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Sex-specific trajectories of molecular cardiometabolic traits from childhood to young adulthood

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ABSTRACT

Background The changes which typically occur in molecular causal risk factors and predictive biomarkers for cardiometabolic diseases across early life are not well characterised.

Methods We quantified sex-specific trajectories of 148 metabolic trait concentrations including various lipoprotein subclasses from age 7 years to 25 years. Data were from 7065 to 7626 offspring (11 702 to14 797 repeated measures) of the Avon Longitudinal Study of Parents and Children birth cohort study. Outcomes were quantified using nuclear magnetic resonance spectroscopy at 7, 15, 18 and 25 years. Sex-specific trajectories of each trait were modelled using linear spline multilevel models.

Results Females had higher very-low-density lipoprotein (VLDL) particle concentrations at 7 years. VLDL particle concentrations decreased from 7 years to 25 years with larger decreases in females, leading to lower VLDL particle concentrations at 25 years in females. For example, females had a 0.25 SD (95% CI 0.20 to 0.31) higher small VLDL particle concentration at 7 years; mean levels decreased by 0.06 SDs (95% CI −0.01 to 0.13) in males and 0.85 SDs (95% CI 0.79 to 0.90) in females from 7 years to 25 years, leading to 0.42 SDs (95% CI 0.35 to 0.48) lower small VLDL particle concentrations in females at 25 years. Females had lower high-density lipoprotein (HDL) particle concentrations at 7 years. HDL particle concentrations increased from 7 years to 25 years with larger increases among females leading to higher HDL particle concentrations in females at 25 years.

Conclusion Childhood and adolescence are important periods for the emergence of sex differences in atherogenic lipids and predictive biomarkers for cardiometabolic disease, mostly to the detriment of males.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Causal risk factors and novel predictive biomarkers for cardiometabolic diseases are increasingly being identified from the recent application of comprehensive metabolomic profiling in epidemiological studies, but the changes which typically occur in these traits across childhood, adolescence and early adulthood are not well understood.

WHAT THIS STUDY ADDS

⇒ In this prospective cohort study with repeat assessments of 148 molecular cardiometabolic traits from comprehensive metabolomic profiling at ages 7, 15, 18 and 25 years, we demonstrate that marked changes in levels of causal risk factors and novel predictive biomarkers for cardiometabolic diseases occur from childhood to early adulthood. These findings suggest that childhood and adolescence are important life stages for the development of sex differences in atherogenic lipids and predictive biomarkers for cardiometabolic disease, mostly to the detriment of males.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Findings suggest that childhood and adolescence should be targeted for prevention of cardiometabolic disease and sex differences in cardiometabolic risk across the life course

INTRODUCTION

Cardiometabolic diseases are a leading cause of death globally.[1] Cardiometabolic risk factors such as adiposity, blood pressure and circulating lipids, as well as underlying subclinical artery disease likely originate in early life, potentially beginning in childhood and tracking through adolescence into adulthood.[2] Understanding how risk factors begin, change and track from childhood to adulthood is important for informing aetiological understanding of cardiometabolic diseases and identifying groups in need of targeted prevention.

To date, longitudinal studies have characterised how conventional cardiometabolic risk factors change over time from childhood to adulthood, including studies of change in adiposity,[3–5] blood pressure,[3–6] and circulating lipids (triglycerides, high-density lipoprotein (HDL) and non-HDL,[3 4 7] as well as glucose and insulin.[3 5 8] In a previous study of the Avon Longitudinal Study of Parents and Children (ALSPAC), we demonstrated distinct patterns of change in conventional cardiometabolic risk factors through the first decades of life, with change for some risk factors coinciding with the sensitive period of puberty.[9] We also demonstrated notable sex differences in circulating lipids that began at birth, including higher HDL and non-HDL among females, which widened further by age

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18 years.[3 5] While these studies provide important insights into early life course development and change in a small number of cardiometabolic risk factors, few studies to date have characterised change in molecular cardiometabolic traits from metabolomics platforms which are now being used for more granular and high-resolution cardiovascular phenotyping to better understand cardiometabolic disease aetiology.[10–12] These platforms include directly measured apolipoprotein B containing lipoprotein subclasses that cause atherosclerotic plaques and lead to coronary heart disease (CHD) and could only previously be indirectly estimated using conventional approaches.[13] As yet, understanding of how these traits typically begin and change from childhood through to adulthood using population-based/non-clinical samples is lacking, despite potential to provide refined understanding of cardiometabolic disease aetiology. In addition, characterising the sex-specific development of these traits is important due to striking sex differences in cardiometabolic disease risk across the life course, which remain poorly understood. The study of sex differences in cardiometabolic health is now widely recognised as an area of unlocked potential for informing improved aetiological understanding and mobilising more effective future prevention opportunities.[14] In particular, the study of sex-specific trajectories from early in the life course through to adulthood has potential to reveal important mechanisms/mediators of these sex differences for future study, which are likely to be complex and multifactorial and driven by both biological (sex hormones, genetics and epigenetics) and social factors (such as health behaviours, adiposity or health service use). For instance, sex differences arising very early in childhood are likely to be mediated by biological factors such as genetics or perhaps early social differences but would be less likely to be mediated by health behaviours such as smoking and alcohol use, which begin in adolescence. In contrast, sex differences that emerge or widen during the sensitive period of adolescence may suggest that both biological factors (sex hormones and puberty timing) and/or perhaps sex differences in the onset and prevalence of health behaviours such as smoking and alcohol use play a role. In addition, studying sex differences in trajectories of absolute levels of key cardiometabolic traits in early life provides opportunity to better understand whether sex differences are driven by this or differences in the relative association of risk factors with cardiometabolic risk, which has been a key focus of much research to date.[15]

Using data from ALSPAC, a large contemporary birth cohort study from South west England, we examined sex-specific trajectories of 148 concentrations of molecular cardiometabolic traits, mostly lipoprotein subclasses and fatty acids, but also including glucose and an inflammatory marker, measured using targeted metabolomics on 4 occasions among the same individuals, from 7 years to 25 years.

METHODS

Study population

The ALSPAC is a prospective birth cohort study in South west England. Pregnant women resident in Avon, UK with expected dates of delivery 1st April 1991 to 31st December 1992 were invited to take part in the study. The initial number of pregnancies enrolled was 14 541. Of these, there was a total of 14 676 fetuses, resulting in 14 062 live births and 13 988 children who were alive at 1 year. Follow-up has included parent and offspring completed questionnaires, links to routine data and clinic attendance. The study has been described elsewhere in detail.[16–18] The study website contains details of all the data that are available through a fully searchable data dictionary (http://www.bristol.ac.uk/alspac/researchers/our-data/). Study data were collected and managed using Research Electronic Data Capture (REDCap) electronic data capture tools hosted at the University of Bristol.[19] REDCap is a secure, web-based software platform designed to support data capture for research studies.

Patient and public involvement

This analysis was performed without patient or public involvement.

Assessment of cardiometabolic traits

Proton nuclear magnetic resonance (NMR) spectroscopy from a targeted metabolomics platform[20] was performed on EDTA plasma samples from blood samples drawn in clinics at ages 7, 15, 18 and 25 years to quantify 148 concentrations including cholesterol, triglyceride, and other lipid content in lipoprotein subclass particles, apolipoproteins, fatty acids, glucose and an inflammatory marker (glycoprotein acetyls). Four traits were not measured at 25 years (diacylglycerol, fatty acid chain length, estimated degree of unsaturation and conjugated linoleic acid). Blood was taken after a minimum of a 6-hour fast (stability in these trait concentrations has been shown over different fasting durations).[21] Laboratory NMR quality control and further data preparation steps are described in online supplemental appendix S1).

Statistical analysis

We used multilevel models to examine sex-specific patterns of change in 148 trait concentrations; 144 traits had measures available from 7 years to 25 years, while 4 traits had measures available from 7 years to 18 years[22]; thus, for these traits, change over time is only modelled to age 18 years. Multilevel models estimate mean trajectories of the outcome while accounting for the non-independence (ie, clustering) of repeated measurements within individuals and differences in the number and timing of measurements between individuals (using all available data from all eligible participants under a missing at random assumption).[23 24] For inclusion in the present analysis, participants required data on sex and at least 1 measure of a metabolic trait between 7 years and 25 years (144 traits) and between 7 years and 18 years (4 traits). Given that sex is the exposure in these analyses, we did not adjust for potential confounders because sex cannot be altered by factors that influence the metabolic traits (outcomes). For example, body mass index is likely to influence many of the metabolic traits, but it could not change participant sex and therefore could not confound the effect of sex on metabolic trait levels (although it might mediate such effects). Change in all 148 traits was estimated here using linear spline multilevel models (2 levels: measurement occasion and individual). Linear splines allow knot points to be fit at different ages to derive periods in which change is approximately linear. All trajectories were modelled in MLwiN V.3.04, called from Stata V.15[25] using the runmlwin command.[26] Data visualisation was performed using R V.3.6.3 using the ggforestplot V.0.0.2 package. Further information on the traits included and our modelling strategy is included in online supplemental appendix S2 and table S1. We also performed several sensitivity analyses and details of these are included in online supplemental appendix S3 and table S2.

RESULTS

Figure 1 provides an overall summary of our study and its findings. The characteristics of participants included in analyses by

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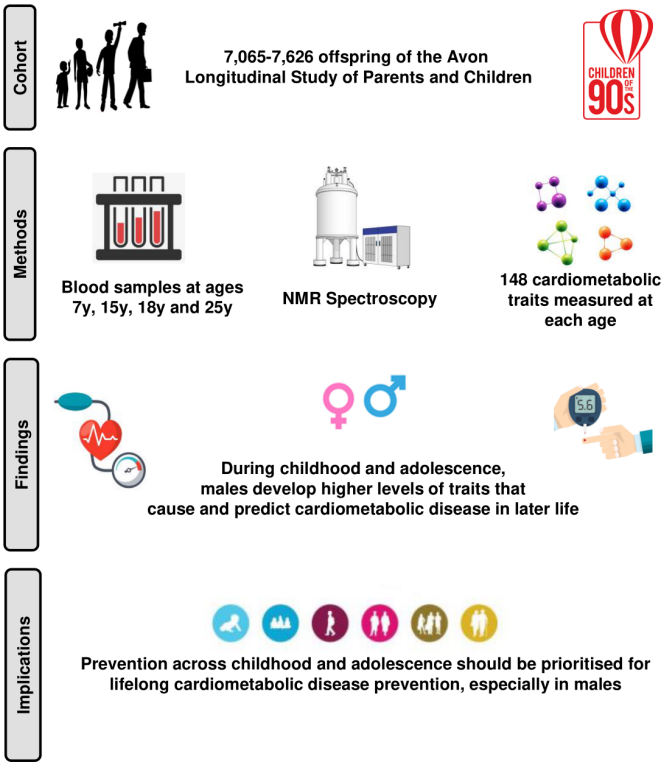

Figure 1 Summary of methods and findings of study. Legend: NMR, nuclear magnetic resonance; y, years.

sex (49% male) are shown in table 1. A total of 148 metabolic trait concentrations were modelled. A total of 7626 participants (14 797 total repeated measures; 5444 at 7 years, 3048 at 15 years, 3121 at 18 years and 3184 at 25 years) were included in the analyses of 144 concentrations. A total of 7065 participants (11 702 total repeated measures; 5395 at 7 years, 3219 at 15 years and 3088 at 18 years) were included in analyses of diacylglycerol, fatty acid chain length, estimated degree of saturation and conjugated linoleic acid as these traits were not available at 25 years.

Very-low-density lipoprotein (VLDL) concentrations

VLDL particle concentrations were higher in females at 7 years, e.g., 0.39 SD (95% CI, 0.34, 0.44) higher for very small VLDL (figure 2 and online supplemental table S3). Except for large and medium concentrations among males which increased over time, most other VLDL particle concentrations decreased from 7 years to 25 years in both sexes (figure 3 and online supplemental table S4), and females had larger decreases compared with males. At 25 years, females had lower levels of most VLDL particle concentrations, except for very small VLDL particle concentrations which remained 0.08 SD (95% CI 0.01 to 0.14) higher in females, although the difference had reduced in magnitude. Patterns were broadly similar for lipid content in VLDL particles over time.

Low-density lipoprotein (LDL) concentrations

Most LDL particle concentrations were higher in females at 7 years (eg, 0.26 SD (95% CI 0.21 to 0.31) higher for large LDL) (figure 2 and online supplemental table S3). LDL particle concentrations increased from 7 years to 25 years (figure 3 and online supplemental table S4). At 25 years, higher levels of LDL particle concentrations persisted in females, for example, 0.17 SD (95% CI, 0.1, 0.23) higher for large LDL but the difference had reduced in magnitude due to smaller increases in females compared with males. These patterns were similar for lipid content in LDL particles, except for triglycerides in LDL; females had higher levels of triglycerides in LDL at 7 years, and this difference widened at 25 years in contrast to a reduction in the difference for other lipid particles in LDL. This reduction appeared to be driven by smaller decreases in triglyceride in LDL particles over time in females.

HDL concentrations

Most HDL particle concentrations were lower in females at age 7 years (eg, −0.1 SD (95% CI, −0.15 to −0.05) lower for very large HDL (figure 4 and online supplemental table S3). Very

Table 1 Characteristics of Avon Longitudinal Study of Parents and Children participants included in the analysis, by sex

	Females n=3909*	Males n=3717*
	n (%)	n (%)
Non-white ethnicity	75 (2.2)	60 (1.8)
Maternal marital status		
Never married	527 (15.1)	467 (13.7)
Widowed	<5	8 (0.2)
Divorced	110 (3.2)	118 (3.5)
Separated	50 (1.4)	36 (1.1)
1st marriage	2581 (73.9)	2544 (74.8)
Marriage 2 or 3	224 (6.4)	229 (6.7)
Household social class†		
Professional	517 (15.8)	532 (16.7)
Managerial and technical	1463 (44.6)	1404 (44.1)
Non-manual	793 (24.2)	792 (24.9)
Manual	343 (10.5)	328 (10.3)
Part skilled and unskilled	161 (4.9)	128 (4.0)
Maternal education		
Less than O level	761 (22.2)	724 (21.6)
O level	1166 (34.1)	1195 (35.7)
A level	926 (27.1)	883 (26.4)
Degree or above	569 (16.6)	548 (16.4)
Mother's partner's highest educational qualification		
Less than O level	965 (28.9)	863 (26.5)
O level	717 (21.5)	724 (22.2)
A level	916 (27.5)	918 (28.2)
Degree or above	737 (22.1)	750 (23.0)
Maternal smoking during pregnancy	660 (18.9)	657 (19.2)
	Mean (SD)	Mean (SD)
Gestational age (weeks)	39.6 (1.8)	39.3 (1.9)
Birth weight (g)	3370 (512)	3469 (578)
Maternal age (years)	28.8 (4.6)	29.1 (4.7)
Maternal prepregnancy body mass index (kg/m^2)	22.8 (3.6)	22.9 (3.8)

*Note that denominators in this table do not sum exactly to N participants included in models due to some missing covariate data, which were not required for inclusion in our analyses.
†Household social class was measured as the highest of the mother's or her partner's occupational social class using data on job title and details of occupation collected about the mother and her partner from the mother's questionnaire at 32 weeks' gestation. Social class was derived using the standard occupational classification codes developed by the UK Office of Population Census and Surveys and classified as I, professional; II, managerial and technical; IIINM, non-manual; IIIM, manual; and IV&V, part skilled occupations and unskilled occupations.

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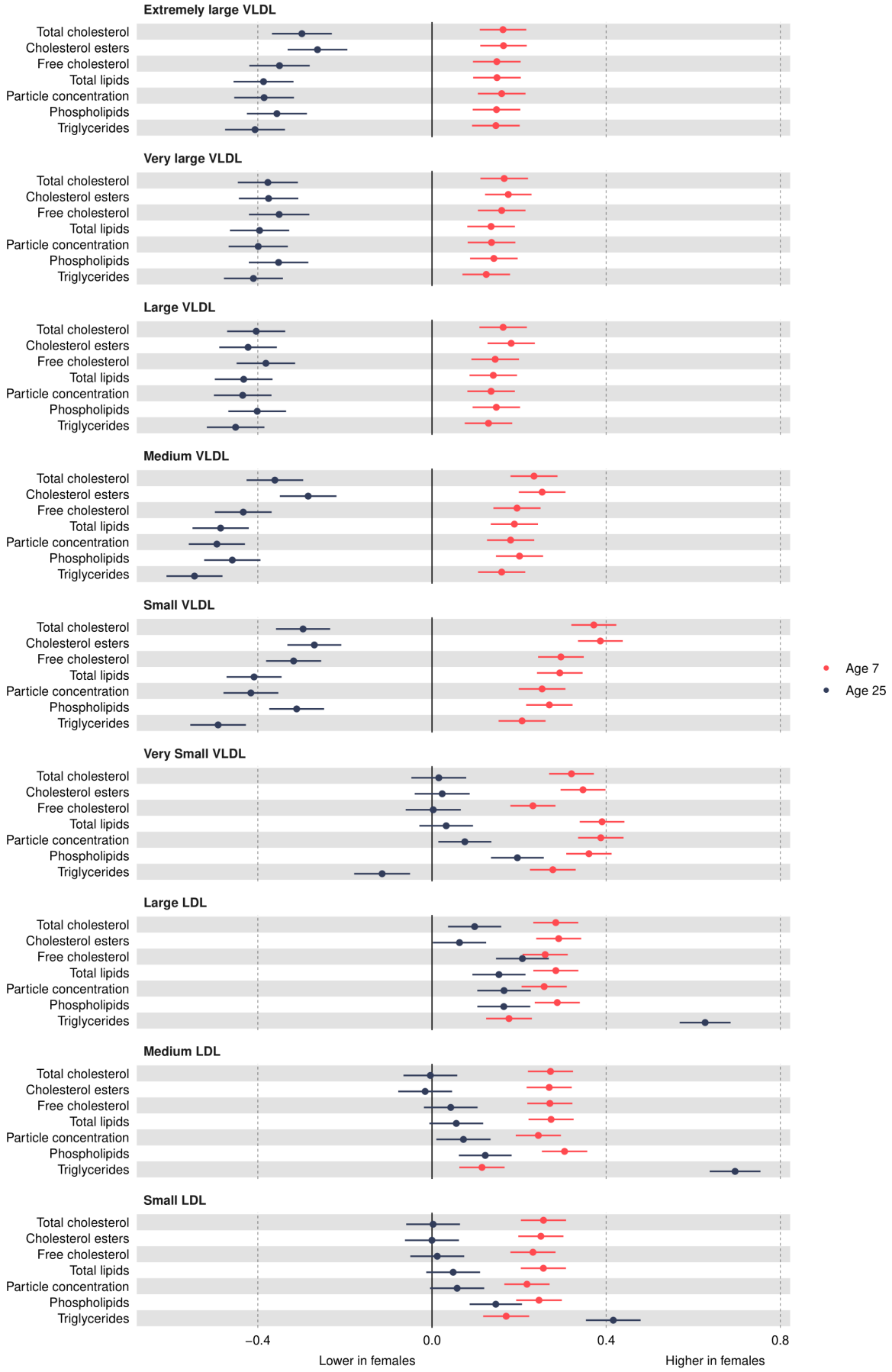

Figure 2 Mean sex difference in VLDL and LDL lipoprotein concentrations in SD units at 7 and 25 years, estimated from multilevel models. Differences shown are for females compared with males. LDL, low-density lipoprotein; VLDL, very-low-density lipoprotein.

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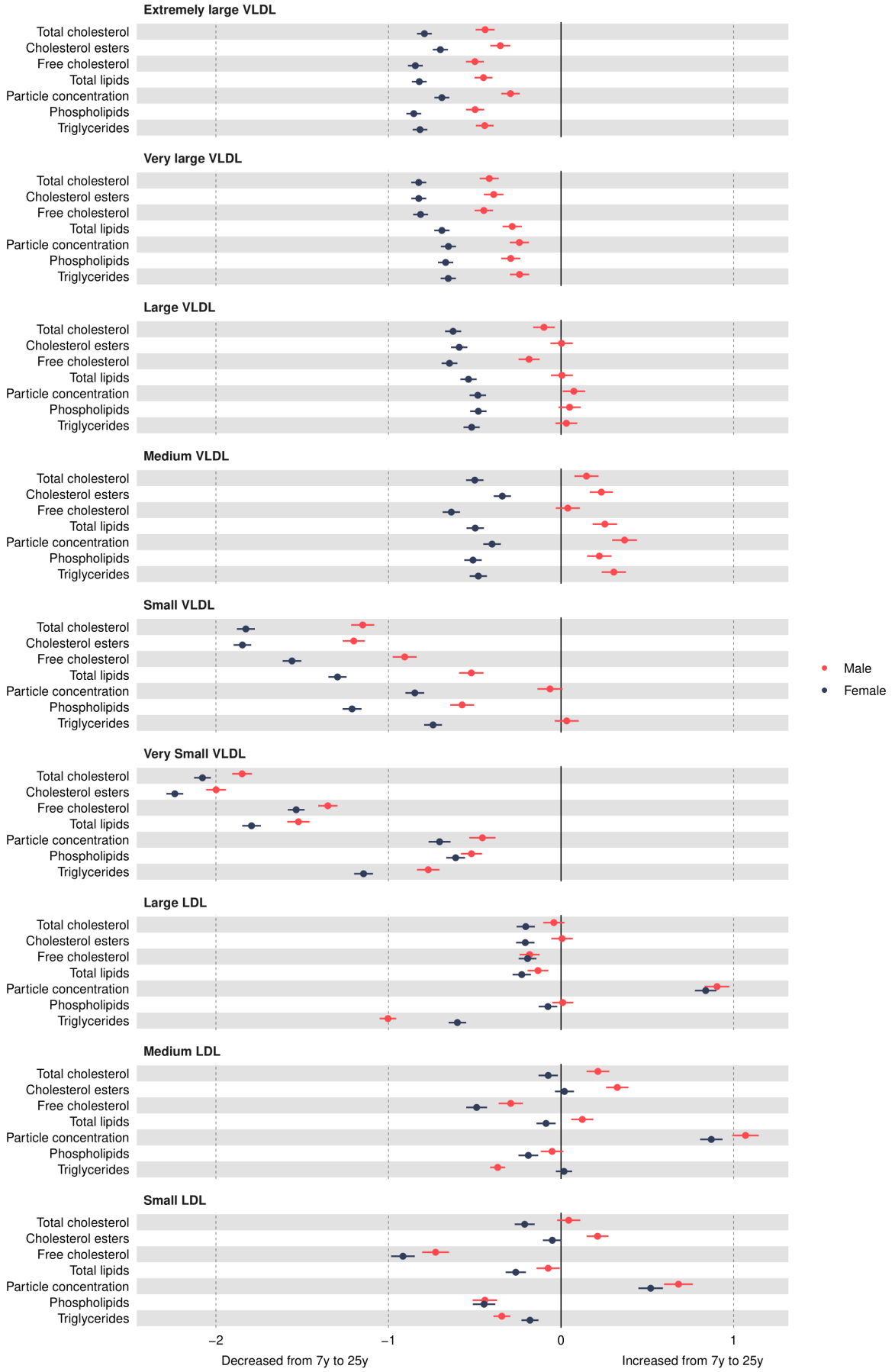

Figure 3 Mean sex-specific change in VLDL and LDL lipid concentrations in SD units from 7 to 25 years, estimated from multilevel models. LDL, low-density lipoprotein; VLDL, very-low-density lipoprotein.

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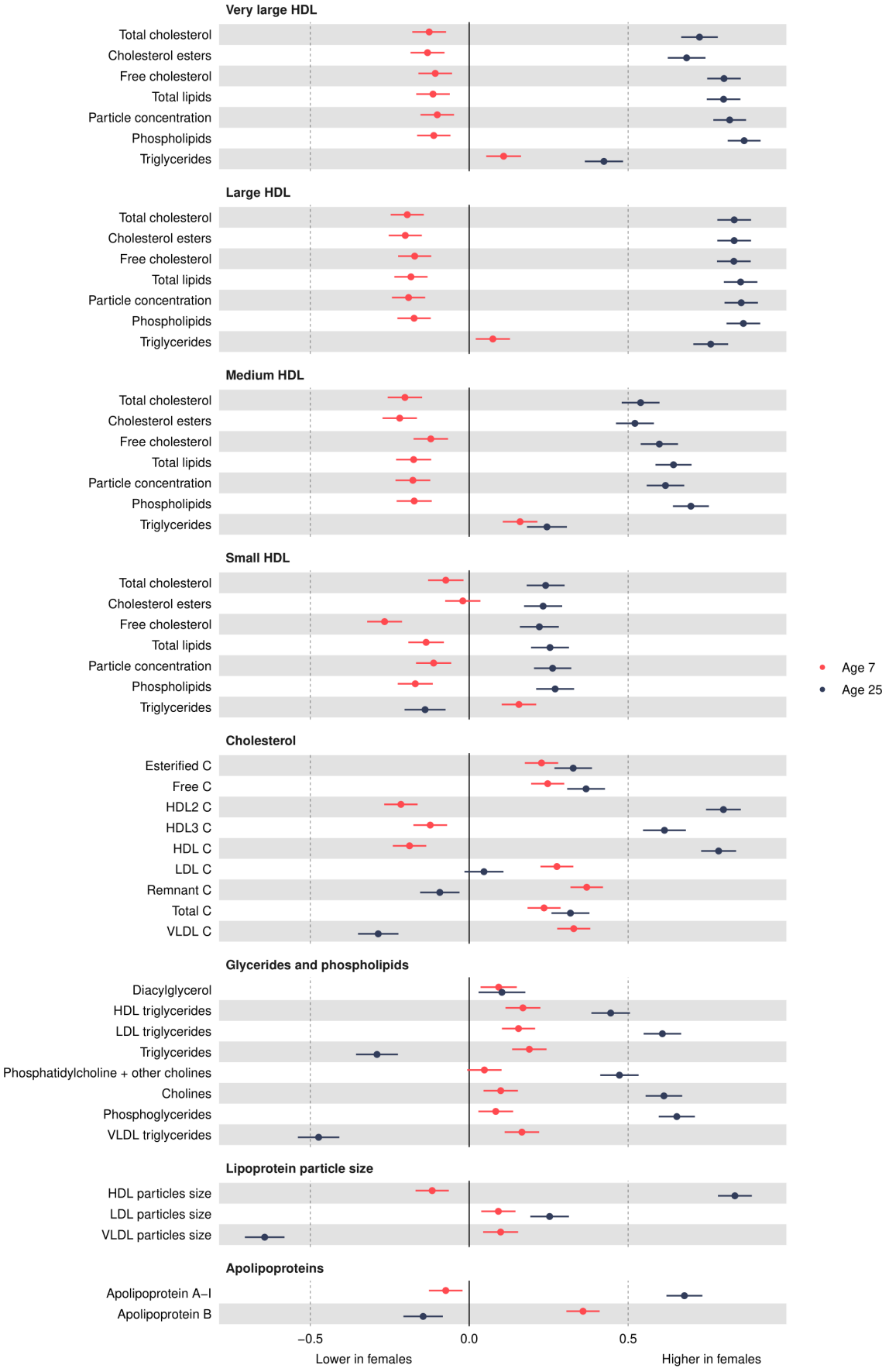

Figure 4 Mean sex difference in lipid concentrations in SD units at 7 and 25 years, estimated from multilevel models. Note that diacylglycerol is measured only up to 18 years. Differences shown are for females compared with males. HDL, high-density lipoprotein; LDL, low-density lipoprotein;VLDL, very-low-density lipoprotein.

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large HDL particle concentrations decreased from 7 years to 25 years in both sexes and females had smaller decreases than males (figure 5 and online supplemental table S4). Large HDL particle concentrations increased from 7 years to 25 years in females but decreased in males. Medium and small HDL particle concentrations increased from 7 years to 25 years in both sexes with larger increases in females. At 25 years, females had higher levels of all HDL particle concentrations, for example, 0.82 SD (95% CI 0.77 to 0.87) higher for very large HDL. Patterns were similar for different lipid contents in HDL particles.

Cholesterol

HDL cholesterol concentrations were lower in females at 7 years (figure 4 and online supplemental table S3). All other cholesterol concentrations were higher in females at 7 years. Most cholesterol concentrations decreased from 7 years to 25 years except for HDL and HDL2 in females and LDL in males, which increased over time (figure 5 and online supplemental table S4). Females had smaller decreases in esterified, free, HDL3 and total cholesterol concentrations and larger decreases in VLDL and remnant cholesterol concentrations. At 25 years, females had higher esterified, free, total and HDL cholesterol concentrations and lower VLDL and remnant cholesterol concentrations, though levels of LDL cholesterol concentrations were similar between the sexes.

Glycerides and phospholipids

All glyceride and phospholipid concentrations were higher in females at 7 years (figure 4 and online supplemental table S3). Concentrations decreased over time in both sexes except for HDL triglyceride concentrations in females which increased over time and VLDL triglycerides which did not change between 7 years and 25 years in males (figure 5 and online supplemental table S4). Females had smaller decreases for most traits, except for total triglyceride concentrations which had a larger decrease. At 25 years, females had higher levels of most glyceride and phospholipid concentrations except total and VLDL triglycerides, which were lower in females.

Particle size and apolipoproteins

LDL and VLDL particle sizes were larger in females at 7 years, but HDL particle size was smaller (figure 4 and online supplemental table S3). HDL and LDL particle sizes decreased in both sexes from 7 years to 25 years, and this decrease was smaller in females (figure 5 and online supplemental table S4). In contrast, VLDL particle size decreased in females and increased in males between 7 years and 25 years. At 25 years, LDL and HDL particle sizes were larger in females, while VLDL particle size was smaller. Apolipoprotein B was higher in females at 7 years and decreased from 7 years to 25 years in both sexes, but females had larger decreases. Apolipoprotein B was lower in females at 25 years. Apolipoprotein A-1 was lower in females at 7 years and increased over time in females but decreased over time in males. Apolipoprotein A-1 was higher in females at 25 years.

