Title: Decreasing severity of obesity from early to late adolescence and young adulthood associates with longitudinal metabolomic changes implicated in lower cardiometabolic disease risk

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Abstract

Background: Obesity in childhood is associated with metabolic dysfunction, adverse subclinical cardiovascular phenotypes and adult cardiovascular disease (CVD). Longitudinal studies of youth with obesity investigating changes in severity of obesity with metabolomic profiles are sparse. We investigated associations between (i) baseline body mass index (BMI) and follow-up metabolomic profiles; (ii) change in BMI with follow-up metabolomic profiles; and (iii) change in BMI with change in metabolomic profiles (mean interval 5.5 years). **Methods:** Participants (n=98, 52% males) were recruited from the Childhood Overweight Biorepository of Australia (COBRA) study. At baseline and follow-up, BMI and the %>95th BMI-centile (percentage above the age-, and sex-specific 95th BMI-centile) indicate severity of obesity, and nuclear magnetic resonance spectroscopy profiling of 72 metabolites/ratios, log-transformed and scaled to standard deviations (SD), was performed in fasting serum. Fully adjusted linear regression analyses were performed. **Results**: Mean (SD) age and %>95th BMI-centile were 10.3 (SD 3.5) years and 134.6% (19.0) at baseline, 15.8 (3.7) years and 130.7% (26.2) at follow-up. Change in BMI over time, but not baseline BMI, was associated with metabolites at follow-up. Each unit (kg/m^2) decrease in sex- and age-adjusted BMI was associated with change (SD; 95%CI; p-value) in metabolites of: alanine (-0.07;-0.11 to -0.04;p<0.001), phenylalanine (-0.07;-0.10 to -0.04;p<0.001), tyrosine (-0.07;-0.10 to -0.04;p<0.001), glycoprotein acetyls (-0.06;-0.09 to -0.04;p<0.001), degree of fatty acid unsaturation (0.06;0.02 to 0.10;p=0.003), monounsaturated fatty acids (-0.04;-0.07 to -0.01;p=0.004), ratio of ApoB/ApoA1 (-0.05;-0.07 to -0.02;p=0.001), VLDL-cholesterol (-0.04;-0.06 to -0.01;p=0.01), HDL-cholesterol (0.05;0.08 to 0.1;p=0.01), pyruvate (-0.08;-0.11 to -0.04;p<0.001), acetoacetate (0.07;0.02 to 0.11;p=0.005), and 3-hydroxybuturate (0.07;0.02 to 0.11;p=0.01). Results using the %>95th BMI-centile were largely consistent with age-, and sex-adjusted BMI measures. **Conclusions:** In children and young adults with obesity, decreasing the severity of obesity was associated with changes in metabolomic profiles consistent with lower cardiovascular and metabolic disease risk in adults.

Introduction

In the United States, approximately one third of those aged 2 to 19 years are overweight or obese, and almost one-fifth are obese, as defined by a body mass index (BMI) ≥ 95th centile (1). Obesity in youth is associated with increased cardiometabolic disease risk, with adverse subclinical cardiovascular phenotypes and arterial injury in adolescence (2-4), and with higher risk of cardiovascular disease (CVD) and diabetes in adulthood (5-7). Improving our understanding of early life obesity-induced metabolic changes that contribute to the development of later cardiometabolic disease may improve risk-prediction and allow targeted treatment, resulting in earlier and effective prevention of adult cardiometabolic disease.

Nuclear Magnetic Resonance (NMR) metabolomic profiling simultaneously quantifies numerous metabolites related to cardiometabolic health and may differentiate adults at higher risk for obesity-related comorbidities (such as insulin resistance, type 2 diabetes mellitus and CVD) beyond stratification by BMI (8-11). However, analogous metabolomic data in childhood and adolescence are sparse, particularly in those with severe obesity who are at high risk of later cardiometabolic disease and are most likely to benefit from primordial and primary prevention (12). In addition, it is unknown whether individual changes in the severity of obesity are associated with changes in metabolomic profiles in youth with obesity.

We have previously reported the cross-sectional association between BMI and metabolomic profile in children and young adults with severe obesity (13). Here, we aimed to investigate the association between i) BMI in early adolescence and metabolomic profiles measured in later adolescence; ii) change in BMI during adolescence and metabolomic profiles in later adolescence; and iii) change in BMI and change in longitudinal metabolomic measures over the same period.

Methods

Study population

The study population was derived from the Childhood Overweight Biorepository of Australia (COBRA) cohort, a total of 408 children and young adults with obesity recruited from the Royal Children's Hospital (RCH Melbourne, Victoria, Australia) Weight Management Service between 2009 and 2018 (14). Between 2017 and 2019, COBRA participants who consented to be recontacted were invited to participate in a sub-study investigating cardiovascular risk phenotypes. Of these 408 individuals, 115 declined to participate, 192 were uncontactable (lapsed contact details, failed to be contacted or relocated interstate), and 101 agreed to participate. The study protocol was approved by the RCH Human Research Ethics Committee (HREC # 28081P). Written, informed consent was obtained from participants aged 18 years or older, or from their legally authorised representative. Assent was obtained from participants aged 14 years or older. Inclusion criteria for the sub-study were; i) weight in the obese category at recruitment, defined as BMI ≥ 95th centile using the United States Centres for Disease Control (CDC) growth reference charts (15)) and, ii) age >3 years at baseline and <25 years at follow-up. Exclusion criteria for the sub-study were; i) inability to provide informed consent due to inadequate level of English language or intellectual impairment, ii) acute infection requiring hospitalisation within the previous 4 weeks, or iii) immunosuppressive medication within the last 3 months. We analysed available data from the initial visit at recruitment for COBRA (baseline) and the subsequent visit later in adolescence (follow-up).

Anthropometric data

Anthropometric measures were obtained at baseline and follow-up using the same protocols and instruments. Height was measured without shoes, using a Harpenden stadiometer (Holtain Ltd., Crymych, Dyfed, UK). Weight was measured in light clothes with a four-point bio-impedance device (Tanita Corporation, Tokyo, Japan). BMI was calculated according to the formula weight (kg) divided by height squared (m^2). The percentage BMI above the 95th centile (%>95th BMI-centile) was calculated

based on age- and sex-matched CDC reference charts for participants younger than 20 years of age. For participants aged 20 years or older, 30kg/m^2 was used as the 95th centile. The %>95th BMI-centile is the ratio of the individual`s BMI divided by the relevant 95th BMI-centile for an age- and sex-matched individual multiplied by 100%: e.g., the 95th BMI-centile for a male adolescent 14 years is 26kg/m^2, such that if this participant's BMI was 32kg/m^2, the %>95th BMI-centile is (32/26) x 100% = 123%). The %>95th BMI-centile is a continuous variable, starting from the 95th BMI-centile (i.e., the cut-off for obesity). The %>95th BMI-centile has advantages in monitoring children and adolescents with severe obesity and it facilitates tracking of adiposity longitudinally compared to BMI z-score (16, 17), particularly in pediatric populations with severe obesity (18). Consequently, only age- and sex-adjusted BMI and %>95th BMI-centile (for sensitivity analysis) were considered in the analysis. Pubertal status at each time point was assessed using simplified Tanner staging by an experienced pediatrician: Tanner stage 1 was considered pre-pubertal, stages 2 or 3 peri-pubertal, and stages 4 or 5 post-pubertal (19).

Metabolomic profile at follow-up

NMR metabolomic analysis was performed on serum from both time points after a 6-hour fast. Blood was processed within 2 hours and stored at -80°C at the Melbourne Children`s Bioresource Centre. We used the same metabolomic platform as described previously (Nightingale Health, Helsinki, Finland) (13). A total of 228 absolute and derived measures, including lipoproteins, amino acids, ketone bodies, glycolysis metabolites, glycoprotein acetyls (GlycA) and related ratios were quantified, of which a subset of 72 measures captured the majority of metabolomic variation (13) and were included in these analyses. Metabolite concentrations were quantified with Nightingale's 2016 bioinformatics pipeline. Definitions of metabolomic measure abbreviations used in figures and tables are listed in **Supp. Table S1**.

Socioeconomic status

Socioeconomic status was assessed using the Socio-Economic Indexes for Areas (SEIFA) score (20) of Relative Socioeconomic Advantage and Disadvantage, which is based on the participant's residential postal code at baseline. SEIFA has a mean of 1000 and standard deviation (SD) of 100; a higher score indicates greater advantage and less disadvantage by area.

Statistical analyses

Prior to analyses, metabolite concentrations were log-transformed and scaled to SD units to allow comparison between different metabolites. There were 98 participants with metabolomics data available at the follow-up timepoint and included in analysis. Of these, 67 participants had metabolomics data available at both time points for the analysis of longitudinal metabolomic changes.

Linear regression modelling was used to investigate the association of BMI and %>95th BMI-centile at baseline on each of the 72 metabolites at follow-up. To investigate the relationship between change in BMI and %>95th BMI-centile between time points and metabolites at follow-up, the BMI measure at follow-up was considered as the exposure and adjusted for the baseline BMI measurement, with each of the 72 metabolites considered as individual outcomes. For investigating the change in BMI and %>95th BMI-centile between time points and the longitudinal change in metabolites between timepoints, models with the metabolomic measure at follow-up as the outcome, adjusted for the metabolomic measure at baseline, were used. Exposure measures for BMI and %>95th BMI-centile were multiplied by -1 in the analysis to describe the results as a per unit decrease of BMI and the %>95th BMI-centile.

All models were adjusted for sex and age at each time point. Associations are reported as the β-coefficient and accompanying 95% confidence interval (95% CI). Additional adjustment for pubertal status at the relevant time points and socioeconomic status was considered to determine if this substantially altered associations between BMI/%>95th BMI-centile and metabolites. In light of our previous findings of differing cross-sectional associations between BMI and metabolites at baseline by

sex and pubertal status (13), we also considered BMI-by-sex and BMI-by-pubertal status (dichotomised as pre-pubertal/other status) interaction effects.

All analyses were performed in R (v3.6.1) (21), and figures were created using the *ggforestplot* package. All statistical tests were two-sided. For each aim, p-values were adjusted for multiple comparisons (72 metabolites) using the Benjamini-Hochberg method (22) with a false-discovery rate (FDR) of 5%.

Code availability

The computer code used in this study is available upon reasonable request, subject to approval by COBRA data custodians.

Results

Cohort characteristics

Cohort characteristics are shown in **Table 1**. At baseline, mean participant age was 10.3 years (SD 3.5, range 3.0 to 16.9 years), mean BMI was 30.9 kg/m^2 (SD 6.2) and mean %>95th BMI-centile was 134.6% (SD 19.0). At follow-up, mean age was 15.8 years (SD 3.7, range 6.1 to 24.3 years), mean BMI was 35.6 kg/m^2 (SD 7.9) and mean %>95th BMI-centile was 130.7% (SD 26.2). The mean age difference between time points was 5.5 years (SD 2.1, range 0.4 to 9.2 years). The mean change in BMI between time points was 4.7 kg/m^2 (SD 5.7), and mean change in %>95th BMI-centile between time points was -3.9% (SD 20.2) (see **Supp. Figure S1**).

Baseline BMI and follow-up metabolites

Baseline BMI was not associated with metabolite concentrations at follow-up in age- and sex-adjusted linear regression models (**Figure 1, Supp. Table S2**). Subsequent adjustment for puberty or economic status at baseline did not alter these findings (**Supp. Table S3**), and there was no evidence for BMI-sex or BMI-pubertal status interaction effects after FDR adjustment (data not shown). Baseline %>95th BMI-centile was similarly not associated with metabolite concentrations at follow-up (**Supp. Figure S2**, **Supp. Table S4**).

Change in BMI and follow-up metabolites

In age- and sex-adjusted models, a decrease in BMI (per unit kg/m^2) from baseline to follow-up was associated with lower measures for phenylalanine (-0.08 SD, 95% CI -0.05 to -0.12), tyrosine (-0.09 SD, 95% CI -0.05 to -0.12), alanine (-0.08 SD, 95% CI -0.04 to -0.12), pyruvate (-0.09 SD, 95% CI -0.05 to -0.12), and GlycA (-0.06 SD, 95% CI -0.02 to -0.10) (**Figure 2, Supp. Table S5**). Also, a decrease in BMI was associated with higher ketone bodies (acetoacetate and 3-hydroxybuturate) (+0.06 SD, 95% CI 0.02 to 0.10, for both). There was more modest evidence of associations between decreases in BMI and other metabolic traits, including lower apolipoprotein B/apolipoprotein A1 (ApoB/ApoA1) ratio,

very-low-density lipoprotein (VLDL) cholesterol and lactate, and lower high-density lipoprotein (HDL) cholesterol, as well as lower monounsaturated fatty acids and lower omega-6 and polyunsaturated fatty acid percentages, but these were not significant after adjustment for FDR. Adjustment for pubertal status at follow-up attenuated the association between change in BMI and ketone body concentrations at follow-up (+0.05 SD, 95% CI 0.01 to 0.09 for acetoacetate; +0.04 SD, 95% CI 0.01 to 0.08 for 3-hydroxybuturate), but otherwise adjustment for pubertal or socioeconomic status did not impact on the above findings (**Supp. Table S6**). There was no evidence for BMI-by-sex or BMI-by-pubertal interaction effects after FDR adjustment (data not shown). Findings using change in %>95th BMI-centile between time-points were similar to those for BMI change (**Supp. Figure S3**, **Supp. Table S7**). For metabolites associated with change in BMI and with the %>95th BMI-centile, relationships were similar in participants who either increased or decreased their %>95th BMI-centile, on average, between time points. For example, for those who increased their %>95th BMI-centile, a greater increase in BMI-centile was associated with higher GlycA and phenylalanine concentrations, and for those who decreased their %>95th BMI-centile, a greater decrease in BMI-centile was associated with lower GlycA and phenylalanine concentrations (**Supp. Figure S4**).

Change in BMI and change in metabolites

Consistent with the associations observed between change in BMI over time and follow-up metabolites, change in age- and sex-adjusted BMI was also associated with several longitudinal changes in metabolite concentrations (**Figure 3, Supp. Table S8**). Decreasing BMI between time points was associated with decreases in alanine, phenylalanine, tyrosine, GlycA, pyruvate, monounsaturated fatty acids, the ratio of ApoB/ApoA1, total triglycerides, the ratio of triglycerides/phosphoglycerides and VLDL-cholesterol, and with increases in acetoacetate, 3-hydroxybutyrate, the degree of fatty acid unsaturation, the percentage of linoleic acid, and HDL-cholesterol. Adjustment for socioeconomic status had no impact on our reported findings, although adjustment for pubertal status modestly attenuated the associations for ketone bodies, cholesterols, and glycerides (**Supp. Table S9**). There

was no evidence for BMI-by-sex or BMI-by-pubertal interaction effects for longitudinal changes in metabolomic measures between time points after FDR adjustment (data not shown). Similar findings were observed for change in %>95th BMI-centile between time-points when compared with change in BMI, adjusted for age and sex (**Supp. Figure S5**, **Supp. Table S10**).

Discussion

In this longitudinal cohort study of children and young adults with obesity, the severity of obesity at baseline and changes to the severity of obesity over a mean 5.5-year interval in adolescence were associated with NMR-derived metabolomic profiles at follow-up and with changes to the metabolomic profiles between time points. In fully adjusted models, BMI at baseline was not associated with metabolites at follow-up, whereas improvement in the severity of obesity over time was associated with lower phenylalanine, tyrosine, alanine, GlycA and pyruvate, with higher ketone bodies at follow-up, and with longitudinal changes in these amino acids, GlycA, pyruvate, VLDL and HDL cholesterol, apolipoprotein ratio and fatty acid ratios. These findings suggest that for children and young adults with obesity, weight management resulting in even modest improvements in the severity of obesity during adolescence may improve metabolic health.

