevention of cardiovascular risk attributable to body fatness.—Wulaningsih, W., P. Proitsi, A. Wong, D. Kuh, and R. Hardy.

Supplementary key words  metabolomics, obesity • nutrition • lipids • epidemiology

Obesity is a major health problem (1–3) and predisposes to CVD (4), but it is unclear which etiological pathways are affected by obesity. Recently, high-throughput analysis of biological samples has allowed quantification of small-molecule metabolites (5) downstream from genome or gene, mRNA, and protein (6), reflecting an integrated metabolic profile (7–9). This metabolome-wide approach has shown aberrations in metabolic profile to be predictive of CVD (10–13). A Mendelian randomization study suggested that higher BMI is associated with altered levels of some CVD-related metabolites, including lipoprotein lipid and cholesterol contents, saturated FAs, branched-chain amino acids (BCAAs) and aromatic amino acids, and inflammatory metabolites (14). However, adults with similar BMI may have different fat distributions (15). It is not clear whether central adiposity is associated with metabolite levels independent of BMI in late adulthood when central adiposity becomes more common. Furthermore, there is an indication that changes in BMI over up to 7 years are associated with metabolic profile (14, 16). However, it is unclear which metabolites are affected by changes in BMI across the life course, which is important, given the effect of childhood BMI changes on cardiovascular function in adulthood (17, 18). Therefore, we assessed the similarities and differences between associations of BMI and central-adiposity measures, as well as body size across the life course, with metabolic profile at age 60–64 in the Medical Research Council (MRC) National Survey of Health and Development (NSHD) birth cohort.

MATERIALS AND METHODS

Study population

The MRC NSHD has been described in detail (19, 20). From this population, we included individuals with measurements of at least one circulating metabolite and information on BMI and waist and hip circumferences at age 60–64 (n = 900). A flowchart depicting

Abbreviations:  AGR, android-to-gynoid fat ratio; BCAA, branched-chain amino acid; CE, cholesteryl ester; MRC, Medical Research Council; NSHD, National Survey of Health and Development; OLS, ordinary least-squares; PL, phospholipid; VIP, variable importance in projection; WHR, waist-to-hip ratio; XL, very large.

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Metabolomics, adiposity, and earlier-life BMI selection of final study population is shown as supplemental Fig. S1. Ethical approval was obtained from the Greater Manchester Local Research Ethics Committee and the Scotland Research Ethics Committee. The study abided by the principles of the Helsinki Declaration. Written informed consent was obtained from each study member for each component of each data collection.

Metabolite quantification

Targeted metabolomics analysis was performed on serum samples collected at age 60–64. Metabolites were quantified by an automated NMR metabolomics platform (Bruker AVANCE III 500 MHz and Bruker AVANCE III HD 600 MHz spectrometers), which have been widely used in published studies (21). A total of 233 metabolite concentrations and derived measures were obtained (supplemental Table S1, supplemental data). Of 233 metabolites, 159 (72%) were measured in all included participants. The remaining metabolites had <1.5% missing values. Metabolite measures that deviated from normality were log-transformed (supplemental Table S1, supplemental data), and all measures were standardized.

Fig. 1. Cross-sectional associations between BMI and systemic metabolites at age 60–64. The outer circle shows predicted SD change in metabolite levels for every kg/m^2 increase in BMI in OLS analysis. The middle circle shows the “Manhattan plot” with green dots indicating significant p-values after Bonferroni adjustment. VIP from OPLS analysis is shown in the inner circle. Metabolites identified by the two analyses were indicated with dark blue points. See supplemental Table S1 for abbreviations and grouping based on metabolic processes. All models were adjusted for sex, age at NMR blood collection, and NMR blood-collection center.
Assessment of adiposity

At ages 60–64, weight (kg), height (m), and waist and hip circumference (cm) were measured using standardized protocols by trained nurses (19). Weight and height were also measured at ages 7, 15, 36, 43, and 53, and BMI (kg/m²) was calculated. Measures of body composition at age 60–64 were obtained in the supine position using a QDR4500 Discovery DXA scanner (Hologic Inc, Bedford, MA) and reviewed using a single operator using APEX 3.1 software (Hologic Inc.) (15). Measures of android and gynoid fat mass were obtained, and the ratio between the two [android-to-gynoid fat ratio (AGR)] was calculated (higher values indicating greater fat distribution in the abdomen than hips).

Other covariates

Systemic metabolites have been reported to be altered with lipid medications (22), diabetes (23), and other chronic diseases (24). Self-reported information on use of statin, diabetes diagnosis, and unintentional weight loss was therefore collected. Unintentional weight loss, which may represent preclinical chronic
disease (25), was defined as losing weight of more than 10 pounds unintentionally in the past year.