Other non-lipid traits

Glycoprotein acetyls was higher in females at 7 years (figure 6 and online supplemental table S3) and decreased in females and increased in males from 7 years to 25 years (figure 7 and online supplemental table S4), such that concentrations remained higher in females at 25 years, with a smaller difference than that observed at age 7 years. Citrate and lactate were higher in females at 7 years and lower (citrate) in females or similar between the sexes (lactate) at 25 years. Glucose was lower in females at 7 years, and this difference widened at 25 years, driven by larger decreases in females from 7 years to 25 years compared with males. All amino acids were higher in females at 7 years or similar between the sexes. Most amino acid concentrations decreased over time, except for alanine and phenylalanine in both sexes and branched chain amino acids in males, which increased over time. At 25 years, all amino acids were lower in females. Except for docosahexaenoic acid and degree of unsaturation, all fatty acids were higher in females at 7 years, and this difference was similar at 25 years due to similar changes from 7 years to 25 years in females and males (all decreased except for fatty acid chain length, which increased over time). Docosahexaenoic acid was higher in females at 7 years, and this difference widened over time. Degree of unsaturation was lower in females at 7 years and higher in females at 18 years (note, 1 of 4 traits only measured to 18 years). Albumin and creatinine were higher in females at 7 years and lower in females at 25 years due to smaller increases in females from 7 years to 25 years. Ketone bodies such as acetoacetate were higher in females at 7 years; this difference was similar at 25 years for beta-hydroxybutyrate but acetoacetate and acetate were lower in females at 25 years.

Sensitivity and additional analyses

Mean rates of change in original units in each linear spline period are shown in online supplemental table S5. Sex differences in each trait at 7 years and 25 years estimated from multilevel models were very similar to those obtained from linear regression (online supplemental table S6). Our findings were also very similar in analyses weighted by the probability of being included in analyses (online supplemental figures S1–S3) and when repeated standardising by the sex-specific mean and SD at 7 years (online supplemental figures S4–S6).

DISCUSSION

In this prospective UK birth cohort study, we examined sex-specific trajectories of 148 molecular traits from a targeted metabolomics platform, each measured repeatedly from childhood to early adulthood. Overall, our findings suggest that childhood and adolescence are important periods for the emergence of sex differences in atherogenic lipids (apolipoprotein B containing VLDL and LDL traits) and predictive biomarkers (glucose and HDL) for cardiometabolic diseases, mostly to the detriment of males.

CHD risk tends to appear higher in males until mid-life, after which risk becomes more similar between females and males.[27] In another study in the parents of participants in this cohort, absolute levels of a number of traits studied here (such as small VLDL) were shown to change little from 25 years to 50 years,[28] suggesting that differences found here may track into mid-life. In addition, recent evidence from a Mendelian randomisation (MR) study[11] of the causal effect of these traits on CHD risk in adults suggests our findings are likely to be clinically meaningful in the long term. For example, in our study, apolipoprotein B decreased by 0.14 SDs from 7 years to 25 years in males compared with a far larger decrease of 0.7 SDs in females during the same time. In the aforementioned MR study,[11] higher genetically predicted apolipoprotein B was associated with 1.68 higher odds (95% CI 1.54 to 1.85) of CHD in mid-life. In our study, apolipoprotein A1 decreased by 1 SD among males compared with an increase of 0.2 SDs in females from 7 years to 25 years; the same MR study showed that higher genetically predicted apolipoprotein A1 was associated with 0.83 lower odds (95% CI 0.77 to 0.89) of CHD

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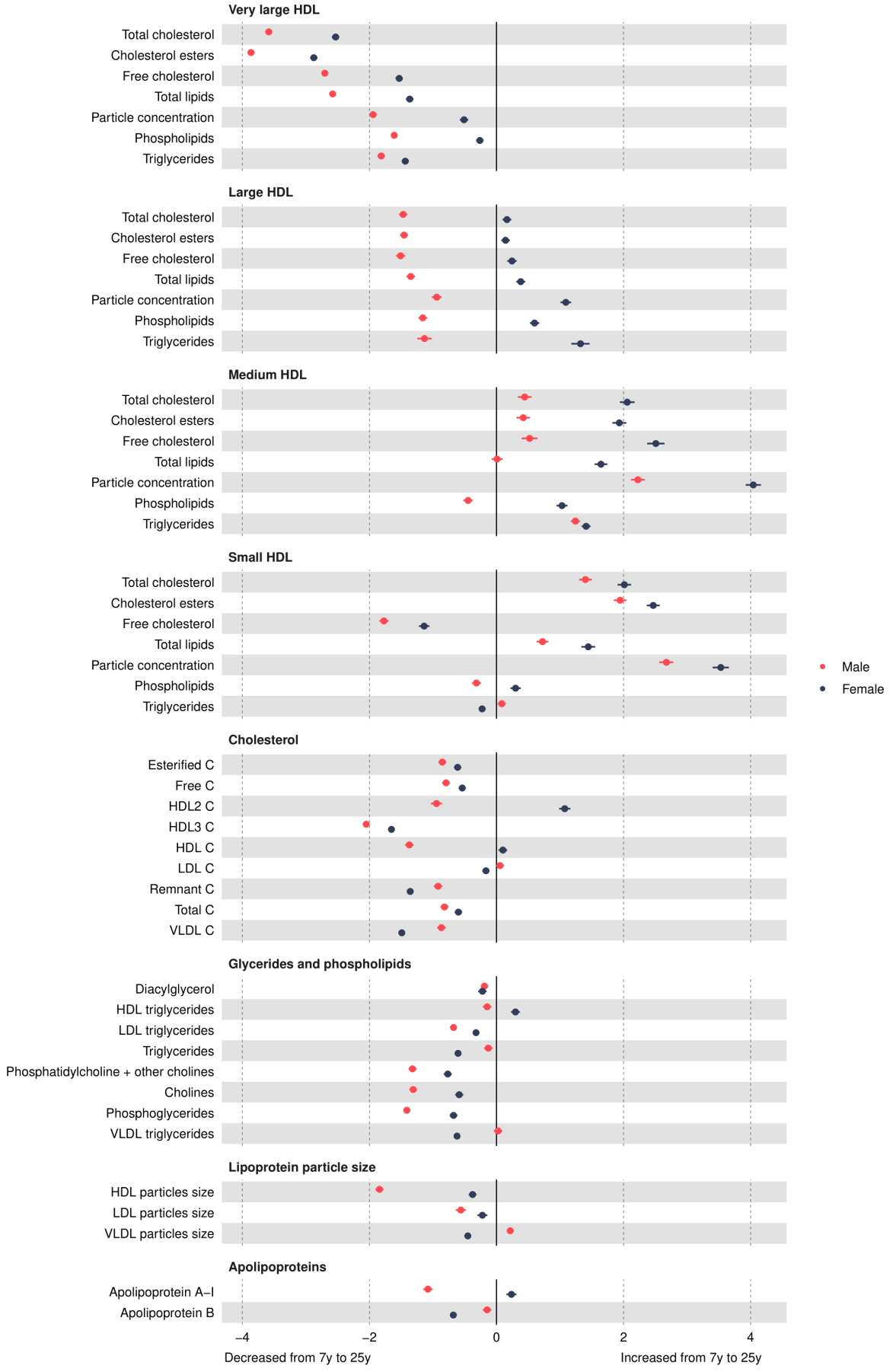

Figure 5 Mean sex-specific change in lipid concentrations in SD units from 7 to 25 years, estimated from multilevel models. Note that diacylglycerol is measured only up to 18 years. HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very-low-density lipoprotein.

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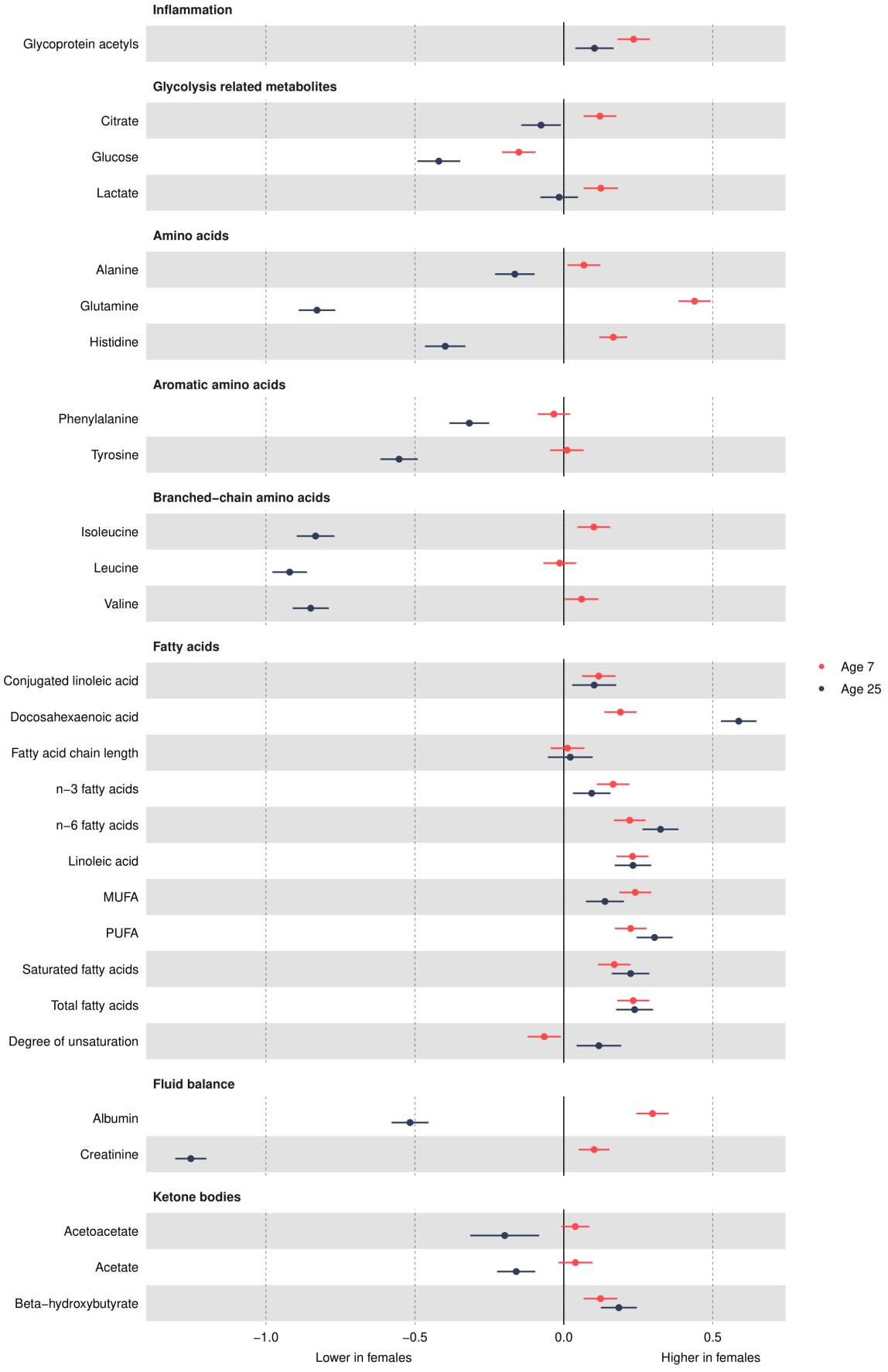

Figure 6 Mean sex difference in other trait concentrations in SD units at 7 and 25 years, estimated from multilevel models. Differences shown are for females compared with males. Note that conjugated linoleic acid, fatty acid chain length and estimated degree of unsaturation are measured only up to 18 years. MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid.

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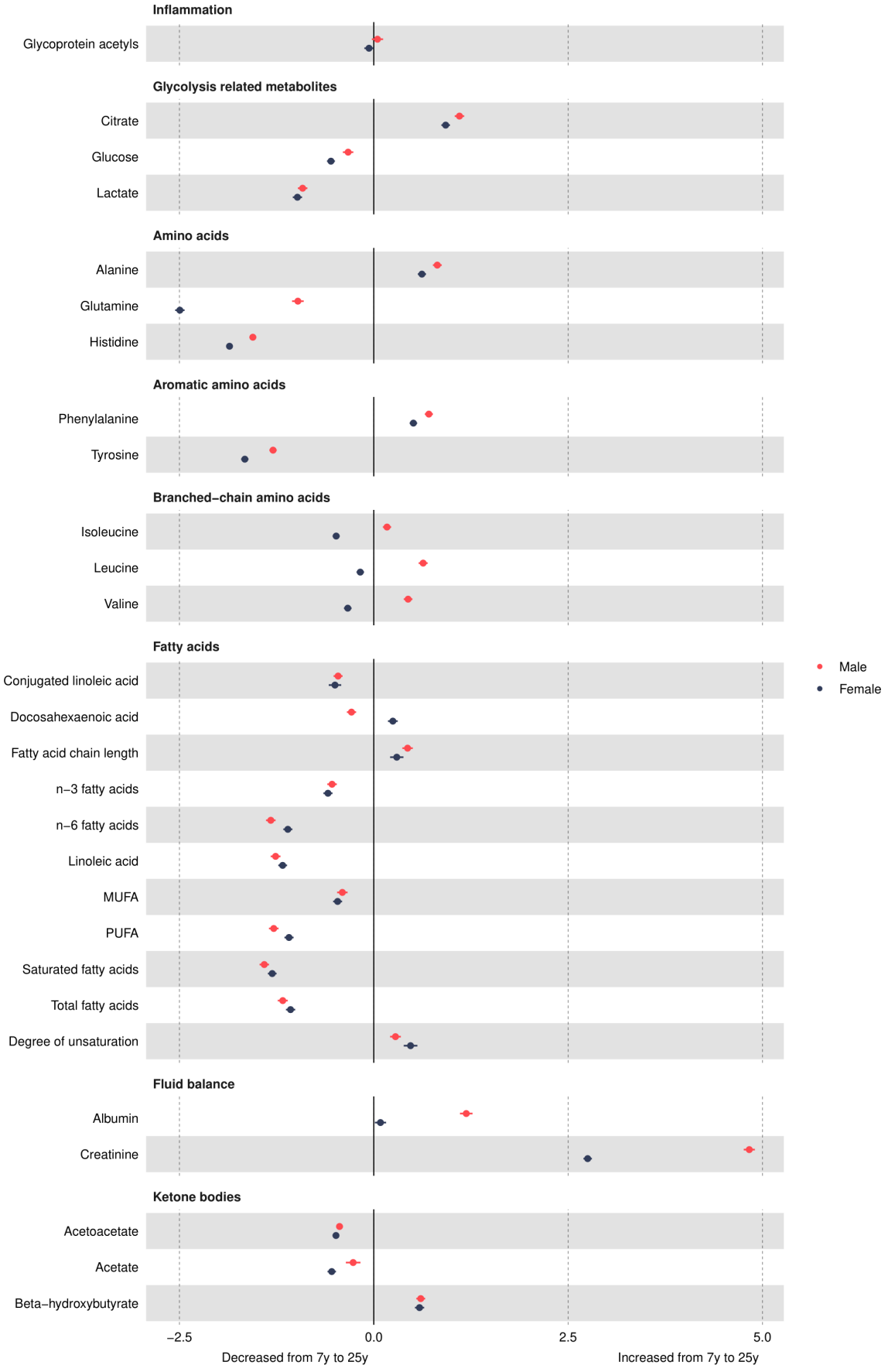

Figure 7 Mean sex-specific change in other trait concentrations in SD units from 7 to 25 years, estimated from multilevel models. Note that conjugated linoleic acid, fatty acid chain length and estimated degree of unsaturation are measured only up to 18 years. MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid.

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in mid-life. This provides indicative evidence of the potential clinical significance of the large, standardised changes and sex differences observed here in early life, particularly as these standardised differences are likely to persist or widen into mid-life as demonstrated in the previous ALSPAC study including parents of the offspring.[29] However, further work is required to study the tracking of early adulthood levels of traits and sex differences in traits into mid-life and to formally quantify the potential clinical significance of these early life trajectories in relation to later life atherosclerotic risk using cohorts with long prospective follow-up and measurement of clinical events. In addition, longitudinal mediation studies investigating multiple mediators related to late childhood and adolescence such as adiposity, puberty timing and other health behaviours are required, given that our study identified that higher levels of causal and predictive cardiometabolic traits were not evident among males at 7 years but emerged in males in late childhood and adolescence.

While few studies to date have quantified change in molecular cardiometabolic traits from childhood to early adulthood, our results are comparable with longitudinal analyses of conventional cardiometabolic risk factors. In the Bogalusa Heart Study (n=4321) which included white and black participants aged 5–26 years,[30] females had higher LDL cholesterol from 5 years to 10 years; however, a male–female cross-over arose for LDL cholesterol during adolescence.[30] Though LDL cholesterol in that study was measured using the Friedwald equation and thus more prone to measurement error due to inability to exclude intermediate-denisty lipoprotein (IDL) particles from measurement; the general pattern of higher levels in females in early childhood and movement toward a cross-over in the sex difference was observed. In addition, males in that study also had higher HDL cholesterol from age 5 years to 10 years; similar to our study, HDL cholesterol decreased over time in both sexes but to a greater degree in males leading to a male–female cross-over in HDL cholesterol at age ~13 or 14, resulting in higher HDL cholesterol in females after this age, which persisted into early adulthood. The male–female cross-over from higher levels of HDL cholesterol in males in childhood to higher levels in females from adolescence/early adulthood was also observed in the Minneapolis Cohort Study[4] and Project Heartbeat![6] Similar to our study, the Minneapolis Cohort Study demonstrated no strong sex differences in LDL cholesterol at 18 years, while in Project Heartbeat! a sex difference to the disadvantage of females emerged between childhood and age 18 years, which contrasts the narrowing of the sex difference that we observed switching from higher levels of LDL cholesterol at 7 years in females to similar levels between females and males at 25 years. The results in both studies for triglycerides, however, were generally compatible with ours, demonstrating no strong sex differences in early childhood and the emergence of higher levels of triglycerides in males around age 14, which widened and persisted until the end of follow-up at age 18/19 years.

Strengths and limitations

There are several strengths to our study including the use of 148 molecular cardiometabolic trait concentrations from a targeted metabolomics platform measured on 4 occasions across the early life course. We used multilevel models which take account of clustering of repeated measures within individuals and the correlation between measures over time. Multilevel models also allow inclusion of all participants with at least 1 measure of a risk factor, thereby minimising selection bias compared with complete case approaches. Limitations include the sparsity of measures for the purposes of trajectory modelling, which meant we were not able to explore non-linear patterns of change. While our modelling approach did minimise bias driven by use of complete case approaches for our outcome, bias may still be introduced due to exclusion of participants who did not attend any NMR clinic. Participants included in our analyses were more advantaged than those excluded from analyses. However, our sensitivity analyses weighted by the probability of inclusion in analyses did not differ from our main analyses, suggesting our results are unlikely to be strongly driven by selection into our analyses. Finally, participants were predominantly of white ethnicity and more socially advantaged, and thus, our results may not be generalisable to other populations.

CONCLUSION

Childhood and adolescence are important periods for the emergence of sex differences in causal atherogenic lipids and predictive biomarkers for cardiometabolic disease, mostly to the detriment of males. Replication in larger independent studies with more repeated measures is required.

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Ethics approval This study involves human participants and was approved by the ALSPAC Ethics and Law Committee and the local research ethics Committees. Details with reference numbers of all approvals are available in the online document (https://www.bristol.ac.uk/media-library/sites/alspac/documents/governance/ResearchEthicsCommitteeapprovalreferences.pdf). The participants gave informed consent to participate in the study before taking part.

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SUPPORTING INFORMATION

Sex-specific trajectories of molecular cardiometabolic trait concentrations through childhood, adolescence and young adulthood

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S1 Appendix Details of quality control

Laboratory

For each sample, the nuclear magnetic resonance (NMR) spectra were analysed for absolute metabolite quantification (molar concentration) in automated fashion. A ridge regression model was applied for quantification of each metabolite to overcome the problems of heavily overlapping spectral data. Quantification of lipoprotein lipid data was performed by calibrating against high performance liquid chromatography methods, and then individually cross-validated against NMR-independent lipid data. Low-molecular-weight metabolites, as well as lipid extract measures, were quantified as mmol/l based on regression modelling calibrated against a set of manually fitted metabolite measures. The calibration data was quantified based on iterative line-shape fitting analysis using PERCH NMR software (PERCH Solutions Ltd., Kuopio, Finland). Absolute quantification could not be directly established for the lipid extract measures due to experimental variation in the lipid extraction protocol. Therefore, serum extract metabolites have been scaled via the total cholesterol as quantified from the native serum LIPO spectrum. We have previously shown strong correlation between the NMR and clinical chemistry measures that are available from both methods.

Data preparation

Prior to statistical analysis, preparation of metabolomics data was performed for each occasion separately using the R package metaboprep (https://github.com/MRCIEU/metaboprep) (version 0.0.1)[1]. Quality control was performed excluding the derived metabolomics measures from missingness and clustering. Briefly, individuals, and then metabolites, with high missingness (>=80%) were removed. Missingness was then re-calculated for individuals and metabolites, with removal based on >=20% missingness. Individuals were then removed based

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on total sum abundance, considering outliers as > 5 standard deviations (SDs) away from the mean.

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S2 Appendix

Model selection

To select the optimal linear spline model for 144 trait concentrations measured from 7y to 25 years (y), we ran a series of models including; model 1: a model with two linear spline periods (7y to 18y and 18y to 25y) model 2: a second model with 2 linear spline periods (7y to 15y and 15y to 25y) and model 3: a single slope model (a single age term which assumed constant change from 7y to 25y). Linear spline periods were chosen to reflect ages in whole years that were closest to mean age at clinics and hence where the density of measures was greatest; note that the same process was carried out to select models for the four traits with measures only available to 18y with a model with two linear spline periods (7y to 15y and 15y to 18y) and single slope (7y to 18y) being compared. For each trait and model, we examined Akaike's Information Criterion (AIC) as an indicator of model fit with lower AIC values indicative of better model fit. Upon selection of the best fitting model based on AIC, we examined, observed and predicted values of models to further assess model fit. Model selection was carried out in both sexes combined to select an optimal model for each trait that would be comparable between the sexes. However, all trajectories were allowed to vary by sex in our final model for each trait by including an interaction term between the linear spline periods/age and sex. S1 Table shows a complete list of all 148 outcomes (144 measured up to 25y and four measured to 18y) and the model details for each outcome). Following the above process of model comparisons, 68 of the 144 outcomes measured to 25y had two linear spline periods from 7-15y and 15-25y, 75 of the 144 outcomes had two linear spline periods from 7-18y and 18-25y and one of the 144 outcomes (acetoacetate) was a single slope model from 7y to 25y. The final models selected for the four outcomes measured only up to 18y had two linear spline periods from 7-15y and 15-18y.

Age (in years) was centred at the first available measure (7y). Models were estimated with robust standard errors for both fixed effects and individual level random effects to account for skewed distributions in some traits. Unstructured variance-covariance matrices for the individual level random effects were used to estimate most trajectories; the optimal linear spline model selected and other model details including details of the variance-covariance matrix for each trait are shown in S1 Table. All models included individual level random effects for the intercept and each linear spline period selected. For 35 of 148 outcomes modelled (S1 Table) the covariance of the individual level random effects (level 2) were set to zero for some parameters to improve model convergence. Models allowing occasion level measurement error to vary with age (level 1 random effects for the slopes) were also explored for each risk factor. However, due to difficulties with convergence given sparsity of measures, our models included only a random effect for the intercept at level 1. The model for each outcome took the form of $metabolite_{ij} = \beta_0 + \beta_1 + u_{0j} + (\beta_2 + u_{1j})s_{ij1} + (\beta_3 + u_{2j})s_{ij2} + (\beta_4 + u_{1j})s_{ij1} + (\beta_5 + u_{2j})s_{ij2} + e_{ij}$ where for person j at measurement occasion i; β_0 represents the fixed effect coefficient for the average intercept in males, β_1 represents the difference between the intercept for females compared with males, β_2 and β_3 represent fixed effect coefficients for the average linear slopes of each linear spline in males, β_4 and β_5 represent the difference in the fixed effect coefficients for the average linear slopes of each linear spline in females compared with males, u_{0j} to u_{2j} indicate person-specific (or individual level/level 2) random effects for the intercept and slopes respectively, and e_{ij} represents the occasion-specific residuals or measurement error which was allowed to vary by the intercept.

For each sex, models directly estimate mean predicted level of each metabolite at 7y (the intercept) and mean predicted slopes in original units (mostly mmol/l), with slopes interpreted as change per year in each metabolite in the respective spline period/age period. Following

analysis, these estimates were then used to calculate mean predicted absolute change in each trait level from 7y to 25y using the slopes given by each model. The mean predicted level of each trait at 25y was also estimated. Post-analysis, all the above estimates were then converted to SD units by dividing by the sex-combined SD of the observed metabolite at 7y, to aid comparison of results between metabolites.

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S1 Table: Metabolic trait subclass, name, units and multilevel model details for each

Molecular class	Lipid, lipoprotein or metabolite name	Units	Knot	Level 2 variance	Level 1 variance
Extremely large VLDL	Concentration of chylomicrons and extremely large VLDL particles	mol/l	15	Intercept & splines; unstructured	Intercept
	Total lipids in chylomicrons and extremely large VLDL	mmol/l	15	Intercept & splines; matrix a = (1, 1, 1, 1, 1, 0)	Intercept
	Phospholipids in chylomicrons and extremely large VLDL	mmol/l	15	Intercept & splines; unstructured	Intercept
	Total cholesterol in chylomicrons and extremely large VLDL	mmol/l	18	Intercept & splines; matrix a = (1, 1, 1, 1, 1, 0)	Intercept
	Cholesterol esters in chylomicrons and extremely large VLDL	mmol/l	18	Intercept & splines; matrix a = (1, 1, 1, 1, 1, 0)	Intercept
	Free cholesterol in chylomicrons and extremely large VLDL	mmol/l	15	Intercept & splines; matrix a = (1, 1, 1, 1, 1, 0)	Intercept
	Triglycerides in chylomicrons and extremely large VLDL	mmol/l	15	Intercept & splines; matrix a = (1, 1, 1, 1, 1, 0)	Intercept
Very large VLDL	Concentration of very large VLDL particles	mol/l	15	Intercept & splines; unstructured	Intercept
	Total lipids in very large VLDL	mmol/l	15	Intercept & splines; unstructured	Intercept
	Phospholipids in very large VLDL	mmol/l	15	Intercept & splines; unstructured	Intercept
	Total cholesterol in very large VLDL	mmol/l	15	Intercept & splines; matrix a = (1, 1, 1, 1, 1, 0)	Intercept
	Cholesterol esters in very large VLDL	mmol/l	18	Intercept & splines; unstructured	Intercept
	Free cholesterol in very large VLDL	mmol/l	15	Intercept & splines; matrix a = (1, 1, 1, 1, 1, 0)	Intercept
	Triglycerides in very large VLDL	mmol/l	15	Intercept & splines; unstructured	Intercept
Large VLDL	Concentration of large VLDL particles	mol/l	15	Intercept & splines; unstructured	Intercept
	Total lipids in large VLDL	mmol/l	15	Intercept & splines; unstructured	Intercept
	Phospholipids in large VLDL	mmol/l	15	Intercept & splines; unstructured	Intercept
	Total cholesterol in large VLDL	mmol/l	15	Intercept & splines; unstructured	Intercept
	Cholesterol esters in large VLDL	mmol/l	15	Intercept & splines; unstructured	Intercept
	Free cholesterol in large VLDL	mmol/l	15	Intercept & splines; unstructured	Intercept
	Triglycerides in large VLDL	mmol/l	15	Intercept & splines; unstructured	Intercept
Medium VLDL	Concentration of large VLDL particles	mol/l	15	Intercept & splines; unstructured	Intercept
	Total lipids in small VLDL	mmol/l	15	Intercept & splines; unstructured	Intercept
	Phospholipids in small VLDL	mmol/l	15	Intercept & splines; unstructured	Intercept
	Total cholesterol in small VLDL	mmol/l	15	Intercept & splines; unstructured	Intercept
	Cholesterol esters in small VLDL	mmol/l	15	Intercept & splines; unstructured	Intercept
	Free cholesterol in small VLDL	mmol/l	15	Intercept & splines; unstructured	Intercept
	Triglycerides in small VLDL	mmol/l	15	Intercept & splines; unstructured	Intercept
Small VLDL	Concentration of small VLDL particles	mol/l	15	Intercept & splines; unstructured	Intercept
	Total lipids in small VLDL	mmol/l	18	Intercept & splines; unstructured	Intercept
	Phospholipids in small VLDL	mmol/l	15	Intercept & splines; matrix a = (1, 1, 0, 1, 1, 1)	Intercept
	Total cholesterol in small VLDL	mmol/l	18	Intercept & splines; unstructured	Intercept
	Cholesterol esters in small VLDL	mmol/l	18	Intercept & splines; unstructured	Intercept

	Free cholesterol in small VLDL	mmol/l	18	Intercept & splines; unstructured	Intercept
	Triglycerides in small VLDL	mmol/l	15	Intercept & splines; unstructured	Intercept
Very small VLDL	Concentration of very small VLDL particles	mmol/l	15	Intercept & splines; matrix a = (1, 1, 0, 1, 1, 1)	Intercept
	Total lipids in very small VLDL	mmol/l	18	Intercept & splines; unstructured	Intercept
	Phospholipids in very small VLDL	mmol/l	15	Intercept & splines; matrix a = (1, 1, 0, 1, 1, 1)	Intercept
	Total cholesterol in very small VLDL	mmol/l	18	Intercept & splines; unstructured	Intercept
	Cholesterol esters in very small VLDL	mmol/l	18	Intercept & splines; unstructured	Intercept
	Free cholesterol in very small VLDL	mmol/l	18	Intercept & splines; unstructured	Intercept
	Triglycerides in very small VLDL	mmol/l	18	Intercept & splines; unstructured	Intercept
IDl	Concentration of IDL particles	mol/l	18	Intercept & splines; unstructured	Intercept
	Total lipids in IDL	mmol/l	18	Intercept & splines; unstructured	Intercept
	Phospholipids in IDL	mmol/l	18	Intercept & splines; unstructured	Intercept
	Total cholesterol in IDL	mmol/l	18	Intercept & splines; unstructured	Intercept
	Cholesterol esters in IDL	mmol/l	18	Intercept & splines; unstructured	Intercept
	Free cholesterol in IDL	mmol/l	18	Intercept & splines; unstructured	Intercept
	Triglycerides in IDL	mmol/l	18	Intercept & splines; unstructured	Intercept
Large LDL	Concentration of large LDL particles	mol/l	18	Intercept & splines; unstructured	Intercept
	Total lipids in large LDL	mmol/l	18	Intercept & splines; unstructured	Intercept
	Phospholipids in large LDL	mmol/l	18	Intercept & splines; unstructured	Intercept
	Total cholesterol in large LDL	mmol/l	18	Intercept & splines; unstructured	Intercept
	Cholesterol esters in large LDL	mmol/l	18	Intercept & splines; unstructured	Intercept
	Free cholesterol in large LDL	mmol/l	18	Intercept & splines; unstructured	Intercept
	Triglycerides in large LDL	mmol/l	18	Intercept & splines; unstructured	Intercept
Medium LDL	Concentration of medium LDL particles	mol/l	18	Intercept & splines; unstructured	Intercept
	Total lipids in medium LDL	mmol/l	18	Intercept & splines; unstructured	Intercept
	Phospholipids in medium LDL	mmol/l	15	Intercept & splines; matrix a = (1, 1, 0, 1, 1, 1)	Intercept
	Total cholesterol in medium LDL	mmol/l	18	Intercept & splines; unstructured	Intercept
	Cholesterol esters in medium LDL	mmol/l	18	Intercept & splines; unstructured	Intercept
	Free cholesterol in medium LDL	mmol/l	18	Intercept & splines; unstructured	Intercept
	Triglycerides in medium LDL	mmol/l	18	Intercept & splines; matrix a = (1, 1, 1, 1, 1, 0)	Intercept
Small LDL	Concentration of small LDL particles	mol/l	18	Intercept & splines; unstructured	Intercept
	Total lipids in small LDL	mmol/l	18	Intercept & splines; unstructured	Intercept
	Phospholipids in small LDL	mmol/l	15	Intercept & splines; matrix a = (1, 1, 0, 1, 1, 1)	Intercept
	Total cholesterol in small LDL	mmol/l	18	Intercept & splines; unstructured	Intercept
	Cholesterol esters in small LDL	mmol/l	18	Intercept & splines; unstructured	Intercept