The current longitudinal findings extend on our previous data from this cohort. We have reported that different measures of increased adiposity (including BMI, BMI z-score, total body fat percentage, truncal fat percentage, and waist circumference) at baseline were cross-sectionally associated with baseline metabolite concentrations, including higher tyrosine, phenylalanine, and GlycA, and lower acetate, with evidence of sex- and puberty-related effects (13). Specifically, associations between higher BMI and higher fatty acids, triglycerides, branched chain acids (BCAAs), LDL cholesterol, and inflammation were particularly evident in post-pubertal males (13). In the current study, we found no evidence for associations between baseline BMI and follow-up metabolite concentrations measured in later adolescence (mean interval 5.5 years). However, changes in BMI from baseline to follow-up were associated with several metabolites at follow-up and with changes to several metabolites between time points implicated in cardiometabolic disease. Adjusting the models for baseline measures of exposure (BMI) and outcome (metabolite) accounted for the potential indirect effect of baseline BMI on follow-up metabolites mediated through associations of baseline BMI with baseline metabolites, which we assumed based on our previous findings from cross-sectional analyses at

baseline in this cohort (13). Consequently, the findings from our three aims emphasize that most of the total effect on follow-up metabolites is not driven by baseline BMI, nor by a mediating effect from baseline BMI on baseline metabolites, but by changes in the severity of obesity between time points. In summary, the main findings of the current study are that in children and young adults with obesity: i) changes in age- and sex- adjusted BMI over time, but not antecedent BMI measures, are associated with specific metabolomic profiles implicated in cardiometabolic disease; and ii) changes in the severity of obesity are driving most of the effect on these changes in metabolomic profiles.

Accumulating evidence from adults indicate specific, obesity-related changes in metabolomic profiles, sometimes referred to as 'metabolic signatures of obesity' (23-25). These profiles are potentially reversible with weight loss (26) and refine CVD prediction beyond BMI alone (27). These NMR or liquid chromatography/mass-spectrometry metabolomic profiles include positive associations between higher BMI levels with levels of BCAAs, aromatic amino acids (AAA), triglycerides, VLDL and LDL-lipoprotein subclasses, GlycA, and negative associations with HDL-lipoprotein subclasses (25, 28, 29). Interestingly, the direction of the association between BMI with BCAA, AAA, all lipoprotein subclasses and with GlycA in this study in adolescents with obesity was consistent with that from a Mendelian randomisation study of BMI on changes in metabolites in 12,664 adolescents and young adults (aged 16-39 years) whose BMI was predominantly in the normal range (mean (SD) 24 (4) kg/m^2) (25). In that study, the effect sizes for individual metabolites from the 6-year longitudinal analysis (n=1,488) were similar to those observed in the current study. Here, we observed modest evidence for relationships between changes in BMI and measures of triglycerides, VLDL lipoproteins, HDL lipoproteins and the ApoB/ApoA1 ratio, in models that only considered these metabolites at follow-up. However, in longitudinal models that included baseline metabolomic measures, these relationships were more evident.

Higher concentrations of AAAs, including phenylalanine and tyrosine, observed in those with more severe obesity, have been linked to insulin resistance and metabolic syndrome in adults (30, 31).

Similarly, elevated BCAAs have also been linked to insulin resistance, and risk of type 2 diabetes (32, 33) and CVD (34, 35). In adults, the inflammatory marker GlycA has been associated both with higher BMI, increased risk of both CVD and all-cause mortality (36, 37), and subclinical cardiovascular phenotypes in adults with chronic inflammatory conditions, such as HIV (38) and psoriasis (39). These findings highlight the importance of inflammatory pathways as potential druggable mediators between adiposity and cardiovascular health (40-42).

Taken together, this study provides evidence for potential significance of intervention to improve BMI for youth and young adults with obesity, and suggests that this would be associated with improvements in metabolic profile regardless of the existing severity of obesity. Ideally, intervention to reduce severity of obesity would occur as early as possible to reduce overall time at risk (43). Earlier interventions are likely to be more effective and feasible while children are in full-time education. Moreover, meta-analytic data suggest that the contribution of childhood and adolescent obesity to CVD risk may be driven primarily by tracking to adulthood obesity, as individuals who have overweight in childhood but normal weight in adulthood have comparable CVD risk measures as adults who were normal weight from childhood (44). Given the high rate of persistence of obesity from childhood into adulthood (45), intervention earlier in life course to manage weight is likely more effective at preventing the later development of CVD risk phenotypes. While similar metabolic changes with improvement in BMI observed in this study may occur in older adults with obesity, irreversible vascular damage may already be present.

The strengths of our study include the combination of longitudinal data on both the severity of obesity and metabolomic profiles in a cohort of children and young adults with obesity followed-up over a mean of 5.5 years, which has not been previously reported. We used a validated metabolomic platform that has been widely used in adults across a wide BMI-range, and in studies of CVD. Limitations include the relatively modest cohort size and the wide age range of participants (range 6.1 to 24.3 years of age at follow-up). Body composition changes substantially over childhood, particularly

during puberty. While changes in metabolomic profile over this age window have not yet been characterised, previous evidence from this cohort suggests that the relationship between severity of obesity and metabolites differs by puberty status in males at baseline (13). We did not observe differences in the relationship between change in severity of obesity and change in metabolites by pubertal status in this current study, but this may be influenced by the small number of pre-pubertal participants at follow-up (n=8). Although there was a wide age range of participants, we observed similar findings for models using age- and sex-adjusted BMI and models using %>95th BMI-centile, which is based on age- and sex-standardised BMI-centiles. Adjustment for pubertal status at both time points only had a modest effect on estimated associations. There was also a lack of participants with BMI in the healthy range, which precludes the generalizability of the findings to all children and adolescents. However, our findings are relevant to a growing proportion of youth with obesity, with approximately 80% of children with obesity will still have obesity by adulthood (46) and therefore represent a population at high risk for later obesity-related co-morbidities. Another consideration is that in this study, we have focused on models with BMI as the exposure and metabolomic measures as the outcome, based on Mendelian randomisation studies that have reported BMI having a casual effect on NMR metabolomic measures (25). However, evidence also shows metabolomic differences could contribute to the development and progression of obesity (47). Assessing causality was beyond the scope of this study, and we report associations only.

In conclusion, improvement in the severity of obesity from early to later adolescence is associated with changes in metabolites consistent with lower cardiometabolic risk and inflammatory profiles in adulthood. Our findings suggest that even for youth with severe obesity, limiting the severity of obesity over time may improve their metabolomic profile, with potential long-term benefits to cardiometabolic health. Replication of our findings and investigation of the longitudinal relationship between obesity, metabolites and cardiovascular phenotypes from childhood through to adulthood are warranted. Future studies are needed to investigate the utility of these metabolites as biomarkers

to gauge the success of interventions for obesity on metabolic health in adolescence and later adulthood.

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Author contributions

TM, DB and CS conceptualised and developed the study. MAS set up the cohort, supervised the data collection and critically revised the manuscript. BEH, ZM and KTK collected data and critically revised the manuscript. TM undertook statistical analysis. CGM assisted with the statistical analysis plan and provided support in interpreting the results. TM, DB and CS drafted the manuscript. JN, TTL, SB, MJ and RS revised the manuscript for important intellectual content. All authors provided expert advice and critical review of the manuscript and approved the final version.

Competing interests

The authors have no conflicts of interest to declare.

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Table and Figure Legends

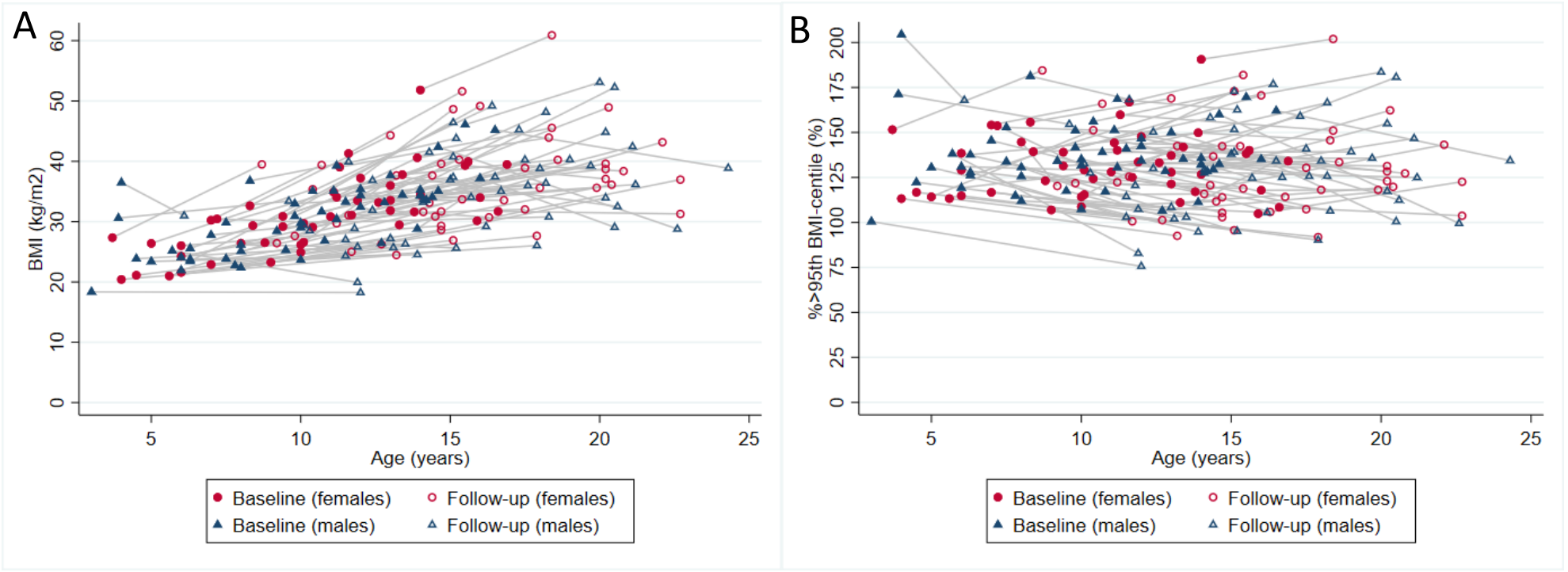
Table 1. Participants characteristics at baseline and follow-up. Results provided in mean, standard deviation (SD) and range (minimum to maximum) for absolute number of individuals (n) and the proportion in percentage(%). The % >95th BMI-centile indicates the severity of obesity based on the age- and sex-adjusted 95th BMI-centile (i.e., the threshold for obesity). Pubertal status was determined according to Tanner stages: Pre-pubertal: Tanner stage 1; Peri-pubertal: Tanner stage 2 & 3; Post-pubertal: Tanner stage 4 & 5. BMI: body mass index; % >95th BMI-centile: severity of obesity in percentage, based on the age- and sex-adjusted 95th BMI-centile.

Figure 1. Longitudinal associations between lower BMI (per one unit kg/m^2) at baseline and metabolite log concentrations (SD units) at follow-up, adjusted for age at each time point and sex. Error bars are 95% confidence intervals. Abbreviations are listed in **Supp. Table S1**.

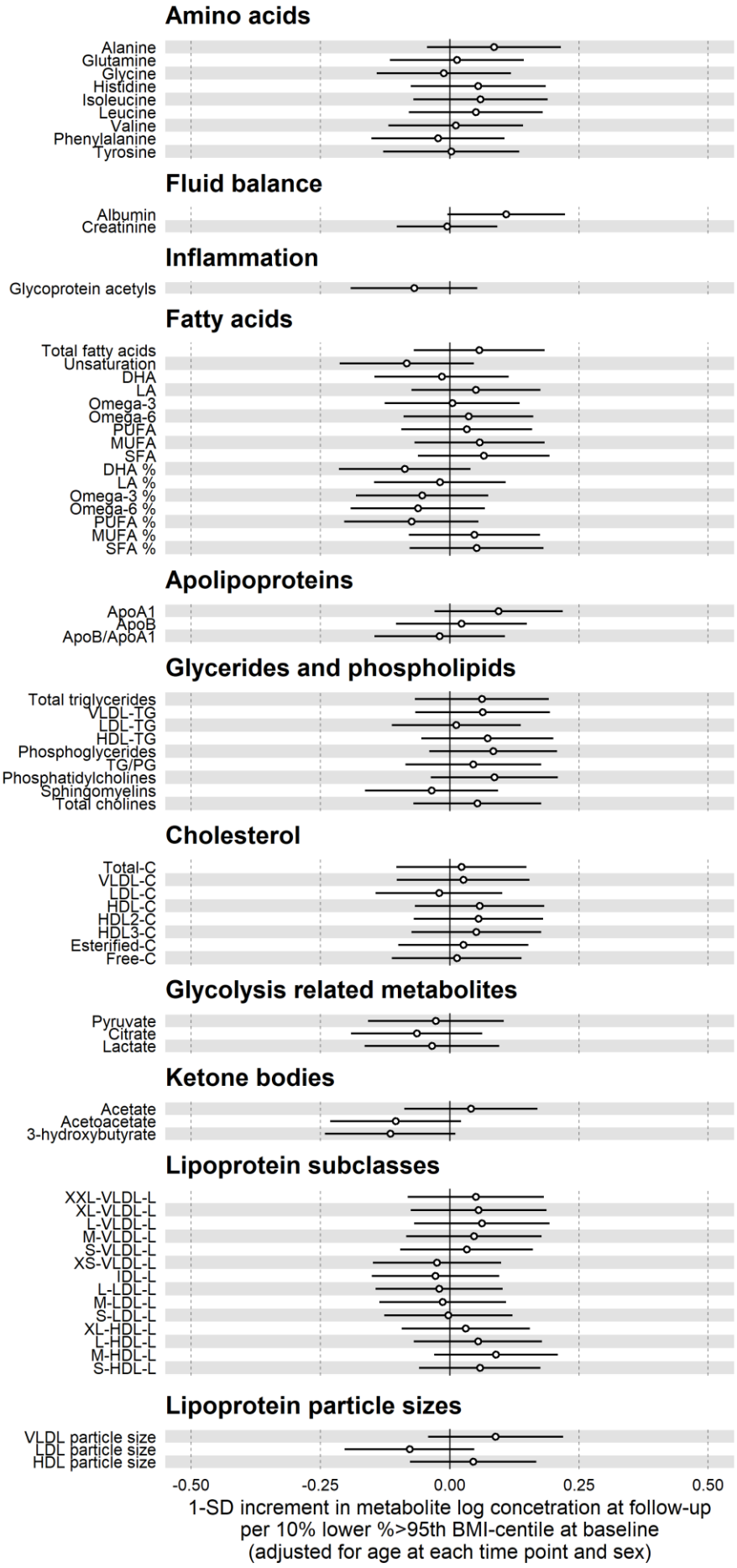
Figure 2. Associations between change in BMI (per 1 kg/m^2 decrease) between time points and metabolite log concentrations (SD units) at follow-up, adjusted for age at each time point and sex. Filled dots indicate a $p<0.05$ after Benjamini-Hochberg adjustment. Error bars are 95% confidence intervals. Abbreviations are listed in **Supp. Table S1**.

Figure 3. Associations between change in BMI (per 1 kg/m^2 decrease) between time points and change in metabolite log concentrations (SD units) between time points, adjusted for age at each time point and sex. Filled dots indicate a $p<0.05$ after Benjamini-Hochberg adjustment. Error bars are 95% confidence intervals. Abbreviations are listed in **Supp. Table S1**.