Data analysis

Association between current adiposity and systemic metabolites. Ordinary least-squares (OLS) regression was used with the adiposity measure [BMI, waist-to-hip ratio (WHR), or AGR] as the predictor for each metabolite, adjusting for sex, age, and clinic. Models for WHR and AGR were further adjusted for BMI. A sensitivity analysis was performed by restricting the models to those without statin use (n = 698), diabetes (n = 849), or unintentional weight loss (n = 856). To address potential correlation between metabolites (9), we repeated the analysis for each adiposity measure using a multivariate approach, orthogonal partial least-squares (OPLS) (26). Metabolites with a variable importance in projection (VIP) ≥ 1 were deemed strongly correlated with adiposity (27).

Association between prior BMI and systemic metabolites. We then investigated how prior BMI was associated with levels of metabolites. OLS regression models were used to assess BMI in childhood (age 7; n = 766), adolescence (age 15; n = 722), and adulthood (ages 36; 43; and 53; n = 836; 855; and 859, respectively) and metabolite levels at age 60–64. Significant associations for prior BMI were further adjusted for BMI at age 60–64 in order to assess whether prior BMI was associated with metabolite level over and above current BMI (28, 29). Because the numbers of participants who had data on prior BMI were smaller than the maximum sample, we performed a sensitivity analysis assessing associations between BMI at all ages and metabolites in participants who had complete data on all BMI measures (n = 569).

Association between BMI gains and systemic metabolites. In the main sample, we assessed whether there were sensitive periods in life during which BMI gains were associated with metabolites in late adulthood. This was conducted for ages 7–15, 15–36, 36–43, 43–53, and 53 to 60–64 by regressing each BMI measure on the BMI measured earlier for each sex. Higher residuals represented greater BMI gains than expected (30). Each set of residuals was standardized and used as predictors of metabolites to address whether there were periods when gain in BMI was associated with later-life metabolites.

For each model, we used a Bonferroni-adjusted significance threshold for 233 tests (p < 0.0002). All analyses were conducted in R statistical software version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Characteristics of study members are shown in supplemental Table S2. The majority had nonmanual occupations and were overweight at age 60–64. Pairwise correlations between metabolites are presented as supplemental Fig. S2.

Association between current adiposity and systemic metabolites

In OLS (n = 900), 168 metabolites were associated with BMI (Fig. 1), 126 with WHR (Fig. 2), and 133 with AGR (supplemental Fig. S3). After adjusting for BMI, 63 metabolites remained associated with WHR and 106 with AGR (supplemental Fig. S4, S5). Associations were strongest for HDL particle diameter (HDL D) and concentration of very large (XL) HDL phospholipids (PLs) (Table 1). Sensitivity analyses excluding participants with statin use, diabetes, or unintentional weight loss yielded similar results (data not shown). We identified 25 metabolites in men and 5 in women that were associated with WHR or AGR when adjusted for BMI, but they were not associated with BMI in the main sex-stratified analysis (Table 2).

In OPLS, six predictors or principal components explained the association between metabolites and each

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**TABLE 1. Ten metabolites associated with each adiposity measure at highest precision**

| BMI | WHR* | AGR* | Prior BMI | Conditional BMI change | Overweight onset |
|-----|------|------|----------|-----------------------|------------------|
| L. HDL FC | L. HDL FC % | HDL D | S HDL C | apoA1 | L. HDL FC | L. HDL FC | HDL TG % | XL HDL FC | apoA1 | L. HDL D | L. HDL PL % | XL HDL PL L |
| HDL D | LA % | XI HDL PL | SM | HDL C % | XI HDL PL | HDL C | HDL D | HDL C % | HDL C | HDL D | HDL C | HDL D |
| XI HDL PL Gp | L. LDL FC % | Faw3 | IDL TG % | apoA1 | L. HDL FC | L. HDL FC | XL HDL FC | L. HDL FC | L. HDL FC | XI HDL PL | HDL D | HDL D |
| L. HDL FC % | L. HDL FC % | TG PG | EstC | HDL C % | HDL C | HDL C | HDL C | Faw6% | HDL D | L. HDL FC | L. HDL FC | M VL DL CE % | L. HDL FC |
| L. HDL C | Faw6% | XI HDL PL | S HDL L | XI HDL FC | XI HDL FC | XI HDL FC | S LDL TG % | HDL D | HDL C | M VL DL TG % | M VL DL TG % | HDL D |
| XL HDL P | HDL C | HDL C | L HDL L | Pufa | Hdl2C | L. HDL FC | HDL C | HDL D | HDL D | L. VL DL TG | XL HDL L | HDL C |
| XL HDL L | XI HDL PL | IIc | Serum C | Hdl2C | XL HDL FC | XL HDL FC | HDL C | HDL D | HDL D | XL HDL FC | HDL C | HDL C |
| XL HDL PL FFA % | L. HDL FC | L. HDL CE | LDL PL | HDL C | HDL C | HDL D | HDL D | HDL D | HDL D | HDL D | HDL D | HDL D |
| L. HDL CE Leu | M VLDL TG | apoA1 | L. LDL TG % | HDL L | HDL L | HDL L | HDL L | XL HDL C | NS VLDL FC % | XL HDL L | HDL D | HDL C |
| L. HDL PL | HDL D | VLDL TG | S LDL C | S LDL C | HDL L | HDL L | HDL L | HDL L | HDL L | HDL L | HDL L | HDL L |