	Free cholesterol in small LDL	mmol/l	18	Intercept & splines; unstructured	Intercept
	Triglycerides in small LDL	mmol/l	15	Intercept & splines; matrix a = (1, 1, 1, 1, 1, 0)	Intercept
Very large HDL	Concentration of very large HDL particles	mol/l	15	Intercept & splines; unstructured	Intercept
	Total lipids in very large HDL	mmol/l	15	Intercept & splines; unstructured	Intercept
	Phospholipids in very large HDL	mmol/l	15	Intercept & splines; unstructured	Intercept
	Total cholesterol in very large HDL	mmol/l	18	Intercept & splines; unstructured	Intercept
	Cholesterol esters in very large HDL	mmol/l	18	Intercept & splines; unstructured	Intercept
	Free cholesterol in very large HDL	mmol/l	15	Intercept & splines; unstructured	Intercept
	Triglycerides in very large HDL	mmol/l	15	Intercept & splines; unstructured	Intercept
Large HDL	Concentration of large HDL particles	mol/l	18	Intercept & splines; unstructured	Intercept
	Total lipids in large HDL	mmol/l	18	Intercept & splines; unstructured	Intercept
	Phospholipids in large HDL	mmol/l	18	Intercept & splines; unstructured	Intercept
	Total cholesterol in large HDL	mmol/l	18	Intercept & splines; unstructured	Intercept
	Cholesterol esters in large HDL	mmol/l	18	Intercept & splines; unstructured	Intercept
	Free cholesterol in large HDL	mmol/l	18	Intercept & splines; unstructured	Intercept
	Triglycerides in large HDL	mmol/l	18	Intercept & splines; unstructured	Intercept
Medium HDL	Concentration of medium HDL particles	mol/l	18	Intercept & splines; unstructured	Intercept
	Total lipids in medium HDL	mmol/l	15	Intercept & splines; matrix a = (1, 1, 0, 1, 1, 1)	Intercept
	Phospholipids in medium HDL	mmol/l	15	Intercept & splines; matrix a = (1, 1, 0, 1, 1, 1)	Intercept
	Total cholesterol in medium HDL	mmol/l	18	Intercept & splines; unstructured	Intercept
	Cholesterol esters in medium HDL	mmol/l	18	Intercept & splines; unstructured	Intercept
	Free cholesterol in medium HDL	mmol/l	18	Intercept & splines; unstructured	Intercept
	Triglycerides in medium HDL	mmol/l	15	Intercept & splines; matrix a = (1, 1, 0, 1, 1, 1)	Intercept
Small HDL	Concentration of small HDL particles	mol/l	15	Intercept & splines; matrix a = (0, 1, 0, 1, 1, 1)	Intercept
	Total lipids in small HDL	mmol/l	15	Intercept & splines; matrix a = (1, 1, 0, 1, 1, 0)	Intercept
	Phospholipids in small HDL	mmol/l	15	Intercept & splines; matrix a = (1, 1, 0, 1, 1, 1)	Intercept
	Total cholesterol in small HDL	mmol/l	15	Intercept & splines; matrix a = (1, 1, 0, 1, 1, 1)	Intercept
	Cholesterol esters in small HDL	mmol/l	15	Intercept & splines; matrix a = (1, 1, 0, 1, 1, 1)	Intercept
	Free cholesterol in small HDL	mmol/l	18	Intercept & splines; unstructured	Intercept
	Triglycerides in small HDL	mmol/l	15	Intercept & splines; unstructured	Intercept
Lipoprotein particle size	Mean diameter for VLDL particles	nm	15	Intercept & splines; unstructured	Intercept
	Mean diameter for LDL particles	nm	15	Intercept & splines; matrix a = (1, 1, 0, 1, 1, 1)	Intercept
	Mean diameter for HDL particles	nm	15	Intercept & splines; unstructured	Intercept
Cholesterol concentrations	Total cholesterol	mmol/l	18	Intercept & splines; unstructured	Intercept
	Total cholesterol in VLDL	mmol/l	18	Intercept & splines; unstructured	Intercept

	Remnant cholesterol (non-HDL and non-LDL cholesterol)	mmol/l	18	Intercept & splines; unstructured	Intercept
	Total cholesterol in LDL	mmol/l	18	Intercept & splines; unstructured	Intercept
	Total cholesterol in HDL	mmol/l	18	Intercept & splines; unstructured	Intercept
	Total cholesterol in HDL2	mmol/l	18	Intercept & splines; unstructured	Intercept
	Total cholesterol in HDL3	mmol/l	18	Intercept & splines; unstructured	Intercept
	Esterified cholesterol	mmol/l	15	Intercept & splines; matrix a = (1, 1, 0, 1, 1, 1)	Intercept
	Free cholesterol	mmol/l	18	Intercept & splines; unstructured	Intercept
Glycerides and phospholipid concentrations	Total triglycerides	mmol/l	15	Intercept & splines; unstructured	Intercept
	Triglycerides in VLDL	mmol/l	15	Intercept & splines; unstructured	Intercept
	Triglycerides in LDL	mmol/l	18	Intercept & splines; matrix a = (1, 1, 1, 1, 1, 0)	Intercept
	Triglycerides in HDL	mmol/l	15	Intercept & splines; unstructured	Intercept
	Diacylglycerol*	mmol/l	15	Intercept & splines; matrix a = (1, 1, 1, 1, 1, 0)	Intercept
	Total phosphoglycerides (mmol/l)	mmol/l	18	Intercept & splines; matrix a = (1, 1, 0, 1, 1, 1)	Intercept
	Phosphatidylcholine and other cholines (mmol/l)	mmol/l	18	Intercept & splines; unstructured	Intercept
	Total cholines (mmol/l)	mmol/l	15	Intercept & splines; unstructured	Intercept
Apolipoprotein concentrations	Apolipoprotein A-1	g/l	18	Intercept & splines; unstructured	Intercept
	Apolipoprotein B	g/l	15	Intercept & splines; unstructured	Intercept
Fatty acid concentrations	Total fatty acids	mmol/l	15	Intercept & splines; unstructured	Intercept
	Fatty acid length*		15	Intercept & splines; unstructured	Intercept
	Estimated degree of saturation*		15	Intercept & splines; unstructured	Intercept
	22:6, docosahexaenoic acid	mmol/l	15	Intercept & splines; matrix a = (1, 1, 0, 1, 1, 1)	Intercept
	18:2 linoleic acid	mmol/l	15	Intercept & splines; unstructured	Intercept
	Conjugated linoleic acid*	mmol/l	15	Intercept & splines; unstructured	Intercept
	Omega-3 fatty acids	mmol/l	15	Intercept & splines; matrix a = (1, 1, 0, 1, 1, 1)	Intercept
	Omega-6 fatty acids	mmol/l	15	Intercept & splines; unstructured	Intercept
	Polyunsaturated fatty acids	mmol/l	15	Intercept & splines; unstructured	Intercept
	Monounsaturated fatty acids; 16:1, 18:1	mmol/l	18	Intercept & splines; unstructured	Intercept
	Saturated fatty acids	mmol/l	15	Intercept & splines; unstructured	Intercept
Glycolysis related metabolite	Glucose	mmol/l	15	Intercept & splines; matrix a = (1, 1, 1, 1, 1, 0)	Intercept
	Lactate	mmol/l	15	Intercept & splines; unstructured	Intercept
	Citrate	mmol/l	18	Intercept & splines; unstructured	Intercept
Amino acid concentrations	Alanine	mmol/l	18	Intercept & splines; unstructured	Intercept
	Glutamine	mmol/l	18	Intercept & splines; unstructured	Intercept

	Histidine	mmol/l	18	Intercept & splines; matrix a = (1, 1, 1, 1, 1, 0)	Intercept
branched	Isoleucine	mmol/l	18	Intercept & splines; matrix a = (1, 1, 1, 1, 1, 0)	Intercept
branched	Leucine	mmol/l	18	Intercept & splines; unstructured	Intercept
branched	Valine	mmol/l	15	Intercept & splines; unstructured	Intercept
aromatic	Phenylalanine	mmol/l	18	Intercept & splines; unstructured	Intercept
aromatic	Tyrosine	mmol/l	15	Intercept & splines; matrix a = (1, 1, 1, 1, 1, 0)	Intercept
	Acetate	mmol/l	15	Intercept & splines; matrix a = (1, 1, 0, 1, 1, 1)	Intercept
Ketone body	Acetoacetate	mmol/l	Linear	Intercept & slope; unstructured	Intercept
concentrations	3-hydroxybutyrate	mmol/l	18	Intercept & splines; matrix a = (0, 1, 1, 1, 1, 1)	Intercept
Fluid balance marker	Creatinine	mmol/l	18	Intercept & splines; unstructured	Intercept
	Albumin	mmol/l	18	Intercept & splines; matrix a = (1, 1, 0, 1, 1, 1)	Intercept
Inflammation marker	Glycoprotein acetyls, mainly a1-acid glycoprotein	mmol/l	18	Intercept & splines; unstructured	Intercept

*These metabolites were not measured at 25y; all models include data only up to aged 18y. HDL: high-density lipoprotein; IDL: intermediate-density lipoprotein; LDL: low-density lipoprotein; VLDL: very-low-density lipoprotein.

S3 Appendix

Characteristics of included vs. included participants

We examined characteristics associated with not being included in our analyses due to missing data on sex or molecular traits. To do this, we compared the socio-demographic characteristics at birth of mothers and partners of participants included in the analyses compared to those excluded from the analyses. All characteristics were measured during pregnancy or at birth through questionnaires or from routine health records.

Marital status was obtained from antenatal questionnaires and classified as never married, widowed, divorced, separated, first marriage, marriage 2 or 3. Household social class was measured as the highest of the mother's or her partner's occupational social class using data on job title and details of occupation collected about the mother and her partner from the mother's questionnaire at 32 weeks gestation. Social class was derived using the standard occupational classification (SOC) codes developed by the United Kingdom Office of Population Census and Surveys and classified as I professional, II managerial and technical, IIINM non-manual, IIIM manual, and IV&V part skilled occupations and unskilled occupations. A questionnaire at 32 weeks gestation asked mothers to report their educational attainment, which was categorized as below O-Level (Ordinary Level; exams taken in different subjects usually at age 15-16 at the completion of legally required school attendance, equivalent to today's UK General Certificate of Secondary Education), O-Level only, A-Level (Advanced-Level; exams taken in different subjects usually at age 18), or university degree or above. A questionnaire at 32 weeks gestation asked partners to report their educational attainment, which was categorized as below O-Level (Ordinary Level; exams taken in different subjects usually at age 15-16 at the completion of legally required school attendance, equivalent to today's UK General Certificate of Secondary Education), O-Level only, A-Level (Advanced-Level; exams taken in different

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subjects usually at age 18), or university degree or above. Smoking in the first trimester of pregnancy was self-reported by mothers at 18 weeks gestation. Birthweight and gestational age were derived from clinical records. Maternal age was reported in the mother's antenatal questionnaires. Maternal pre-pregnancy weight and height were self-reported in antenatal questionnaires.

Sensitivity analyses

We compared sex differences in metabolic traits at 7y and 25y from the multilevel models with the same differences generated from linear regression analyses at each age separately. This was done to explore the appropriateness of our modelling strategy, compared with more conventional analytic approaches. As outlined, participants included in our analyses required data on sex and at least one measure of each metabolite from 7y to 25y. Mothers of participants included in the analyses tended be of higher household social class and more educated than mothers of participants excluded due to missing data and these differences were similar between females and males (S2 Table). Thus, we performed sensitivity analyses weighted by the probability of being included in our analyses to account for the higher probability of being included due to greater social advantage. The participant level weights were estimated using logistic regression using all socio-demographic characteristics listed above with the addition of sex and were subsequently incorporated into the multilevel models as level two weights which adjust for the unequal probability of selection of the participants. We repeated all SD unit analyses standardising with the sex-specific SD of each metabolite at 7y to examine whether our main results (standardised with sex-combined SDs) were similar.

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S2 Table: Characteristics of offspring included in analyses compared to those excluded due to missing sex, cardiometabolic trait data or attrition from the cohort

	Female participants included n=3,909*	Female participants excluded	N excluded females	Male participants included n=3,717*	Male participants excluded	N excluded males
	n (%)	n (%)	n	n (%)	n (%)	n
Non-white ethnicity	75 (2.2)	77 (2.99)	2573	60 (1.8)	112 (3.7)	3050
Maternal marital status			2887			3433
Never married	527 (15.1)	680 (23.6)		467 (13.7)	853 (24.9)	
Widowed	<5	6 (0.2)		8 (0.2)	<5	
Divorced	110 (3.2)	143 (5.0)		118 (3.5)	188 (5.5)	
Separated	50 (1.4)	58 (2.0)		36 (1.1)	70 (2.0)	
1st Marriage	2581 (73.9)	1832 (63.5)		2544 (74.8)	2086 (60.8)	
Marriage 2 or 3	224 (6.4)	168 (5.8)		229 (6.7)	234 (6.8)	
Household social class †			2337			2758
Professional	517 (15.8)	213 (9.1)		532 (16.7)	275 (10.0)	
Managerial & Technical	1463 (44.6)	893 (38.2)		1404 (44.1)	1062 (38.5)	
Non-Manual	793 (24.2)	637 (27.3)		792 (24.9)	723 (26.2)	
Manual	343 (10.5)	411 (17.6)		328 (10.3)	479 (17.4)	
Part Skilled & Unskilled	161 (4.9)	183 (7.8)		128 (4.0)	219 (7.9)	
Maternal education			2605			3088
Less than O level	761 (22.2)	1025 (39.4)		724 (21.6)	1238 (40.1)	
O level	1166 (34.1)	920 (35.3)		1195 (35.7)	1036 (33.6)	
A level	926 (27.1)	435 (16.7)		883 (26.4)	550 (17.8)	
Degree or above	569 (16.6)	225 (8.6)		548 (16.4)	264 (8.6)	
Mother's Partner's highest educational qualification			2479			2915
Less than O level	965 (28.9)	1056 (42.6)		863 (26.5)	1258 (43.2)	
O level	717 (21.5)	501 (20.2)		724 (22.2)	609 (20.9)	
A level	916 (27.5)	625 (25.2)		918 (28.2)	657 (22.5)	
Degree or Above	737 (22.1)	297 (12.0)		750 (23.0)	391 (13.4)	
Maternal smoking during pregnancy	660 (18.9)	891 (30.5)	2992	657 (19.2)	1126 (32.8)	3438
	Mean (SD)	***Mean (SD)***		***Mean (SD)***	***Mean (SD)***	
Birthweight (g)	3370 (512)	3283 (579)	3158	3469 (578)	3395 (631)	3723
Gestational age (weeks)	39.6 (1.8)	39.2 (2.9)	3230	39.3 (1.9)	39.0 (3.0)	3812
Maternal age (years)	28.8 (4.6)	26.8 (5.0)	3198	29.1 (4.7)	27.1 (5.1)	3778
Maternal pre-pregnancy BMI (kg/m²)	22.8 (3.6)	23.1 (4.1)	2448	22.9 (3.8)	23.0 (3.9)	2845

*Represents participants included in models of 144 concentrations with data at all four time points; exact denominators in this table will vary due to missing data for characteristics which were not required for inclusion in analyses.

S3 Table: Mean difference in traits at 7y and 25y comparing females with males

	Original units		SD units	
	Difference (95% CI) in trait at 7y comparing females to males	**Difference (95% CI) in trait at 25y comparing females to males**	**Difference (95% CI) in trait at 7y comparing females to males**	**Difference (95% CI) in trait at 25y comparing females to males**
Concentration of chylomicrons and extremely large VLDL particles (mol/l)	1.68E-11 (1.11E-11,2.26E-11)	-2.63E-11 (-3.10E-11,-2.16E-11)	0.16(0.11,0.21)	-0.39(-0.45,-0.32)
Total lipids in chylomicrons and extremely large VLDL (mmol/l)	3.51E-03 (2.22E-03,4.79E-03)	-5.65E-03 (-6.65E-03,-4.64E-03)	0.15(0.09,0.2)	-0.39(-0.46,-0.32)
Phospholipids in chylomicrons and extremely large VLDL (mmol/l)	4.25E-04 (2.68E-04,5.81E-04)	-6.51E-04 (-7.77E-04,-5.25E-04)	0.15(0.09,0.2)	-0.36(-0.43,-0.29)
Total cholesterol in chylomicrons and extremely large VLDL (mmol/l)	5.91E-04 (3.97E-04,7.84E-04)	-7.50E-04 (-9.22E-04,-5.77E-04)	0.16(0.11,0.22)	-0.3(-0.37,-0.23)
Cholesterol esters in chylomicrons and extremely large VLDL (mmol/l)	2.97E-04 (2.01E-04,3.94E-04)	-3.59E-04 (-4.52E-04,-2.65E-04)	0.16(0.11,0.22)	-0.26(-0.33,-0.19)
Free cholesterol in chylomicrons and extremely large VLDL (mmol/l)	2.84E-04 (1.79E-04,3.88E-04)	-4.12E-04 (-4.94E-04,-3.31E-04)	0.15(0.09,0.2)	-0.35(-0.42,-0.28)
Triglycerides in chylomicrons and extremely large VLDL (mmol/l)	2.51E-03 (1.57E-03,3.45E-03)	-4.20E-03 (-4.90E-03,-3.49E-03)	0.15(0.09,0.2)	-0.41(-0.48,-0.34)
Concentration of very large VLDL particles (mol/l)	7.96E-11 (4.77E-11,1.11E-10)	-1.66E-10 (-1.94E-10,-1.37E-10)	0.14(0.08,0.19)	-0.4(-0.47,-0.33)
Total lipids in very large VLDL (mmol/l)	7.62E-03 (4.55E-03,1.07E-02)	-1.59E-02 (-1.86E-02,-1.32E-02)	0.14(0.08,0.19)	-0.4(-0.46,-0.33)
Phospholipids in very large VLDL (mmol/l)	1.34E-03 (8.22E-04,1.85E-03)	-2.33E-03 (-2.78E-03,-1.88E-03)	0.14(0.09,0.2)	-0.35(-0.42,-0.28)
Total cholesterol in very large VLDL (mmol/l)	1.79E-03 (1.20E-03,2.38E-03)	-2.82E-03 (-3.33E-03,-2.30E-03)	0.17(0.11,0.22)	-0.38(-0.45,-0.31)
Cholesterol esters in very large VLDL (mmol/l)	9.61E-04 (6.68E-04,1.25E-03)	-1.51E-03 (-1.79E-03,-1.24E-03)	0.18(0.12,0.23)	-0.38(-0.44,-0.31)
Free cholesterol in very large VLDL (mmol/l)	8.59E-04 (5.66E-04,1.15E-03)	-1.21E-03 (-1.45E-03,-9.74E-04)	0.16(0.11,0.21)	-0.35(-0.42,-0.28)
Triglycerides in very large VLDL (mmol/l)	4.49E-03 (2.52E-03,6.46E-03)	-1.07E-02 (-1.25E-02,-8.97E-03)	0.12(0.07,0.18)	-0.41(-0.48,-0.34)
Concentration of large VLDL particles (mol/l)	3.61E-10 (2.16E-10,5.06E-10)	-1.11E-09 (-1.28E-09,-9.44E-10)	0.14(0.08,0.19)	-0.43(-0.5,-0.37)
Total lipids in large VLDL (mmol/l)	2.25E-02 (1.38E-02,3.12E-02)	-6.39E-02 (-7.37E-02,-5.41E-02)	0.14(0.09,0.2)	-0.43(-0.5,-0.37)
Phospholipids in large VLDL (mmol/l)	4.22E-03 (2.66E-03,5.78E-03)	-1.08E-02 (-1.26E-02,-9.04E-03)	0.15(0.09,0.2)	-0.4(-0.47,-0.34)
Total cholesterol in large VLDL (mmol/l)	5.87E-03 (3.91E-03,7.83E-03)	-1.32E-02 (-1.54E-02,-1.10E-02)	0.16(0.11,0.22)	-0.4(-0.47,-0.34)
Cholesterol esters in large VLDL (mmol/l)	3.05E-03 (2.14E-03,3.96E-03)	-6.89E-03 (-7.97E-03,-5.82E-03)	0.18(0.13,0.24)	-0.42(-0.49,-0.36)
Free cholesterol in large VLDL (mmol/l)	2.83E-03 (1.76E-03,3.89E-03)	-6.30E-03 (-7.41E-03,-5.19E-03)	0.15(0.09,0.2)	-0.38(-0.45,-0.31)
Triglycerides in large VLDL (mmol/l)	1.24E-02 (7.18E-03,1.76E-02)	-3.99E-02 (-4.58E-02,-3.41E-02)	0.13(0.08,0.18)	-0.45(-0.52,-0.38)
Concentration of medium VLDL particles (mol/l)	1.05E-09 (7.37E-10,1.37E-09)	-3.34E-09 (-3.78E-09,-2.90E-09)	0.18(0.13,0.23)	-0.49(-0.56,-0.43)
Total lipids in medium VLDL (mmol/l)	3.73E-02 (2.66E-02,4.80E-02)	-1.09E-01 (-1.23E-01,-9.44E-02)	0.19(0.14,0.24)	-0.49(-0.55,-0.42)
Phospholipids in medium VLDL (mmol/l)	7.60E-03 (5.56E-03,9.65E-03)	-1.97E-02 (-2.25E-02,-1.70E-02)	0.2(0.15,0.26)	-0.46(-0.52,-0.39)
Total cholesterol in medium VLDL (mmol/l)	1.19E-02 (9.16E-03,1.46E-02)	-2.07E-02 (-2.44E-02,-1.70E-02)	0.23(0.18,0.29)	-0.36(-0.43,-0.3)
Cholesterol esters in medium VLDL (mmol/l)	7.01E-03 (5.52E-03,8.49E-03)	-8.63E-03 (-1.06E-02,-6.66E-03)	0.25(0.2,0.31)	-0.28(-0.35,-0.22)
Free cholesterol in medium VLDL (mmol/l)	4.91E-03 (3.54E-03,6.27E-03)	-1.20E-02 (-1.38E-02,-1.02E-02)	0.2(0.14,0.25)	-0.43(-0.5,-0.37)
Triglycerides in medium VLDL (mmol/l)	1.78E-02 (1.18E-02,2.39E-02)	-6.84E-02 (-7.65E-02,-6.04E-02)	0.16(0.11,0.21)	-0.55(-0.61,-0.48)
Concentration of small VLDL particles (mol/l)	1.46E-09 (1.15E-09,1.77E-09)	-3.08E-09 (-3.55E-09,-2.62E-09)	0.25(0.2,0.31)	-0.42(-0.48,-0.35)
Total lipids in small VLDL (mmol/l)	3.40E-02 (2.79E-02,4.01E-02)	-5.84E-02 (-6.74E-02,-4.94E-02)	0.29(0.24,0.35)	-0.41(-0.47,-0.35)
Phospholipids in small VLDL (mmol/l)	6.19E-03 (4.97E-03,7.42E-03)	-8.95E-03 (-1.08E-02,-7.14E-03)	0.27(0.22,0.32)	-0.31(-0.37,-0.25)
Total cholesterol in small VLDL (mmol/l)	1.58E-02 (1.36E-02,1.80E-02)	-1.56E-02 (-1.88E-02,-1.23E-02)	0.37(0.32,0.42)	-0.3(-0.36,-0.23)
Cholesterol esters in small VLDL (mmol/l)	1.12E-02 (9.71E-03,1.27E-02)	-9.38E-03 (-1.15E-02,-7.23E-03)	0.39(0.34,0.44)	-0.27(-0.33,-0.21)

S3 Table: Mean difference in traits at 7y and 25y comparing females with males

	Original units		SD units	
	Difference (95% CI) in trait at 7y comparing females to males	**Difference (95% CI) in trait at 25y comparing females to males**	**Difference (95% CI) in trait at 7y comparing females to males**	**Difference (95% CI) in trait at 25y comparing females to males**
Free cholesterol in small VLDL (mmol/l)	4.61E-03 (3.80E-03,5.43E-03)	-6.15E-03 (-7.37E-03,-4.93E-03)	0.3(0.24,0.35)	-0.32(-0.38,-0.25)
Triglycerides in small VLDL (mmol/l)	1.21E-02 (8.97E-03,1.53E-02)	-3.32E-02 (-3.75E-02,-2.89E-02)	0.21(0.15,0.26)	-0.49(-0.56,-0.43)
Concentration of very small VLDL particles (mol/l)	1.79E-09 (1.55E-09,2.03E-09)	5.40E-10 (1.04E-10,9.77E-10)	0.39(0.34,0.44)	0.08(0.01,0.14)
Total lipids in very small VLDL (mmol/l)	2.84E-02 (2.47E-02,3.21E-02)	2.98E-03 (-2.65E-03,8.60E-03)	0.39(0.34,0.44)	0.03(-0.03,0.09)
Phospholipids in very small VLDL (mmol/l)	8.72E-03 (7.46E-03,9.98E-03)	5.91E-03 (4.08E-03,7.74E-03)	0.36(0.31,0.41)	0.2(0.14,0.26)
Total cholesterol in very small VLDL (mmol/l)	1.43E-02 (1.20E-02,1.66E-02)	7.17E-04 (-2.18E-03,3.61E-03)	0.32(0.27,0.37)	0.02(-0.05,0.08)
Cholesterol esters in very small VLDL (mmol/l)	1.06E-02 (9.07E-03,1.22E-02)	7.42E-04 (-1.26E-03,2.74E-03)	0.35(0.3,0.4)	0.02(-0.04,0.09)
Free cholesterol in very small VLDL (mmol/l)	3.65E-03 (2.84E-03,4.47E-03)	4.21E-05 (-9.04E-04,9.88E-04)	0.23(0.18,0.28)	0.02(-0.06,0.07)
Triglycerides in very small VLDL (mmol/l)	5.41E-03 (4.39E-03,6.43E-03)	-2.49E-03 (-3.89E-03,-1.10E-03)	0.28(0.22,0.33)	-0.11(-0.18,-0.05)
Concentration of IDL particles (mol/l)	4.19E-09 (3.47E-09,4.90E-09)	4.78E-09 (3.52E-09,6.03E-09)	0.3(0.25,0.36)	0.23(0.17,0.29)
Total lipids in IDL (mmol/l)	5.60E-02 (4.69E-02,6.51E-02)	4.73E-02 (3.44E-02,6.02E-02)	0.32(0.27,0.37)	0.22(0.16,0.28)
Phospholipids in IDL (mmol/l)	1.28E-02 (1.04E-02,1.53E-02)	1.41E-02 (1.09E-02,1.74E-02)	0.27(0.22,0.32)	0.26(0.2,0.32)
Total cholesterol in IDL (mmol/l)	3.79E-02 (3.18E-02,4.41E-02)	2.44E-02 (1.55E-02,3.32E-02)	0.32(0.27,0.37)	0.17(0.11,0.23)
Cholesterol esters in IDL (mmol/l)	2.82E-02 (2.38E-02,3.25E-02)	1.27E-02 (6.27E-03,1.91E-02)	0.33(0.28,0.38)	0.12(0.06,0.18)
Free cholesterol in IDL (mmol/l)	9.70E-03 (7.77E-03,1.16E-02)	1.17E-02 (9.21E-03,1.42E-02)	0.26(0.21,0.31)	0.28(0.22,0.34)
Triglycerides in IDL (mmol/l)	5.19E-03 (4.10E-03,6.28E-03)	8.87E-03 (7.62E-03,1.01E-02)	0.25(0.2,0.3)	0.43(0.37,0.49)
Concentration of large LDL particles (mol/l)	6.66E-09 (5.32E-09,8.00E-09)	6.20E-09 (3.89E-09,8.50E-09)	0.26(0.21,0.31)	0.17(0.1,0.23)
Total lipids in large LDL (mmol/l)	6.39E-02 (5.23E-02,7.55E-02)	4.14E-02 (2.50E-02,5.78E-02)	0.28(0.23,0.34)	0.15(0.09,0.21)
Phospholipids in large LDL (mmol/l)	1.32E-02 (1.08E-02,1.55E-02)	9.27E-03 (5.85E-03,1.27E-02)	0.29(0.24,0.34)	0.16(0.1,0.23)
Total cholesterol in large LDL (mmol/l)	4.66E-02 (3.81E-02,5.50E-02)	1.95E-02 (7.36E-03,3.17E-02)	0.28(0.23,0.34)	0.1(0.04,0.16)
Cholesterol esters in large LDL (mmol/l)	3.58E-02 (2.95E-02,4.22E-02)	9.62E-03 (2.99E-04,1.89E-02)	0.29(0.24,0.34)	0.06(0.01,0.12)
Free cholesterol in large LDL (mmol/l)	1.07E-02 (8.59E-03,1.29E-02)	9.91E-03 (7.02E-03,1.28E-02)	0.26(0.21,0.31)	0.21(0.15,0.27)
Triglycerides in large LDL (mmol/l)	4.09E-03 (2.88E-03,5.31E-03)	1.26E-02 (1.14E-02,1.37E-02)	0.18(0.12,0.23)	0.63(0.57,0.69)
Concentration of medium LDL particles (mol/l)	5.57E-09 (4.39E-09,6.76E-09)	2.46E-09 (3.41E-10,4.59E-09)	0.24(0.19,0.3)	0.07(0.01,0.13)
Total lipids in medium LDL (mmol/l)	3.81E-02 (3.09E-02,4.54E-02)	9.72E-03 (-1.04E-03,2.05E-02)	0.27(0.22,0.33)	0.06(-0.01,0.12)
Phospholipids in medium LDL (mmol/l)	8.01E-03 (6.64E-03,9.38E-03)	4.33E-03 (2.19E-03,6.47E-03)	0.3(0.25,0.36)	0.12(0.06,0.18)
Total cholesterol in medium LDL (mmol/l)	2.83E-02 (2.29E-02,3.37E-02)	-5.03E-04 (-8.72E-03,7.72E-03)	0.27(0.22,0.32)	-0.01(-0.07,0.06)
Cholesterol esters in medium LDL (mmol/l)	2.31E-02 (1.86E-02,2.75E-02)	-1.68E-03 (-8.26E-03,4.91E-03)	0.27(0.22,0.32)	-0.02(-0.08,0.05)
Free cholesterol in medium LDL (mmol/l)	5.22E-03 (4.22E-03,6.22E-03)	1.17E-03 (-5.04E-04,2.85E-03)	0.27(0.22,0.32)	0.04(-0.02,0.1)
Triglycerides in medium LDL (mmol/l)	1.77E-03 (9.68E-04,2.57E-03)	7.42E-03 (6.80E-03,8.05E-03)	0.11(0.06,0.17)	0.7(0.64,0.75)
Concentration of small LDL particles (mol/l)	5.42E-09 (4.13E-09,6.72E-09)	2.37E-09 (-1.85E-10,4.93E-09)	0.22(0.17,0.27)	0.06(0.002,0.12)
Total lipids in small LDL (mmol/l)	2.27E-02 (1.81E-02,2.73E-02)	5.67E-03 (-1.54E-03,1.29E-02)	0.26(0.2,0.31)	0.05(-0.01,0.11)
Phospholipids in small LDL (mmol/l)	4.50E-03 (3.54E-03,5.46E-03)	4.06E-03 (2.39E-03,5.72E-03)	0.25(0.19,0.3)	0.15(0.09,0.21)