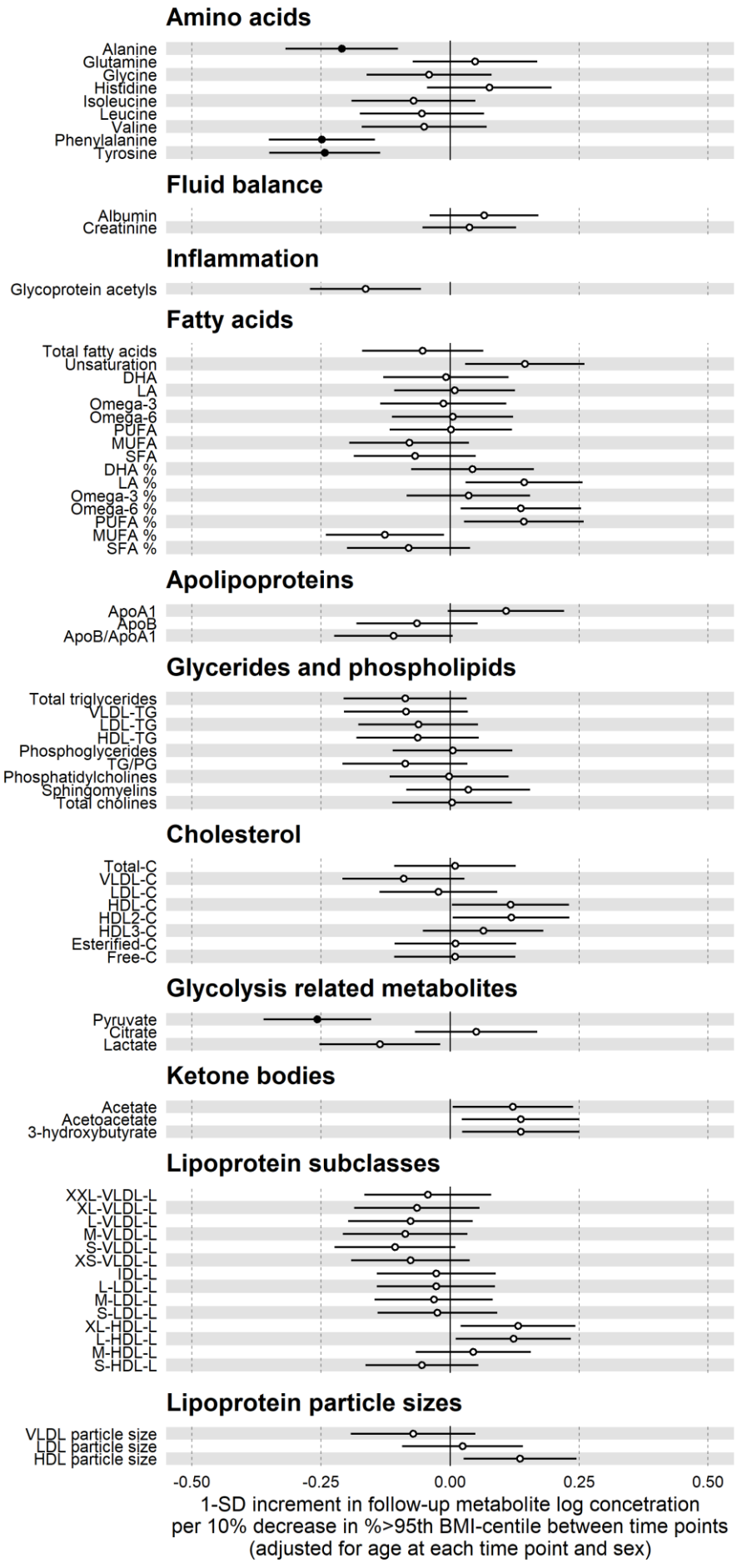
Supplementary Figures



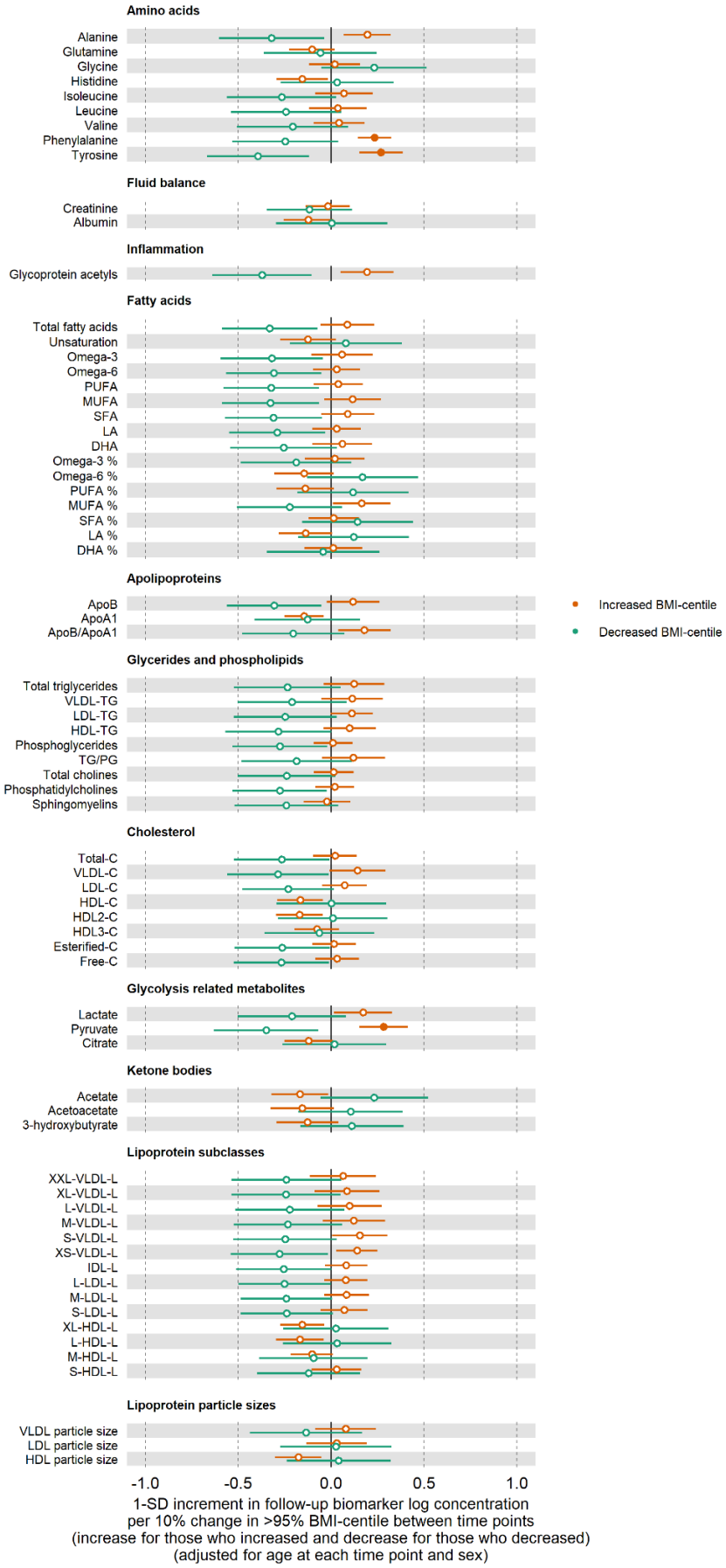
Supp. Figure S1. Change in (A) BMI and (B) %>95th BMI-centile between timepoints for each participant. Baseline timepoint is solid, follow-up time point is hollow. Females are red, males are in blue. The connecting grey line represents the change in BMI or %>95th BMI-centile.



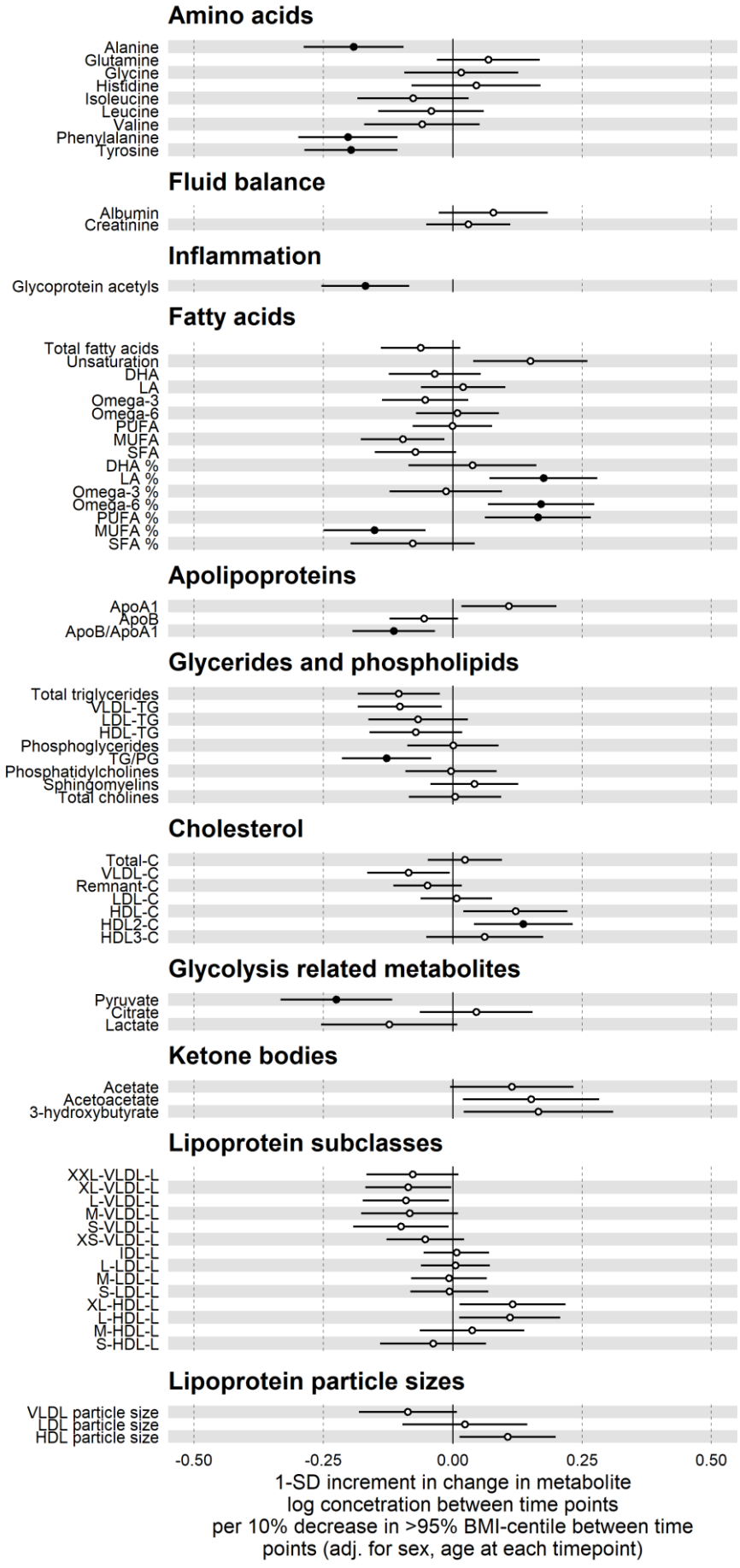
Supp. Figure S2. Associations between lower %>95th BMI-centile (per 10%) at baseline and metabolite log concentrations (SD units) at follow-up, adjusted for age at each time point and sex. Error bars are 95% confidence intervals. Abbreviations are listed in **Supp. Table S1.**


Amino acids
Alanine
Glutamine
Glycine
Histidine
Isoleucine
Leucine
Valine
Phenylalanine
Tyrosine
Fluid balance
Albumin
Creatinine
Inflammation
Glycoprotein acetyls
Fatty acids
Total fatty acids
Unsaturation
DHA
LA
Omega-3
Omega-6
PUFA
MUFA
SFA
DHA %
LA %
Omega-3 %
Omega-6 %
PUFA %
MUFA %
SFA %
Apolipoproteins
ApoA1
ApoB
ApoB/ApoA1
Glycerides and phospholipids
Total triglycerides
VLDL-TG
LDL-TG
HDL-TG
Phosphoglycerides
TG/PG
Phosphatidylcholines
Sphingomyelins
Total cholines
Cholesterol
Total-C
VLDL-C
LDL-C
HDL-C
HDL2-C
HDL3-C
Esterified-C
Free-C
Glycolysis related metabolites
Pyruvate
Citrate
Lactate
Ketone bodies
Acetate
Acetoacetate
3-hydroxybutyrate
Lipoprotein subclasses
XXL-VLDL-L
XL-VLDL-L
L-VLDL-L
M-VLDL-L
S-VLDL-L
XS-VLDL-L
IDL-L
L-LDL-L
M-LDL-L
S-LDL-L
XL-HDL-L
L-HDL-L
M-HDL-L
S-HDL-L
Lipoprotein particle sizes
VLDL particle size
LDL particle size
HDL particle size
-0.50
-0.25
0.00
0.25
0.50
1-SD increment in follow-up metabolite log concetration
per 10% decrease in %>95th BMI-centile between time points
(adjusted for age at each time point and sex)

Supp. Figure S3. Associations between change in %>95th BMI-centile (per 10% decrease) between time points and metabolite log concentrations (SD units) at follow-up, adjusted for age at each time point and sex. Filled dots indicate a p<0.05 after Benjamini-Hochberg adjustment. Error bars are 95% confidence intervals. Abbreviations are listed in **Supp. Table S1.**



Supp. Figure S4. Associations between increase (orange) and decrease (green) in %>95th BMI-centile (per 10% change) between time points and log metabolite concentrations (SD units) at follow-up, stratified by whether the participant increased (orange) or decreased (green) their %>95th BMI-centile between time points. Filled dots indicate a p<0.05 after Benjamini-Hochberg adjustment. Error bars are 95% confidence intervals. Abbreviations are listed in **Supp. Table S1.**



Supp. Figure S5. Associations between change in %>95th BMI-centile (per 10% decrease) between time points and change in log metabolite concentrations (SD units) between time points, adjusted for age at each time point and sex. Filled dots indicate a p<0.05 after Benjamini-Hochberg adjustment. Error bars are 95% confidence intervals. Abbreviations are listed in **Supp. Table S1.**

Supplementary Tables

Supp. Table S1. Definitions of metabolomic measure abbreviations.

Abbreviation	Definition
XXL-VLDL-L	Extra extra large subclass of very-low-density lipoprotein lipids
XL-VLDL-L	Extra large subclass of very-low-density lipoprotein lipids
L-VLDL-L	Large subclass of very-low-density lipoprotein lipids
M-VLDL-L	Medium subclass of very-low-density lipoprotein lipids
S-VLDL-L	Small subclass of very-low-density lipoprotein lipids
XS-VLDL-L	Extra small subclass of very-low-density lipoprotein lipids
IDL-L	Intermediate-density lipoprotein lipids
L-LDL-L	Large subclass of low-density lipoprotein lipids
M-LDL-L	Medium subclass of low-density lipoprotein lipids
S-LDL-L	Small subclass of low-density lipoprotein lipids
XL-HDL-L	Extra large subclass of high-density lipoprotein lipids
L-HDL-L	Large subclass of high-density lipoprotein lipids
M-HDL-L	Medium subclass of high-density lipoprotein lipids
S-HDL-L	Small subclass of high-density lipoprotein lipids
VLDL particle size	Very-low-density lipoprotein particle size
LDL particle size	Low-density lipoprotein particle size
HDL particle size	High-density lipoprotein particle size
ApoA1	Apolipoprotein A1
ApoB	Apolipoprotein B
ApoB/ApoA1	Ratio of Apolipoprotein B to Apolipoprotein A1
Total-C	Total cholesterol
VLDL-C	Very-low-density lipoprotein cholesterol
Remnant-C	Remnant cholesterol
LDL-C	Low-density lipoprotein cholesterol
HDL-C	High-density lipoprotein cholesterol
HDL2-C	High-density lipoprotein 2 subclass cholesterol
HDL3-C	High-density lipoprotein 3 subclass cholesterol
Esterified-C	Esterified cholesterol
Free-C	Free cholesterol
Unsaturation	Unsaturation degree of fatty acids
DHA	Docosahexaenoic acid
LA	Linoleic acid
PUFA	Polyunsaturated fatty acids
MUFA	Monounsaturated fatty acids
SFA	Saturated fatty acids
DHA %	Docosahexaenoic acid as percentage of total fatty acids
LA %	Linoleic acid as percentage of total fatty acids
Omega-3 %	Omega-3 fatty acids as percentage of total fatty acids
Omega-6 %	Omega-6 fatty acids as percentage of total fatty acids
PUFA %	Polyunsaturated fatty acids as percentage of total fatty acids
MUFA %	Monounsaturated fatty acids as percentage of total fatty acids
SFA %	Saturated fatty acids as percentage of total fatty acids
VLDL-TG	Very-low-density lipoprotein triglycerides
LDL-TG	Low-density lipoprotein triglycerides
HDL-TG	High-density lipoprotein triglycerides
TG/PG	Ratio of triglycerides to phosphoglycerides

Supp. Table S2. Coefficients of the log concentrations of metabolites in SD units at follow-up per unit BMI (kg/m^2) lower at baseline from linear regression models (n=98).