Positive (inverse) associations were highlighted in blue (red), respectively. Significant results with adjustment for multiple testing are indicated in white. For abbreviations, see supplemental Table S1.

*Adjusted for BMI.
measure of adiposity. Taking such clustering into account, a total of 99 metabolites were shown to be associated with BMI (VIP ≥ 1), 87 with WHR, and 90 with AGR. Common metabolites identified by both the hypothesis-testing approach and OPLS are indicated in Figs. 1, 2, supplemental Fig. S3 for BMI, WHR, and AGR, respectively. Agreement between the two methods was high for associations of BMI, WHR, and AGR with metabolite markers of XL and large HDL, large and medium VLDL, lipoprotein particle size, and BCAAs. HDL D was consistently among the top 10 metabolite correlates of BMI, WHR, and AGR in the OPLS analysis (supplemental Table S3).

Association between prior BMI and systemic metabolites

Associations between prior adult BMI and metabolites showed similar, albeit weaker, trends to current BMI (supplemental Fig. S6 and Table 2). More metabolites were associated with more recent BMI, with 125; 147; and 162 metabolite correlates seen for BMI at age 36, 43, and 53, respectively. Of these, only three remained associated with BMI at age 43 and 11 with BMI at age 53 when adjusted for BMI at age 60–64 (supplemental Table S3). No association was observed between BMI at age 7 or 15 with systemic metabolites at age 60–64. However, upon adjustment with BMI at age 60–64, we found BMI at age 7 to be inversely related with 0.11 SD decrease in glucose (95% CI: −0.06 to −0.15) and 0.10 SD decrease in glycoprotein (−0.05 to −0.15).

The sensitivity analysis in the subset of participants who had complete data of prior BMI showed similar results (data not shown), and after adjustment with current BMI, only one metabolite, small (S) LDL PLs (S LDL PL) remained associated with previous BMI, i.e., BMI at age 43.

Association between BMI gains and systemic metabolites

BMI gains from adolescence through adulthood were consistently related to XL and large HDL metabolites (Fig. 3). Apart from these, BMI gains at the latter ages were also associated with larger VLDL metabolites, and adolescent gains with relative contents of smaller VLDL and LDL metabolites, medium HDL, FAs, and aromatic amino acids (Fig. 3). One metabolite, relatively large LDL cholesteryl ester (L LDL CE %), decreased with greater BMI gain between age 15 and 36 but was not associated with change at other ages or BMI at age 60–64. Small HDL total lipids (S HDL L) was associated with BMI gains between age 43 and 53, but not with other periods or current BMI.

DISCUSSION

We showed associations between current adiposity and systemic metabolites in late adulthood and BMI in earlier ages. Most consistent associations were observed for HDL metabolism. We identified 25 metabolite measures

| Metabolite | n | Estimate | CI               | n | Estimate | CI               |
|------------|---|----------|------------------|---|----------|------------------|
|**Men**     |   |          |                  |   |          |                  |
| Medium VLDL CEs | 368 | 1.30 | 0.70–1.90 | 465 | 3.56 | 1.88–5.24 |
| Medium VLDL free cholesterol (%) | 368 | 1.24 | 0.73–1.76 | 465 | 3.80 | 2.05–5.45 |
| Small VLDL PLs | 368 | 1.39 | 1.06–2.12 | 465 | 3.61 | 1.81–5.40 |
| Small VLDL total cholesterol | 368 | 1.35 | 0.79–1.91 | 465 | 3.67 | 1.97–5.36 |
| Small VLDL CEs | 368 | 1.66 | 1.13–2.19 | 465 | 3.48 | 1.68–5.26 |
| Small LDL free cholesterol (%) | 368 | 1.24 | 0.63–1.84 | 465 | 1.25 | 0.86 to 1.86 |
| HDL triglycerides | 368 | 1.27 | 0.65–1.90 | 465 | 1.31 | 0.66–1.76 |
| Medium LDL triglycerides | 368 | 1.21 | 0.66–1.76 | 465 | 1.24 | 0.84–2.00 |
| VLDL cholesterol | 368 | 1.42 | 0.84–2.00 | 465 | 1.42 | 0.84–2.00 |
| RemNAt cholesterol | 368 | 1.36 | 0.56–1.76 | 465 | 1.53 | 1.16–2.76 |
| Lipoprotein acetyls | 368 | 1.83 | 1.23–2.43 | 465 | 1.53 | 1.16–2.76 |
|**Women**   |   |          |                  |   |          |                  |
| Small HDL concentration | 365 | 2.03 | 1.23–2.83 | 465 | 2.01 | 1.23–2.83 |
| Small HDL PLs | 365 | 1.98 | 1.18–2.78 | 465 | 2.03 | 1.23–2.83 |
| Small HDL total lipids | 365 | 1.96 | 1.16–2.76 | 465 | 2.03 | 1.23–2.83 |
| XXL VLDL PLs (%) | 365 | 1.88 | 1.00–2.76 | 465 | 2.03 | 1.23–2.83 |
| Diacylglycerol | 365 | 1.55 | 0.80–2.29 | 465 | 2.03 | 1.23–2.83 |