S3 Table: Mean difference in traits at 7y and 25y comparing females with males

	Original units		SD units	
	Difference (95% CI) in trait at 7y comparing females to males	**Difference (95% CI) in trait at 25y comparing females to males**	**Difference (95% CI) in trait at 7y comparing females to males**	**Difference (95% CI) in trait at 25y comparing females to males**
Total cholesterol in small LDL (mmol/l)	1.67E-02 (1.34E-02,2.01E-02)	2.15E-04 (-5.06E-03,5.49E-03)	0.26(0.2,0.31)	0.02(-0.06,0.06)
Cholesterol esters in small LDL (mmol/l)	1.40E-02 (1.11E-02,1.68E-02)	-9.53E-06 (-4.15E-03,4.13E-03)	0.25(0.2,0.3)	0.02(-0.06,0.06)
Free cholesterol in small LDL (mmol/l)	2.77E-03 (2.15E-03,3.39E-03)	2.32E-04 (-9.59E-04,1.42E-03)	0.23(0.18,0.28)	0.01(-0.05,0.07)
Triglycerides in small LDL (mmol/l)	1.59E-03 (1.10E-03,2.09E-03)	2.97E-03 (2.52E-03,3.42E-03)	0.17(0.12,0.22)	0.42(0.35,0.48)
Concentration of very large HDL particles (mol/l)	-1.16E-08 (-1.77E-08,-5.51E-09)	1.53E-07 (1.44E-07,1.63E-07)	-0.1(-0.15,-0.05)	0.82(0.77,0.87)
Total lipids in very large HDL (mmol/l)	-1.58E-02 (-2.31E-02,-8.47E-03)	1.51E-01 (1.41E-01,1.61E-01)	-0.11(-0.17,-0.06)	0.8(0.75,0.85)
Phospholipids in very large HDL (mmol/l)	-8.35E-03 (-1.23E-02,-4.43E-03)	9.26E-02 (8.71E-02,9.81E-02)	-0.11(-0.16,-0.06)	0.87(0.81,0.92)
Total cholesterol in very large HDL (mmol/l)	-8.26E-03 (-1.17E-02,-4.78E-03)	5.78E-02 (5.33E-02,6.24E-02)	-0.13(-0.18,-0.07)	0.72(0.67,0.78)
Cholesterol esters in very large HDL (mmol/l)	-6.22E-03 (-8.75E-03,-3.68E-03)	3.80E-02 (3.47E-02,4.13E-02)	-0.13(-0.18,-0.08)	0.68(0.62,0.74)
Free cholesterol in very large HDL (mmol/l)	-2.03E-03 (-3.03E-03,-1.03E-03)	1.98E-02 (1.85E-02,2.11E-02)	-0.11(-0.16,-0.05)	0.8(0.75,0.85)
Triglycerides in very large HDL (mmol/l)	5.59E-04 (2.76E-04,8.41E-04)	2.46E-03 (2.11E-03,2.81E-03)	0.11(0.05,0.16)	0.42(0.36,0.48)
Concentration of large HDL particles (mol/l)	-4.38E-08 (-5.58E-08,-3.18E-08)	4.22E-07 (3.96E-07,4.48E-07)	-0.19(-0.24,-0.14)	0.86(0.8,0.91)
Total lipids in large HDL (mmol/l)	-3.19E-02 (-4.10E-02,-2.28E-02)	2.69E-01 (2.53E-01,2.86E-01)	-0.18(-0.24,-0.13)	0.85(0.8,0.91)
Phospholipids in large HDL (mmol/l)	-1.33E-02 (-1.73E-02,-9.29E-03)	1.22E-01 (1.14E-01,1.29E-01)	-0.17(-0.23,-0.12)	0.86(0.81,0.92)
Total cholesterol in large HDL (mmol/l)	-1.88E-02 (-2.39E-02,-1.38E-02)	1.39E-01 (1.30E-01,1.48E-01)	-0.2(-0.25,-0.14)	0.83(0.78,0.89)
Cholesterol esters in large HDL (mmol/l)	-1.53E-02 (-1.92E-02,-1.13E-02)	1.06E-01 (9.90E-02,1.12E-01)	-0.2(-0.25,-0.15)	0.83(0.78,0.89)
Free cholesterol in large HDL (mmol/l)	-3.58E-03 (-4.67E-03,-2.50E-03)	3.31E-02 (3.10E-02,3.52E-02)	-0.17(-0.22,-0.12)	0.83(0.78,0.89)
Triglycerides in large HDL (mmol/l)	2.59E-04 (7.13E-05,4.47E-04)	8.79E-03 (8.16E-03,9.42E-03)	0.07(0.02,0.13)	0.76(0.71,0.81)
Concentration of medium HDL particles (mol/l)	-2.98E-08 (-3.90E-08,-2.06E-08)	2.75E-07 (2.48E-07,3.01E-07)	-0.18(-0.23,-0.12)	0.62(0.56,0.68)
Total lipids in medium HDL (mmol/l)	-1.49E-02 (-1.96E-02,-1.02E-02)	1.25E-01 (1.14E-01,1.36E-01)	-0.17(-0.23,-0.12)	0.64(0.59,0.7)
Phospholipids in medium HDL (mmol/l)	-8.09E-03 (-1.07E-02,-5.51E-03)	6.09E-02 (5.60E-02,6.58E-02)	-0.17(-0.23,-0.12)	0.7(0.64,0.75)
Total cholesterol in medium HDL (mmol/l)	-8.22E-03 (-1.04E-02,-6.02E-03)	5.73E-02 (5.10E-02,6.36E-02)	-0.2(-0.26,-0.15)	0.54(0.48,0.6)
Cholesterol esters in medium HDL (mmol/l)	-7.33E-03 (-9.14E-03,-5.52E-03)	4.33E-02 (3.84E-02,4.83E-02)	-0.22(-0.27,-0.16)	0.52(0.46,0.58)
Free cholesterol in medium HDL (mmol/l)	-9.05E-04 (-1.31E-03,-4.99E-04)	1.39E-02 (1.26E-02,1.53E-02)	-0.12(-0.18,-0.07)	0.6(0.54,0.66)
Triglycerides in medium HDL (mmol/l)	1.26E-03 (8.34E-04,1.70E-03)	2.73E-03 (2.03E-03,3.43E-03)	0.16(0.11,0.21)	0.24(0.18,0.31)
Concentration of small HDL particles (mol/l)	-2.83E-08 (-4.23E-08,-1.43E-08)	1.87E-07 (1.46E-07,2.29E-07)	-0.11(-0.17,-0.06)	0.26(0.2,0.32)
Total lipids in small HDL (mmol/l)	-9.61E-03 (-1.36E-02,-5.65E-03)	4.13E-02 (3.16E-02,5.10E-02)	-0.14(-0.19,-0.08)	0.25(0.19,0.31)
Phospholipids in small HDL (mmol/l)	-7.62E-03 (-1.01E-02,-5.15E-03)	2.02E-02 (1.57E-02,2.46E-02)	-0.17(-0.22,-0.11)	0.27(0.21,0.33)
Total cholesterol in small HDL (mmol/l)	-3.28E-03 (-5.76E-03,-8.05E-04)	2.45E-02 (1.84E-02,3.05E-02)	-0.07(-0.13,-0.02)	0.24(0.18,0.3)
Cholesterol esters in small HDL (mmol/l)	-8.07E-04 (-3.02E-03,1.41E-03)	2.08E-02 (1.54E-02,2.61E-02)	-0.02(-0.08,0.04)	0.23(0.17,0.29)
Free cholesterol in small HDL (mmol/l)	-2.55E-03 (-3.07E-03,-2.02E-03)	3.45E-03 (2.50E-03,4.41E-03)	-0.27(-0.32,-0.21)	0.22(0.16,0.28)
Triglycerides in small HDL (mmol/l)	1.34E-03 (8.78E-04,1.81E-03)	-1.30E-03 (-1.90E-03,-6.97E-04)	0.16(0.1,0.21)	-0.14(-0.2,-0.07)
Mean diameter for VLDL particles (mm)	1.28E-01 (5.69E-02,2.00E-01)	-7.44E-01 (-8.16E-01,-6.72E-01)	0.1(0.04,0.15)	-0.64(-0.71,-0.58)

S3 Table: Mean difference in traits at 7y and 25y comparing females with males

	Original units		SD units	
	Difference (95% CI) in trait at 7y comparing females to males	**Difference (95% CI) in trait at 25y comparing females to males**	**Difference (95% CI) in trait at 7y comparing females to males**	**Difference (95% CI) in trait at 25y comparing females to males**
Mean diameter for LDL particles (mm)	9.55E-03 (3.94E-03,1.52E-02)	4.54E-02 (3.45E-02,5.63E-02)	0.09(0.04,0.15)	0.25(0.19,0.31)
Mean diameter for HDL particles (mm)	-1.77E-02 (-2.57E-02,-9.76E-03)	2.05E-01 (1.92E-01,2.18E-01)	-0.12(-0.17,-0.06)	0.84(0.78,0.89)
Serum total cholesterol (mmol/l)	1.41E-01 (1.10E-01,1.72E-01)	2.57E-01 (2.08E-01,3.05E-01)	0.24(0.18,0.29)	0.32(0.26,0.38)
Total cholesterol in VLDL (mmol/l)	5.08E-02 (4.27E-02,5.88E-02)	-5.20E-02 (-6.35E-02,-4.04E-02)	0.33(0.28,0.38)	-0.29(-0.35,-0.22)
Remnant cholesterol (non-HDL, non-LDL -cholesterol) (mmol/l)	8.86E-02 (7.64E-02,1.01E-01)	-2.78E-02 (-4.65E-02,-9.20E-03)	0.37(0.32,0.42)	-0.09(-0.15,-0.03)
Total cholesterol in LDL (mmol/l)	9.17E-02 (7.45E-02,1.09E-01)	1.92E-02 (-6.21E-03,4.47E-02)	0.28(0.22,0.33)	0.05(-0.01,0.11)
Total cholesterol in HDL (mmol/l)	-3.90E-02 (-5.00E-02,-2.81E-02)	2.67E-01 (2.48E-01,2.85E-01)	-0.19(-0.24,-0.14)	0.78(0.73,0.84)
Total cholesterol in HDL2 (mmol/l)	-2.97E-02 (-3.70E-02,-2.25E-02)	2.48E-01 (2.31E-01,2.65E-01)	-0.21(-0.27,-0.16)	0.8(0.75,0.85)
Total cholesterol in HDL3 (mmol/l)	-9.15E-03 (-1.31E-02,-5.19E-03)	2.17E-02 (1.93E-02,2.41E-02)	-0.12(-0.18,-0.07)	0.61(0.55,0.68)
Esterified cholesterol (mmol/l)	9.74E-02 (7.49E-02,1.20E-01)	1.88E-01 (1.54E-01,2.22E-01)	0.23(0.18,0.28)	0.33(0.27,0.39)
Free cholesterol (mmol/l)	4.48E-02 (3.54E-02,5.43E-02)	8.63E-02 (7.24E-02,1.00E-01)	0.25(0.19,0.3)	0.37(0.31,0.43)
Serum total triglycerides (mmol/l)	7.20E-02 (5.14E-02,9.26E-02)	-1.11E-01 (-1.36E-01,-8.56E-02)	0.19(0.14,0.24)	-0.29(-0.36,-0.22)
Triglycerides in VLDL (mmol/l)	5.49E-02 (3.70E-02,7.29E-02)	-1.59E-01 (-1.81E-01,-1.37E-01)	0.17(0.11,0.22)	-0.47(-0.54,-0.41)
Triglycerides in LDL (mmol/l)	7.31E-03 (4.85E-03,9.78E-03)	2.27E-02 (2.05E-02,2.49E-02)	0.16(0.1,0.21)	0.61(0.55,0.67)
Triglycerides in HDL (mmol/l)	3.49E-03 (2.36E-03,4.62E-03)	1.26E-02 (1.09E-02,1.44E-02)	0.17(0.11,0.22)	0.45(0.38,0.51)
Diacylglycerol (mmol/l)*	1.00E-03 (3.85E-04,1.62E-03)	9.52E-04 (2.71E-04,1.63E-03)	0.09(0.04,0.15)	0.1(0.03,0.18)
Total phosphoglycerides (mmol/l)	2.27E-02 (7.82E-03,3.75E-02)	2.15E-01 (1.97E-01,2.34E-01)	0.08(0.03,0.14)	0.65(0.6,0.71)
Phosphatidylcholine and other cholines (mmol/l)	1.31E-02 (-1.70E-03,2.78E-02)	1.65E-01 (1.44E-01,1.86E-01)	0.05(-0.01,0.1)	0.47(0.41,0.53)
Total cholines (mmol/l)	2.95E-02 (1.34E-02,4.56E-02)	2.40E-01 (2.17E-01,2.62E-01)	0.1(0.05,0.15)	0.61(0.56,0.67)
Apolipoprotein A-I (g/l)	-8.28E-03 (-1.42E-02,-2.36E-03)	1.40E-01 (1.28E-01,1.51E-01)	-0.07(-0.13,-0.02)	0.68(0.62,0.73)
Apolipoprotein B (g/l)	4.42E-02 (3.77E-02,5.06E-02)	-2.25E-02 (-3.21E-02,-1.29E-02)	0.36(0.31,0.41)	-0.15(-0.21,-0.08)
Total fatty acids (mmol/l)	3.72E-01 (2.86E-01,4.58E-01)	4.61E-01 (3.41E-01,5.81E-01)	0.23(0.18,0.29)	0.24(0.18,0.3)
Fatty acid length*	4.51E-03 (-1.56E-02,2.46E-02)	7.86E-03 (-1.94E-02,3.51E-02)	0.01(-0.04,0.07)	0.02(-0.05,0.1)
Estimated degree of unsaturation*	-3.97E-03 (-7.38E-03,-5.72E-04)	7.57E-03 (2.75E-03,1.24E-02)	-0.07(-0.12,-0.01)	0.12(0.04,0.19)
22:6, docosahexaenoic acid (mmol/l)	5.08E-03 (3.64E-03,6.53E-03)	1.91E-02 (1.72E-02,2.11E-02)	0.19(0.14,0.24)	0.59(0.53,0.65)
18:2, linoleic acid (mmol/l)	1.02E-01 (7.83E-02,1.26E-01)	1.25E-01 (9.22E-02,1.58E-01)	0.23(0.18,0.28)	0.23(0.17,0.29)
Conjugated linoleic acid (mmol/l)*	2.09E-03 (1.08E-03,3.09E-03)	1.42E-03 (3.96E-04,2.45E-03)	0.12(0.06,0.17)	0.1(0.03,0.18)
Omega-3 fatty acids (mmol/l)	1.13E-02 (7.59E-03,1.50E-02)	7.34E-03 (2.41E-03,1.23E-02)	0.17(0.11,0.22)	0.09(0.03,0.16)
Omega-6 fatty acids (mmol/l)	1.09E-01 (8.28E-02,1.35E-01)	1.98E-01 (1.61E-01,2.35E-01)	0.22(0.17,0.27)	0.32(0.26,0.38)
Polyunsaturated fatty acids (mmol/l)	1.20E-01 (9.18E-02,1.49E-01)	2.06E-01 (1.65E-01,2.46E-01)	0.22(0.17,0.28)	0.3(0.24,0.37)
Monounsaturated fatty acids; 16:1, 18:1 (mmol/l)	1.34E-01 (1.04E-01,1.64E-01)	8.93E-02 (4.82E-02,1.30E-01)	0.24(0.19,0.29)	0.14(0.07,0.2)
Saturated fatty acids (mmol/l)	1.14E-01 (7.69E-02,1.50E-01)	1.59E-01 (1.15E-01,2.04E-01)	0.17(0.11,0.22)	0.22(0.16,0.29)
Glucose (mmol/l)	-7.74E-02 (-1.06E-01,-4.84E-02)	-1.92E-01 (-2.25E-01,-1.59E-01)	-0.15(-0.21,-0.09)	-0.42(-0.49,-0.35)

S3 Table: Mean difference in traits at 7y and 25y comparing females with males

	Original units		SD units	
	Difference (95% CI) in trait at 7y comparing females to males	**Difference (95% CI) in trait at 25y comparing females to males**	**Difference (95% CI) in trait at 7y comparing females to males**	**Difference (95% CI) in trait at 25y comparing females to males**
Lactate (mmol/l)	5.99E-02 (3.24E-02,8.73E-02)	-7.08E-03 (-3.62E-02,2.20E-02)	0.12(0.07,0.18)	-0.02(-0.08,0.05)
Citrate (mmol/l)	3.05E-03 (1.67E-03,4.42E-03)	-1.88E-03 (-3.51E-03,-2.46E-04)	0.12(0.07,0.18)	-0.08(-0.14,-0.01)
Alanine (mmol/l)	4.33E-03 (7.96E-04,7.87E-03)	-9.16E-03 (-1.29E-02,-5.47E-03)	0.07(0.01,0.12)	-0.16(-0.23,-0.1)
Glutamine (mmol/l)	2.54E-02 (2.23E-02,2.86E-02)	-6.36E-02 (-6.83E-02,-5.89E-02)	0.44(0.39,0.49)	-0.83(-0.89,-0.77)
Histidine (mmol/l)	2.38E-03 (1.71E-03,3.05E-03)	-3.20E-03 (-3.75E-03,-2.66E-03)	0.17(0.12,0.21)	-0.4(-0.47,-0.33)
Isoleucine (mmol/l)	1.81E-03 (8.22E-04,2.81E-03)	-9.90E-03 (-1.07E-02,-9.15E-03)	0.1(0.05,0.16)	-0.83(-0.9,-0.77)
Leucine (mmol/l)	-2.03E-04 (-1.03E-03,6.23E-04)	-1.22E-02 (-1.30E-02,-1.14E-02)	-0.01(-0.07,0.04)	-0.92(-0.98,-0.86)
Valine (mmol/l)	2.09E-03 (1.20E-04,4.06E-03)	-2.49E-02 (-2.67E-02,-2.32E-02)	0.06(-0.004,0.12)	-0.85(-0.91,-0.79)
Phenylalanine (mmol/l)	-2.86E-04 (-7.56E-04,1.84E-04)	-2.00E-03 (-2.42E-03,-1.58E-03)	-0.03(-0.09,0.02)	-0.32(-0.38,-0.25)
Tyrosine (mmol/l)	1.67E-04 (-7.27E-04,1.06E-03)	-5.41E-03 (-6.02E-03,-4.80E-03)	0.01(-0.05,0.07)	-0.55(-0.62,-0.49)
Acetate (mmol/l)	9.42E-04 (-4.36E-04,2.32E-03)	-5.65E-03 (-7.92E-03,-3.38E-03)	0.04(-0.02,0.1)	-0.16(-0.22,-0.1)
Acetoacetate (mmol/l)	1.82E-03 (-3.99E-04,4.05E-03)	-2.05E-03 (-3.25E-03,-8.54E-04)	0.04(-0.01,0.09)	-0.2(-0.31,-0.08)
3-hydroxybutyrate (mmol/l)	1.21E-02 (6.54E-03,1.76E-02)	1.61E-02 (1.09E-02,2.14E-02)	0.12(0.07,0.18)	0.18(0.12,0.25)
Creatinine (mmol/l)	6.22E-04 (3.06E-04,9.38E-04)	-1.17E-02 (-1.22E-02,-1.12E-02)	0.1(0.05,0.15)	-1.25(-1.3,-1.2)
Albumin (mmol/l)	1.08E-03 (8.79E-04,1.27E-03)	-2.89E-03 (-3.24E-03,-2.54E-03)	0.3(0.24,0.35)	-0.52(-0.58,-0.45)
Glycoprotein acetyls, mainly a1-acid glycoprotein (mmol/l)	3.23E-02 (2.48E-02,3.98E-02)	1.75E-02 (6.60E-03,2.85E-02)	0.23(0.18,0.29)	0.1(0.04,0.17)

*These metabolites (diacylglycerol, fatty acid chain length, estimated degree of saturation and conjugated linoleic acid) were not measured at 25y; all models include data only up to aged 18y and values in this table for these traits are at 7y and 18y respectively. HDL: high-density lipoprotein; IDL: intermediate-density lipoprotein; LDL: low-density lipoprotein; VLDL: very-low-density lipoprotein.

S4 Table: Mean absolute difference in traits between 7y and 25y in males and females

	Original units		SD units	
	Mean absolute difference between 7y and 25y (95% CI)		Mean absolute difference between 7y and 25y (95% CI)	
	Males	Females	Males	Females
	Beta	Beta		
Concentration of chylomicrons and extremely large VLDL particles (mol/l)	-2.95E-11 (-3.48E-11,-2.41E-11)	-7.26E-11 (-7.71E-11,-6.81E-11)	-0.28(-0.33,-0.23)	-0.69(-0.73,-0.65)
Total lipids in chylomicrons and extremely large VLDL (mmol/l)	-1.02E-02 (-1.13E-02,-8.99E-03)	-1.93E-02 (-2.03E-02,-1.83E-02)	-0.43(-0.48,-0.38)	-0.82(-0.86,-0.78)
Phospholipids in chylomicrons and extremely large VLDL (mmol/l)	-1.37E-03 (-1.52E-03,-1.23E-03)	-2.45E-03 (-2.57E-03,-2.32E-03)	-0.48(-0.53,-0.43)	-0.85(-0.9,-0.81)
Total cholesterol in chylomicrons and extremely large VLDL (mmol/l)	-1.53E-03 (-1.72E-03,-1.34E-03)	-2.87E-03 (-3.02E-03,-2.71E-03)	-0.42(-0.47,-0.37)	-0.79(-0.84,-0.75)
Cholesterol esters in chylomicrons and extremely large VLDL (mmol/l)	-6.10E-04 (-7.10E-04,-5.11E-04)	-1.27E-03 (-1.35E-03,-1.19E-03)	-0.34(-0.39,-0.28)	-0.7(-0.74,-0.66)
Free cholesterol in chylomicrons and extremely large VLDL (mmol/l)	-9.13E-04 (-1.01E-03,-8.18E-04)	-1.61E-03 (-1.69E-03,-1.53E-03)	-0.48(-0.53,-0.43)	-0.84(-0.89,-0.8)
Triglycerides in chylomicrons and extremely large VLDL (mmol/l)	-7.28E-03 (-8.13E-03,-6.44E-03)	-1.40E-02 (-1.47E-02,-1.33E-02)	-0.43(-0.47,-0.38)	-0.82(-0.86,-0.78)
Concentration of very large VLDL particles (mol/l)	-1.35E-10 (-1.66E-10,-1.04E-10)	-3.80E-10 (-4.05E-10,-3.54E-10)	-0.23(-0.28,-0.18)	-0.65(-0.7,-0.61)
Total lipids in very large VLDL (mmol/l)	-1.53E-02 (-1.82E-02,-1.23E-02)	-3.88E-02 (-4.12E-02,-3.63E-02)	-0.27(-0.33,-0.22)	-0.69(-0.73,-0.65)
Phospholipids in very large VLDL (mmol/l)	-2.62E-03 (-3.12E-03,-2.12E-03)	-6.29E-03 (-6.70E-03,-5.88E-03)	-0.28(-0.33,-0.23)	-0.67(-0.71,-0.62)
Total cholesterol in very large VLDL (mmol/l)	-4.30E-03 (-4.87E-03,-3.73E-03)	-8.90E-03 (-9.37E-03,-8.44E-03)	-0.4(-0.45,-0.35)	-0.82(-0.87,-0.78)
Cholesterol esters in very large VLDL (mmol/l)	-2.05E-03 (-2.35E-03,-1.75E-03)	-4.52E-03 (-4.76E-03,-4.29E-03)	-0.37(-0.43,-0.32)	-0.82(-0.87,-0.78)
Free cholesterol in very large VLDL (mmol/l)	-2.30E-03 (-2.57E-03,-2.02E-03)	-4.37E-03 (-4.60E-03,-4.14E-03)	-0.43(-0.48,-0.38)	-0.81(-0.86,-0.77)
Triglycerides in very large VLDL (mmol/l)	-8.33E-03 (-1.03E-02,-6.40E-03)	-2.36E-02 (-2.52E-02,-2.20E-02)	-0.23(-0.28,-0.18)	-0.65(-0.7,-0.61)
Concentration of large VLDL particles (mol/l)	1.90E-10 (2.41E-11,3.57E-10)	-1.28E-09 (-1.41E-09,-1.16E-09)	0.07(0.01,0.13)	-0.48(-0.53,-0.43)
Total lipids in large VLDL (mmol/l)	7.76E-04 (-8.96E-03,1.05E-02)	-8.56E-02 (-9.32E-02,-7.81E-02)	0.004(-0.06,0.07)	-0.54(-0.58,-0.49)
Phospholipids in large VLDL (mmol/l)	1.36E-03 (-4.06E-04,3.12E-03)	-1.37E-02 (-1.51E-02,-1.23E-02)	0.05(-0.01,0.11)	-0.48(-0.53,-0.43)
Total cholesterol in large VLDL (mmol/l)	-3.42E-03 (-5.59E-03,-1.25E-03)	-2.25E-02 (-2.42E-02,-2.08E-02)	-0.1(-0.16,-0.03)	-0.63(-0.67,-0.58)
Cholesterol esters in large VLDL (mmol/l)	4.91E-05 (-9.97E-04,1.09E-03)	-9.89E-03 (-1.07E-02,-9.10E-03)	0.002(-0.06,0.07)	-0.59(-0.64,-0.54)
Free cholesterol in large VLDL (mmol/l)	-3.47E-03 (-4.60E-03,-2.33E-03)	-1.26E-02 (-1.35E-02,-1.17E-02)	-0.18(-0.24,-0.12)	-0.65(-0.69,-0.6)
Triglycerides in large VLDL (mmol/l)	2.82E-03 (-3.00E-03,8.64E-03)	-4.95E-02 (-5.40E-02,-4.50E-02)	0.03(-0.03,0.09)	-0.52(-0.57,-0.47)
Concentration of medium VLDL particles (mol/l)	2.06E-09 (1.66E-09,2.47E-09)	-2.33E-09 (-2.63E-09,-2.03E-09)	0.35(0.28,0.42)	-0.4(-0.45,-0.35)
Total lipids in medium VLDL (mmol/l)	4.81E-02 (3.46E-02,6.15E-02)	-9.81E-02 (-1.08E-01,-8.82E-02)	0.24(0.18,0.31)	-0.5(-0.55,-0.45)
Phospholipids in medium VLDL (mmol/l)	8.05E-03 (5.47E-03,1.06E-02)	-1.93E-02 (-2.12E-02,-1.74E-02)	0.21(0.14,0.28)	-0.51(-0.56,-0.46)
Total cholesterol in medium VLDL (mmol/l)	7.18E-03 (3.77E-03,1.06E-02)	-2.54E-02 (-2.80E-02,-2.28E-02)	0.14(0.07,0.21)	-0.5(-0.55,-0.45)
Cholesterol esters in medium VLDL (mmol/l)	6.21E-03 (4.41E-03,8.01E-03)	-9.43E-03 (-1.08E-02,-8.05E-03)	0.22(0.16,0.29)	-0.34(-0.39,-0.29)
Free cholesterol in medium VLDL (mmol/l)	9.50E-04 (-7.32E-04,2.63E-03)	-1.60E-02 (-1.73E-02,-1.47E-02)	0.04(-0.03,0.1)	-0.64(-0.69,-0.59)
Triglycerides in medium VLDL (mmol/l)	3.28E-02 (2.53E-02,4.04E-02)	-5.35E-02 (-5.90E-02,-4.79E-02)	0.29(0.23,0.36)	-0.48(-0.53,-0.43)
Concentration of small VLDL particles (mol/l)	-3.56E-10 (-7.61E-10,4.85E-11)	-4.90E-09 (-5.21E-09,-4.59E-09)	-0.06(-0.13,0.01)	-0.85(-0.9,-0.79)
Total lipids in small VLDL (mmol/l)	-5.76E-02 (-6.55E-02,-4.98E-02)	-1.50E-01 (-1.56E-01,-1.44E-01)	-0.5(-0.57,-0.43)	-1.3(-1.35,-1.24)
Phospholipids in small VLDL (mmol/l)	-1.27E-02 (-1.42E-02,-1.12E-02)	-2.78E-02 (-2.91E-02,-2.66E-02)	-0.55(-0.62,-0.49)	-1.21(-1.27,-1.16)
Total cholesterol in small VLDL (mmol/l)	-4.64E-02 (-4.91E-02,-4.37E-02)	-7.78E-02 (-8.00E-02,-7.56E-02)	-1.09(-1.15,-1.03)	-1.83(-1.88,-1.77)
Cholesterol esters in small VLDL (mmol/l)	-3.29E-02 (-3.47E-02,-3.11E-02)	-5.35E-02 (-5.50E-02,-5.20E-02)	-1.14(-1.2,-1.08)	-1.85(-1.9,-1.8)
Free cholesterol in small VLDL (mmol/l)	-1.35E-02 (-1.46E-02,-1.25E-02)	-2.43E-02 (-2.51E-02,-2.35E-02)	-0.87(-0.94,-0.8)	-1.56(-1.61,-1.51)
Triglycerides in small VLDL (mmol/l)	1.85E-03 (-2.08E-03,5.78E-03)	-4.35E-02 (-4.65E-02,-4.05E-02)	0.03(-0.04,0.1)	-0.74(-0.79,-0.69)
Concentration of very small VLDL particles (mol/l)	-2.00E-09 (-2.33E-09,-1.67E-09)	-3.25E-09 (-3.54E-09,-2.95E-09)	-0.43(-0.51,-0.36)	-0.7(-0.77,-0.64)
Total lipids in very small VLDL (mmol/l)	-1.05E-01 (-1.09E-01,-1.00E-01)	-1.30E-01 (-1.34E-01,-1.26E-01)	-1.44(-1.51,-1.38)	-1.79(-1.85,-1.74)
Phospholipids in very small VLDL (mmol/l)	-1.20E-02 (-1.34E-02,-1.06E-02)	-1.48E-02 (-1.61E-02,-1.35E-02)	-0.49(-0.55,-0.44)	-0.61(-0.67,-0.56)
Total cholesterol in very small VLDL (mmol/l)	-7.94E-02 (-8.18E-02,-7.69E-02)	-9.30E-02 (-9.52E-02,-9.08E-02)	-1.77(-1.83,-1.72)	-2.08(-2.13,-2.03)
Cholesterol esters in very small VLDL (mmol/l)	-5.88E-02 (-6.05E-02,-5.71E-02)	-6.87E-02 (-7.02E-02,-6.72E-02)	-1.92(-1.97,-1.86)	-2.24(-2.29,-2.19)
Free cholesterol in very small VLDL (mmol/l)	-2.06E-02 (-2.14E-02,-1.97E-02)	-2.42E-02 (-2.50E-02,-2.34E-02)	-1.31(-1.36,-1.25)	-1.54(-1.58,-1.49)
Triglycerides in very small VLDL (mmol/l)	-1.44E-02 (-1.56E-02,-1.32E-02)	-2.23E-02 (-2.34E-02,-2.12E-02)	-0.74(-0.8,-0.68)	-1.14(-1.2,-1.09)
Concentration of IDL particles (mol/l)	2.41E-09 (1.46E-09,3.36E-09)	3.00E-09 (2.13E-09,3.87E-09)	0.18(0.11,0.24)	0.22(0.16,0.28)
Total lipids in IDL (mmol/l)	-1.22E-01 (-1.32E-01,-1.12E-01)	-1.31E-01 (-1.40E-01,-1.22E-01)	-0.69(-0.75,-0.64)	-0.74(-0.8,-0.69)