Name	Estimate	95% CI	p-value	Adj. p-value
Lipoprotein subclasses				
XXL-VLDL-L	0.021	-0.035 to 0.076	0.47	0.95
XL-VLDL-L	0.024	-0.031 to 0.08	0.39	0.95
L-VLDL-L	0.027	-0.028 to 0.083	0.34	0.95
M-VLDL-L	0.022	-0.034 to 0.077	0.45	0.95
S-VLDL-L	0.015	-0.039 to 0.07	0.58	0.95
XS-VLDL-L	-0.014	-0.067 to 0.038	0.60	0.95
IDL-L	-0.015	-0.067 to 0.037	0.57	0.95
L-LDL-L	-0.010	-0.062 to 0.042	0.70	0.97
M-LDL-L	-0.005	-0.057 to 0.047	0.86	1.00
S-LDL-L	0.000	-0.053 to 0.052	0.99	1.00
XL-HDL-L	-0.001	-0.053 to 0.052	0.97	1.00
L-HDL-L	0.011	-0.042 to 0.064	0.69	0.97
M-HDL-L	0.029	-0.022 to 0.08	0.27	0.95
S-HDL-L	0.030	-0.02 to 0.079	0.24	0.95
Lipoprotein particle sizes				
VLDL particle size	0.041	-0.015 to 0.096	0.15	0.95
LDL particle size	-0.043	-0.096 to 0.01	0.11	0.95
HDL particle size	0.004	-0.048 to 0.056	0.87	1.00
Apolipoproteins				
ApoA1	0.029	-0.024 to 0.082	0.28	0.95
ApoB	0.009	-0.044 to 0.063	0.74	0.98
ApoB/ApoA1	-0.004	-0.057 to 0.05	0.89	1.00
Cholesterols				
Total-C	0.004	-0.049 to 0.058	0.87	1.00
VLDL-C	0.011	-0.043 to 0.066	0.69	0.97
Remnant-C	0.002	-0.051 to 0.055	0.94	1.00
LDL-C	-0.008	-0.06 to 0.043	0.75	0.98
HDL-C	0.014	-0.039 to 0.067	0.61	0.95
HDL2-C	0.013	-0.04 to 0.066	0.64	0.97
HDL3-C	0.018	-0.035 to 0.071	0.52	0.95
Esterified-C	0.006	-0.047 to 0.059	0.82	0.99
Free-C	0.000	-0.053 to 0.053	1.00	1.00
Fatty acids				
Total fatty acids	0.020	-0.034 to 0.073	0.48	0.95
Unsaturation	-0.035	-0.09 to 0.02	0.21	0.95
DHA	-0.007	-0.062 to 0.048	0.81	0.99
LA	0.017	-0.036 to 0.07	0.52	0.95
Omega-3	0.003	-0.052 to 0.059	0.91	1.00
Omega-6	0.011	-0.043 to 0.064	0.70	0.97
PUFA	0.010	-0.044 to 0.064	0.71	0.97
MUFA	0.021	-0.033 to 0.074	0.45	0.95
SFA	0.023	-0.031 to 0.077	0.41	0.95
DHA %	-0.034	-0.088 to 0.02	0.23	0.95
LA %	-0.007	-0.061 to 0.047	0.80	0.99
Omega-3 %	-0.017	-0.071 to 0.037	0.54	0.95
Omega-6 %	-0.025	-0.08 to 0.03	0.38	0.95

PUFA %	-0.028	-0.083 to 0.027	0.31	0.95
MUFA %	0.019	-0.035 to 0.073	0.49	0.95
SFA %	0.019	-0.036 to 0.074	0.50	0.95
Amino acids				
Alanine	0.036	-0.019 to 0.09	0.21	0.95
Glutamine	-0.001	-0.056 to 0.054	0.98	1.00
Glycine	-0.008	-0.063 to 0.047	0.77	0.98
Histidine	0.015	-0.04 to 0.071	0.59	0.95
Isoleucine	0.031	-0.023 to 0.086	0.27	0.95
Leucine	0.025	-0.03 to 0.08	0.37	0.95
Valine	0.015	-0.04 to 0.07	0.59	0.95
Phenylalanine	-0.016	-0.07 to 0.039	0.57	0.95
Tyrosine	0.000	-0.055 to 0.056	0.99	1.00
Glycerides and phospholipids				
Total triglycerides	0.026	-0.029 to 0.081	0.35	0.95
VLDL-TG	0.028	-0.027 to 0.083	0.32	0.95
LDL-TG	-0.001	-0.054 to 0.052	0.98	1.00
HDL-TG	0.026	-0.028 to 0.08	0.35	0.95
Phosphoglycerides	0.028	-0.024 to 0.081	0.30	0.95
TG/PG	0.021	-0.035 to 0.077	0.46	0.95
Phosphatidylcholines	0.028	-0.025 to 0.08	0.31	0.95
Sphingomyelins	-0.022	-0.077 to 0.032	0.43	0.95
Total cholines	0.014	-0.039 to 0.067	0.60	0.95
Glycolysis related metabolites				
Pyruvate	-0.018	-0.073 to 0.037	0.53	0.95
Citrate	-0.032	-0.086 to 0.021	0.24	0.95
Lactate	-0.012	-0.067 to 0.043	0.67	0.97
Ketone bodies				
Acetate	0.018	-0.036 to 0.072	0.52	0.95
Acetoacetate	-0.048	-0.102 to 0.005	0.08	0.95
3-hydroxybutyrate	-0.046	-0.1 to 0.008	0.10	0.95
Fluid balance				
Albumin	0.047	-0.001 to 0.095	0.06	0.95
Creatinine	-0.006	-0.048 to 0.035	0.77	0.98
Inflammation				
Glycoprotein acetyls	-0.030	-0.082 to 0.022	0.27	0.95

Adjusted for age at each time point and sex. Adjusted p-values are based on Benjamini-Hochberg adjustment. Abbreviations are listed in **Supp. Table S1.**

Supp. Table S3. Coefficients of the log concentrations of metabolites in SD units at follow-up per unit BMI (kg/m^2) lower at baseline from linear regression models, additionally adjusted for pubertal status or socioeconomic status (n=98).

Name	Adjusted for pubertal status				Adjusted for socioeconomic status			
	Estimate	**95% CI**	**p-value**	**Adj. p-value**	**Estimate**	**95% CI**	**p-value**	**Adj. p-value**
Lipoprotein subclasses								
XXL-VLDL-L	0.017	-0.038 to 0.072	0.543	0.994	0.023	-0.033 to 0.079	0.427	0.953
XL-VLDL-L	0.022	-0.033 to 0.077	0.429	0.994	0.027	-0.029 to 0.083	0.344	0.953
L-VLDL-L	0.025	-0.029 to 0.079	0.367	0.994	0.031	-0.024 to 0.086	0.272	0.953
M-VLDL-L	0.020	-0.033 to 0.072	0.467	0.994	0.026	-0.029 to 0.081	0.362	0.953
S-VLDL-L	0.015	-0.037 to 0.067	0.578	0.994	0.020	-0.033 to 0.074	0.457	0.953
XS-VLDL-L	-0.016	-0.069 to 0.037	0.555	0.994	-0.010	-0.062 to 0.042	0.710	0.953
IDL-L	-0.015	-0.069 to 0.038	0.579	0.994	-0.013	-0.065 to 0.04	0.633	0.953
L-LDL-L	-0.009	-0.062 to 0.045	0.754	0.994	-0.008	-0.06 to 0.044	0.766	0.953
M-LDL-L	-0.002	-0.055 to 0.051	0.954	0.994	-0.003	-0.055 to 0.05	0.923	0.981
S-LDL-L	0.003	-0.051 to 0.057	0.910	0.994	0.002	-0.051 to 0.055	0.947	0.981
XL-HDL-L	-0.005	-0.058 to 0.048	0.857	0.994	-0.003	-0.056 to 0.05	0.904	0.981
L-HDL-L	0.007	-0.045 to 0.06	0.786	0.994	0.008	-0.045 to 0.061	0.760	0.953
M-HDL-L	0.026	-0.027 to 0.079	0.339	0.994	0.029	-0.023 to 0.081	0.276	0.953
S-HDL-L	0.033	-0.018 to 0.084	0.207	0.994	0.032	-0.018 to 0.082	0.211	0.953
Lipoprotein particle sizes								
VLDL particle size	0.040	-0.013 to 0.094	0.147	0.994	0.043	-0.013 to 0.098	0.135	0.953
LDL particle size	-0.053	-0.104 to -0.002	0.045	0.994	-0.042	-0.095 to 0.011	0.128	0.953
HDL particle size	0.000	-0.052 to 0.052	0.994	0.994	0.002	-0.05 to 0.054	0.954	0.981
Apolipoproteins								
ApoA1	0.026	-0.029 to 0.081	0.361	0.994	0.028	-0.026 to 0.081	0.311	0.953
ApoB	0.009	-0.043 to 0.06	0.740	0.994	0.013	-0.04 to 0.066	0.639	0.953
ApoB/ApoA1	-0.002	-0.053 to 0.049	0.929	0.994	0.000	-0.053 to 0.053	0.995	0.995
Cholesterols								
Total-C	0.004	-0.051 to 0.06	0.878	0.994	0.006	-0.048 to 0.06	0.831	0.953
VLDL-C	0.009	-0.042 to 0.06	0.737	0.994	0.016	-0.038 to 0.069	0.575	0.953
Remnant-C	0.000	-0.05 to 0.051	0.992	0.994	0.006	-0.047 to 0.059	0.834	0.953
LDL-C	-0.005	-0.058 to 0.048	0.852	0.994	-0.007	-0.059 to 0.045	0.802	0.953
HDL-C	0.012	-0.042 to 0.066	0.669	0.994	0.012	-0.042 to 0.065	0.667	0.953
HDL2-C	0.010	-0.044 to 0.064	0.710	0.994	0.010	-0.043 to 0.064	0.703	0.953
HDL3-C	0.021	-0.034 to 0.076	0.457	0.994	0.018	-0.036 to 0.072	0.522	0.953
Esterified-C	0.006	-0.049 to 0.062	0.826	0.994	0.008	-0.046 to 0.061	0.781	0.953
Free-C	0.000	-0.055 to 0.055	0.993	0.994	0.002	-0.052 to 0.055	0.949	0.981
Fatty acids								
Total fatty acids	0.017	-0.037 to 0.07	0.543	0.994	0.023	-0.03 to 0.077	0.392	0.953
Unsaturation	-0.034	-0.091 to 0.023	0.250	0.994	-0.041	-0.094 to 0.012	0.136	0.953
DHA	-0.013	-0.069 to 0.043	0.659	0.994	-0.006	-0.062 to 0.049	0.827	0.953
LA	0.016	-0.037 to 0.069	0.552	0.994	0.020	-0.034 to 0.073	0.472	0.953
Omega-3	-0.003	-0.058 to 0.053	0.927	0.994	0.005	-0.051 to 0.06	0.871	0.977
Omega-6	0.009	-0.045 to 0.063	0.753	0.994	0.013	-0.041 to 0.066	0.637	0.953
PUFA	0.007	-0.047 to 0.062	0.789	0.994	0.012	-0.042 to 0.066	0.658	0.953
MUFA	0.019	-0.034 to 0.072	0.486	0.994	0.025	-0.028 to 0.078	0.359	0.953
SFA	0.018	-0.035 to 0.072	0.506	0.994	0.027	-0.026 to 0.081	0.319	0.953
DHA %	-0.038	-0.093 to 0.016	0.174	0.994	-0.037	-0.091 to 0.017	0.185	0.953
LA %	-0.002	-0.058 to 0.054	0.939	0.994	-0.011	-0.064 to 0.043	0.693	0.953

Omega-3 %	-0.023	-0.078 to 0.033	0.428	0.994	-0.019	-0.074 to 0.036	0.496	0.953
Omega-6 %	-0.021	-0.077 to 0.035	0.468	0.994	-0.029	-0.084 to 0.025	0.294	0.953
PUFA %	-0.027	-0.083 to 0.03	0.360	0.994	-0.033	-0.087 to 0.021	0.229	0.953
MUFA %	0.022	-0.032 to 0.076	0.427	0.994	0.023	-0.03 to 0.076	0.399	0.953
SFA %	0.011	-0.045 to 0.068	0.697	0.994	0.022	-0.033 to 0.077	0.439	0.953
Amino acids								
Alanine	0.038	-0.016 to 0.092	0.170	0.994	0.037	-0.018 to 0.093	0.189	0.953
Glutamine	0.004	-0.046 to 0.055	0.869	0.994	0.000	-0.056 to 0.055	0.995	0.995
Glycine	-0.007	-0.062 to 0.049	0.812	0.994	-0.011	-0.066 to 0.044	0.694	0.953
Histidine	0.020	-0.038 to 0.077	0.503	0.994	0.017	-0.04 to 0.073	0.564	0.953
Isoleucine	0.030	-0.027 to 0.087	0.311	0.994	0.036	-0.018 to 0.09	0.193	0.953
Leucine	0.024	-0.033 to 0.081	0.418	0.994	0.029	-0.025 to 0.083	0.297	0.953
Valine	0.017	-0.039 to 0.074	0.547	0.994	0.018	-0.037 to 0.073	0.523	0.953
Phenylalanine	-0.014	-0.071 to 0.042	0.620	0.994	-0.011	-0.064 to 0.043	0.698	0.953
Tyrosine	0.003	-0.055 to 0.061	0.913	0.994	0.007	-0.047 to 0.06	0.808	0.953
Glycerides and phospholipids								
Total triglycerides	0.025	-0.028 to 0.078	0.362	0.994	0.031	-0.024 to 0.085	0.274	0.953
VLDL-TG	0.027	-0.026 to 0.081	0.326	0.994	0.032	-0.023 to 0.087	0.255	0.953
LDL-TG	-0.001	-0.056 to 0.053	0.959	0.994	0.004	-0.048 to 0.056	0.882	0.977
HDL-TG	0.022	-0.031 to 0.074	0.420	0.994	0.030	-0.024 to 0.084	0.278	0.953
Phosphoglycerides	0.024	-0.031 to 0.079	0.402	0.994	0.030	-0.024 to 0.083	0.279	0.953
TG/PG	0.020	-0.034 to 0.074	0.473	0.994	0.025	-0.03 to 0.08	0.383	0.953
Phosphatidylcholines	0.023	-0.031 to 0.078	0.407	0.994	0.029	-0.024 to 0.082	0.284	0.953
Sphingomyelins	-0.024	-0.082 to 0.033	0.408	0.994	-0.022	-0.077 to 0.033	0.443	0.953
Total cholines	0.010	-0.045 to 0.064	0.735	0.994	0.015	-0.038 to 0.068	0.578	0.953
Glycolysis related metabolites								
Pyruvate	-0.013	-0.071 to 0.044	0.652	0.994	-0.017	-0.073 to 0.039	0.559	0.953
Citrate	-0.036	-0.089 to 0.018	0.196	0.994	-0.030	-0.084 to 0.024	0.278	0.953
Lactate	-0.011	-0.068 to 0.047	0.720	0.994	-0.010	-0.066 to 0.045	0.718	0.953
Ketone bodies								
Acetate	0.023	-0.03 to 0.077	0.395	0.994	0.014	-0.04 to 0.069	0.604	0.953
Acetoacetate	-0.052	-0.105 to 0.002	0.062	0.994	-0.049	-0.103 to 0.005	0.080	0.953
3-hydroxybutyrate	-0.048	-0.099 to 0.004	0.078	0.994	-0.047	-0.101 to 0.007	0.094	0.953
Fluid balance								
Albumin	0.049	-0.001 to 0.1	0.061	0.994	0.045	-0.004 to 0.093	0.075	0.953
Creatinine	0.000	-0.041 to 0.041	0.985	0.994	-0.005	-0.047 to 0.036	0.798	0.953
Inflammation								
Glycoprotein acetyls	-0.031	-0.084 to 0.022	0.256	0.994	-0.028	-0.081 to 0.024	0.298	0.953

All models adjusted for age at each time point and sex. Adjusted p-values are based on Benjamini-Hochberg adjustment. Abbreviations are listed in **Supp. Table S1.**

Supp. Table S4. Coefficients of the log concentrations of metabolites in SD units at follow-up per 10% lower %>95th BMI-centile at baseline from linear regression models (n=98).