Percentage for lipoprotein lipid components refers to proportion against total lipid contents. RemNAt, remnant cholesterol; XS, very small; XXL, extremely large.
Fig 3. Associations between conditional BMI change and systemic metabolites at age 60–64. Point estimates indicate SD change in metabolite levels for every z-score increase in BMI at each age interval, conditioned by BMI at the earlier age. Associations that remained after Bonferroni correction are displayed. All models were adjusted for sex, age at NMR blood collection, and NMR blood collection center.

independently associated with central adiposity but not BMI. When controlling for BMI at age 60–64, greater BMI at age 7 was correlated with lower glucose and glycoprotein at age 60–64. We also revealed lower relatively large LDL CE at age 60–64 with greater adolescent-to-adulthood BMI gains.

Our cross-sectional findings for BMI and metabolites in early old age corroborate prior findings linking body size and metabolites, including causal associations observed using a Mendelian randomization study of young adults (31). Similar to that study, we found associations between BMI
and a number of metabolites including HDL metabolites, BCAAs, markers of glycolysis, and inflammation. This may suggest that BMI influences metabolites in a similar manner throughout adulthood. Metabolite correlates of central adiposity also align with those identified in previous studies, such as lipoprotein concentration, HDL particle size, and BCAAs (32–35). We added to these findings by presenting data in late adulthood in which central obesity is common, including specific lipoprotein components, and identifying associations independent of BMI. Central adiposity may represent visceral rather than overall accumulation of fat (36). There were more metabolites specifically linked to central adiposity in men compared with women. This may support sexual dimorphism in regulation of fat depot and systemic metabolism (32, 37).

A similar pattern to current BMI was observed with greater past BMI or its increments, which is in line with a previous study assessing metabolites linked to a 7 year weight change in adults aged 62–77 (16). Although this may indicate BMI tracking, there were remaining associations between past BMI in adulthood and current metabolites after taking into account current BMI. Plausible mechanisms by which high BMI in earlier adulthood may affect metabolites in early old age may involve excess adiposity affecting systemic processes such as inflammation and oxidative stress (38) or predisposing to maladaptive lifestyles such as physical inactivity (39). Additionally, we identified specific metabolite correlates of BMI at age 7 after adjusting for BMI at age 60–64 and of BMI gains from adolescence to early adulthood, which were different from late adulthood. The inverse associations of BMI at age 7 with glucose and glycoprotein, both of which are greater with higher BMI at age 60–64, may indicate that they were particularly responsive to greater gains in BMI between childhood and adulthood. These metabolites have been associated with adverse metabolic pathways, including insulin resistance and advanced glycated end products, which are often activated in obesity (38, 40).

**Strengths and limitations**

The strength of this study lies in the longitudinal measurements of BMI from childhood through adulthood and measurements of body fat distribution in early old age. A limitation of this study is the smaller number of those with information on prior BMI. However, findings comparing prior BMI were similar in a sensitivity analysis limited to those with complete lifelong BMI information. Metabolites were only measured on one occasion. Individuals who had higher BMI were at higher risk of CVD and may have died or dropped out of the study prior to metabolite quantification at age 60–64, and this may result in underestimation of the observed associations. Our NMR platform only included absolute or relative quantification of metabolites. Future studies of adiposity could investigate other characteristics of metabolites such as aggregation susceptibility because LDL aggregation has been shown to be associated with CVD and is potentially modifiable by treatment (41).

**CONCLUSION**

We found metabolite correlates of current and past measures of BMI, which imply that metabolic profiling may be valuable for interventions aiming to mitigate the impacts of excess adiposity across adult life. The suggestion of alternative mechanisms for central adiposity and childhood BMI, which are independent of current BMI at age 60–64, indicates the importance of future research on body composition and longitudinal measures of adiposity.

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