S4 Table: Mean absolute difference in traits between 7y and 25y in males and females

	Original units		SD units	
	Mean absolute difference between 7y and 25y (95% CI)		Mean absolute difference between 7y and 25y (95% CI)	
	Males	Females	Males	Females
Phospholipids in IDL (mmol/l)	-2.06E-02 (-2.32E-02,-1.80E-02)	-1.93E-02 (-2.17E-02,-1.68E-02)	-0.43(-0.49,-0.38)	-0.41(-0.46,-0.35)
Total cholesterol in IDL (mmol/l)	-8.18E-02 (-8.87E-02,-7.50E-02)	-9.53E-02 (-1.02E-01,-8.91E-02)	-0.68(-0.74,-0.63)	-0.8(-0.85,-0.74)
Cholesterol esters in IDL (mmol/l)	-6.02E-02 (-6.52E-02,-5.52E-02)	-7.57E-02 (-8.02E-02,-7.13E-02)	-0.71(-0.77,-0.65)	-0.89(-0.94,-0.84)
Free cholesterol in IDL (mmol/l)	-2.16E-02 (-2.36E-02,-1.96E-02)	-1.96E-02 (-2.15E-02,-1.77E-02)	-0.58(-0.64,-0.53)	-0.53(-0.58,-0.48)
Triglycerides in IDL (mmol/l)	-1.99E-02 (-2.09E-02,-1.88E-02)	-1.62E-02 (-1.73E-02,-1.51E-02)	-0.96(-1.01,-0.9)	-0.78(-0.83,-0.73)
Concentration of large LDL particles (mol/l)	2.21E-08 (2.04E-08,2.39E-08)	2.17E-08 (2.01E-08,2.33E-08)	0.86(0.79,0.92)	0.84(0.78,0.9)
Total lipids in large LDL (mmol/l)	-2.86E-02 (-4.16E-02,-1.57E-02)	-5.12E-02 (-6.31E-02,-3.93E-02)	-0.13(-0.18,-0.07)	-0.23(-0.28,-0.17)
Phospholipids in large LDL (mmol/l)	4.26E-04 (-2.24E-03,3.09E-03)	-3.47E-03 (-5.94E-03,-1.01E-03)	0.01(-0.05,0.07)	-0.08(-0.13,-0.02)
Total cholesterol in large LDL (mmol/l)	-6.51E-03 (-1.61E-02,3.06E-03)	-3.35E-02 (-4.22E-02,-2.49E-02)	-0.04(-0.1,0.02)	-0.2(-0.26,-0.15)
Cholesterol esters in large LDL (mmol/l)	6.79E-04 (-6.64E-03,8.00E-03)	-2.55E-02 (-3.21E-02,-1.90E-02)	0.01(-0.05,0.06)	-0.21(-0.26,-0.15)
Free cholesterol in large LDL (mmol/l)	-7.20E-03 (-9.50E-03,-4.90E-03)	-8.02E-03 (-1.01E-02,-5.90E-03)	-0.17(-0.23,-0.12)	-0.19(-0.25,-0.14)
Triglycerides in large LDL (mmol/l)	-2.24E-02 (-2.34E-02,-2.13E-02)	-1.39E-02 (-1.51E-02,-1.27E-02)	-0.97(-1.01,-0.92)	-0.6(-0.65,-0.55)
Concentration of medium LDL particles (mol/l)	2.30E-08 (2.13E-08,2.46E-08)	1.99E-08 (1.84E-08,2.14E-08)	1.01(0.93,1.08)	0.87(0.81,0.94)
Total lipids in medium LDL (mmol/l)	1.63E-02 (7.76E-03,2.48E-02)	-1.21E-02 (-1.99E-02,-4.39E-03)	0.12(0.06,0.18)	-0.09(-0.14,-0.03)
Phospholipids in medium LDL (mmol/l)	-1.31E-03 (-2.94E-03,3.21E-04)	-4.99E-03 (-6.49E-03,-3.49E-03)	-0.05(-0.11,0.01)	-0.19(-0.25,-0.13)
Total cholesterol in medium LDL (mmol/l)	2.11E-02 (1.46E-02,2.76E-02)	-7.76E-03 (-1.36E-02,-1.92E-03)	0.2(0.14,0.26)	-0.07(-0.13,-0.02)
Cholesterol esters in medium LDL (mmol/l)	2.64E-02 (2.12E-02,3.17E-02)	1.68E-03 (-3.04E-03,6.41E-03)	0.31(0.25,0.37)	0.02(-0.04,0.07)
Free cholesterol in medium LDL (mmol/l)	-5.38E-03 (-6.67E-03,-4.10E-03)	-9.43E-03 (-1.06E-02,-8.27E-03)	-0.28(-0.35,-0.21)	-0.49(-0.55,-0.43)
Triglycerides in medium LDL (mmol/l)	-5.39E-03 (-6.04E-03,-4.75E-03)	2.65E-04 (-4.62E-04,9.91E-04)	-0.35(-0.39,-0.31)	0.02(-0.03,0.06)
Concentration of small LDL particles (mol/l)	1.60E-08 (1.40E-08,1.79E-08)	1.29E-08 (1.12E-08,1.47E-08)	0.64(0.56,0.72)	0.52(0.45,0.59)
Total lipids in small LDL (mmol/l)	-6.26E-03 (-1.19E-02,-6.28E-04)	-2.33E-02 (-2.85E-02,-1.81E-02)	-0.07(-0.13,-0.01)	-0.26(-0.32,-0.2)
Phospholipids in small LDL (mmol/l)	-7.73E-03 (-8.97E-03,-6.49E-03)	-8.17E-03 (-9.36E-03,-6.98E-03)	-0.42(-0.49,-0.35)	-0.45(-0.51,-0.38)
Total cholesterol in small LDL (mmol/l)	2.74E-03 (-1.41E-03,6.88E-03)	-1.38E-02 (-1.76E-02,-1.00E-02)	0.04(-0.02,0.11)	-0.21(-0.27,-0.15)
Cholesterol esters in small LDL (mmol/l)	1.11E-02 (7.80E-03,1.45E-02)	-2.83E-03 (-5.88E-03,2.26E-04)	0.2(0.14,0.26)	-0.05(-0.11,0.004)
Free cholesterol in small LDL (mmol/l)	-8.42E-03 (-9.32E-03,-7.52E-03)	-1.10E-02 (-1.18E-02,-1.01E-02)	-0.7(-0.78,-0.63)	-0.92(-0.98,-0.85)
Triglycerides in small LDL (mmol/l)	-3.06E-03 (-3.49E-03,-2.62E-03)	-1.68E-03 (-2.14E-03,-1.22E-03)	-0.33(-0.37,-0.28)	-0.18(-0.23,-0.13)
Concentration of very large HDL particles (mol/l)	-2.24E-07 (-2.30E-07,-2.17E-07)	-5.89E-08 (-6.64E-08,-5.13E-08)	-1.94(-2,-1.88)	-0.51(-0.58,-0.45)
Total lipids in very large HDL (mmol/l)	-3.56E-01 (-3.63E-01,-3.49E-01)	-1.89E-01 (-1.97E-01,-1.81E-01)	-2.57(-2.62,-2.52)	-1.37(-1.42,-1.31)
Phospholipids in very large HDL (mmol/l)	-1.21E-01 (-1.25E-01,-1.17E-01)	-1.96E-02 (-2.40E-02,-1.53E-02)	-1.61(-1.66,-1.56)	-0.26(-0.32,-0.2)
Total cholesterol in very large HDL (mmol/l)	-2.32E-01 (-2.36E-01,-2.29E-01)	-1.66E-01 (-1.70E-01,-1.62E-01)	-3.54(-3.59,-3.49)	-2.53(-2.59,-2.47)
Cholesterol esters in very large HDL (mmol/l)	-1.80E-01 (-1.83E-01,-1.78E-01)	-1.36E-01 (-1.39E-01,-1.33E-01)	-3.81(-3.86,-3.75)	-2.88(-2.93,-2.82)
Free cholesterol in very large HDL (mmol/l)	-5.09E-02 (-5.19E-02,-4.99E-02)	-2.90E-02 (-3.01E-02,-2.80E-02)	-2.68(-2.74,-2.63)	-1.53(-1.59,-1.47)
Triglycerides in very large HDL (mmol/l)	-9.31E-03 (-9.61E-03,-9.01E-03)	-7.41E-03 (-7.70E-03,-7.12E-03)	-1.8(-1.86,-1.75)	-1.44(-1.49,-1.38)
Concentration of large HDL particles (mol/l)	-2.15E-07 (-2.33E-07,-1.98E-07)	2.50E-07 (2.31E-07,2.69E-07)	-0.94(-1.02,-0.86)	1.09(1.01,1.17)
Total lipids in large HDL (mmol/l)	-2.35E-01 (-2.47E-01,-2.23E-01)	6.63E-02 (5.39E-02,7.88E-02)	-1.35(-1.42,-1.28)	0.38(0.31,0.45)
Phospholipids in large HDL (mmol/l)	-8.91E-02 (-9.43E-02,-8.39E-02)	4.60E-02 (4.04E-02,5.16E-02)	-1.16(-1.23,-1.09)	0.6(0.53,0.67)
Total cholesterol in large HDL (mmol/l)	-1.42E-01 (-1.48E-01,-1.36E-01)	1.59E-02 (9.30E-03,2.25E-02)	-1.47(-1.53,-1.4)	0.16(0.1,0.23)
Cholesterol esters in large HDL (mmol/l)	-1.10E-01 (-1.15E-01,-1.05E-01)	1.08E-02 (5.75E-03,1.59E-02)	-1.45(-1.52,-1.39)	0.14(0.08,0.21)
Free cholesterol in large HDL (mmol/l)	-3.16E-02 (-3.31E-02,-3.02E-02)	5.09E-03 (3.55E-03,6.63E-03)	-1.52(-1.59,-1.44)	0.24(0.17,0.32)
Triglycerides in large HDL (mmol/l)	-3.93E-03 (-4.32E-03,-3.54E-03)	4.60E-03 (4.10E-03,5.11E-03)	-1.13(-1.24,-1.02)	1.32(1.18,1.47)
Concentration of medium HDL particles (mol/l)	3.76E-07 (3.58E-07,3.94E-07)	6.80E-07 (6.60E-07,7.00E-07)	2.23(2.13,2.34)	4.04(3.92,4.16)
Total lipids in medium HDL (mmol/l)	7.71E-04 (-6.79E-03,8.33E-03)	1.40E-01 (1.32E-01,1.49E-01)	0.01(-0.08,0.1)	1.64(1.54,1.74)
Phospholipids in medium HDL (mmol/l)	-2.09E-02 (-2.43E-02,-1.74E-02)	4.81E-02 (4.41E-02,5.22E-02)	-0.45(-0.52,-0.37)	1.03(0.94,1.12)
Total cholesterol in medium HDL (mmol/l)	1.80E-02 (1.36E-02,2.25E-02)	8.35E-02 (7.89E-02,8.82E-02)	0.44(0.34,0.55)	2.06(1.94,2.17)
Cholesterol esters in medium HDL (mmol/l)	1.41E-02 (1.06E-02,1.76E-02)	6.48E-02 (6.11E-02,6.85E-02)	0.42(0.32,0.53)	1.93(1.82,2.04)

S4 Table: Mean absolute difference in traits between 7y and 25y in males and females

	Original units		SD units	
	Mean absolute difference between 7y and 25y (95% CI)		Mean absolute difference between 7y and 25y (95% CI)	
	Males	Females	Males	Females
Free cholesterol in medium HDL (mmol/l)	3.93E-03 (2.99E-03,4.87E-03)	1.88E-02 (1.77E-02,1.98E-02)	0.53(0.4,0.65)	2.51(2.37,2.64)
Triglycerides in medium HDL (mmol/l)	9.68E-03 (9.12E-03,1.02E-02)	1.11E-02 (1.06E-02,1.17E-02)	1.22(1.15,1.3)	1.41(1.34,1.48)
Concentration of small HDL particles (mol/l)	6.77E-07 (6.49E-07,7.04E-07)	8.92E-07 (8.60E-07,9.24E-07)	2.68(2.57,2.79)	3.53(3.4,3.66)
Total lipids in small HDL (mmol/l)	5.14E-02 (4.48E-02,5.80E-02)	1.02E-01 (9.47E-02,1.10E-01)	0.73(0.63,0.82)	1.44(1.34,1.55)
Phospholipids in small HDL (mmol/l)	-1.43E-02 (-1.75E-02,-1.11E-02)	1.35E-02 (9.84E-03,1.71E-02)	-0.32(-0.39,-0.25)	0.3(0.22,0.38)
Total cholesterol in small HDL (mmol/l)	6.17E-02 (5.74E-02,6.61E-02)	8.95E-02 (8.48E-02,9.42E-02)	1.39(1.29,1.49)	2.01(1.91,2.12)
Cholesterol esters in small HDL (mmol/l)	7.68E-02 (7.29E-02,8.07E-02)	9.84E-02 (9.43E-02,1.02E-01)	1.93(1.83,2.02)	2.47(2.36,2.57)
Free cholesterol in small HDL (mmol/l)	-1.69E-02 (-1.76E-02,-1.62E-02)	-1.09E-02 (-1.17E-02,-1.01E-02)	-1.77(-1.84,-1.69)	-1.14(-1.22,-1.06)
Triglycerides in small HDL (mmol/l)	7.00E-04 (1.63E-04,1.24E-03)	-1.94E-03 (-2.42E-03,-1.47E-03)	0.08(0.02,0.14)	-0.23(-0.28,-0.17)
Mean diameter for VLDL particles (mm)	2.84E-01 (2.12E-01,3.57E-01)	-5.88E-01 (-6.48E-01,-5.27E-01)	0.22(0.16,0.27)	-0.45(-0.5,-0.41)
Mean diameter for LDL particles (mm)	-5.89E-02 (-6.73E-02,-5.05E-02)	-2.31E-02 (-3.13E-02,-1.49E-02)	-0.57(-0.65,-0.48)	-0.22(-0.3,-0.14)
Mean diameter for HDL particles (mm)	-2.80E-01 (-2.90E-01,-2.70E-01)	-5.72E-02 (-6.65E-02,-4.79E-02)	-1.84(-1.91,-1.78)	-0.38(-0.44,-0.32)
Serum total cholesterol (mmol/l)	-4.74E-01 (-5.11E-01,-4.38E-01)	-3.59E-01 (-3.94E-01,-3.24E-01)	-0.79(-0.85,-0.73)	-0.6(-0.66,-0.54)
Total cholesterol in VLDL (mmol/l)	-1.27E-01 (-1.37E-01,-1.17E-01)	-2.30E-01 (-2.38E-01,-2.22E-01)	-0.83(-0.89,-0.76)	-1.49(-1.54,-1.44)
Remnant cholesterol (non-HDL, non-LDL -cholesterol) (mmol/l)	-2.09E-01 (-2.24E-01,-1.94E-01)	-3.25E-01 (-3.38E-01,-3.13E-01)	-0.87(-0.93,-0.81)	-1.36(-1.41,-1.31)
Total cholesterol in LDL (mmol/l)	1.73E-02 (-2.74E-03,3.74E-02)	-5.51E-02 (-7.32E-02,-3.71E-02)	0.05(-0.01,0.11)	-0.17(-0.22,-0.11)
Total cholesterol in HDL (mmol/l)	-2.85E-01 (-2.99E-01,-2.71E-01)	2.09E-02 (6.63E-03,3.51E-02)	-1.37(-1.44,-1.31)	0.1(0.03,0.17)
Total cholesterol in HDL2 (mmol/l)	-1.30E-01 (-1.41E-01,-1.18E-01)	1.48E-01 (1.36E-01,1.61E-01)	-0.94(-1.02,-0.85)	1.07(0.99,1.16)
Total cholesterol in HDL3 (mmol/l)	-1.54E-01 (-1.57E-01,-1.51E-01)	-1.23E-01 (-1.26E-01,-1.20E-01)	-2.07(-2.11,-2.03)	-1.65(-1.7,-1.61)
Esterified cholesterol (mmol/l)	-3.52E-01 (-3.78E-01,-3.27E-01)	-2.62E-01 (-2.87E-01,-2.37E-01)	-0.82(-0.88,-0.76)	-0.61(-0.67,-0.55)
Free cholesterol (mmol/l)	-1.39E-01 (-1.50E-01,-1.29E-01)	-9.78E-02 (-1.08E-01,-8.75E-02)	-0.77(-0.83,-0.71)	-0.54(-0.6,-0.48)
Serum total triglycerides (mmol/l)	-4.75E-02 (-7.13E-02,-2.37E-02)	-2.30E-01 (-2.49E-01,-2.11E-01)	-0.12(-0.19,-0.06)	-0.61(-0.65,-0.56)
Triglycerides in VLDL (mmol/l)	7.82E-03 (-1.31E-02,2.87E-02)	-2.06E-01 (-2.22E-01,-1.90E-01)	0.02(-0.04,0.09)	-0.62(-0.67,-0.57)
Triglycerides in LDL (mmol/l)	-3.06E-02 (-3.27E-02,-2.85E-02)	-1.52E-02 (-1.75E-02,-1.29E-02)	-0.65(-0.69,-0.6)	-0.32(-0.37,-0.27)
Triglycerides in HDL (mmol/l)	-2.98E-03 (-4.35E-03,-1.61E-03)	6.17E-03 (4.76E-03,7.57E-03)	-0.14(-0.21,-0.08)	0.3(0.23,0.37)
Diacylglycerol (mmol/l)*	-1.97E-03 (-2.57E-03,-1.37E-03)	-2.40E-03 (-3.11E-03,-1.68E-03)	-0.18(-0.24,-0.13)	-0.22(-0.29,-0.16)
Total phosphoglycerides (mmol/l)	-3.76E-01 (-3.91E-01,-3.62E-01)	-1.84E-01 (-2.00E-01,-1.67E-01)	-1.39(-1.44,-1.33)	-0.68(-0.74,-0.61)
Phosphatidylcholine and other cholines (mmol/l)	-3.62E-01 (-3.79E-01,-3.45E-01)	-2.10E-01 (-2.27E-01,-1.93E-01)	-1.32(-1.38,-1.26)	-0.77(-0.83,-0.7)
Total cholines (mmol/l)	-3.85E-01 (-4.02E-01,-3.68E-01)	-1.75E-01 (-1.94E-01,-1.56E-01)	-1.29(-1.35,-1.23)	-0.59(-0.65,-0.52)
Apolipoprotein A-I (g/l)	-1.22E-01 (-1.30E-01,-1.13E-01)	2.63E-02 (1.75E-02,3.52E-02)	-1.09(-1.16,-1.01)	0.23(0.16,0.31)
Apolipoprotein B (g/l)	-1.72E-02 (-2.50E-02,-9.40E-03)	-8.39E-02 (-9.04E-02,-7.73E-02)	-0.14(-0.2,-0.08)	-0.68(-0.73,-0.63)
Total fatty acids (mmol/l)	-1.80E+00 (-1.90E+00,-1.70E+00)	-1.71E+00 (-1.80E+00,-1.61E+00)	-1.13(-1.19,-1.07)	-1.07(-1.13,-1.01)
Fatty acid length*	1.57E-01 (1.33E-01,1.81E-01)	1.05E-01 (7.44E-02,1.35E-01)	0.44(0.38,0.51)	0.3(0.21,0.38)
Estimated degree of unsaturation*	1.72E-02 (1.30E-02,2.15E-02)	2.86E-02 (2.33E-02,3.39E-02)	0.28(0.21,0.36)	0.47(0.39,0.56)
22:6, docosahexaenoic acid (mmol/l)	-7.50E-03 (-9.04E-03,-5.95E-03)	6.54E-03 (4.87E-03,8.21E-03)	-0.28(-0.34,-0.22)	0.24(0.18,0.31)
18:2, linoleic acid (mmol/l)	-5.42E-01 (-5.68E-01,-5.15E-01)	-5.18E-01 (-5.43E-01,-4.93E-01)	-1.23(-1.29,-1.16)	-1.17(-1.23,-1.12)
Conjugated linoleic acid (mmol/l)*	-7.74E-03 (-8.71E-03,-6.78E-03)	-8.89E-03 (-1.03E-02,-7.46E-03)	-0.44(-0.49,-0.38)	-0.5(-0.58,-0.42)
Omega-3 fatty acids (mmol/l)	-3.63E-02 (-4.05E-02,-3.22E-02)	-4.03E-02 (-4.43E-02,-3.63E-02)	-0.53(-0.59,-0.47)	-0.59(-0.65,-0.53)
Omega-6 fatty acids (mmol/l)	-6.34E-01 (-6.63E-01,-6.04E-01)	-5.44E-01 (-5.73E-01,-5.16E-01)	-1.29(-1.35,-1.23)	-1.11(-1.16,-1.05)
Polyunsaturated fatty acids (mmol/l)	-6.70E-01 (-7.02E-01,-6.38E-01)	-5.85E-01 (-6.16E-01,-5.53E-01)	-1.25(-1.31,-1.19)	-1.09(-1.15,-1.03)
Monounsaturated fatty acids; 16:1, 18:1 (mmol/l)	-2.16E-01 (-2.51E-01,-1.80E-01)	-2.61E-01 (-2.93E-01,-2.28E-01)	-0.39(-0.45,-0.32)	-0.47(-0.52,-0.41)
Saturated fatty acids (mmol/l)	-9.22E-01 (-9.61E-01,-8.82E-01)	-8.76E-01 (-9.13E-01,-8.38E-01)	-1.38(-1.43,-1.32)	-1.31(-1.36,-1.25)
Glucose (mmol/l)	-1.68E-01 (-2.02E-01,-1.34E-01)	-2.82E-01 (-3.08E-01,-2.57E-01)	-0.33(-0.39,-0.26)	-0.55(-0.6,-0.5)
Lactate (mmol/l)	-4.06E-01 (-4.33E-01,-3.79E-01)	-4.73E-01 (-5.01E-01,-4.44E-01)	-0.84(-0.9,-0.79)	-0.98(-1.04,-0.92)
Citrate (mmol/l)	2.81E-02 (2.66E-02,2.96E-02)	2.32E-02 (2.18E-02,2.45E-02)	1.12(1.06,1.18)	0.92(0.87,0.98)

S4 Table: Mean absolute difference in traits between 7y and 25y in males and females

	Original units		SD units	
	Mean absolute difference between 7y and 25y (95% CI)		Mean absolute difference between 7y and 25y (95% CI)	
	Males	Females	Males	Females
Alanine (mmol/l)	5.32E-02 (4.95E-02,5.69E-02)	3.97E-02 (3.64E-02,4.30E-02)	0.83(0.77,0.89)	0.62(0.57,0.67)
Glutamine (mmol/l)	-5.55E-02 (-5.97E-02,-5.12E-02)	-1.45E-01 (-1.48E-01,-1.41E-01)	-0.96(-1.03,-0.88)	-2.49(-2.56,-2.43)
Histidine (mmol/l)	-2.10E-02 (-2.16E-02,-2.04E-02)	-2.66E-02 (-2.72E-02,-2.60E-02)	-1.47(-1.51,-1.42)	-1.86(-1.9,-1.81)
Isoleucine (mmol/l)	3.01E-03 (2.08E-03,3.94E-03)	-8.71E-03 (-9.52E-03,-7.90E-03)	0.17(0.12,0.22)	-0.48(-0.53,-0.44)
Leucine (mmol/l)	9.37E-03 (8.52E-03,1.02E-02)	-2.61E-03 (-3.33E-03,-1.89E-03)	0.62(0.57,0.68)	-0.17(-0.22,-0.13)
Valine (mmol/l)	1.53E-02 (1.34E-02,1.73E-02)	-1.17E-02 (-1.34E-02,-9.99E-03)	0.44(0.38,0.49)	-0.33(-0.38,-0.29)
Phenylalanine (mmol/l)	6.10E-03 (5.65E-03,6.55E-03)	4.39E-03 (3.98E-03,4.80E-03)	0.71(0.66,0.76)	0.51(0.46,0.56)
Tyrosine (mmol/l)	-2.07E-02 (-2.15E-02,-2.00E-02)	-2.63E-02 (-2.70E-02,-2.55E-02)	-1.31(-1.35,-1.26)	-1.66(-1.71,-1.61)
Acetate (mmol/l)	-6.45E-03 (-8.73E-03,-4.17E-03)	-1.30E-02 (-1.43E-02,-1.17E-02)	-0.27(-0.36,-0.17)	-0.54(-0.59,-0.49)
Acetoacetate (mmol/l)	-1.91E-02 (-2.10E-02,-1.72E-02)	-2.30E-02 (-2.50E-02,-2.10E-02)	-0.4(-0.44,-0.36)	-0.49(-0.53,-0.44)
3-hydroxybutyrate (mmol/l)	5.34E-02 (4.84E-02,5.84E-02)	5.75E-02 (5.17E-02,6.33E-02)	0.55(0.5,0.6)	0.59(0.53,0.65)
Creatinine (mmol/l)	2.92E-02 (2.87E-02,2.96E-02)	1.68E-02 (1.65E-02,1.71E-02)	4.77(4.7,4.84)	2.75(2.7,2.81)
Albumin (mmol/l)	4.28E-03 (3.99E-03,4.57E-03)	3.09E-04 (4.88E-05,5.70E-04)	1.18(1.1,1.27)	0.09(0.01,0.16)
Glycoprotein acetyls, mainly a1-acid glycoprotein (mmol/l)	6.33E-03 (-3.30E-03,1.60E-02)	-8.46E-03 (-1.67E-02,-1.73E-04)	0.05(-0.02,0.12)	-0.06(-0.12,-0.001)

*These metabolites (diacylglycerol, fatty acid chain length, estimated degree of saturation and conjugated linoleic acid) were not measured at 25y; all models include data only up to aged 18y and values in this table for these traits are at 7y and 18y respectively. HDL: high-density lipoprotein; IDL: intermediate-density lipoprotein; LDL: low-density lipoprotein; VLDL: very-low-density lipoprotein.