Name	Estimate (per 10%)	95% CI	p-value	Adj. p-value
Lipoprotein subclasses				
XXL-VLDL-L	0.051	-0.081 to 0.183	0.45	0.86
XL-VLDL-L	0.056	-0.075 to 0.187	0.41	0.86
L-VLDL-L	0.063	-0.068 to 0.193	0.35	0.86
M-VLDL-L	0.047	-0.084 to 0.178	0.49	0.87
S-VLDL-L	0.033	-0.095 to 0.161	0.62	0.92
XS-VLDL-L	-0.025	-0.149 to 0.099	0.70	0.92
IDL-L	-0.028	-0.151 to 0.096	0.66	0.92
L-LDL-L	-0.021	-0.143 to 0.102	0.74	0.92
M-LDL-L	-0.014	-0.136 to 0.109	0.83	0.93
S-LDL-L	-0.003	-0.127 to 0.122	0.97	0.97
XL-HDL-L	0.031	-0.093 to 0.155	0.62	0.92
L-HDL-L	0.055	-0.069 to 0.178	0.39	0.86
M-HDL-L	0.090	-0.03 to 0.209	0.15	0.86
S-HDL-L	0.058	-0.059 to 0.176	0.33	0.86
Lipoprotein particle sizes				
VLDL particle size	0.089	-0.042 to 0.219	0.19	0.86
LDL particle size	-0.078	-0.203 to 0.048	0.23	0.86
HDL particle size	0.046	-0.077 to 0.168	0.47	0.86
Apolipoproteins				
ApoA1	0.095	-0.029 to 0.219	0.14	0.86
ApoB	0.023	-0.104 to 0.149	0.73	0.92
ApoB/ApoA1	-0.020	-0.146 to 0.107	0.76	0.92
Cholesterols				
Total-C	0.023	-0.103 to 0.149	0.72	0.92
VLDL-C	0.026	-0.103 to 0.155	0.69	0.92
Remnant-C	0.008	-0.118 to 0.133	0.90	0.96
LDL-C	-0.021	-0.143 to 0.101	0.74	0.92
HDL-C	0.058	-0.067 to 0.183	0.37	0.86
HDL2-C	0.056	-0.069 to 0.181	0.38	0.86
HDL3-C	0.052	-0.074 to 0.177	0.42	0.86
Esterified-C	0.026	-0.1 to 0.152	0.68	0.92
Free-C	0.014	-0.112 to 0.139	0.83	0.93
Fatty acids				
Total fatty acids	0.057	-0.069 to 0.183	0.38	0.86
Unsaturation	-0.083	-0.213 to 0.047	0.21	0.86
DHA	-0.016	-0.145 to 0.114	0.82	0.93
LA	0.051	-0.074 to 0.176	0.43	0.86
Omega-3	0.005	-0.126 to 0.136	0.94	0.97
Omega-6	0.036	-0.089 to 0.162	0.57	0.92
PUFA	0.033	-0.094 to 0.159	0.61	0.92
MUFA	0.058	-0.068 to 0.184	0.37	0.86
SFA	0.066	-0.061 to 0.193	0.31	0.86
DHA %	-0.087	-0.215 to 0.041	0.19	0.86
LA %	-0.019	-0.146 to 0.108	0.77	0.92
Omega-3 %	-0.053	-0.181 to 0.075	0.42	0.86
Omega-6 %	-0.062	-0.192 to 0.068	0.36	0.86

PUFA %	-0.074	-0.204 to 0.056	0.27	0.86
MUFA %	0.048	-0.079 to 0.175	0.46	0.86
SFA %	0.052	-0.077 to 0.181	0.43	0.86
Amino acids				
Alanine	0.086	-0.043 to 0.215	0.20	0.86
Glutamine	0.014	-0.115 to 0.144	0.83	0.93
Glycine	-0.011	-0.141 to 0.119	0.86	0.93
Histidine	0.055	-0.075 to 0.186	0.41	0.86
Isoleucine	0.060	-0.07 to 0.189	0.37	0.86
Leucine	0.051	-0.079 to 0.18	0.45	0.86
Valine	0.012	-0.118 to 0.142	0.86	0.93
Phenylalanine	-0.023	-0.151 to 0.106	0.73	0.92
Tyrosine	0.003	-0.129 to 0.135	0.97	0.97
Glycerides and phospholipids				
Total triglycerides	0.062	-0.068 to 0.192	0.35	0.86
VLDL-TG	0.064	-0.067 to 0.194	0.34	0.86
LDL-TG	0.013	-0.112 to 0.138	0.84	0.93
HDL-TG	0.073	-0.055 to 0.201	0.27	0.86
Phosphoglycerides	0.084	-0.04 to 0.208	0.19	0.86
TG/PG	0.046	-0.085 to 0.177	0.50	0.87
Phosphatidylcholines	0.086	-0.037 to 0.209	0.17	0.86
Sphingomyelins	-0.035	-0.163 to 0.094	0.60	0.92
Total cholines	0.053	-0.07 to 0.177	0.40	0.86
Glycolysis related metabolites				
Pyruvate	-0.027	-0.158 to 0.104	0.69	0.92
Citrate	-0.064	-0.191 to 0.063	0.33	0.86
Lactate	-0.035	-0.165 to 0.096	0.60	0.92
Ketone bodies				
Acetate	0.041	-0.088 to 0.17	0.54	0.92
Acetoacetate	-0.104	-0.231 to 0.022	0.11	0.86
3-hydroxybutyrate	-0.115	-0.241 to 0.011	0.08	0.86
Fluid balance				
Albumin	0.109	-0.005 to 0.223	0.06	0.86
Creatinine	-0.005	-0.103 to 0.093	0.92	0.96
Inflammation				
Glycoprotein acetyls	-0.069	-0.192 to 0.054	0.28	0.86

Adjusted for age at each time point and sex. Adjusted p-values are based on Benjamini-Hochberg adjustment. Abbreviations are listed in **Supp. Table S1**.

Supp. Table S5. Coefficients of the log concentrations of metabolites in SD units at follow-up per unit decrease in BMI (kg/m^2) between time points from linear regression models (n=98).

Name	Estimate	95% CI	p-value	Adj. p-value
Lipoprotein subclasses				
XXL-VLDL-L	-0.026	-0.068 to 0.016	0.24	0.38
XL-VLDL-L	-0.034	-0.075 to 0.008	0.12	0.24
L-VLDL-L	-0.037	-0.078 to 0.004	0.08	0.21
M-VLDL-L	-0.041	-0.081 to 0	0.06	0.16
S-VLDL-L	-0.047	-0.087 to -0.007	0.02	0.10
XS-VLDL-L	-0.032	-0.071 to 0.008	0.12	0.24
IDL-L	-0.016	-0.055 to 0.024	0.45	0.57
L-LDL-L	-0.017	-0.056 to 0.022	0.40	0.56
M-LDL-L	-0.019	-0.059 to 0.02	0.34	0.51
S-LDL-L	-0.018	-0.057 to 0.022	0.39	0.56
XL-HDL-L	0.046	0.007 to 0.084	0.02	0.10
L-HDL-L	0.045	0.006 to 0.083	0.03	0.11
M-HDL-L	0.013	-0.026 to 0.052	0.51	0.64
S-HDL-L	-0.024	-0.061 to 0.013	0.21	0.37
Lipoprotein particle sizes				
VLDL particle size	-0.035	-0.076 to 0.006	0.10	0.22
LDL particle size	0.016	-0.024 to 0.056	0.44	0.57
HDL particle size	0.049	0.012 to 0.087	0.01	0.07
Apolipoproteins				
ApoA1	0.031	-0.008 to 0.071	0.12	0.24
ApoB	-0.034	-0.074 to 0.006	0.10	0.23
ApoB/ApoA1	-0.046	-0.085 to -0.007	0.02	0.11
Cholesterols				
Total-C	-0.006	-0.047 to 0.035	0.78	0.79
VLDL-C	-0.042	-0.082 to -0.002	0.04	0.15
Remnant-C	-0.035	-0.074 to 0.005	0.09	0.22
LDL-C	-0.016	-0.055 to 0.023	0.42	0.57
HDL-C	0.040	0.001 to 0.08	0.05	0.15
HDL2-C	0.041	0.002 to 0.081	0.04	0.15
HDL3-C	0.016	-0.024 to 0.056	0.44	0.57
Esterified-C	-0.006	-0.046 to 0.035	0.78	0.79
Free-C	-0.006	-0.046 to 0.035	0.78	0.79
Fatty acids				
Total fatty acids	-0.031	-0.072 to 0.009	0.13	0.24
Unsaturation	0.055	0.016 to 0.095	0.01	0.06
DHA	-0.009	-0.051 to 0.033	0.66	0.72
LA	-0.010	-0.05 to 0.031	0.64	0.72
Omega-3	-0.016	-0.058 to 0.026	0.46	0.58
Omega-6	-0.010	-0.051 to 0.03	0.62	0.70
PUFA	-0.012	-0.053 to 0.029	0.56	0.66
MUFA	-0.040	-0.08 to -0.001	0.05	0.15
SFA	-0.036	-0.076 to 0.004	0.09	0.21
DHA %	0.018	-0.023 to 0.059	0.39	0.56
LA %	0.051	0.012 to 0.09	0.01	0.07
Omega-3 %	0.006	-0.036 to 0.047	0.79	0.79
Omega-6 %	0.054	0.015 to 0.094	0.01	0.06

PUFA %	0.055	0.015 to 0.094	0.01	0.06
MUFA %	-0.053	-0.092 to -0.015	0.01	0.06
SFA %	-0.021	-0.063 to 0.02	0.31	0.48
Amino acids				
Alanine	-0.080	-0.117 to -0.044	<0.001	0.001
Glutamine	0.016	-0.025 to 0.058	0.44	0.57
Glycine	-0.013	-0.055 to 0.029	0.55	0.66
Histidine	0.026	-0.016 to 0.068	0.23	0.38
Isoleucine	-0.034	-0.075 to 0.007	0.11	0.23
Leucine	-0.025	-0.066 to 0.016	0.24	0.38
Valine	-0.026	-0.067 to 0.016	0.23	0.38
Phenylalanine	-0.083	-0.119 to -0.047	<0.001	0.001
Tyrosine	-0.086	-0.122 to -0.049	<0.001	0.001
Glycerides and phospholipids				
Total triglycerides	-0.041	-0.081 to 0	0.05	0.16
VLDL-TG	-0.040	-0.081 to 0	0.06	0.16
LDL-TG	-0.025	-0.064 to 0.015	0.23	0.38
HDL-TG	-0.030	-0.07 to 0.011	0.16	0.29
Phosphoglycerides	-0.009	-0.049 to 0.031	0.66	0.72
TG/PG	-0.040	-0.081 to 0.002	0.06	0.17
Phosphatidylcholines	-0.011	-0.05 to 0.029	0.60	0.70
Sphingomyelins	0.006	-0.036 to 0.047	0.79	0.79
Total cholines	-0.007	-0.047 to 0.033	0.74	0.79
Glycolysis related metabolites				
Pyruvate	-0.087	-0.123 to -0.051	<0.001	0.001
Citrate	0.033	-0.007 to 0.073	0.12	0.24
Lactate	-0.046	-0.086 to -0.005	0.03	0.11
Ketone bodies				
Acetate	0.048	0.008 to 0.087	0.02	0.10
Acetoacetate	0.058	0.02 to 0.096	0.004	0.05
3-hydroxybutyrate	0.057	0.019 to 0.096	0.005	0.05
Fluid balance				
Albumin	0.019	-0.017 to 0.056	0.30	0.47
Creatinine	0.009	-0.022 to 0.041	0.56	0.66
Inflammation				
Glycoprotein acetyls	-0.061	-0.097 to -0.024	0.002	0.03

Adjusted for age at each time point and sex. Adjusted p-values are based on Benjamini-Hochberg adjustment. Abbreviations are listed in **Supp. Table S1**.

Supp. Table S6. Coefficients of the log concentrations of metabolites in SD units at follow-up per unit decrease in BMI (kg/m^2) between time points from linear regression models, additionally adjusted for pubertal status or socioeconomic status (n=98).

Name	Adjusted for pubertal status				Adjusted for socioeconomic status			
	Estimate	**95% CI**	**p-value**	**Adj. p-value**	**Estimate**	**95% CI**	**p-value**	**Adj. p-value**
Lipoprotein subclasses								
XXL-VLDL-L	-0.013	-0.057 to 0.031	0.555	0.800	-0.023	-0.066 to 0.019	0.288	0.492
XL-VLDL-L	-0.021	-0.065 to 0.022	0.339	0.547	-0.031	-0.073 to 0.011	0.151	0.311
L-VLDL-L	-0.023	-0.066 to 0.019	0.283	0.523	-0.033	-0.075 to 0.008	0.119	0.290
M-VLDL-L	-0.024	-0.066 to 0.017	0.249	0.487	-0.036	-0.078 to 0.005	0.087	0.232
S-VLDL-L	-0.032	-0.073 to 0.008	0.125	0.417	-0.042	-0.082 to -0.003	0.040	0.152
XS-VLDL-L	-0.022	-0.064 to 0.019	0.300	0.540	-0.027	-0.066 to 0.012	0.179	0.345
IDL-L	-0.006	-0.049 to 0.037	0.790	0.887	-0.013	-0.053 to 0.027	0.527	0.632
L-LDL-L	-0.006	-0.049 to 0.036	0.766	0.880	-0.015	-0.055 to 0.025	0.468	0.620
M-LDL-L	-0.009	-0.051 to 0.034	0.695	0.879	-0.017	-0.057 to 0.023	0.399	0.586
S-LDL-L	-0.007	-0.05 to 0.036	0.740	0.880	-0.016	-0.056 to 0.025	0.451	0.613
XL-HDL-L	0.040	-0.001 to 0.081	0.059	0.285	0.044	0.005 to 0.083	0.031	0.152
L-HDL-L	0.036	-0.005 to 0.077	0.088	0.353	0.043	0.003 to 0.082	0.037	0.152
M-HDL-L	0.005	-0.037 to 0.048	0.800	0.887	0.013	-0.027 to 0.052	0.525	0.632
S-HDL-L	-0.031	-0.07 to 0.009	0.137	0.417	-0.022	-0.06 to 0.016	0.255	0.448
Lipoprotein particle sizes								
VLDL particle size	-0.021	-0.064 to 0.022	0.342	0.547	-0.033	-0.075 to 0.008	0.121	0.290
LDL particle size	0.012	-0.029 to 0.052	0.572	0.808	0.018	-0.023 to 0.058	0.392	0.586
HDL particle size	0.043	0.003 to 0.082	0.041	0.225	0.047	0.009 to 0.085	0.019	0.108
Apolipoproteins								
ApoA1	0.028	-0.015 to 0.072	0.205	0.476	0.031	-0.01 to 0.071	0.141	0.306
ApoB	-0.018	-0.058 to 0.023	0.401	0.602	-0.030	-0.07 to 0.01	0.145	0.306
ApoB/ApoA1	-0.030	-0.07 to 0.01	0.151	0.417	-0.042	-0.081 to -0.003	0.040	0.152
Cholesterols								
Total-C	0.003	-0.041 to 0.047	0.896	0.935	-0.004	-0.045 to 0.037	0.843	0.859
VLDL-C	-0.026	-0.067 to 0.014	0.203	0.476	-0.038	-0.078 to 0.002	0.070	0.230
Remnant-C	-0.019	-0.059 to 0.021	0.359	0.550	-0.031	-0.071 to 0.009	0.133	0.300
LDL-C	-0.004	-0.046 to 0.038	0.842	0.904	-0.015	-0.055 to 0.025	0.474	0.620
HDL-C	0.032	-0.011 to 0.074	0.150	0.417	0.039	-0.001 to 0.078	0.063	0.215
HDL2-C	0.032	-0.01 to 0.074	0.141	0.417	0.039	0 to 0.079	0.056	0.200
HDL3-C	0.014	-0.029 to 0.058	0.525	0.772	0.016	-0.025 to 0.057	0.439	0.607
Esterified-C	0.002	-0.042 to 0.047	0.919	0.946	-0.004	-0.045 to 0.037	0.842	0.859
Free-C	0.004	-0.04 to 0.048	0.854	0.904	-0.004	-0.045 to 0.037	0.847	0.859
Fatty acids								
Total fatty acids	-0.021	-0.063 to 0.021	0.331	0.547	-0.028	-0.068 to 0.013	0.182	0.345
Unsaturation	0.056	0.012 to 0.099	0.015	0.151	0.050	0.011 to 0.088	0.015	0.106
DHA	-0.010	-0.055 to 0.034	0.655	0.879	-0.009	-0.052 to 0.034	0.679	0.776
LA	0.004	-0.038 to 0.046	0.850	0.904	-0.007	-0.048 to 0.034	0.731	0.798
Omega-3	-0.011	-0.055 to 0.033	0.628	0.870	-0.015	-0.057 to 0.028	0.504	0.632
Omega-6	0.000	-0.043 to 0.044	0.983	0.983	-0.008	-0.049 to 0.033	0.705	0.794
PUFA	-0.002	-0.045 to 0.042	0.935	0.948	-0.010	-0.051 to 0.032	0.644	0.760
MUFA	-0.029	-0.071 to 0.012	0.169	0.433	-0.036	-0.076 to 0.003	0.077	0.232
SFA	-0.028	-0.07 to 0.014	0.202	0.476	-0.031	-0.071 to 0.009	0.132	0.300
DHA %	0.010	-0.034 to 0.053	0.665	0.879	0.015	-0.027 to 0.056	0.491	0.631