S5 Table: Mean rate of change in concentration per year in males and females

	Males		Females	
	Mean change in concentration per year from 7 to 15y/ 18y(95%CI)	**Mean change in concentration per year from 15y/18y to 25y (95%CI)**	**Mean change in concentration per year from 7 to 15y/ 18y(95%CI)**	**Mean change in concentration per year from 15y/18y to 25y (95%CI)**
Concentration of chylomicrons and extremely large VLDL particles (mol/l)	-3.48E-12 (-4.11E-12,-2.85E-12)	-1.80E-13 (-7.41E-13,3.81E-13)	-6.18E-12 (-6.76E-12,-5.59E-12)	-2.58E-12 (-2.93E-12,-2.22E-12)
Total lipids in chylomicrons and extremely large VLDL (mmol/l)	-7.84E-04 (-9.25E-04,-6.43E-04)	-4.32E-04 (-5.55E-04,-3.10E-04)	-1.35E-03 (-1.49E-03,-1.22E-03)	-9.43E-04 (-1.02E-03,-8.65E-04)
Phospholipids in chylomicrons and extremely large VLDL (mmol/l)	-1.01E-04 (-1.18E-04,-8.35E-05)	-6.28E-05 (-7.81E-05,-4.76E-05)	-1.65E-04 (-1.81E-04,-1.49E-04)	-1.25E-04 (-1.35E-04,-1.16E-04)
Total cholesterol in chylomicrons and extremely large VLDL (mmol/l)	-8.79E-05 (-1.05E-04,-7.06E-05)	-9.34E-05 (-1.21E-04,-6.54E-05)	-1.69E-04 (-1.85E-04,-1.53E-04)	-1.68E-04 (-1.87E-04,-1.50E-04)
Cholesterol esters in chylomicrons and extremely large VLDL (mmol/l)	-3.52E-05 (-4.42E-05,-2.63E-05)	-3.71E-05 (-5.21E-05,-2.21E-05)	-7.15E-05 (-7.97E-05,-6.33E-05)	-8.00E-05 (-9.02E-05,-6.97E-05)
Free cholesterol in chylomicrons and extremely large VLDL (mmol/l)	-6.13E-05 (-7.28E-05,-4.98E-05)	-4.70E-05 (-5.70E-05,-3.70E-05)	-1.03E-04 (-1.14E-04,-9.27E-05)	-8.69E-05 (-9.33E-05,-8.05E-05)
Triglycerides in chylomicrons and extremely large VLDL (mmol/l)	-5.68E-04 (-6.70E-04,-4.65E-04)	-3.05E-04 (-3.92E-04,-2.18E-04)	-1.00E-03 (-1.10E-03,-9.07E-04)	-6.64E-04 (-7.19E-04,-6.08E-04)
Concentration of very large VLDL particles (mol/l)	-1.82E-11 (-2.17E-11,-1.47E-11)	1.20E-12 (-2.10E-12,4.50E-12)	-3.37E-11 (-3.69E-11,-3.05E-11)	-1.22E-11 (-1.43E-11,-1.02E-11)
Total lipids in very large VLDL (mmol/l)	-1.83E-03 (-2.17E-03,-1.49E-03)	-7.20E-05 (-3.93E-04,2.49E-04)	-3.26E-03 (-3.57E-03,-2.94E-03)	-1.41E-03 (-1.61E-03,-1.21E-03)
Phospholipids in very large VLDL (mmol/l)	-3.47E-04 (-4.03E-04,-2.90E-04)	1.69E-05 (-3.64E-05,7.01E-05)	-5.48E-04 (-6.01E-04,-4.96E-04)	-2.12E-04 (-2.45E-04,-1.79E-04)
Total cholesterol in very large VLDL (mmol/l)	-3.16E-04 (-3.82E-04,-2.50E-04)	-1.97E-04 (-2.58E-04,-1.35E-04)	-5.91E-04 (-6.52E-04,-5.30E-04)	-4.64E-04 (-5.03E-04,-4.25E-04)
Cholesterol esters in very large VLDL (mmol/l)	-1.03E-04 (-1.29E-04,-7.68E-05)	-1.53E-04 (-1.97E-04,-1.10E-04)	-2.70E-04 (-2.94E-04,-2.46E-04)	-2.59E-04 (-2.87E-04,-2.31E-04)
Free cholesterol in very large VLDL (mmol/l)	-1.81E-04 (-2.13E-04,-1.48E-04)	-9.48E-05 (-1.24E-04,-6.57E-05)	-2.96E-04 (-3.26E-04,-2.65E-04)	-2.23E-04 (-2.41E-04,-2.04E-04)
Triglycerides in very large VLDL (mmol/l)	-1.16E-03 (-1.38E-03,-9.44E-04)	1.08E-04 (-9.96E-05,3.15E-04)	-2.12E-03 (-2.32E-03,-1.92E-03)	-7.36E-04 (-8.66E-04,-6.06E-04)
Concentration of large VLDL particles (mol/l)	-9.61E-11 (-1.13E-10,-7.95E-11)	1.07E-10 (8.79E-11,1.25E-10)	-1.62E-10 (-1.77E-10,-1.47E-10)	1.72E-12 (-1.01E-11,1.35E-11)
Total lipids in large VLDL (mmol/l)	-5.64E-03 (-6.63E-03,-4.65E-03)	5.10E-03 (4.01E-03,6.19E-03)	-9.56E-03 (-1.05E-02,-8.66E-03)	-1.02E-03 (-1.71E-03,-3.25E-04)
Phospholipids in large VLDL (mmol/l)	-1.14E-03 (-1.31E-03,-9.59E-04)	1.16E-03 (9.63E-04,1.36E-03)	-1.77E-03 (-1.93E-03,-1.61E-03)	5.08E-05 (-7.57E-05,1.77E-04)
Total cholesterol in large VLDL (mmol/l)	-1.40E-03 (-1.62E-03,-1.17E-03)	8.61E-04 (6.18E-04,1.10E-03)	-2.14E-03 (-2.35E-03,-1.94E-03)	-5.93E-04 (-7.48E-04,-4.39E-04)
Cholesterol esters in large VLDL (mmol/l)	-6.43E-04 (-7.48E-04,-5.38E-04)	5.77E-04 (4.59E-04,6.95E-04)	-9.71E-04 (-1.07E-03,-8.74E-04)	-2.36E-04 (-3.13E-04,-1.59E-04)
Free cholesterol in large VLDL (mmol/l)	-7.51E-04 (-8.71E-04,-6.32E-04)	2.82E-04 (1.57E-04,4.08E-04)	-1.17E-03 (-1.28E-03,-1.06E-03)	-3.57E-04 (-4.36E-04,-2.78E-04)
Triglycerides in large VLDL (mmol/l)	-3.11E-03 (-3.70E-03,-2.51E-03)	3.08E-03 (2.43E-03,3.73E-03)	-5.65E-03 (-6.19E-03,-5.11E-03)	-4.76E-04 (-8.90E-04,-6.28E-05)
Concentration of medium VLDL particles (mol/l)	-1.98E-10 (-2.34E-10,-1.61E-10)	4.05E-10 (3.58E-10,4.52E-10)	-3.58E-10 (-3.91E-10,-3.24E-10)	5.89E-11 (2.86E-11,8.91E-11)
Total lipids in medium VLDL (mmol/l)	-6.58E-03 (-7.83E-03,-5.33E-03)	1.12E-02 (9.64E-03,1.27E-02)	-1.17E-02 (-1.28E-02,-1.05E-02)	-5.47E-04 (-1.56E-03,4.70E-04)
Phospholipids in medium VLDL (mmol/l)	-1.58E-03 (-1.81E-03,-1.34E-03)	2.29E-03 (2.00E-03,2.59E-03)	-2.37E-03 (-2.59E-03,-2.14E-03)	-4.23E-05 (-2.39E-04,1.55E-04)
Total cholesterol in medium VLDL (mmol/l)	-2.62E-03 (-2.94E-03,-2.30E-03)	3.13E-03 (2.73E-03,3.52E-03)	-3.21E-03 (-3.51E-03,-2.91E-03)	2.97E-05 (-2.42E-04,3.01E-04)
Cholesterol esters in medium VLDL (mmol/l)	-1.57E-03 (-1.74E-03,-1.40E-03)	2.09E-03 (1.88E-03,2.30E-03)	-1.70E-03 (-1.87E-03,-1.54E-03)	4.65E-04 (3.15E-04,6.14E-04)
Free cholesterol in medium VLDL (mmol/l)	-1.04E-03 (-1.20E-03,-8.85E-04)	1.03E-03 (8.39E-04,1.23E-03)	-1.50E-03 (-1.65E-03,-1.36E-03)	-4.41E-04 (-5.69E-04,-3.12E-04)
Triglycerides in medium VLDL (mmol/l)	-2.37E-03 (-3.08E-03,-1.67E-03)	5.75E-03 (4.88E-03,6.62E-03)	-6.07E-03 (-6.71E-03,-5.43E-03)	-5.43E-04 (-1.10E-03,1.79E-05)
Concentration of small VLDL particles (mol/l)	-2.93E-10 (-3.28E-10,-2.58E-10)	2.21E-10 (1.74E-10,2.68E-10)	-3.78E-10 (-4.13E-10,-3.43E-10)	-2.09E-10 (-2.43E-10,-1.74E-10)
Total lipids in small VLDL (mmol/l)	-3.67E-03 (-4.20E-03,-3.13E-03)	-2.89E-03 (-4.08E-03,-1.69E-03)	-6.28E-03 (-6.83E-03,-5.73E-03)	-1.35E-02 (-1.44E-02,-1.26E-02)
Phospholipids in small VLDL (mmol/l)	-1.38E-03 (-1.51E-03,-1.24E-03)	-1.87E-04 (-3.66E-04,-8.70E-06)	-1.46E-03 (-1.61E-03,-1.32E-03)	-1.79E-03 (-1.94E-03,-1.65E-03)
Total cholesterol in small VLDL (mmol/l)	-1.44E-03 (-1.62E-03,-1.25E-03)	-5.10E-03 (-5.52E-03,-4.68E-03)	-2.22E-03 (-2.42E-03,-2.01E-03)	-8.90E-03 (-9.26E-03,-8.55E-03)
Cholesterol esters in small VLDL (mmol/l)	-6.73E-04 (-7.98E-04,-5.48E-04)	-4.25E-03 (-4.53E-03,-3.97E-03)	-1.28E-03 (-1.42E-03,-1.14E-03)	-6.56E-03 (-6.81E-03,-6.32E-03)
Free cholesterol in small VLDL (mmol/l)	-7.66E-04 (-8.38E-04,-6.95E-04)	-8.52E-04 (-1.01E-03,-6.93E-04)	-9.33E-04 (-1.01E-03,-8.57E-04)	-2.34E-03 (-2.47E-03,-2.21E-03)
Triglycerides in small VLDL (mmol/l)	-2.16E-03 (-2.53E-03,-1.80E-03)	2.13E-03 (1.67E-03,2.58E-03)	-3.32E-03 (-3.67E-03,-2.97E-03)	-1.89E-03 (-2.20E-03,-1.57E-03)
Concentration of very small VLDL particles (mol/l)	-4.17E-10 (-4.42E-10,-3.92E-10)	1.48E-10 (1.08E-10,1.89E-10)	-2.95E-10 (-3.24E-10,-2.66E-10)	-9.82E-11 (-1.34E-10,-6.21E-11)
Total lipids in very small VLDL (mmol/l)	-3.75E-03 (-4.05E-03,-3.45E-03)	-1.06E-02 (-1.13E-02,-9.92E-03)	-3.78E-03 (-4.13E-03,-3.44E-03)	-1.48E-02 (-1.54E-02,-1.41E-02)
Phospholipids in very small VLDL (mmol/l)	-2.10E-03 (-2.22E-03,-1.97E-03)	5.32E-04 (3.61E-04,7.04E-04)	-1.21E-03 (-1.35E-03,-1.06E-03)	-5.70E-04 (-7.29E-04,-4.10E-04)
Total cholesterol in very small VLDL (mmol/l)	-1.17E-03 (-1.37E-03,-9.79E-04)	-1.11E-02 (-1.15E-02,-1.07E-02)	-1.95E-03 (-2.16E-03,-1.75E-03)	-1.19E-02 (-1.23E-02,-1.16E-02)
Cholesterol esters in very small VLDL (mmol/l)	-4.68E-04 (-6.04E-04,-3.33E-04)	-8.95E-03 (-9.21E-03,-8.68E-03)	-1.40E-03 (-1.55E-03,-1.25E-03)	-8.89E-03 (-9.14E-03,-8.64E-03)
Free cholesterol in very small VLDL (mmol/l)	-7.13E-04 (-7.79E-04,-6.46E-04)	-2.13E-03 (-2.25E-03,-2.00E-03)	-5.56E-04 (-6.28E-04,-4.84E-04)	-3.02E-03 (-3.13E-03,-2.90E-03)
Triglycerides in very small VLDL (mmol/l)	-9.96E-04 (-1.09E-03,-9.04E-04)	-5.76E-04 (-7.61E-04,-3.90E-04)	-8.71E-04 (-9.73E-04,-7.69E-04)	-2.12E-03 (-2.29E-03,-1.96E-03)
Concentration of IDL particles (mol/l)	-1.10E-09 (-1.16E-09,-1.05E-09)	2.43E-09 (2.28E-09,2.57E-09)	-6.93E-10 (-7.56E-10,-6.29E-10)	1.77E-09 (1.63E-09,1.91E-09)

S5 Table: Mean rate of change in concentration per year in males and females

	Males		Females	
	Mean change in concentration per year from 7 to 15y/ 18y(95%CI)	**Mean change in concentration per year from 15y/18y to 25y (95%CI)**	**Mean change in concentration per year from 7 to 15y/ 18y(95%CI)**	**Mean change in concentration per year from 15y/18y to 25y (95%CI)**
Total lipids in IDL (mmol/l)	-1.33E-02 (-1.40E-02,-1.26E-02)	4.04E-03 (2.48E-03,5.60E-03)	-8.22E-03 (-9.02E-03,-7.42E-03)	-6.77E-03 (-8.27E-03,-5.27E-03)
Phospholipids in IDL (mmol/l)	-3.56E-03 (-3.74E-03,-3.37E-03)	3.08E-03 (2.69E-03,3.48E-03)	-1.86E-03 (-2.08E-03,-1.64E-03)	1.97E-04 (-1.87E-04,5.81E-04)
Total cholesterol in IDL (mmol/l)	-8.18E-03 (-8.65E-03,-7.71E-03)	1.36E-03 (2.93E-04,2.43E-03)	-5.82E-03 (-6.35E-03,-5.30E-03)	-5.21E-03 (-6.22E-03,-4.20E-03)
Cholesterol esters in IDL (mmol/l)	-5.44E-03 (-5.78E-03,-5.10E-03)	-6.70E-05 (-8.45E-04,7.11E-04)	-4.35E-03 (-4.72E-03,-3.98E-03)	-4.65E-03 (-5.37E-03,-3.92E-03)
Free cholesterol in IDL (mmol/l)	-2.75E-03 (-2.89E-03,-2.60E-03)	1.44E-03 (1.13E-03,1.74E-03)	-1.47E-03 (-1.64E-03,-1.31E-03)	-5.66E-04 (-8.60E-04,-2.72E-04)
Triglycerides in IDL (mmol/l)	-1.59E-03 (-1.69E-03,-1.50E-03)	-3.91E-04 (-5.57E-04,-2.26E-04)	-5.13E-04 (-6.26E-04,-3.99E-04)	-1.76E-03 (-1.94E-03,-1.57E-03)
Concentration of large LDL particles (mol/l)	-1.98E-09 (-2.08E-09,-1.88E-09)	7.32E-09 (7.04E-09,7.60E-09)	-1.01E-09 (-1.13E-09,-8.88E-10)	5.46E-09 (5.21E-09,5.71E-09)
Total lipids in large LDL (mmol/l)	-1.80E-02 (-1.89E-02,-1.72E-02)	2.83E-02 (2.63E-02,3.03E-02)	-9.53E-03 (-1.06E-02,-8.49E-03)	8.93E-03 (7.04E-03,1.08E-02)
Phospholipids in large LDL (mmol/l)	-3.44E-03 (-3.62E-03,-3.26E-03)	6.37E-03 (5.95E-03,6.79E-03)	-1.78E-03 (-1.99E-03,-1.57E-03)	2.68E-03 (2.29E-03,3.07E-03)
Total cholesterol in large LDL (mmol/l)	-1.27E-02 (-1.34E-02,-1.21E-02)	2.23E-02 (2.08E-02,2.38E-02)	-7.23E-03 (-7.97E-03,-6.48E-03)	7.66E-03 (6.27E-03,9.04E-03)
Cholesterol esters in large LDL (mmol/l)	-9.62E-03 (-1.01E-02,-9.13E-03)	1.77E-02 (1.66E-02,1.89E-02)	-5.63E-03 (-6.19E-03,-5.07E-03)	6.07E-03 (5.02E-03,7.12E-03)
Free cholesterol in large LDL (mmol/l)	-3.13E-03 (-3.29E-03,-2.96E-03)	4.53E-03 (4.18E-03,4.89E-03)	-1.59E-03 (-1.78E-03,-1.41E-03)	1.59E-03 (1.25E-03,1.92E-03)
Triglycerides in large LDL (mmol/l)	-1.87E-03 (-1.97E-03,-1.77E-03)	-2.99E-04 (-4.57E-04,-1.40E-04)	-5.02E-04 (-6.25E-04,-3.79E-04)	-1.39E-03 (-1.58E-03,-1.21E-03)
Concentration of medium LDL particles (mol/l)	-1.68E-09 (-1.78E-09,-1.59E-09)	6.92E-09 (6.66E-09,7.18E-09)	-8.88E-10 (-9.97E-10,-7.80E-10)	4.94E-09 (4.71E-09,5.17E-09)
Total lipids in medium LDL (mmol/l)	-1.11E-02 (-1.16E-02,-1.05E-02)	2.30E-02 (2.16E-02,2.43E-02)	-6.03E-03 (-6.68E-03,-5.37E-03)	9.03E-03 (7.79E-03,1.03E-02)
Phospholipids in medium LDL (mmol/l)	-3.39E-03 (-3.53E-03,-3.24E-03)	2.86E-03 (2.66E-03,3.07E-03)	-1.98E-03 (-2.14E-03,-1.82E-03)	1.20E-03 (1.02E-03,1.39E-03)
Total cholesterol in medium LDL (mmol/l)	-7.78E-03 (-8.19E-03,-7.36E-03)	1.78E-02 (1.67E-02,1.88E-02)	-4.61E-03 (-5.08E-03,-4.13E-03)	7.15E-03 (6.22E-03,8.08E-03)
Cholesterol esters in medium LDL (mmol/l)	-6.13E-03 (-6.48E-03,-5.79E-03)	1.56E-02 (1.48E-02,1.65E-02)	-3.60E-03 (-3.99E-03,-3.20E-03)	6.88E-03 (6.13E-03,7.62E-03)
Free cholesterol in medium LDL (mmol/l)	-1.65E-03 (-1.72E-03,-1.57E-03)	2.12E-03 (1.92E-03,2.33E-03)	-1.00E-03 (-1.09E-03,-9.18E-04)	2.70E-04 (8.05E-05,4.60E-04)
Triglycerides in medium LDL (mmol/l)	-1.01E-03 (-1.08E-03,-9.46E-04)	9.56E-04 (8.66E-04,1.05E-03)	-1.26E-04 (-2.04E-04,-4.81E-05)	2.75E-04 (1.72E-04,3.78E-04)
Concentration of small LDL particles (mol/l)	-2.15E-09 (-2.25E-09,-2.05E-09)	6.61E-09 (6.29E-09,6.92E-09)	-1.30E-09 (-1.42E-09,-1.18E-09)	4.54E-09 (4.26E-09,4.82E-09)
Total lipids in small LDL (mmol/l)	-7.41E-03 (-7.77E-03,-7.06E-03)	1.25E-02 (1.17E-02,1.34E-02)	-4.45E-03 (-4.86E-03,-4.03E-03)	4.28E-03 (3.45E-03,5.10E-03)
Phospholipids in small LDL (mmol/l)	-2.55E-03 (-2.65E-03,-2.45E-03)	1.41E-03 (1.25E-03,1.57E-03)	-1.63E-03 (-1.74E-03,-1.52E-03)	5.42E-04 (3.96E-04,6.88E-04)
Total cholesterol in small LDL (mmol/l)	-4.96E-03 (-5.22E-03,-4.70E-03)	9.55E-03 (8.90E-03,1.02E-02)	-3.04E-03 (-3.34E-03,-2.74E-03)	3.27E-03 (2.67E-03,3.86E-03)
Cholesterol esters in small LDL (mmol/l)	-3.92E-03 (-4.14E-03,-3.70E-03)	9.04E-03 (8.52E-03,9.56E-03)	-2.31E-03 (-2.57E-03,-2.05E-03)	3.76E-03 (3.29E-03,4.23E-03)
Free cholesterol in small LDL (mmol/l)	-1.05E-03 (-1.09E-03,-9.98E-04)	5.14E-04 (3.69E-04,6.58E-04)	-7.20E-04 (-7.74E-04,-6.67E-04)	-5.06E-04 (-6.41E-04,-3.72E-04)
Triglycerides in small LDL (mmol/l)	-8.23E-04 (-8.79E-04,-7.68E-04)	3.92E-04 (3.44E-04,4.41E-04)	-3.99E-04 (-4.59E-04,-3.39E-04)	1.68E-04 (1.21E-04,2.14E-04)
Concentration of very large HDL particles (mol/l)	-8.69E-09 (-9.30E-09,-8.07E-09)	-1.71E-08 (-1.79E-08,-1.63E-08)	-9.70E-10 (-1.65E-09,-2.95E-10)	-5.68E-09 (-6.59E-09,-4.77E-09)
Total lipids in very large HDL (mmol/l)	-9.16E-03 (-9.91E-03,-8.41E-03)	-3.14E-02 (-3.23E-02,-3.06E-02)	-4.20E-04 (-1.24E-03,3.96E-04)	-2.06E-02 (-2.16E-02,-1.97E-02)
Phospholipids in very large HDL (mmol/l)	-5.18E-03 (-5.57E-03,-4.79E-03)	-8.79E-03 (-9.25E-03,-8.34E-03)	5.53E-04 (1.28E-04,9.77E-04)	-2.67E-03 (-3.19E-03,-2.15E-03)
Total cholesterol in very large HDL (mmol/l)	-6.97E-03 (-7.26E-03,-6.67E-03)	-2.59E-02 (-2.65E-02,-2.54E-02)	-3.79E-03 (-4.11E-03,-3.48E-03)	-2.07E-02 (-2.13E-02,-2.01E-02)
Cholesterol esters in very large HDL (mmol/l)	-5.07E-03 (-5.29E-03,-4.85E-03)	-2.08E-02 (-2.12E-02,-2.03E-02)	-3.05E-03 (-3.28E-03,-2.81E-03)	-1.71E-02 (-1.76E-02,-1.67E-02)
Free cholesterol in very large HDL (mmol/l)	-1.25E-03 (-1.35E-03,-1.15E-03)	-4.54E-03 (-4.65E-03,-4.43E-03)	-1.81E-04 (-2.92E-04,-7.01E-05)	-3.07E-03 (-3.19E-03,-2.94E-03)
Triglycerides in very large HDL (mmol/l)	-3.76E-04 (-4.08E-04,-3.44E-04)	-7.01E-04 (-7.34E-04,-6.67E-04)	-2.01E-04 (-2.34E-04,-1.69E-04)	-6.44E-04 (-6.77E-04,-6.12E-04)
Concentration of large HDL particles (mol/l)	-2.10E-08 (-2.19E-08,-2.01E-08)	2.66E-09 (5.96E-11,5.26E-09)	1.59E-09 (5.56E-10,2.62E-09)	3.88E-08 (3.58E-08,4.18E-08)
Total lipids in large HDL (mmol/l)	-1.54E-02 (-1.61E-02,-1.47E-02)	-1.09E-02 (-1.26E-02,-9.22E-03)	1.13E-03 (3.56E-04,1.90E-03)	8.99E-03 (7.06E-03,1.09E-02)
Phospholipids in large HDL (mmol/l)	-7.07E-03 (-7.37E-03,-6.77E-03)	-1.88E-03 (-2.65E-03,-1.12E-03)	7.68E-04 (4.20E-04,1.12E-03)	6.25E-03 (5.38E-03,7.13E-03)
Total cholesterol in large HDL (mmol/l)	-7.97E-03 (-8.34E-03,-7.59E-03)	-9.03E-03 (-9.94E-03,-8.13E-03)	4.95E-04 (7.30E-05,9.17E-04)	1.74E-03 (7.20E-04,2.76E-03)
Cholesterol esters in large HDL (mmol/l)	-6.23E-03 (-6.52E-03,-5.93E-03)	-6.95E-03 (-7.64E-03,-6.26E-03)	4.74E-04 (1.41E-04,8.07E-04)	9.32E-04 (1.49E-04,1.71E-03)
Free cholesterol in large HDL (mmol/l)	-1.74E-03 (-1.82E-03,-1.66E-03)	-2.08E-03 (-2.30E-03,-1.86E-03)	2.04E-05 (-6.94E-05,1.10E-04)	8.11E-04 (5.71E-04,1.05E-03)
Triglycerides in large HDL (mmol/l)	-3.73E-04 (-3.89E-04,-3.57E-04)	2.85E-05 (-3.51E-05,9.21E-05)	-1.38E-04 (-1.55E-04,-1.20E-04)	1.02E-03 (9.38E-04,1.10E-03)
Concentration of medium HDL particles (mol/l)	-1.43E-08 (-1.51E-08,-1.34E-08)	8.88E-08 (8.59E-08,9.17E-08)	5.23E-09 (4.16E-09,6.29E-09)	1.04E-07 (1.01E-07,1.07E-07)
Total lipids in medium HDL (mmol/l)	-1.09E-02 (-1.15E-02,-1.04E-02)	9.80E-03 (8.86E-03,1.07E-02)	-7.53E-04 (-1.42E-03,-9.00E-05)	1.63E-02 (1.52E-02,1.73E-02)
Phospholipids in medium HDL (mmol/l)	-5.56E-03 (-5.86E-03,-5.26E-03)	2.63E-03 (2.21E-03,3.04E-03)	2.76E-04 (-8.66E-05,6.38E-04)	5.10E-03 (4.62E-03,5.59E-03)

S5 Table: Mean rate of change in concentration per year in males and females

	Males		Females	
	Mean change in concentration per year from 7 to 15y/ 18y(95%CI)	**Mean change in concentration per year from 15y/18y to 25y (95%CI)**	**Mean change in concentration per year from 7 to 15y/ 18y(95%CI)**	**Mean change in concentration per year from 15y/18y to 25y (95%CI)**
Total cholesterol in medium HDL (mmol/l)	-3.00E-03 (-3.21E-03,-2.79E-03)	8.50E-03 (7.79E-03,9.22E-03)	1.13E-03 (8.83E-04,1.37E-03)	1.19E-02 (1.11E-02,1.26E-02)
Cholesterol esters in medium HDL (mmol/l)	-2.29E-03 (-2.47E-03,-2.12E-03)	6.55E-03 (5.99E-03,7.12E-03)	1.05E-03 (8.50E-04,1.25E-03)	8.87E-03 (8.26E-03,9.48E-03)
Free cholesterol in medium HDL (mmol/l)	-7.09E-04 (-7.47E-04,-6.71E-04)	1.95E-03 (1.80E-03,2.11E-03)	7.82E-05 (3.33E-05,1.23E-04)	2.98E-03 (2.82E-03,3.15E-03)
Triglycerides in medium HDL (mmol/l)	-5.78E-04 (-6.28E-04,-5.28E-04)	1.59E-03 (1.52E-03,1.66E-03)	-3.63E-04 (-4.16E-04,-3.11E-04)	1.56E-03 (1.50E-03,1.63E-03)
Concentration of small HDL particles (mol/l)	-3.34E-08 (-3.53E-08,-3.15E-08)	1.05E-07 (1.01E-07,1.08E-07)	-1.66E-08 (-1.87E-08,-1.44E-08)	1.14E-07 (1.10E-07,1.18E-07)
Total lipids in small HDL (mmol/l)	-8.08E-03 (-8.61E-03,-7.56E-03)	1.28E-02 (1.19E-02,1.37E-02)	3.58E-04 (-2.85E-04,1.00E-03)	1.05E-02 (9.48E-03,1.15E-02)
Phospholipids in small HDL (mmol/l)	-2.08E-03 (-2.39E-03,-1.77E-03)	2.58E-04 (-1.29E-04,6.45E-04)	5.88E-06 (-3.48E-04,3.60E-04)	1.49E-03 (1.04E-03,1.94E-03)
Total cholesterol in small HDL (mmol/l)	-5.40E-03 (-5.70E-03,-5.09E-03)	1.17E-02 (1.11E-02,1.22E-02)	6.93E-04 (3.54E-04,1.03E-03)	9.33E-03 (8.73E-03,9.92E-03)
Cholesterol esters in small HDL (mmol/l)	-4.66E-03 (-4.93E-03,-4.39E-03)	1.27E-02 (1.22E-02,1.32E-02)	5.09E-04 (2.21E-04,7.97E-04)	1.05E-02 (9.96E-03,1.10E-02)
Free cholesterol in small HDL (mmol/l)	-7.00E-04 (-7.50E-04,-6.50E-04)	-1.53E-03 (-1.65E-03,-1.42E-03)	9.54E-05 (3.21E-05,1.59E-04)	-1.99E-03 (-2.12E-03,-1.85E-03)
Triglycerides in small HDL (mmol/l)	-4.05E-04 (-4.60E-04,-3.50E-04)	4.38E-04 (3.76E-04,5.00E-04)	-2.64E-04 (-3.22E-04,-2.07E-04)	1.89E-05 (-3.56E-05,7.33E-05)
Mean diameter for VLDL particles (mm)	-1.92E-02 (-2.79E-02,-1.06E-02)	4.87E-02 (4.05E-02,5.69E-02)	-7.13E-02 (-7.90E-02,-6.37E-02)	-1.88E-03 (-8.08E-03,4.32E-03)
Mean diameter for LDL particles (mm)	1.53E-02 (1.45E-02,1.61E-02)	-2.01E-02 (-2.12E-02,-1.90E-02)	9.00E-03 (8.26E-03,9.74E-03)	-1.06E-02 (-1.16E-02,-9.52E-03)
Mean diameter for HDL particles (mm)	-1.01E-02 (-1.10E-02,-9.31E-03)	-2.21E-02 (-2.32E-02,-2.09E-02)	5.30E-04 (-3.42E-04,1.40E-03)	-6.83E-03 (-7.95E-03,-5.71E-03)
Serum total cholesterol (mmol/l)	-5.89E-02 (-6.12E-02,-5.65E-02)	2.88E-02 (2.31E-02,3.45E-02)	-2.90E-02 (-3.18E-02,-2.63E-02)	-6.59E-03 (-1.22E-02,-9.76E-04)
Total cholesterol in VLDL (mmol/l)	-5.24E-03 (-5.95E-03,-4.54E-03)	-1.16E-02 (-1.31E-02,-1.01E-02)	-9.10E-03 (-9.81E-03,-8.40E-03)	-2.17E-02 (-2.28E-02,-2.05E-02)
Remnant cholesterol (non-HDL, non-LDL -cholesterol) (mmol/l)	-1.34E-02 (-1.44E-02,-1.24E-02)	-1.02E-02 (-1.26E-02,-7.89E-03)	-1.49E-02 (-1.60E-02,-1.38E-02)	-2.69E-02 (-2.89E-02,-2.49E-02)
Total cholesterol in LDL (mmol/l)	-2.55E-02 (-2.68E-02,-2.42E-02)	4.96E-02 (4.64E-02,5.27E-02)	-1.49E-02 (-1.64E-02,-1.34E-02)	1.81E-02 (1.52E-02,2.10E-02)
Total cholesterol in HDL (mmol/l)	-2.00E-02 (-2.08E-02,-1.92E-02)	-1.09E-02 (-1.29E-02,-8.83E-03)	6.93E-04 (-2.76E-04,1.66E-03)	2.20E-03 (-2.14E-05,4.43E-03)
Total cholesterol in HDL2 (mmol/l)	-1.15E-02 (-1.21E-02,-1.10E-02)	-4.88E-04 (-2.31E-03,1.33E-03)	1.68E-03 (1.05E-03,2.32E-03)	2.17E-02 (1.97E-02,2.36E-02)
Total cholesterol in HDL3 (mmol/l)	-8.59E-03 (-8.89E-03,-8.30E-03)	-9.92E-03 (-1.04E-02,-9.48E-03)	-1.31E-03 (-1.67E-03,-9.47E-04)	-1.81E-02 (-1.87E-02,-1.76E-02)
Esterified cholesterol (mmol/l)	-5.48E-02 (-5.71E-02,-5.25E-02)	9.56E-03 (6.42E-03,1.27E-02)	-2.90E-02 (-3.15E-02,-2.64E-02)	-3.32E-03 (-6.29E-03,-3.42E-04)
Free cholesterol (mmol/l)	-1.63E-02 (-1.70E-02,-1.56E-02)	6.63E-03 (4.94E-03,8.31E-03)	-7.04E-03 (-7.89E-03,-6.20E-03)	-3.39E-03 (-5.08E-03,-1.70E-03)
Serum total triglycerides (mmol/l)	-1.84E-02 (-2.08E-02,-1.60E-02)	1.11E-02 (8.35E-03,1.38E-02)	-2.20E-02 (-2.43E-02,-1.98E-02)	-5.99E-03 (-7.88E-03,-4.10E-03)
Triglycerides in VLDL (mmol/l)	-1.06E-02 (-1.27E-02,-8.54E-03)	1.03E-02 (7.92E-03,1.27E-02)	-1.91E-02 (-2.10E-02,-1.72E-02)	-5.93E-03 (-7.48E-03,-4.37E-03)
Triglycerides in LDL (mmol/l)	-3.48E-03 (-3.69E-03,-3.28E-03)	1.29E-03 (9.87E-04,1.60E-03)	-8.64E-04 (-1.11E-03,-6.19E-04)	-9.47E-04 (-1.29E-03,-6.02E-04)
Triglycerides in HDL (mmol/l)	-1.77E-03 (-1.90E-03,-1.64E-03)	1.24E-03 (1.08E-03,1.40E-03)	-1.12E-03 (-1.26E-03,-9.79E-04)	1.68E-03 (1.51E-03,1.84E-03)
Diacylglycerol (mmol/l)*	-3.33E-04 (-4.11E-04,-2.56E-04)	2.32E-04 (6.66E-06,4.56E-04)	-4.10E-04 (-4.93E-04,-3.27E-04)	4.18E-04 (1.70E-04,6.66E-04)
Total phosphoglycerides (mmol/l)	-4.28E-02 (-4.43E-02,-4.13E-02)	-3.76E-03 (-5.47E-03,-2.05E-03)	-2.07E-02 (-2.25E-02,-1.88E-02)	-2.05E-03 (-3.99E-03,-1.04E-04)
Phosphatidylcholine and other cholines (mmol/l)	-2.65E-02 (-2.77E-02,-2.53E-02)	-1.17E-02 (-1.43E-02,-9.09E-03)	-5.41E-03 (-6.88E-03,-3.93E-03)	-2.51E-02 (-2.78E-02,-2.23E-02)
Total cholines (mmol/l)	-4.19E-02 (-4.36E-02,-4.02E-02)	-5.52E-03 (-7.60E-03,-3.45E-03)	-1.83E-02 (-2.02E-02,-1.63E-02)	-3.20E-03 (-5.43E-03,-9.79E-04)
Apolipoprotein A-I (g/l)	-1.33E-02 (-1.38E-02,-1.29E-02)	4.18E-03 (2.91E-03,5.44E-03)	-2.12E-03 (-2.65E-03,-1.58E-03)	8.27E-03 (6.85E-03,9.68E-03)
Apolipoprotein B (g/l)	-1.01E-02 (-1.08E-02,-9.34E-03)	7.02E-03 (6.09E-03,7.96E-03)	-9.85E-03 (-1.06E-02,-9.12E-03)	-5.59E-04 (-1.31E-03,1.94E-04)
Total fatty acids (mmol/l)	-2.09E-01 (-2.19E-01,-2.00E-01)	-1.36E-02 (-2.53E-02,-1.99E-03)	-1.35E-01 (-1.46E-01,-1.25E-01)	-6.94E-02 (-8.00E-02,-5.88E-02)
Fatty acid length*	3.08E-02 (2.72E-02,3.43E-02)	-2.97E-02 (-4.08E-02,-1.86E-02)	2.07E-02 (1.74E-02,2.41E-02)	-1.80E-03 (-1.19E-02,8.33E-03)
Estimated degree of unsaturation*	4.04E-03 (3.45E-03,4.62E-03)	-5.02E-03 (-6.99E-03,-3.06E-03)	5.45E-03 (4.87E-03,6.02E-03)	-4.94E-03 (-6.66E-03,-3.22E-03)
22:6, docosahexaenoic acid (mmol/l)	-3.04E-03 (-3.21E-03,-2.87E-03)	1.87E-03 (1.67E-03,2.06E-03)	-1.23E-03 (-1.43E-03,-1.02E-03)	1.82E-03 (1.61E-03,2.03E-03)
18:2, linoleic acid (mmol/l)	-6.69E-02 (-6.93E-02,-6.44E-02)	-7.25E-04 (-3.92E-03,2.47E-03)	-4.15E-02 (-4.41E-02,-3.89E-02)	-2.07E-02 (-2.35E-02,-1.79E-02)
Conjugated linoleic acid (mmol/l)*	-8.57E-04 (-1.02E-03,-6.90E-04)	-2.96E-04 (-7.78E-04,1.85E-04)	-1.03E-03 (-1.20E-03,-8.63E-04)	-5.71E-05 (-5.17E-04,4.03E-04)
Omega-3 fatty acids (mmol/l)	-7.65E-03 (-8.11E-03,-7.20E-03)	2.77E-03 (2.26E-03,3.27E-03)	-4.66E-03 (-5.14E-03,-4.18E-03)	-3.36E-04 (-8.13E-04,1.41E-04)
Omega-6 fatty acids (mmol/l)	-7.41E-02 (-7.68E-02,-7.14E-02)	-4.53E-03 (-8.04E-03,-1.03E-03)	-4.32E-02 (-4.61E-02,-4.02E-02)	-2.21E-02 (-2.53E-02,-1.88E-02)
Polyunsaturated fatty acids (mmol/l)	-8.18E-02 (-8.47E-02,-7.88E-02)	-1.77E-03 (-5.63E-03,2.09E-03)	-4.79E-02 (-5.11E-02,-4.47E-02)	-2.24E-02 (-2.60E-02,-1.88E-02)
Monounsaturated fatty acids; 16:1, 18:1 (mmol/l)	-1.73E-02 (-2.00E-02,-1.45E-02)	-4.25E-03 (-9.70E-03,1.19E-03)	-6.00E-03 (-8.91E-03,-3.09E-03)	-3.24E-02 (-3.73E-02,-2.76E-02)
Saturated fatty acids (mmol/l)	-1.04E-01 (-1.08E-01,-1.00E-01)	-9.71E-03 (-1.43E-02,-5.09E-03)	-7.91E-02 (-8.35E-02,-7.47E-02)	-2.70E-02 (-3.12E-02,-2.28E-02)

S5 Table: Mean rate of change in concentration per year in males and females

	Males		Females	
	Mean change in concentration per year from 7 to 15y/ 18y(95%CI)	**Mean change in concentration per year from 15y/18y to 25y (95%CI)**	**Mean change in concentration per year from 7 to 15y/ 18y(95%CI)**	**Mean change in concentration per year from 15y/18y to 25y (95%CI)**
Glucose (mmol/l)	2.00E-02 (1.66E-02,2.34E-02)	-3.64E-02 (-3.97E-02,-3.31E-02)	1.16E-02 (8.45E-03,1.48E-02)	-4.17E-02 (-4.40E-02,-3.94E-02)
Lactate (mmol/l)	-2.29E-02 (-2.68E-02,-1.91E-02)	-2.47E-02 (-2.84E-02,-2.10E-02)	-2.65E-02 (-3.06E-02,-2.24E-02)	-2.90E-02 (-3.25E-02,-2.54E-02)
Citrate (mmol/l)	-2.49E-03 (-2.62E-03,-2.36E-03)	9.25E-03 (9.01E-03,9.48E-03)	-3.34E-03 (-3.46E-03,-3.22E-03)	9.99E-03 (9.78E-03,1.02E-02)
Alanine (mmol/l)	-4.59E-03 (-4.91E-03,-4.27E-03)	1.73E-02 (1.68E-02,1.78E-02)	-5.20E-03 (-5.52E-03,-4.88E-03)	1.62E-02 (1.57E-02,1.66E-02)
Glutamine (mmol/l)	3.92E-03 (3.63E-03,4.21E-03)	-1.64E-02 (-1.71E-02,-1.58E-02)	-3.80E-03 (-4.12E-03,-3.48E-03)	-1.71E-02 (-1.77E-02,-1.65E-02)
Histidine (mmol/l)	-1.34E-04 (-2.01E-04,-6.67E-05)	-3.26E-03 (-3.36E-03,-3.15E-03)	-7.73E-04 (-8.44E-04,-7.02E-04)	-3.01E-03 (-3.11E-03,-2.92E-03)
Isoleucine (mmol/l)	-1.16E-04 (-2.02E-04,-2.98E-05)	7.14E-04 (5.88E-04,8.39E-04)	-1.13E-03 (-1.21E-03,-1.05E-03)	6.18E-04 (5.32E-04,7.04E-04)
Leucine (mmol/l)	1.97E-04 (1.27E-04,2.68E-04)	1.20E-03 (1.08E-03,1.32E-03)	-8.51E-04 (-9.18E-04,-7.83E-04)	1.12E-03 (1.04E-03,1.21E-03)
Valine (mmol/l)	1.99E-03 (1.76E-03,2.22E-03)	-6.33E-05 (-2.67E-04,1.41E-04)	-6.33E-04 (-8.48E-04,-4.17E-04)	-7.36E-04 (-9.00E-04,-5.72E-04)
Phenylalanine (mmol/l)	-5.33E-04 (-5.73E-04,-4.94E-04)	1.99E-03 (1.93E-03,2.06E-03)	-7.01E-04 (-7.40E-04,-6.62E-04)	2.02E-03 (1.97E-03,2.07E-03)
Tyrosine (mmol/l)	-1.07E-03 (-1.16E-03,-9.73E-04)	-1.35E-03 (-1.42E-03,-1.29E-03)	-1.52E-03 (-1.62E-03,-1.43E-03)	-1.57E-03 (-1.63E-03,-1.50E-03)
Acetate (mmol/l)	-2.12E-03 (-2.28E-03,-1.97E-03)	1.17E-03 (8.98E-04,1.44E-03)	-2.47E-03 (-2.62E-03,-2.33E-03)	7.48E-04 (6.27E-04,8.69E-04)
Acetoacetate (mmol/l)	-1.11E-03 (-1.23E-03,-9.95E-04)		-2.22E-03 (-2.46E-03,-1.99E-03)	
3-hydroxybutyrate (mmol/l)	1.17E-03 (6.35E-04,1.71E-03)	6.75E-03 (5.89E-03,7.61E-03)	2.90E-03 (2.24E-03,3.57E-03)	4.26E-03 (3.26E-03,5.26E-03)
Creatinine (mmol/l)	3.34E-03 (3.30E-03,3.38E-03)	-1.27E-03 (-1.34E-03,-1.19E-03)	2.26E-03 (2.23E-03,2.30E-03)	-1.35E-03 (-1.40E-03,-1.29E-03)
Albumin (mmol/l)	1.01E-04 (8.04E-05,1.21E-04)	5.28E-04 (4.80E-04,5.76E-04)	-1.92E-04 (-2.14E-04,-1.71E-04)	4.04E-04 (3.61E-04,4.48E-04)
Glycoprotein acetyls, mainly a1-acid glycoprotein (mmol/l)	-3.32E-03 (-4.01E-03,-2.63E-03)	7.13E-03 (5.68E-03,8.58E-03)	-5.11E-04 (-1.22E-03,2.00E-04)	-4.73E-04 (-1.68E-03,7.35E-04)

*These metabolites (diacylglycerol, fatty acid chain length, estimated degree of saturation and conjugated linoleic acid) were not measured at 25y; all models include data only up to aged 18y. HDL: high-density lipoprotein; IDL: intermediate-density lipoprotein; LDL: low-density lipoprotein; VLDL: very-low-density lipoprotein.

S6 Table: Mean absolute difference in traits in SD units between 7y and 25y in males and females comparing i)findings from multilevel models implemented here to ii)linear regression of traits at 7y and 25y

	7y		25y	
	Mean absolute sex difference in SD units (95% CI)		Mean absolute sex difference in SD units (95% CI)	
	MLM	Regression	MLM	Regression
Concentration of chylomicrons and extremely large VLDL particles (mol/l)	0.16(0.11,0.21)	0.14(0.09,0.2)	-0.39(-0.45,-0.32)	-0.39(-0.46,-0.31)
Total lipids in chylomicrons and extremely large VLDL (mmol/l)	0.15(0.09,0.2)	0.13(0.08,0.19)	-0.39(-0.46,-0.32)	-0.38(-0.46,-0.31)
Phospholipids in chylomicrons and extremely large VLDL (mmol/l)	0.15(0.09,0.2)	0.13(0.08,0.19)	-0.36(-0.43,-0.29)	-0.35(-0.43,-0.28)
Total cholesterol in chylomicrons and extremely large VLDL (mmol/l)	0.16(0.11,0.22)	0.14(0.09,0.2)	-0.3(-0.37,-0.23)	-0.31(-0.39,-0.24)
Cholesterol esters in chylomicrons and extremely large VLDL (mmol/l)	0.16(0.11,0.22)	0.15(0.1,0.2)	-0.26(-0.33,-0.19)	-0.28(-0.35,-0.2)
Free cholesterol in chylomicrons and extremely large VLDL (mmol/l)	0.15(0.09,0.2)	0.13(0.08,0.19)	-0.35(-0.42,-0.28)	-0.35(-0.42,-0.27)
Triglycerides in chylomicrons and extremely large VLDL (mmol/l)	0.15(0.09,0.2)	0.13(0.08,0.18)	-0.41(-0.48,-0.34)	-0.4(-0.48,-0.33)
Concentration of very large VLDL particles (mol/l)	0.14(0.08,0.19)	0.12(0.07,0.17)	-0.4(-0.47,-0.33)	-0.4(-0.47,-0.32)
Total lipids in very large VLDL (mmol/l)	0.14(0.08,0.19)	0.12(0.07,0.17)	-0.4(-0.46,-0.33)	-0.39(-0.47,-0.32)
Phospholipids in very large VLDL (mmol/l)	0.14(0.09,0.2)	0.13(0.08,0.18)	-0.35(-0.42,-0.28)	-0.36(-0.43,-0.28)
Total cholesterol in very large VLDL (mmol/l)	0.17(0.11,0.22)	0.15(0.1,0.2)	-0.38(-0.45,-0.31)	-0.37(-0.45,-0.29)
Cholesterol esters in very large VLDL (mmol/l)	0.18(0.12,0.23)	0.15(0.1,0.2)	-0.38(-0.44,-0.31)	-0.39(-0.46,-0.31)
Free cholesterol in very large VLDL (mmol/l)	0.16(0.11,0.21)	0.15(0.09,0.2)	-0.35(-0.42,-0.28)	-0.35(-0.43,-0.27)
Triglycerides in very large VLDL (mmol/l)	0.12(0.07,0.18)	0.11(0.06,0.16)	-0.41(-0.48,-0.34)	-0.41(-0.48,-0.33)
Concentration of large VLDL particles (mol/l)	0.14(0.08,0.19)	0.12(0.07,0.17)	-0.43(-0.5,-0.37)	-0.45(-0.52,-0.37)
Total lipids in large VLDL (mmol/l)	0.14(0.09,0.2)	0.12(0.07,0.18)	-0.43(-0.5,-0.37)	-0.44(-0.52,-0.37)
Phospholipids in large VLDL (mmol/l)	0.15(0.09,0.2)	0.13(0.08,0.18)	-0.4(-0.47,-0.34)	-0.41(-0.49,-0.34)
Total cholesterol in large VLDL (mmol/l)	0.16(0.11,0.22)	0.15(0.1,0.2)	-0.4(-0.47,-0.34)	-0.41(-0.49,-0.34)
Cholesterol esters in large VLDL (mmol/l)	0.18(0.13,0.24)	0.17(0.12,0.22)	-0.42(-0.49,-0.36)	-0.44(-0.51,-0.36)
Free cholesterol in large VLDL (mmol/l)	0.15(0.09,0.2)	0.13(0.08,0.18)	-0.38(-0.45,-0.31)	-0.39(-0.46,-0.31)
Triglycerides in large VLDL (mmol/l)	0.13(0.08,0.18)	0.11(0.06,0.16)	-0.45(-0.52,-0.38)	-0.46(-0.53,-0.38)
Concentration of medium VLDL particles (mol/l)	0.18(0.13,0.23)	0.16(0.11,0.21)	-0.49(-0.56,-0.43)	-0.52(-0.59,-0.44)
Total lipids in medium VLDL (mmol/l)	0.19(0.14,0.24)	0.17(0.12,0.22)	-0.49(-0.55,-0.42)	-0.51(-0.58,-0.43)
Phospholipids in medium VLDL (mmol/l)	0.2(0.15,0.26)	0.19(0.13,0.24)	-0.46(-0.52,-0.39)	-0.49(-0.56,-0.41)
Total cholesterol in medium VLDL (mmol/l)	0.23(0.18,0.29)	0.22(0.17,0.28)	-0.36(-0.43,-0.3)	-0.39(-0.46,-0.31)
Cholesterol esters in medium VLDL (mmol/l)	0.25(0.2,0.31)	0.25(0.19,0.3)	-0.28(-0.35,-0.22)	-0.31(-0.39,-0.24)
Free cholesterol in medium VLDL (mmol/l)	0.2(0.14,0.25)	0.18(0.13,0.23)	-0.43(-0.5,-0.37)	-0.46(-0.53,-0.38)
Triglycerides in medium VLDL (mmol/l)	0.16(0.11,0.21)	0.14(0.09,0.19)	-0.55(-0.61,-0.48)	-0.56(-0.63,-0.49)
Concentration of small VLDL particles (mol/l)	0.25(0.2,0.31)	0.24(0.19,0.29)	-0.42(-0.48,-0.35)	-0.45(-0.52,-0.38)
Total lipids in small VLDL (mmol/l)	0.29(0.24,0.35)	0.28(0.23,0.33)	-0.41(-0.47,-0.35)	-0.43(-0.5,-0.36)

S6 Table: Mean absolute difference in traits in SD units between 7y and 25y in males and females comparing i)findings from multilevel models implemented here to ii)linear regression of traits at 7y and 25y

	7y		25y	
	Mean absolute sex difference in SD units (95% CI)		Mean absolute sex difference in SD units (95% CI)	
	MLM	Regression	MLM	Regression
Phospholipids in small VLDL (mmol/l)	0.27(0.22,0.32)	0.26(0.21,0.31)	-0.31(-0.37,-0.25)	-0.34(-0.41,-0.27)
Total cholesterol in small VLDL (mmol/l)	0.37(0.32,0.42)	0.36(0.3,0.41)	-0.3(-0.36,-0.23)	-0.31(-0.38,-0.24)
Cholesterol esters in small VLDL (mmol/l)	0.39(0.34,0.44)	0.37(0.32,0.42)	-0.27(-0.33,-0.21)	-0.28(-0.35,-0.21)
Free cholesterol in small VLDL (mmol/l)	0.3(0.24,0.35)	0.29(0.24,0.34)	-0.32(-0.38,-0.25)	-0.34(-0.41,-0.27)
Triglycerides in small VLDL (mmol/l)	0.21(0.15,0.26)	0.19(0.14,0.24)	-0.49(-0.56,-0.43)	-0.53(-0.6,-0.46)
Concentration of very small VLDL particles (mol/l)	0.39(0.34,0.44)	0.39(0.34,0.44)	0.08(0.01,0.14)	0.03(-0.04,0.1)
Total lipids in very small VLDL (mmol/l)	0.39(0.34,0.44)	0.39(0.34,0.44)	0.03(-0.03,0.09)	0.04(-0.03,0.11)
Phospholipids in very small VLDL (mmol/l)	0.36(0.31,0.41)	0.37(0.32,0.42)	0.2(0.14,0.26)	0.15(0.08,0.22)
Total cholesterol in very small VLDL (mmol/l)	0.32(0.27,0.37)	0.31(0.25,0.36)	0.02(-0.05,0.08)	0.04(-0.03,0.12)
Cholesterol esters in very small VLDL (mmol/l)	0.35(0.3,0.4)	0.32(0.27,0.37)	0.02(-0.04,0.09)	0.06(-0.01,0.13)
Free cholesterol in very small VLDL (mmol/l)	0.23(0.18,0.28)	0.24(0.19,0.29)	0.01(-0.06,0.07)	0.01(-0.06,0.08)
Triglycerides in very small VLDL (mmol/l)	0.28(0.22,0.33)	0.29(0.24,0.34)	-0.11(-0.18,-0.05)	-0.14(-0.22,-0.07)
Concentration of IDL particles (mol/l)	0.3(0.25,0.36)	0.32(0.27,0.37)	0.23(0.17,0.29)	0.21(0.14,0.28)
Total lipids in IDL (mmol/l)	0.32(0.27,0.37)	0.33(0.28,0.39)	0.22(0.16,0.28)	0.2(0.13,0.27)
Phospholipids in IDL (mmol/l)	0.27(0.22,0.32)	0.29(0.24,0.34)	0.26(0.2,0.32)	0.24(0.17,0.31)
Total cholesterol in IDL (mmol/l)	0.32(0.27,0.37)	0.32(0.27,0.38)	0.17(0.11,0.23)	0.15(0.08,0.23)
Cholesterol esters in IDL (mmol/l)	0.33(0.28,0.38)	0.33(0.28,0.38)	0.12(0.06,0.18)	0.11(0.04,0.18)
Free cholesterol in IDL (mmol/l)	0.26(0.21,0.31)	0.28(0.23,0.33)	0.28(0.22,0.34)	0.26(0.19,0.33)
Triglycerides in IDL (mmol/l)	0.25(0.2,0.3)	0.29(0.24,0.35)	0.43(0.37,0.49)	0.4(0.34,0.47)
Concentration of large LDL particles (mol/l)	0.26(0.21,0.31)	0.28(0.23,0.33)	0.17(0.1,0.23)	0.13(0.06,0.2)
Total lipids in large LDL (mmol/l)	0.28(0.23,0.34)	0.31(0.25,0.36)	0.15(0.09,0.21)	0.12(0.04,0.19)
Phospholipids in large LDL (mmol/l)	0.29(0.24,0.34)	0.31(0.26,0.36)	0.16(0.1,0.23)	0.13(0.06,0.2)
Total cholesterol in large LDL (mmol/l)	0.28(0.23,0.34)	0.3(0.25,0.35)	0.1(0.04,0.16)	0.06(-0.01,0.13)
Cholesterol esters in large LDL (mmol/l)	0.29(0.24,0.34)	0.31(0.26,0.36)	0.06(0.01,0.12)	0.02(-0.05,0.09)
Free cholesterol in large LDL (mmol/l)	0.26(0.21,0.31)	0.28(0.23,0.33)	0.21(0.15,0.27)	0.17(0.1,0.24)
Triglycerides in large LDL (mmol/l)	0.18(0.12,0.23)	0.23(0.18,0.28)	0.63(0.57,0.69)	0.6(0.54,0.67)
Concentration of medium LDL particles (mol/l)	0.24(0.19,0.3)	0.27(0.22,0.32)	0.07(0.01,0.13)	0.03(-0.04,0.1)
Total lipids in medium LDL (mmol/l)	0.27(0.22,0.33)	0.3(0.24,0.35)	0.06(-0.01,0.12)	0.01(-0.06,0.08)
Phospholipids in medium LDL (mmol/l)	0.3(0.25,0.36)	0.32(0.27,0.37)	0.12(0.06,0.18)	0.04(-0.03,0.11)
Total cholesterol in medium LDL (mmol/l)	0.27(0.22,0.32)	0.29(0.24,0.34)	-0.05(-0.07,0.06)	-0.05(-0.12,0.02)
Cholesterol esters in medium LDL (mmol/l)	0.27(0.22,0.32)	0.29(0.23,0.34)	-0.02(-0.08,0.05)	-0.06(-0.14,0.01)

S6 Table: Mean absolute difference in traits in SD units between 7y and 25y in males and females comparing i)findings from multilevel models implemented here to ii)linear regression of traits at 7y and 25y

	7y		25y	
	Mean absolute sex difference in SD units (95% CI)		Mean absolute sex difference in SD units (95% CI)	
	MLM	Regression	MLM	Regression
Free cholesterol in medium LDL (mmol/l)	0.27(0.22,0.32)	0.29(0.24,0.34)	0.04(-0.02,0.1)	0.01(-0.06,0.08)
Triglycerides in medium LDL (mmol/l)	0.11(0.06,0.17)	0.17(0.12,0.22)	0.7(0.64,0.75)	0.65(0.59,0.72)
Concentration of small LDL particles (mol/l)	0.22(0.17,0.27)	0.24(0.19,0.29)	0.06(0.002,0.12)	0.02(-0.05,0.09)
Total lipids in small LDL (mmol/l)	0.26(0.2,0.31)	0.28(0.22,0.33)	0.05(-0.01,0.11)	0.01(-0.06,0.08)
Phospholipids in small LDL (mmol/l)	0.25(0.19,0.3)	0.26(0.21,0.32)	0.15(0.09,0.21)	0.08(0.01,0.15)
Total cholesterol in small LDL (mmol/l)	0.26(0.2,0.31)	0.27(0.22,0.33)	-0.04 (-0.06,0.06)	-0.04(-0.11,0.03)
Cholesterol esters in small LDL (mmol/l)	0.25(0.2,0.3)	0.27(0.22,0.32)	-0.05 (-0.06,0.06)	-0.05(-0.12,0.02)
Free cholesterol in small LDL (mmol/l)	0.23(0.18,0.28)	0.25(0.19,0.3)	0.01(-0.05,0.07)	0.01(-0.07,0.07)
Triglycerides in small LDL (mmol/l)	0.17(0.12,0.22)	0.19(0.14,0.24)	0.42(0.35,0.48)	0.33(0.26,0.4)
Concentration of very large HDL particles (mol/l)	-0.1(-0.15,-0.05)	-0.05(-0.1,0.0008)	0.82(0.77,0.87)	0.85(0.79,0.91)
Total lipids in very large HDL (mmol/l)	-0.11(-0.17,-0.06)	-0.07(-0.12,-0.02)	0.8(0.75,0.85)	0.85(0.79,0.91)
Phospholipids in very large HDL (mmol/l)	-0.11(-0.16,-0.06)	-0.06(-0.11,-0.005)	0.87(0.81,0.92)	0.88(0.81,0.94)
Total cholesterol in very large HDL (mmol/l)	-0.13(-0.18,-0.07)	-0.09(-0.14,-0.04)	0.72(0.67,0.78)	0.79(0.73,0.85)
Cholesterol esters in very large HDL (mmol/l)	-0.13(-0.18,-0.08)	-0.1(-0.15,-0.05)	0.68(0.62,0.74)	0.76(0.7,0.82)
Free cholesterol in very large HDL (mmol/l)	-0.11(-0.16,-0.05)	-0.07(-0.12,-0.01)	0.8(0.75,0.85)	0.86(0.8,0.92)
Triglycerides in very large HDL (mmol/l)	0.11(0.05,0.16)	0.13(0.08,0.18)	0.42(0.36,0.48)	0.44(0.37,0.51)
Concentration of large HDL particles (mol/l)	-0.19(-0.24,-0.14)	-0.12(-0.17,-0.07)	0.86(0.8,0.91)	0.89(0.82,0.95)
Total lipids in large HDL (mmol/l)	-0.18(-0.24,-0.13)	-0.12(-0.17,-0.06)	0.85(0.8,0.91)	0.88(0.82,0.94)
Phospholipids in large HDL (mmol/l)	-0.17(-0.23,-0.12)	-0.1(-0.16,-0.05)	0.86(0.81,0.92)	0.89(0.83,0.95)
Total cholesterol in large HDL (mmol/l)	-0.2(-0.25,-0.14)	-0.13(-0.19,-0.08)	0.83(0.78,0.89)	0.87(0.81,0.93)
Cholesterol esters in large HDL (mmol/l)	-0.2(-0.25,-0.15)	-0.14(-0.19,-0.09)	0.83(0.78,0.89)	0.87(0.8,0.93)
Free cholesterol in large HDL (mmol/l)	-0.17(-0.22,-0.12)	-0.11(-0.17,-0.06)	0.83(0.78,0.89)	0.87(0.81,0.93)
Triglycerides in large HDL (mmol/l)	0.07(0.02,0.13)	0.12(0.07,0.17)	0.76(0.71,0.81)	0.8(0.74,0.86)
Concentration of medium HDL particles (mol/l)	-0.18(-0.23,-0.12)	-0.1(-0.15,-0.05)	0.62(0.56,0.68)	0.61(0.55,0.68)
Total lipids in medium HDL (mmol/l)	-0.17(-0.23,-0.12)	-0.11(-0.16,-0.06)	0.64(0.59,0.7)	0.61(0.54,0.67)
Phospholipids in medium HDL (mmol/l)	-0.17(-0.23,-0.12)	-0.11(-0.16,-0.05)	0.7(0.64,0.75)	0.66(0.6,0.73)
Total cholesterol in medium HDL (mmol/l)	-0.2(-0.26,-0.15)	-0.14(-0.19,-0.09)	0.54(0.48,0.6)	0.54(0.48,0.61)
Cholesterol esters in medium HDL (mmol/l)	-0.22(-0.27,-0.16)	-0.16(-0.21,-0.11)	0.52(0.46,0.58)	0.53(0.46,0.59)
Free cholesterol in medium HDL (mmol/l)	-0.12(-0.18,-0.07)	-0.06(-0.11,-0.004)	0.6(0.54,0.66)	0.61(0.54,0.67)
Triglycerides in medium HDL (mmol/l)	0.16(0.11,0.21)	0.17(0.12,0.23)	0.24(0.18,0.31)	0.19(0.12,0.26)
Concentration of small HDL particles (mol/l)	-0.11(-0.17,-0.06)	-0.08(-0.13,-0.03)	0.26(0.2,0.32)	0.16(0.1,0.23)