LA %	0.059	0.017 to 0.101	0.008	0.094	0.048	0.009 to 0.087	0.020	0.108
Omega-3 %	0.007	-0.038 to 0.051	0.770	0.880	0.003	-0.039 to 0.045	0.883	0.883
Omega-6 %	0.052	0.009 to 0.095	0.021	0.163	0.050	0.01 to 0.09	0.016	0.106
PUFA %	0.052	0.008 to 0.095	0.023	0.163	0.050	0.01 to 0.089	0.016	0.106
MUFA %	-0.043	-0.084 to -0.001	0.048	0.246	-0.050	-0.089 to -0.011	0.015	0.106
SFA %	-0.034	-0.078 to 0.01	0.132	0.417	-0.019	-0.061 to 0.023	0.385	0.586
Amino acids								
Alanine	-0.072	-0.11 to -0.033	0.001	0.010	-0.080	-0.117 to -0.043	<0.001	0.001
Glutamine	0.036	-0.004 to 0.075	0.081	0.353	0.017	-0.025 to 0.06	0.424	0.607
Glycine	-0.007	-0.051 to 0.037	0.758	0.880	-0.017	-0.059 to 0.025	0.437	0.607
Histidine	0.037	-0.008 to 0.082	0.113	0.406	0.028	-0.014 to 0.07	0.201	0.372
Isoleucine	-0.032	-0.077 to 0.012	0.162	0.433	-0.029	-0.07 to 0.011	0.165	0.329
Leucine	-0.026	-0.072 to 0.019	0.254	0.487	-0.021	-0.062 to 0.021	0.329	0.539
Valine	-0.026	-0.071 to 0.018	0.250	0.487	-0.023	-0.064 to 0.019	0.294	0.492
Phenylalanine	-0.089	-0.128 to -0.05	<0.001	0.001	-0.078	-0.114 to -0.043	<0.001	0.001
Tyrosine	-0.091	-0.131 to -0.051	<0.001	0.001	-0.080	-0.116 to -0.044	<0.001	0.001
Glycerides and phospholipids								
Total triglycerides	-0.027	-0.069 to 0.015	0.214	0.477	-0.036	-0.077 to 0.004	0.084	0.232
VLDL-TG	-0.026	-0.069 to 0.016	0.225	0.477	-0.037	-0.077 to 0.004	0.085	0.232
LDL-TG	-0.022	-0.064 to 0.021	0.330	0.547	-0.019	-0.059 to 0.02	0.339	0.542
HDL-TG	-0.020	-0.061 to 0.022	0.358	0.550	-0.026	-0.067 to 0.015	0.218	0.392
Phosphoglycerides	-0.009	-0.053 to 0.035	0.696	0.879	-0.008	-0.048 to 0.033	0.718	0.795
TG/PG	-0.025	-0.067 to 0.018	0.257	0.487	-0.036	-0.077 to 0.006	0.095	0.243
Phosphatidylcholines	-0.009	-0.053 to 0.034	0.682	0.879	-0.009	-0.049 to 0.032	0.667	0.774
Sphingomyelins	0.007	-0.039 to 0.053	0.759	0.880	0.006	-0.036 to 0.048	0.769	0.827
Total cholines	-0.008	-0.051 to 0.036	0.738	0.880	-0.006	-0.046 to 0.035	0.790	0.837
Glycolysis related metabolites								
Pyruvate	-0.085	-0.125 to -0.046	<0.001	0.002	-0.088	-0.124 to -0.051	<0.001	0.001
Citrate	0.026	-0.016 to 0.068	0.225	0.477	0.036	-0.004 to 0.076	0.086	0.232
Lactate	-0.039	-0.084 to 0.005	0.087	0.353	-0.045	-0.086 to -0.004	0.037	0.152
Ketone bodies								
Acetate	0.050	0.009 to 0.091	0.020	0.163	0.044	0.004 to 0.084	0.034	0.152
Acetoacetate	0.047	0.006 to 0.088	0.027	0.177	0.058	0.02 to 0.097	0.004	0.053
3-hydroxybutyrate	0.044	0.005 to 0.084	0.032	0.195	0.057	0.018 to 0.096	0.006	0.057
Fluid balance								
Albumin	0.020	-0.02 to 0.06	0.334	0.547	0.018	-0.019 to 0.054	0.357	0.559
Creatinine	0.027	-0.005 to 0.058	0.109	0.406	0.011	-0.021 to 0.042	0.518	0.632
Inflammation								
Glycoprotein acetyls	-0.059	-0.098 to -0.019	0.005	0.078	-0.060	-0.097 to -0.023	0.002	0.034

All models adjusted for age at each time point and sex. Adjusted p-values are based on Benjamini-Hochberg adjustment. Abbreviations are listed in **Supp. Table S1.**

Supp. Table S7. Coefficients of the log concentrations of metabolites in SD units at follow-up per 10% decrease in %>95th BMI-centile between time points from linear regression models (n=98).

Name	Estimate (per 10%)	95% CI	p-value	Adj. p-value
Lipoprotein subclasses				
XXL-VLDL-L	-0.043	-0.166 to 0.08	0.50	0.69
XL-VLDL-L	-0.064	-0.186 to 0.057	0.30	0.52
L-VLDL-L	-0.077	-0.198 to 0.044	0.22	0.49
M-VLDL-L	-0.087	-0.208 to 0.033	0.16	0.45
S-VLDL-L	-0.107	-0.224 to 0.011	0.08	0.26
XS-VLDL-L	-0.077	-0.191 to 0.038	0.19	0.47
IDL-L	-0.027	-0.142 to 0.089	0.65	0.81
L-LDL-L	-0.027	-0.142 to 0.087	0.64	0.81
M-LDL-L	-0.031	-0.146 to 0.083	0.59	0.76
S-LDL-L	-0.025	-0.141 to 0.092	0.68	0.83
XL-HDL-L	0.132	0.021 to 0.243	0.02	0.14
L-HDL-L	0.123	0.011 to 0.234	0.04	0.16
M-HDL-L	0.045	-0.067 to 0.157	0.43	0.63
S-HDL-L	-0.054	-0.164 to 0.055	0.33	0.56
Lipoprotein particle sizes				
VLDL particle size	-0.071	-0.192 to 0.049	0.25	0.50
LDL particle size	0.024	-0.093 to 0.141	0.69	0.83
HDL particle size	0.136	0.026 to 0.245	0.02	0.14
Apolipoproteins				
ApoA1	0.109	-0.004 to 0.221	0.06	0.23
ApoB	-0.064	-0.181 to 0.053	0.29	0.52
ApoB/ApoA1	-0.110	-0.224 to 0.005	0.07	0.23
Cholesterols				
Total-C	0.010	-0.108 to 0.128	0.87	0.96
VLDL-C	-0.090	-0.208 to 0.028	0.14	0.44
Remnant-C	-0.069	-0.185 to 0.047	0.25	0.50
LDL-C	-0.022	-0.137 to 0.092	0.70	0.83
HDL-C	0.117	0.004 to 0.231	0.05	0.18
HDL2-C	0.118	0.005 to 0.232	0.04	0.18
HDL3-C	0.064	-0.052 to 0.181	0.28	0.52
Esterified-C	0.010	-0.108 to 0.128	0.87	0.96
Free-C	0.009	-0.108 to 0.127	0.88	0.96
Fatty acids				
Total fatty acids	-0.053	-0.171 to 0.064	0.38	0.61
Unsaturation	0.145	0.029 to 0.261	0.02	0.14
DHA	-0.008	-0.13 to 0.114	0.90	0.96
LA	0.009	-0.108 to 0.126	0.89	0.96
Omega-3	-0.013	-0.135 to 0.109	0.84	0.96
Omega-6	0.005	-0.113 to 0.122	0.94	0.98
PUFA	0.001	-0.117 to 0.12	0.98	0.98
MUFA	-0.079	-0.195 to 0.037	0.19	0.47
SFA	-0.068	-0.186 to 0.05	0.26	0.51
DHA %	0.043	-0.075 to 0.162	0.48	0.67
LA %	0.143	0.03 to 0.257	0.02	0.14
Omega-3 %	0.036	-0.084 to 0.155	0.56	0.75
Omega-6 %	0.137	0.02 to 0.254	0.02	0.14

PUFA %	0.143	0.027 to 0.259	0.02	0.14
MUFA %	-0.126	-0.241 to -0.012	0.03	0.16
SFA %	-0.080	-0.2 to 0.039	0.19	0.47
Amino acids				
Alanine	-0.210	-0.319 to -0.101	0.00	0.01
Glutamine	0.048	-0.072 to 0.169	0.44	0.63
Glycine	-0.041	-0.162 to 0.081	0.51	0.70
Histidine	0.076	-0.045 to 0.197	0.22	0.49
Isoleucine	-0.071	-0.191 to 0.049	0.25	0.50
Leucine	-0.054	-0.175 to 0.066	0.38	0.61
Valine	-0.050	-0.171 to 0.071	0.42	0.63
Phenylalanine	-0.248	-0.351 to -0.145	<0.001	0.001
Tyrosine	-0.243	-0.35 to -0.136	<0.001	0.001
Glycerides and phospholipids				
Total triglycerides	-0.087	-0.206 to 0.032	0.16	0.45
VLDL-TG	-0.086	-0.206 to 0.034	0.17	0.45
LDL-TG	-0.062	-0.178 to 0.054	0.30	0.52
HDL-TG	-0.063	-0.181 to 0.056	0.30	0.52
Phosphoglycerides	0.005	-0.111 to 0.121	0.93	0.98
TG/PG	-0.087	-0.208 to 0.034	0.16	0.45
Phosphatidylcholines	-0.002	-0.117 to 0.113	0.97	0.98
Sphingomyelins	0.035	-0.085 to 0.155	0.57	0.75
Total cholines	0.004	-0.112 to 0.12	0.95	0.98
Glycolysis related metabolites				
Pyruvate	-0.257	-0.361 to -0.153	<0.001	0.001
Citrate	0.050	-0.068 to 0.169	0.41	0.63
Lactate	-0.136	-0.253 to -0.019	0.03	0.14
Ketone bodies				
Acetate	0.122	0.005 to 0.238	0.05	0.18
Acetoacetate	0.137	0.023 to 0.25	0.02	0.14
3-hydroxybutyrate	0.137	0.024 to 0.25	0.02	0.14
Fluid balance				
Albumin	0.066	-0.04 to 0.171	0.23	0.49
Creatinine	0.038	-0.053 to 0.128	0.42	0.63
Inflammation				
Glycoprotein acetyls	-0.164	-0.271 to -0.056	0.00	0.06

Adjusted for age at each time point and sex. Adjusted p-values are based on Benjamini-Hochberg adjustment. Abbreviations are listed in **Supp. Table S1.**

Supp. Table S8. Coefficients of the change in log concentrations of metabolites in SD units between time points per unit decrease in BMI (kg/m^2) between time points from linear regression models (n=67).

Name	Estimate	95% CI	p-value	Adj. p-value
Lipoprotein subclasses				
XXL-VLDL-L	-0.036	-0.066 to -0.006	0.02	0.06
XL-VLDL-L	-0.038	-0.066 to -0.01	0.01	0.04
L-VLDL-L	-0.038	-0.066 to -0.01	0.01	0.04
M-VLDL-L	-0.034	-0.066 to -0.002	0.04	0.09
S-VLDL-L	-0.039	-0.071 to -0.008	0.02	0.05
XS-VLDL-L	-0.022	-0.048 to 0.004	0.10	0.18
IDL-L	-0.002	-0.024 to 0.02	0.87	0.92
L-LDL-L	-0.001	-0.024 to 0.022	0.91	0.93
M-LDL-L	-0.006	-0.031 to 0.019	0.64	0.79
S-LDL-L	-0.006	-0.032 to 0.02	0.63	0.79
XL-HDL-L	0.041	0.006 to 0.076	0.03	0.07
L-HDL-L	0.041	0.007 to 0.074	0.02	0.06
M-HDL-L	0.013	-0.022 to 0.048	0.48	0.65
S-HDL-L	-0.016	-0.051 to 0.02	0.38	0.56
Lipoprotein particle sizes				
VLDL particle size	-0.037	-0.069 to -0.005	0.03	0.07
LDL particle size	0.016	-0.025 to 0.057	0.45	0.62
HDL particle size	0.039	0.007 to 0.071	0.02	0.06
Apolipoproteins				
ApoA1	0.035	0.003 to 0.067	0.04	0.08
ApoB	-0.026	-0.048 to -0.003	0.03	0.07
ApoB/ApoA1	-0.046	-0.073 to -0.019	0.001	0.01
Cholesterols				
Total-C	0.005	-0.02 to 0.03	0.69	0.83
VLDL-C	-0.035	-0.062 to -0.008	0.01	0.05
Remnant-C	-0.022	-0.044 to 0.001	0.06	0.12
LDL-C	-0.001	-0.025 to 0.023	0.94	0.95
HDL-C	0.045	0.011 to 0.08	0.01	0.04
HDL2-C	0.049	0.016 to 0.082	0.01	0.02
HDL3-C	0.015	-0.024 to 0.054	0.44	0.62
Esterified-C	0.007	-0.019 to 0.033	0.60	0.77
Free-C	-0.003	-0.027 to 0.021	0.81	0.90
Fatty acids				
Total fatty acids	-0.028	-0.054 to -0.002	0.04	0.09
Unsaturation	0.059	0.022 to 0.097	0.003	0.02
DHA	-0.014	-0.045 to 0.016	0.36	0.54
LA	0.003	-0.026 to 0.031	0.85	0.92
Omega-3	-0.024	-0.053 to 0.004	0.10	0.18
Omega-6	-0.001	-0.028 to 0.027	0.97	0.97
PUFA	-0.004	-0.03 to 0.023	0.78	0.89
MUFA	-0.041	-0.068 to -0.014	0.004	0.02
SFA	-0.032	-0.058 to -0.005	0.02	0.06
DHA %	0.016	-0.026 to 0.059	0.45	0.62
LA %	0.065	0.03 to 0.101	0.001	0.01
Omega-3 %	-0.008	-0.045 to 0.029	0.67	0.81

Omega-6 %	0.069	0.034 to 0.103	<0.001	0.003
PUFA %	0.065	0.03 to 0.1	0.001	0.01
MUFA %	-0.061	-0.094 to -0.028	0.001	0.01
SFA %	-0.022	-0.064 to 0.019	0.29	0.45
Amino acids				
Alanine	-0.072	-0.105 to -0.04	<0.001	0.002
Glutamine	0.024	-0.011 to 0.058	0.18	0.29
Glycine	0.005	-0.033 to 0.042	0.82	0.90
Histidine	0.012	-0.031 to 0.054	0.60	0.77
Isoleucine	-0.035	-0.071 to 0.001	0.06	0.12
Leucine	-0.021	-0.055 to 0.014	0.25	0.39
Valine	-0.027	-0.065 to 0.011	0.17	0.29
Phenylalanine	-0.069	-0.102 to -0.037	<0.001	0.002
Tyrosine	-0.068	-0.099 to -0.037	<0.001	0.002
Glycerides and phospholipids				
Total triglycerides	-0.043	-0.069 to -0.016	0.003	0.02
VLDL-TG	-0.042	-0.07 to -0.015	0.003	0.02
LDL-TG	-0.023	-0.057 to 0.01	0.17	0.29
HDL-TG	-0.030	-0.06 to 0.001	0.06	0.12
Phosphoglycerides	-0.005	-0.036 to 0.025	0.75	0.87
TG/PG	-0.052	-0.081 to -0.023	0.001	0.01
Phosphatidylcholines	-0.006	-0.036 to 0.024	0.70	0.83
Sphingomyelins	0.011	-0.018 to 0.041	0.46	0.62
Total cholines	-0.002	-0.033 to 0.029	0.90	0.93
Glycolysis related metabolites				
Pyruvate	-0.077	-0.114 to -0.039	<0.001	0.002
Citrate	0.032	-0.004 to 0.069	0.09	0.17
Lactate	-0.039	-0.085 to 0.006	0.09	0.17
Ketone bodies				
Acetate	0.045	0.004 to 0.086	0.04	0.08
Acetoacetate	0.065	0.021 to 0.109	0.005	0.02
3-hydroxybutyrate	0.066	0.018 to 0.113	0.01	0.04
Fluid balance				
Albumin	0.026	-0.011 to 0.062	0.17	0.29
Creatinine	0.003	-0.026 to 0.031	0.85	0.92
Inflammation				
Glycoprotein acetyls	-0.063	-0.092 to -0.035	<0.001	0.002

All models adjusted for age at each time point and sex. Adjusted p-values are based on Benjamini-Hochberg adjustment. Abbreviations are listed in **Supp. Table S1.**

Supp. Table S9. Coefficients of the change in log concentrations of metabolites in SD units between time points per unit decrease in BMI (kg/m^2) between time points from linear regression models, additionally adjusted for pubertal status or socioeconomic status (n=67).

Name	Adjusted for pubertal status				Adjusted for socioeconomic status			
	Estimate	**95% CI**	**p-value**	**Adj. p-value**	**Estimate**	**95% CI**	**p-value**	**Adj. p-value**
Lipoprotein subclasses								
XXL-VLDL-L	-0.025	-0.056 to 0.007	0.129	0.266	-0.038	-0.069 to -0.008	0.017	0.055
XL-VLDL-L	-0.028	-0.058 to 0.001	0.066	0.164	-0.040	-0.068 to -0.012	0.008	0.031
L-VLDL-L	-0.028	-0.058 to 0.002	0.072	0.172	-0.038	-0.067 to -0.01	0.011	0.040
M-VLDL-L	-0.025	-0.059 to 0.008	0.146	0.277	-0.032	-0.065 to 0	0.054	0.115
S-VLDL-L	-0.032	-0.065 to 0.001	0.065	0.164	-0.036	-0.067 to -0.004	0.030	0.079
XS-VLDL-L	-0.017	-0.044 to 0.009	0.209	0.335	-0.018	-0.043 to 0.007	0.164	0.288
IDL-L	0.003	-0.02 to 0.026	0.788	0.854	0.000	-0.022 to 0.022	0.992	0.992
L-LDL-L	0.004	-0.021 to 0.029	0.767	0.849	0.000	-0.024 to 0.023	0.976	0.992
M-LDL-L	0.000	-0.027 to 0.027	0.999	0.999	-0.006	-0.031 to 0.02	0.675	0.810
S-LDL-L	-0.001	-0.029 to 0.028	0.971	0.998	-0.006	-0.032 to 0.02	0.660	0.805
XL-HDL-L	0.037	-0.001 to 0.075	0.061	0.164	0.039	0.003 to 0.075	0.035	0.085
L-HDL-L	0.035	-0.001 to 0.072	0.064	0.164	0.040	0.006 to 0.074	0.024	0.070
M-HDL-L	0.007	-0.031 to 0.044	0.729	0.826	0.013	-0.023 to 0.048	0.482	0.655
S-HDL-L	-0.022	-0.06 to 0.016	0.265	0.381	-0.015	-0.051 to 0.021	0.426	0.602
Lipoprotein particle sizes								
VLDL particle size	-0.026	-0.061 to 0.008	0.139	0.276	-0.037	-0.07 to -0.005	0.028	0.078
LDL particle size	0.011	-0.03 to 0.053	0.590	0.746	0.018	-0.024 to 0.06	0.403	0.592
HDL particle size	0.035	0 to 0.069	0.057	0.164	0.039	0.006 to 0.071	0.023	0.069
Apolipoproteins								
ApoA1	0.035	0 to 0.07	0.057	0.164	0.035	0.002 to 0.068	0.040	0.094
ApoB	-0.017	-0.04 to 0.007	0.168	0.303	-0.025	-0.048 to -0.002	0.035	0.085
ApoB/ApoA1	-0.036	-0.065 to -0.007	0.017	0.101	-0.045	-0.073 to -0.018	0.002	0.012
Cholesterols								
Total-C	0.008	-0.019 to 0.036	0.550	0.707	0.006	-0.019 to 0.031	0.654	0.805
VLDL-C	-0.028	-0.056 to 0.001	0.063	0.164	-0.033	-0.06 to -0.005	0.023	0.069
Remnant-C	-0.016	-0.04 to 0.008	0.190	0.319	-0.020	-0.043 to 0.002	0.085	0.162
LDL-C	0.005	-0.021 to 0.031	0.717	0.826	0.000	-0.025 to 0.024	0.978	0.992
HDL-C	0.039	0.002 to 0.076	0.045	0.161	0.045	0.01 to 0.08	0.015	0.053
HDL2-C	0.043	0.007 to 0.079	0.023	0.116	0.049	0.015 to 0.083	0.006	0.026
HDL3-C	0.013	-0.029 to 0.056	0.536	0.707	0.016	-0.024 to 0.055	0.442	0.613
Esterified-C	0.010	-0.018 to 0.038	0.486	0.660	0.008	-0.018 to 0.034	0.556	0.715
Free-C	0.002	-0.025 to 0.028	0.909	0.948	-0.003	-0.027 to 0.022	0.829	0.933
Fatty acids								
Total fatty acids	-0.023	-0.05 to 0.005	0.118	0.250	-0.027	-0.053 to 0	0.052	0.114
Unsaturation	0.058	0.017 to 0.099	0.008	0.057	0.055	0.017 to 0.092	0.006	0.026
DHA	-0.016	-0.048 to 0.015	0.316	0.446	-0.014	-0.045 to 0.017	0.372	0.558
LA	0.009	-0.021 to 0.04	0.544	0.707	0.004	-0.024 to 0.033	0.760	0.883
Omega-3	-0.024	-0.051 to 0.004	0.101	0.227	-0.027	-0.055 to 0.002	0.076	0.152
Omega-6	0.004	-0.026 to 0.034	0.807	0.854	0.001	-0.027 to 0.029	0.941	0.982
PUFA	0.000	-0.029 to 0.029	0.995	0.999	-0.003	-0.03 to 0.024	0.842	0.933
MUFA	-0.035	-0.064 to -0.005	0.023	0.116	-0.040	-0.068 to -0.013	0.006	0.026
SFA	-0.027	-0.055 to 0.001	0.062	0.164	-0.031	-0.058 to -0.003	0.031	0.079
DHA %	0.008	-0.037 to 0.053	0.725	0.826	0.014	-0.029 to 0.057	0.525	0.697
LA %	0.072	0.034 to 0.11	<0.001	0.008	0.064	0.027 to 0.101	0.001	0.010

Omega-3 %	-0.010	-0.049 to 0.029	0.609	0.755	-0.012	-0.05 to 0.025	0.533	0.697
Omega-6 %	0.065	0.027 to 0.102	0.001	0.013	0.067	0.031 to 0.102	0.001	0.006
PUFA %	0.061	0.023 to 0.099	0.003	0.024	0.062	0.027 to 0.098	0.001	0.009
MUFA %	-0.051	-0.087 to -0.016	0.006	0.050	-0.059	-0.093 to -0.025	0.001	0.009
SFA %	-0.034	-0.078 to 0.011	0.142	0.276	-0.020	-0.062 to 0.022	0.356	0.545
Amino acids								
Alanine	-0.064	-0.099 to -0.029	0.001	0.011	-0.074	-0.107 to -0.041	<0.001	0.002
Glutamine	0.035	0.003 to 0.068	0.038	0.145	0.023	-0.012 to 0.057	0.209	0.351
Glycine	0.008	-0.032 to 0.049	0.685	0.822	0.002	-0.036 to 0.039	0.931	0.982
Histidine	0.027	-0.017 to 0.07	0.234	0.358	0.012	-0.032 to 0.056	0.600	0.758
Isoleucine	-0.036	-0.076 to 0.003	0.078	0.180	-0.032	-0.069 to 0.005	0.093	0.172
Leucine	-0.022	-0.058 to 0.014	0.243	0.364	-0.019	-0.054 to 0.016	0.298	0.466
Valine	-0.030	-0.07 to 0.01	0.151	0.278	-0.025	-0.064 to 0.013	0.207	0.351
Phenylalanine	-0.071	-0.106 to -0.037	<0.001	0.006	-0.067	-0.1 to -0.034	<0.001	0.003
Tyrosine	-0.074	-0.106 to -0.043	<0.001	0.002	-0.064	-0.095 to -0.034	<0.001	0.003
Glycerides and phospholipids								
Total triglycerides	-0.032	-0.06 to -0.004	0.027	0.122	-0.042	-0.07 to -0.015	0.003	0.020
VLDL-TG	-0.032	-0.061 to -0.003	0.033	0.140	-0.043	-0.071 to -0.015	0.004	0.020
LDL-TG	-0.022	-0.057 to 0.013	0.229	0.358	-0.020	-0.053 to 0.013	0.243	0.389
HDL-TG	-0.021	-0.053 to 0.011	0.208	0.335	-0.028	-0.059 to 0.003	0.081	0.158
Phosphoglycerides	-0.007	-0.04 to 0.026	0.678	0.822	-0.005	-0.036 to 0.026	0.773	0.884
TG/PG	-0.039	-0.07 to -0.009	0.015	0.098	-0.053	-0.082 to -0.023	0.001	0.009
Phosphatidylcholines	-0.006	-0.039 to 0.027	0.734	0.826	-0.006	-0.037 to 0.025	0.728	0.860
Sphingomyelins	0.012	-0.02 to 0.044	0.471	0.652	0.012	-0.018 to 0.042	0.426	0.602
Total cholines	-0.004	-0.038 to 0.029	0.795	0.854	-0.001	-0.033 to 0.03	0.927	0.982
Glycolysis related metabolites								
Pyruvate	-0.073	-0.114 to -0.031	0.001	0.013	-0.076	-0.114 to -0.039	<0.001	0.003
Citrate	0.022	-0.016 to 0.061	0.258	0.379	0.035	-0.002 to 0.072	0.067	0.137
Lactate	-0.035	-0.085 to 0.015	0.178	0.309	-0.039	-0.085 to 0.007	0.103	0.186
Ketone bodies								
Acetate	0.049	0.008 to 0.091	0.024	0.116	0.042	0 to 0.083	0.052	0.114
Acetoacetate	0.052	0.004 to 0.1	0.037	0.145	0.065	0.021 to 0.11	0.006	0.026
3-hydroxybutyrate	0.052	0.001 to 0.102	0.050	0.164	0.066	0.017 to 0.114	0.011	0.040
Fluid balance								
Albumin	0.028	-0.012 to 0.068	0.181	0.309	0.023	-0.014 to 0.06	0.222	0.363
Creatinine	0.022	-0.005 to 0.049	0.117	0.250	0.001	-0.028 to 0.03	0.932	0.982
Inflammation								
Glycoprotein acetyls	-0.061	-0.093 to -0.03	<0.001	0.008	-0.065	-0.094 to -0.036	<0.001	0.002

All models adjusted for age at each time point and sex. Adjusted p-values are based on Benjamini-Hochberg adjustment. Abbreviations are listed in **Supp. Table S1.**

Supp. Table S10. Coefficients of the change in log concentrations of metabolites in SD units between time points per 10% decrease in %>95th BMI-centile between time points from linear regression models (n=67).

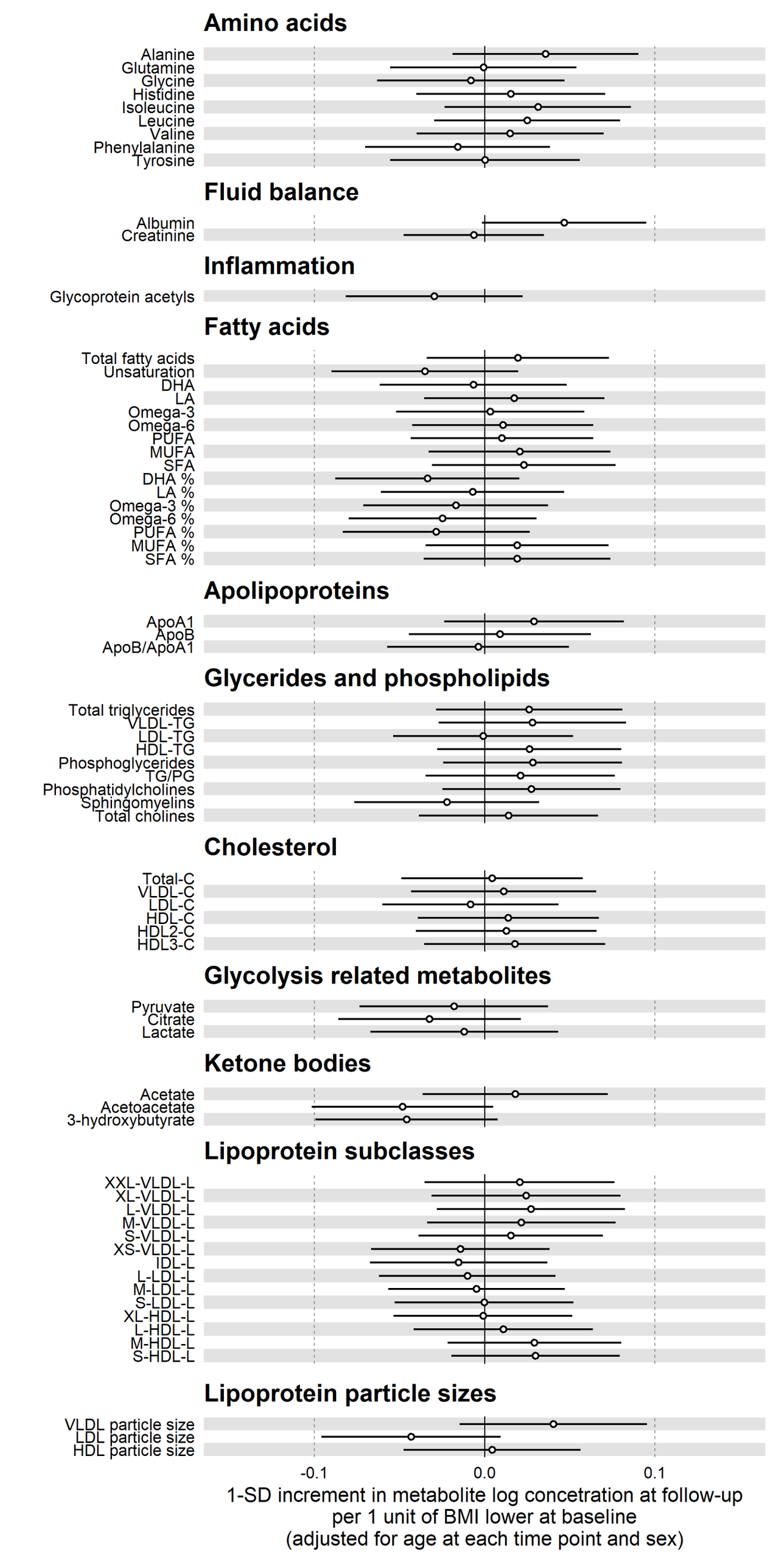
Name	Estimate	95% CI	p-value	Adj. p-value
Lipoprotein subclasses				
XXL-VLDL-L	-0.078	-0.166 to 0.011	0.092	0.202
XL-VLDL-L	-0.086	-0.169 to -0.003	0.047	0.126
L-VLDL-L	-0.090	-0.174 to -0.007	0.037	0.108
M-VLDL-L	-0.083	-0.177 to 0.01	0.086	0.194
S-VLDL-L	-0.100	-0.193 to -0.008	0.037	0.108
XS-VLDL-L	-0.053	-0.128 to 0.022	0.172	0.308
IDL-L	0.007	-0.056 to 0.071	0.821	0.937
L-LDL-L	0.005	-0.061 to 0.072	0.877	0.943
M-LDL-L	-0.007	-0.08 to 0.066	0.846	0.937
S-LDL-L	-0.007	-0.082 to 0.069	0.865	0.943
XL-HDL-L	0.116	0.014 to 0.218	0.030	0.097
L-HDL-L	0.110	0.012 to 0.208	0.031	0.097
M-HDL-L	0.037	-0.064 to 0.138	0.471	0.629
S-HDL-L	-0.038	-0.14 to 0.065	0.472	0.629
Lipoprotein particle sizes				
VLDL particle size	-0.087	-0.181 to 0.008	0.077	0.180
LDL particle size	0.023	-0.097 to 0.144	0.707	0.862
HDL particle size	0.106	0.013 to 0.199	0.029	0.097
Apolipoproteins				
ApoA1	0.109	0.017 to 0.2	0.023	0.094
ApoB	-0.056	-0.122 to 0.011	0.104	0.221
ApoB/ApoA1	-0.114	-0.193 to -0.034	0.007	0.041
Cholesterols				
Total-C	0.023	-0.049 to 0.095	0.528	0.679
VLDL-C	-0.086	-0.165 to -0.006	0.040	0.110
Remnant-C	-0.049	-0.115 to 0.018	0.155	0.294
LDL-C	0.007	-0.062 to 0.076	0.842	0.937
HDL-C	0.121	0.021 to 0.222	0.021	0.094
HDL2-C	0.136	0.041 to 0.232	0.007	0.041
HDL3-C	0.062	-0.051 to 0.175	0.288	0.460
Esterified-C	0.028	-0.046 to 0.102	0.456	0.629
Free-C	0.005	-0.066 to 0.075	0.892	0.944
Fatty acids				
Total fatty acids	-0.062	-0.139 to 0.015	0.119	0.245
Unsaturation	0.150	0.04 to 0.261	0.010	0.055
DHA	-0.035	-0.124 to 0.054	0.446	0.629
LA	0.020	-0.062 to 0.102	0.631	0.784
Omega-3	-0.053	-0.137 to 0.03	0.217	0.355
Omega-6	0.009	-0.071 to 0.089	0.827	0.937
PUFA	-0.001	-0.077 to 0.076	0.989	0.991
MUFA	-0.097	-0.178 to -0.016	0.022	0.094
SFA	-0.072	-0.151 to 0.006	0.077	0.180
DHA %	0.038	-0.085 to 0.161	0.548	0.693
LA %	0.175	0.071 to 0.279	0.002	0.019
Omega-3 %	-0.013	-0.122 to 0.095	0.811	0.937

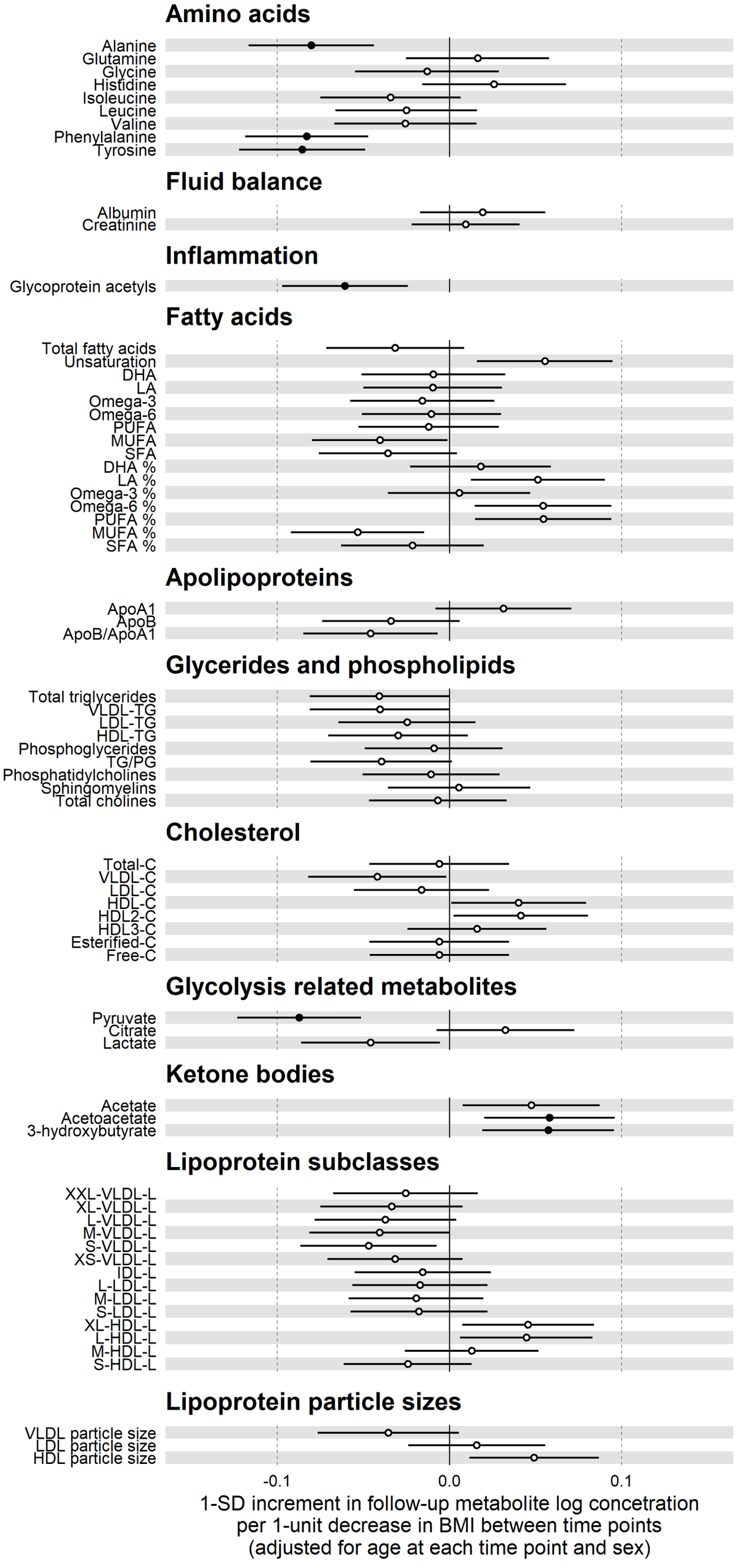
Omega-6 %	0.171	0.068 to 0.274	0.002	0.019
PUFA %	0.165	0.062 to 0.267	0.003	0.023
MUFA %	-0.151	-0.249 to -0.053	0.004	0.030
SFA %	-0.078	-0.198 to 0.042	0.210	0.351
Amino acids				
Alanine	-0.192	-0.288 to -0.095	<0.001	0.004
Glutamine	0.069	-0.031 to 0.169	0.180	0.308
Glycine	0.017	-0.094 to 0.127	0.770	0.924
Histidine	0.045	-0.079 to 0.17	0.481	0.629
Isoleucine	-0.076	-0.184 to 0.031	0.169	0.308
Leucine	-0.042	-0.144 to 0.06	0.425	0.624
Valine	-0.059	-0.171 to 0.052	0.301	0.471
Phenylalanine	-0.203	-0.298 to -0.107	<0.001	0.003
Tyrosine	-0.197	-0.286 to -0.107	<0.001	0.003
Glycerides and phospholipids				
Total triglycerides	-0.104	-0.184 to -0.025	0.013	0.066
VLDL-TG	-0.102	-0.183 to -0.021	0.017	0.079
LDL-TG	-0.067	-0.163 to 0.029	0.177	0.308
HDL-TG	-0.071	-0.161 to 0.018	0.124	0.247
Phosphoglycerides	0.001	-0.088 to 0.089	0.991	0.991
TG/PG	-0.128	-0.214 to -0.042	0.005	0.037
Phosphatidylcholines	-0.003	-0.091 to 0.085	0.941	0.968
Sphingomyelins	0.042	-0.043 to 0.127	0.340	0.521
Total cholines	0.004	-0.085 to 0.093	0.928	0.968
Glycolysis related metabolites				
Pyruvate	-0.225	-0.333 to -0.117	0.000	0.003
Citrate	0.045	-0.063 to 0.154	0.416	0.624
Lactate	-0.123	-0.254 to 0.009	0.073	0.180
Ketone bodies				
Acetate	0.114	-0.005 to 0.234	<0.001	0.169
Acetoacetate	0.152	0.02 to 0.283	0.027	0.097
3-hydroxybutyrate	0.166	0.021 to 0.31	0.029	0.097
Fluid balance				
Albumin	0.079	-0.027 to 0.184	0.149	0.290
Creatinine	0.030	-0.051 to 0.111	0.473	0.629
Inflammation				
Glycoprotein acetyls	-0.169	-0.254 to -0.084	<0.001	0.004

All models adjusted for age at each time point and sex. Adjusted p-values are based on Benjamini-Hochberg adjustment. Abbreviations are listed in **Supp. Table S1.**

Table 1. Participant characteristics.

	Baseline			Follow-up		
Characteristic	**n**	**Mean (SD)**	**Range**	**n**	**Mean (SD)**	**Range**
Sex, males (%)	98	51 (52)		98	51 (52)	
Age (y)	98	10.3 (3.5)	3.0-16.9	98	15.8 (3.7)	6.1-24.3
Weight (kg)	98	72.1 (29.6)	19.1-157.7	98	101.8 (30.5)	40.8-187.8
BMI (kg/m^2)	98	30.9 (6.2)	18.4-51.8	98	35.6 (7.9)	18.2-60.9
% >95th centile	98	134.6 (19.0)	100.5-204.4	98	130.7 (26.2)	75.6-202.0
n <100%	0			9		
n ≥100% - <120%	24			26		
n ≥120% - <140%	43			32		
n ≥140%	31			31		
Tanner stage (%)	93			98		
n pre-pubertal	47 (50)			8 (8)		
n peri-pubertal	22 (24)			16 (16)		
n post-pubertal	24 (26)			74 (76)		


Amino acids
Alanine
Glutamine
Glycine
Histidine
Isoleucine
Leucine
Valine
Phenylalanine
Tyrosine
Fluid balance
Albumin
Creatinine
Inflammation
Glycoprotein acetyls
Fatty acids
Total fatty acids
Unsaturation
DHA
LA
Omega-3
Omega-6
PUFA
MUFA
SFA
DHA %
LA %
Omega-3 %
Omega-6 %
PUFA %
MUFA %
SFA %
Apolipoproteins
ApoA1
ApoB
ApoB/ApoA1
Glycerides and phospholipids
Total triglycerides
VLDL-TG
LDL-TG
HDL-TG
Phosphoglycerides
TG/PG
Phosphatidylcholines
Sphingomyelins
Total cholines
Cholesterol
Total-C
VLDL-C
LDL-C
HDL-C
HDL2-C
HDL3-C
Glycolysis related metabolites
Pyruvate
Citrate
Lactate
Ketone bodies
Acetate
Acetoacetate
3-hydroxybutyrate
Lipoprotein subclasses
XXL-VLDL-L
XL-VLDL-L
L-VLDL-L
M-VLDL-L
S-VLDL-L
XS-VLDL-L
IDL-L
L-LDL-L
M-LDL-L
S-LDL-L
XL-HDL-L
L-HDL-L
M-HDL-L
S-HDL-L
Lipoprotein particle sizes
VLDL particle size
LDL particle size
HDL particle size
-0.1
0.0
0.1
1-SD increment in metabolite log concetration at follow-up
per 1 unit of BMI lower at baseline
(adjusted for age at each time point and sex)


Amino acids
Alanine
Glutamine
Glycine
Histidine
Isoleucine
Leucine
Valine
Phenylalanine
Tyrosine
Fluid balance
Albumin
Creatinine
Inflammation
Glycoprotein acetyls
Fatty acids
Total fatty acids
Unsaturation
DHA
LA
Omega-3
Omega-6
PUFA
MUFA
SFA
DHA %
LA %
Omega-3 %
Omega-6 %
PUFA %
MUFA %
SFA %
Apolipoproteins
ApoA1
ApoB
ApoB/ApoA1
Glycerides and phospholipids
Total triglycerides
VLDL-TG
LDL-TG
HDL-TG
Phosphoglycerides
TG/PG
Phosphatidylcholines
Sphingomyelins
Total cholines
Cholesterol
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VLDL-C
LDL-C
HDL-C
HDL2-C
HDL3-C
Esterified-C
Free-C
Glycolysis related metabolites
Pyruvate
Citrate
Lactate
Ketone bodies
Acetate
Acetoacetate
3-hydroxybutyrate
Lipoprotein subclasses
XXL-VLDL-L
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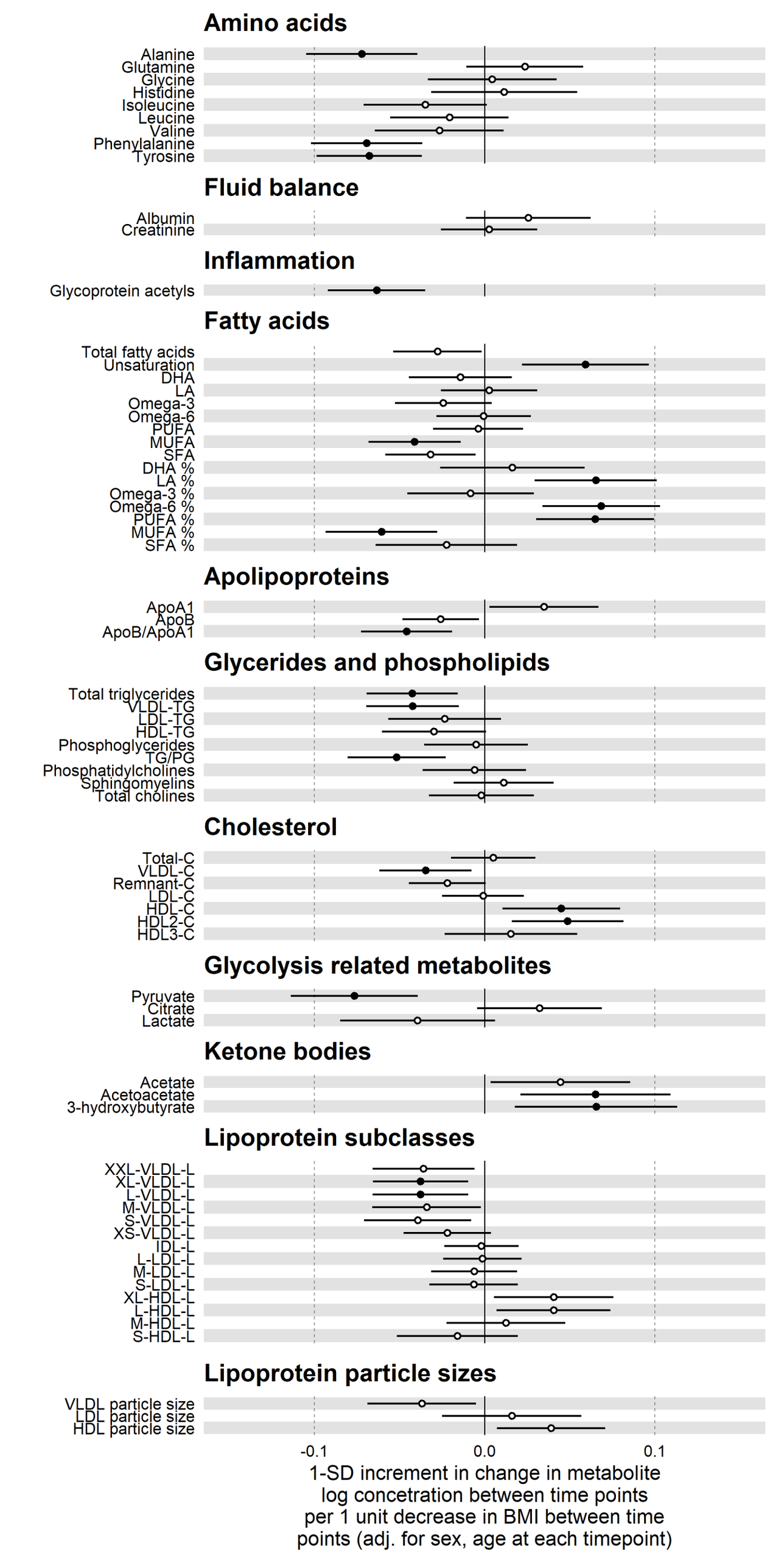
L-VLDL-L
M-VLDL-L
S-VLDL-L
XS-VLDL-L
IDL-L
L-LDL-L
M-LDL-L
S-LDL-L
XL-HDL-L
L-HDL-L
M-HDL-L
S-HDL-L
Lipoprotein particle sizes
VLDL particle size
LDL particle size
HDL particle size
-0.1
0.0
0.1
1-SD increment in follow-up metabolite log concetration
per 1-unit decrease in BMI between time points
(adjusted for age at each time point and sex)


Amino acids
Alanine
Glutamine
Glycine
Histidine
Isoleucine
Leucine
Valine
Phenylalanine
Tyrosine
Fluid balance
Albumin
Creatinine
Inflammation
Glycoprotein acetyls
Fatty acids
Total fatty acids
Unsaturation
DHA
LA
Omega-3
Omega-6
PUFA
MUFA
SFA
DHA %
LA %
Omega-3 %
Omega-6 %
PUFA %
MUFA %
SFA %
Apolipoproteins
ApoA1
ApoB
ApoB/ApoA1
Glycerides and phospholipids
Total triglycerides
VLDL-TG
LDL-TG
HDL-TG
Phosphoglycerides
TG/PG
Phosphatidylcholines
Sphingomyelins
Total cholines
Cholesterol
Total-C
VLDL-C
Remnant-C
LDL-C
HDL-C
HDL2-C
HDL3-C
Glycolysis related metabolites
Pyruvate
Citrate
Lactate
Ketone bodies
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Acetoacetate
3-hydroxybutyrate
Lipoprotein subclasses
XXL-VLDL-L
XL-VLDL-L
L-VLDL-L
M-VLDL-L
S-VLDL-L
XS-VLDL-L
IDL-L
L-LDL-L
M-LDL-L
S-LDL-L
XL-HDL-L
L-HDL-L
M-HDL-L
S-HDL-L
Lipoprotein particle sizes
VLDL particle size
LDL particle size
HDL particle size
-0.1
0.0
0.1
1-SD increment in change in metabolite log concetration between time points per 1 unit decrease in BMI between time points (adj. for sex, age at each timepoint)