S6 Table: Mean absolute difference in traits in SD units between 7y and 25y in males and females comparing i)findings from multilevel models implemented here to ii)linear regression of traits at 7y and 25y

	7y		25y	
	Mean absolute sex difference in SD units (95% CI)		Mean absolute sex difference in SD units (95% CI)	
	MLM	Regression	MLM	Regression
Total lipids in small HDL (mmol/l)	-0.14(-0.19,-0.08)	-0.08(-0.13,-0.02)	0.25(0.19,0.31)	0.17(0.1,0.23)
Phospholipids in small HDL (mmol/l)	-0.17(-0.22,-0.11)	-0.15(-0.2,-0.09)	0.27(0.21,0.33)	0.27(0.2,0.33)
Total cholesterol in small HDL (mmol/l)	-0.07(-0.13,-0.02)	-0.01(-0.06,0.05)	0.24(0.18,0.3)	0.09(0.02,0.16)
Cholesterol esters in small HDL (mmol/l)	-0.02(-0.08,0.04)	0.04(-0.01,0.09)	0.23(0.17,0.29)	0.06(-0.01,0.13)
Free cholesterol in small HDL (mmol/l)	-0.27(-0.32,-0.21)	-0.2(-0.26,-0.15)	0.22(0.16,0.28)	0.22(0.16,0.29)
Triglycerides in small HDL (mmol/l)	0.16(0.1,0.21)	0.16(0.11,0.21)	-0.14(-0.2,-0.07)	-0.21(-0.28,-0.14)
Mean diameter for VLDL particles (mm)	0.1(0.04,0.15)	0.07(0.02,0.13)	-0.64(-0.71,-0.58)	-0.65(-0.72,-0.58)
Mean diameter for LDL particles (mm)	0.09(0.04,0.15)	0.06(0.01,0.12)	0.25(0.19,0.31)	0.36(0.29,0.42)
Mean diameter for HDL particles (mm)	-0.12(-0.17,-0.06)	-0.07(-0.12,-0.01)	0.84(0.78,0.89)	0.86(0.8,0.92)
Serum total cholesterol (mmol/l)	0.24(0.18,0.29)	0.27(0.21,0.32)	0.32(0.26,0.38)	0.31(0.24,0.37)
Total cholesterol in VLDL (mmol/l)	0.33(0.28,0.38)	0.31(0.26,0.36)	-0.29(-0.35,-0.22)	-0.29(-0.37,-0.22)
Remnant cholesterol (non-HDL, non-LDL -cholesterol) (mmol/l)	0.37(0.32,0.42)	0.36(0.31,0.41)	-0.09(-0.15,-0.03)	-0.1(-0.17,-0.03)
Total cholesterol in LDL (mmol/l)	0.28(0.22,0.33)	0.29(0.24,0.35)	0.05(-0.01,0.11)	0.05(-0.07,0.08)
Total cholesterol in HDL (mmol/l)	-0.19(-0.24,-0.14)	-0.12(-0.17,-0.07)	0.78(0.73,0.84)	0.81(0.75,0.87)
Total cholesterol in HDL2 (mmol/l)	-0.21(-0.27,-0.16)	-0.15(-0.2,-0.1)	0.8(0.75,0.85)	0.83(0.76,0.89)
Total cholesterol in HDL3 (mmol/l)	-0.12(-0.18,-0.07)	-0.06(-0.11,-0.005)	0.61(0.55,0.68)	0.51(0.44,0.57)
Esterified cholesterol (mmol/l)	0.23(0.18,0.28)	0.25(0.2,0.31)	0.33(0.27,0.39)	0.28(0.21,0.35)
Free cholesterol (mmol/l)	0.25(0.19,0.3)	0.28(0.22,0.33)	0.37(0.31,0.43)	0.35(0.29,0.42)
Serum total triglycerides (mmol/l)	0.19(0.14,0.24)	0.18(0.13,0.23)	-0.29(-0.36,-0.22)	-0.32(-0.4,-0.25)
Triglycerides in VLDL (mmol/l)	0.17(0.11,0.22)	0.15(0.1,0.2)	-0.47(-0.54,-0.41)	-0.49(-0.56,-0.42)
Triglycerides in LDL (mmol/l)	0.16(0.1,0.21)	0.2(0.15,0.26)	0.61(0.55,0.67)	0.57(0.51,0.64)
Triglycerides in HDL (mmol/l)	0.17(0.11,0.22)	0.19(0.13,0.24)	0.45(0.38,0.51)	0.42(0.36,0.49)
Diacylglycerol (mmol/l)*	0.09(0.04,0.15)	0.08(0.03,0.13)	0.1(0.03,0.18)	0.11(0.04,0.18)
Total phosphoglycerides (mmol/l)	0.08(0.03,0.14)	0.12(0.07,0.18)	0.65(0.6,0.71)	0.63(0.57,0.7)
Phosphatidylcholine and other cholines (mmol/l)	0.05(-0.01,0.1)	0.1(0.05,0.16)	0.47(0.41,0.53)	0.46(0.4,0.53)
Total cholines (mmol/l)	0.1(0.05,0.15)	0.14(0.09,0.19)	0.61(0.56,0.67)	0.57(0.51,0.63)
Apolipoprotein A-I (g/l)	-0.07(-0.13,-0.02)	-0.01(-0.06,0.04)	0.68(0.62,0.73)	0.69(0.62,0.75)
Apolipoprotein B (g/l)	0.36(0.31,0.41)	0.35(0.3,0.4)	-0.15(-0.21,-0.08)	-0.19(-0.26,-0.12)
Total fatty acids (mmol/l)	0.23(0.18,0.29)	0.25(0.2,0.31)	0.24(0.18,0.3)	0.2(0.13,0.27)
Fatty acid length*	0.01(-0.04,0.07)	-0.01(-0.06,0.04)	0.02(-0.05,0.1)	0.01(-0.06,0.08)
Estimated degree of unsaturation*	-0.07(-0.12,-0.01)	-0.05(-0.1,0.01)	0.12(0.04,0.19)	0.12(0.05,0.19)

S6 Table: Mean absolute difference in traits in SD units between 7y and 25y in males and females comparing i)findings from multilevel models implemented here to ii)linear regression of traits at 7y and 25y

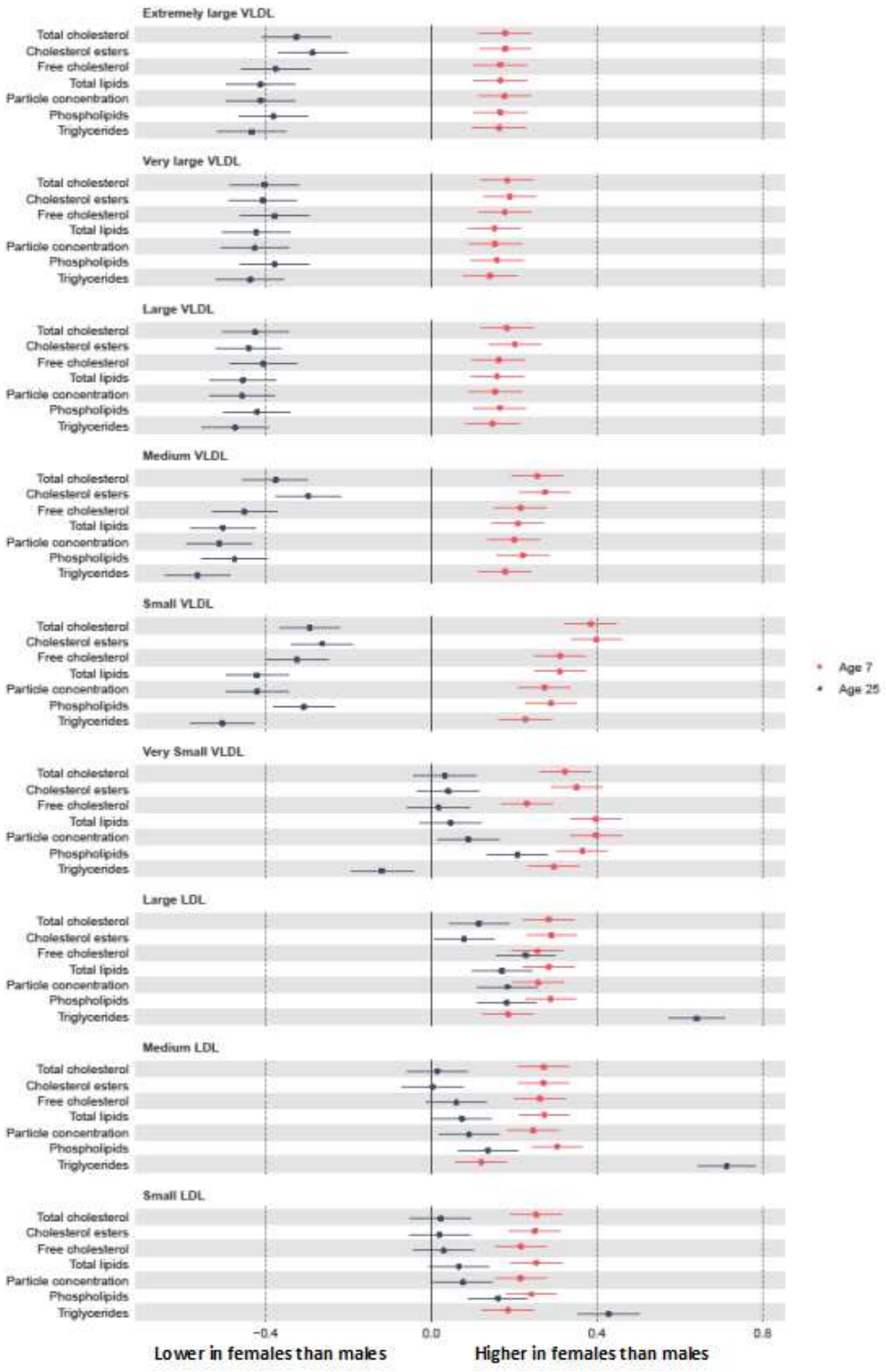
	7y		25y	
	Mean absolute sex difference in SD units (95% CI)		Mean absolute sex difference in SD units (95% CI)	
	MLM	Regression	MLM	Regression
22:6, docosahexaenoic acid (mmol/l)	0.19(0.14,0.24)	0.23(0.18,0.28)	0.59(0.53,0.65)	0.54(0.48,0.61)
18:2, linoleic acid (mmol/l)	0.23(0.18,0.28)	0.26(0.21,0.31)	0.23(0.17,0.29)	0.17(0.1,0.24)
Conjugated linoleic acid (mmol/l)*	0.12(0.06,0.17)	0.12(0.07,0.17)	0.1(0.03,0.18)	0.1(0.03,0.17)
Omega-3 fatty acids (mmol/l)	0.17(0.11,0.22)	0.19(0.14,0.24)	0.09(0.03,0.16)	0.06(-0.01,0.13)
Omega-6 fatty acids (mmol/l)	0.22(0.17,0.27)	0.25(0.2,0.31)	0.32(0.26,0.38)	0.28(0.21,0.35)
Polyunsaturated fatty acids (mmol/l)	0.22(0.17,0.28)	0.26(0.2,0.31)	0.3(0.24,0.37)	0.26(0.19,0.33)
Monounsaturated fatty acids; 16:1, 18:1 (mmol/l)	0.24(0.19,0.29)	0.25(0.2,0.31)	0.14(0.07,0.2)	0.13(0.05,0.2)
Saturated fatty acids (mmol/l)	0.17(0.11,0.22)	0.19(0.14,0.24)	0.22(0.16,0.29)	0.19(0.12,0.26)
Glucose (mmol/l)	-0.15(-0.21,-0.09)	-0.15(-0.21,-0.1)	-0.42(-0.49,-0.35)	-0.41(-0.48,-0.33)
Lactate (mmol/l)	0.12(0.07,0.18)	0.12(0.07,0.17)	-0.02(-0.08,0.05)	0.01(-0.05,0.08)
Citrate (mmol/l)	0.12(0.07,0.18)	0.12(0.07,0.18)	-0.08(-0.14,-0.01)	-0.1(-0.17,-0.03)
Alanine (mmol/l)	0.07(0.01,0.12)	0.03(-0.02,0.09)	-0.16(-0.23,-0.1)	-0.19(-0.26,-0.12)
Glutamine (mmol/l)	0.44(0.39,0.49)	0.35(0.3,0.4)	-0.83(-0.89,-0.77)	-0.8(-0.87,-0.74)
Histidine (mmol/l)	0.17(0.12,0.21)	0.14(0.09,0.18)	-0.4(-0.47,-0.33)	-0.33(-0.4,-0.26)
Isoleucine (mmol/l)	0.1(0.05,0.16)	0.06(0.01,0.11)	-0.83(-0.9,-0.77)	-0.83(-0.9,-0.77)
Leucine (mmol/l)	-0.01(-0.07,0.04)	-0.06(-0.11,-0.004)	-0.92(-0.98,-0.86)	-0.93(-0.99,-0.86)
Valine (mmol/l)	0.06(-0.004,0.12)	0.02(-0.03,0.08)	-0.85(-0.91,-0.79)	-0.83(-0.89,-0.76)
Phenylalanine (mmol/l)	-0.03(-0.09,0.02)	-0.05(-0.1,0.01)	-0.32(-0.38,-0.25)	-0.35(-0.41,-0.28)
Tyrosine (mmol/l)	0.01(-0.05,0.07)	-0.01(-0.06,0.05)	-0.55(-0.62,-0.49)	-0.52(-0.58,-0.45)
Acetate (mmol/l)	0.04(-0.02,0.1)	0.03(-0.02,0.08)	-0.16(-0.22,-0.1)	-0.17(-0.24,-0.1)
Acetoacetate (mmol/l)	0.04(-0.01,0.09)	0.08(0.03,0.13)	-0.2(-0.31,-0.08)	-0.11(-0.18,-0.04)
3-hydroxybutyrate (mmol/l)	0.12(0.07,0.18)	0.14(0.09,0.2)	0.18(0.12,0.25)	0.16(0.1,0.22)
Creatinine (mmol/l)	0.1(0.05,0.15)	-0.02(-0.07,0.03)	-1.25(-1.3,-1.2)	-1.24(-1.3,-1.18)
Albumin (mmol/l)	0.3(0.24,0.35)	0.23(0.18,0.28)	-0.52(-0.58,-0.45)	-0.53(-0.6,-0.46)
Glycoprotein acetyls, mainly a1-acid glycoprotein (mmol/l)	0.23(0.18,0.29)	0.24(0.19,0.29)	0.1(0.04,0.17)	0.08(0.01,0.15)

*These metabolites (diacylglycerol, fatty acid chain length, estimated degree of saturation and conjugated linoleic acid) were not measured at 25y; all models include data only up to aged 18y and values in this table for these traits are at 7y and 18y respectively. HDL: high-density lipoprotein; IDL: intermediate-density lipoprotein; LDL: low-density lipoprotein; MLM; multilevel model; VLDL: very-low-density lipoprotein.

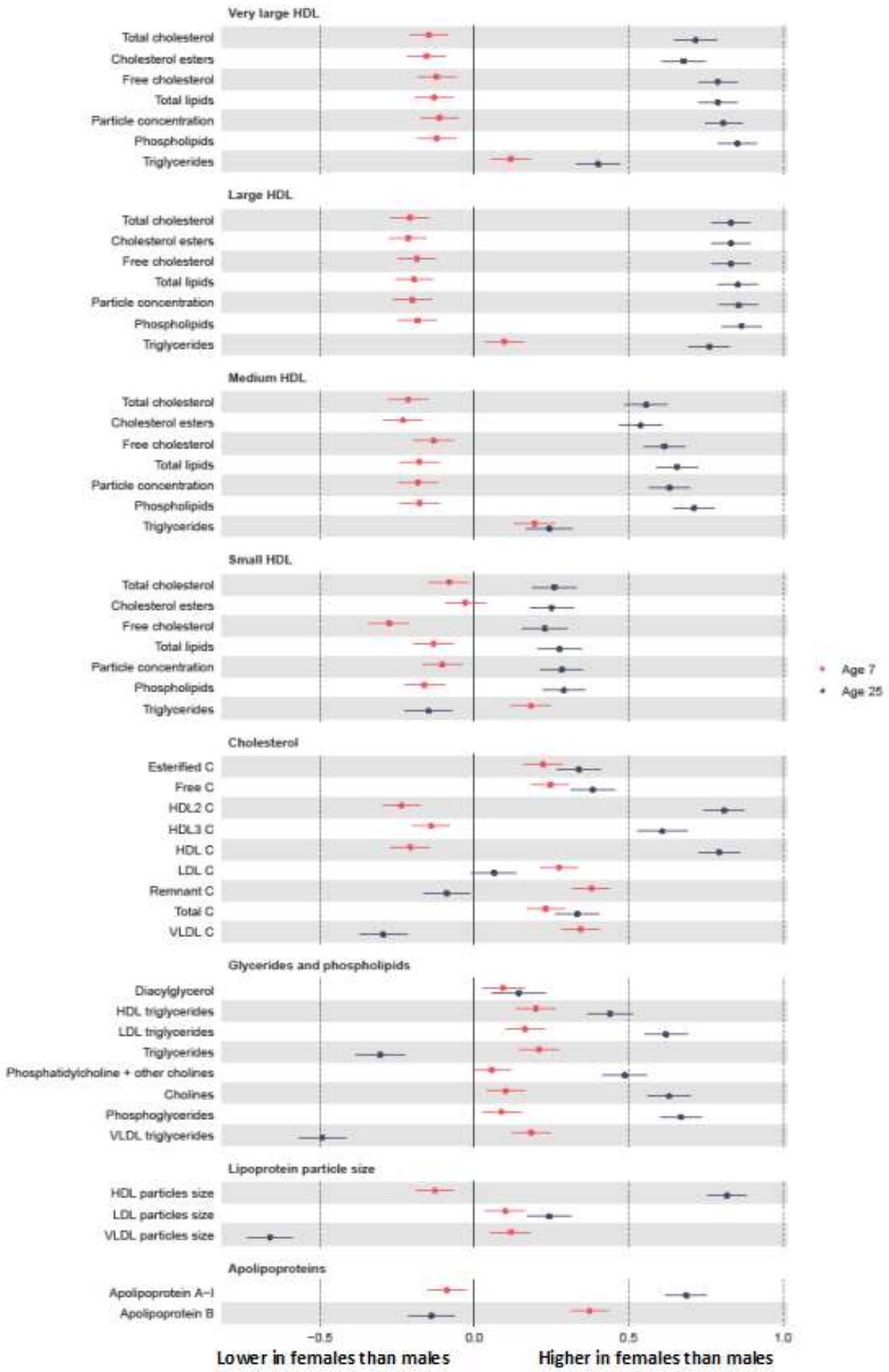
S2 Table: Characteristics of offspring included in analyses compared to those excluded due to missing sex, cardiometabolic trait data or attrition from the cohort

	Female participants included n=3,909*	Female participants excluded	N excluded females	Male participants included n=3,717*	Male participants excluded	N excluded males
	n (%)	n (%)	n	n (%)	n (%)	n
Non-white ethnicity	75 (2.2)	77 (2.99)	2573	60 (1.8)	112 (3.7)	3050
Maternal marital status			2887			3433
Never married	527 (15.1)	680 (23.6)		467 (13.7)	853 (24.9)	
Widowed	<5	6 (0.2)		8 (0.2)	<5	
Divorced	110 (3.2)	143 (5.0)		118 (3.5)	188 (5.5)	
Separated	50 (1.4)	58 (2.0)		36 (1.1)	70 (2.0)	
1st Marriage	2581 (73.9)	1832 (63.5)		2544 (74.8)	2086 (60.8)	
Marriage 2 or 3	224 (6.4)	168 (5.8)		229 (6.7)	234 (6.8)	
Household social class †			2337			2758
Professional	517 (15.8)	213 (9.1)		532 (16.7)	275 (10.0)	
Managerial & Technical	1463 (44.6)	893 (38.2)		1404 (44.1)	1062 (38.5)	
Non-Manual	793 (24.2)	637 (27.3)		792 (24.9)	723 (26.2)	
Manual	343 (10.5)	411 (17.6)		328 (10.3)	479 (17.4)	
Part Skilled & Unskilled	161 (4.9)	183 (7.8)		128 (4.0)	219 (7.9)	
Maternal education			2605			3088
Less than O level	761 (22.2)	1025 (39.4)		724 (21.6)	1238 (40.1)	
O level	1166 (34.1)	920 (35.3)		1195 (35.7)	1036 (33.6)	
A level	926 (27.1)	435 (16.7)		883 (26.4)	550 (17.8)	
Degree or above	569 (16.6)	225 (8.6)		548 (16.4)	264 (8.6)	
Mother's Partner's highest educational qualification			2479			2915
Less than O level	965 (28.9)	1056 (42.6)		863 (26.5)	1258 (43.2)	
O level	717 (21.5)	501 (20.2)		724 (22.2)	609 (20.9)	
A level	916 (27.5)	625 (25.2)		918 (28.2)	657 (22.5)	
Degree or Above	737 (22.1)	297 (12.0)		750 (23.0)	391 (13.4)	
Maternal smoking during pregnancy	660 (18.9)	891 (30.5)	2992	657 (19.2)	1126 (32.8)	3438
	Mean (SD)	***Mean (SD)***		***Mean (SD)***	***Mean (SD)***	
Birthweight (g)	3370 (512)	3283 (579)	3158	3469 (578)	3395 (631)	3723
Gestational age (weeks)	39.6 (1.8)	39.2 (2.9)	3230	39.3 (1.9)	39.0 (3.0)	3812
Maternal age (years)	28.8 (4.6)	26.8 (5.0)	3198	29.1 (4.7)	27.1 (5.1)	3778
Maternal pre-pregnancy BMI (kg/m²)	22.8 (3.6)	23.1 (4.1)	2448	22.9 (3.8)	23.0 (3.9)	2845

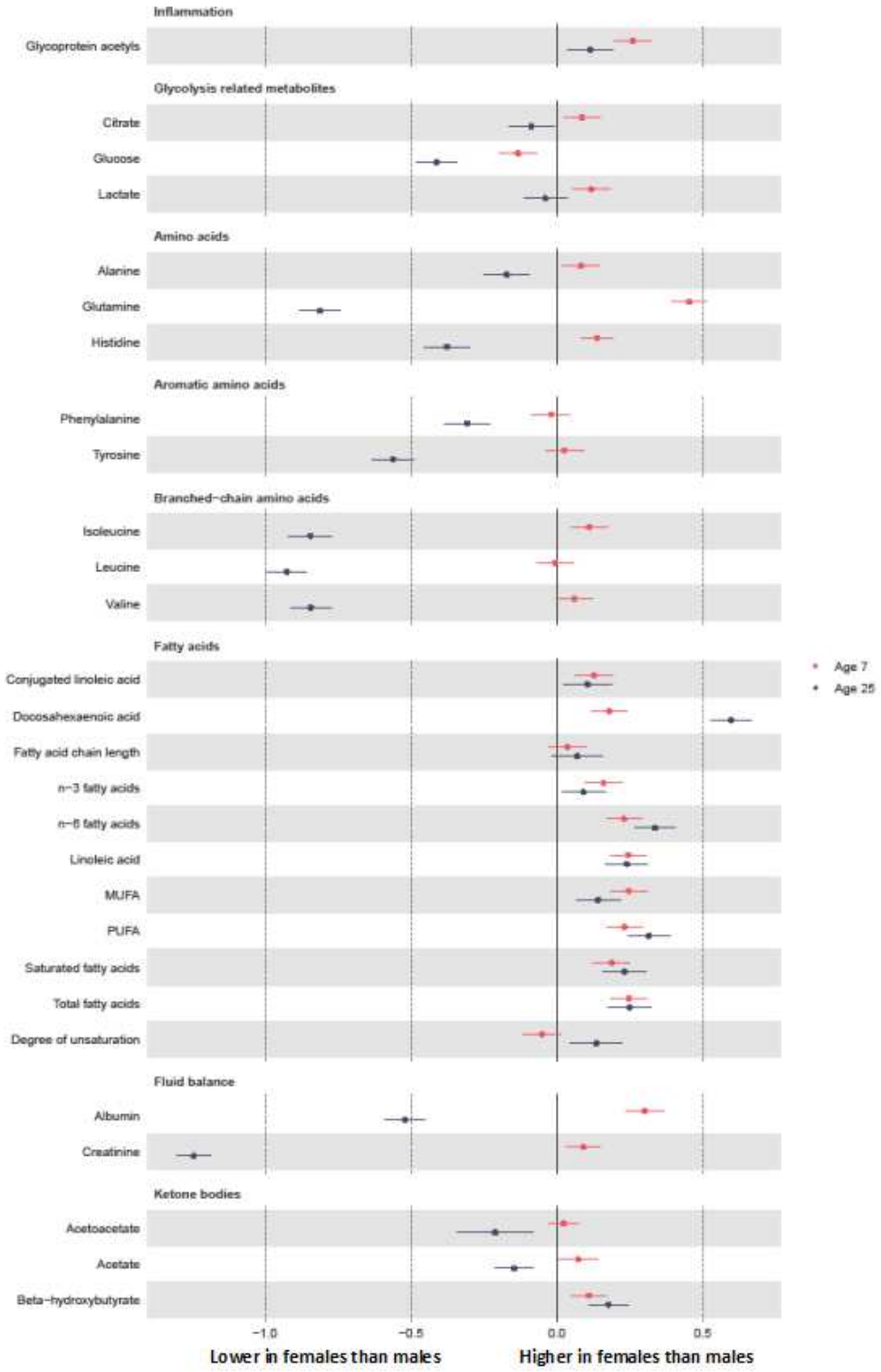
*Represents participants included in models of 144 concentrations with data at all four time points; exact denominators in this table will vary due to missing data for characteristics which were not required for inclusion in analyses.



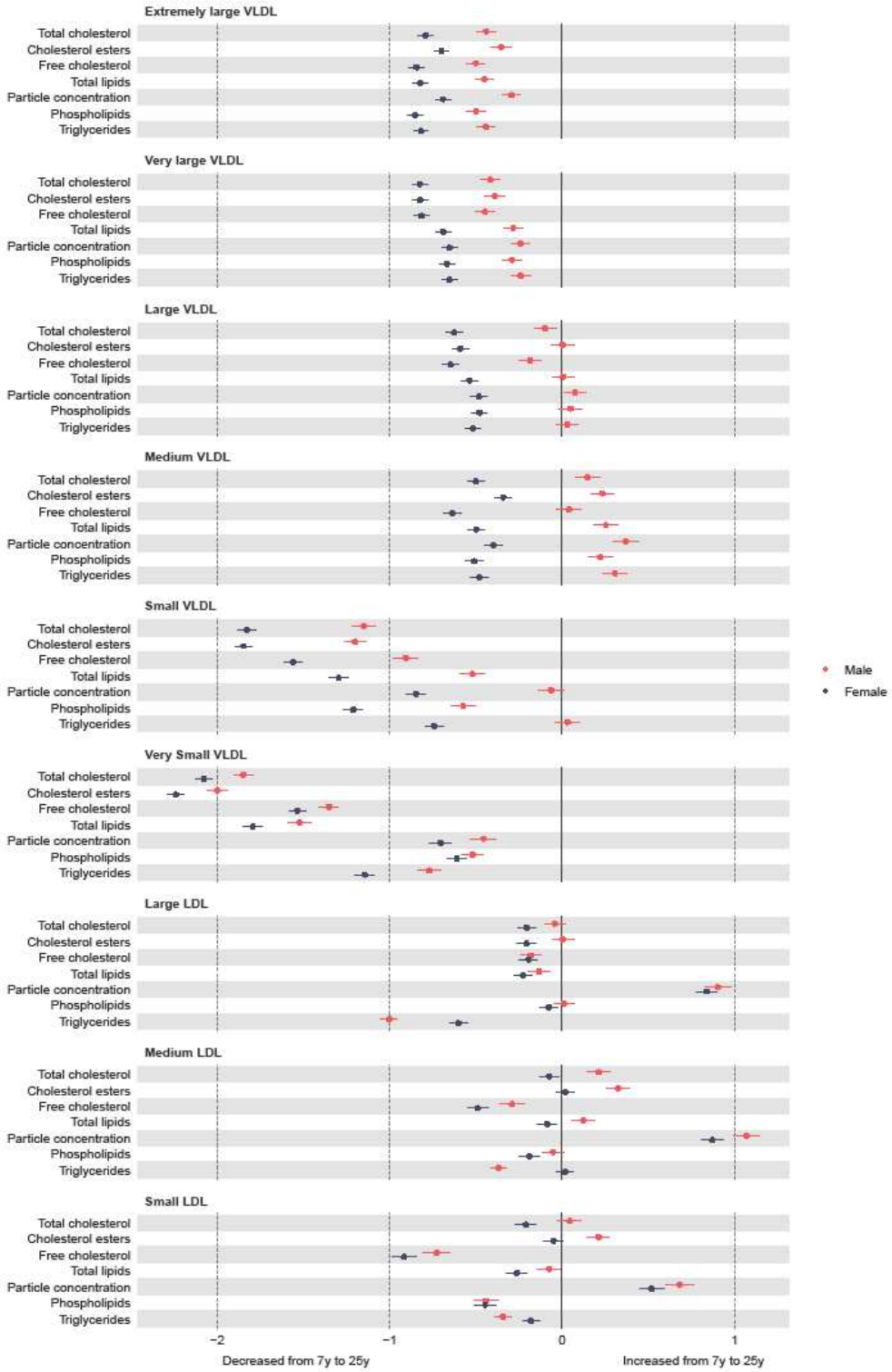
S1 Figure Mean sex difference in VLDL and LDL lipoprotein concentrations in SD units at 7y and 25y, estimated from multilevel models weighted by the probability of inclusion in analysis. Legend: LDL, low-density lipoprotein; VLDL, very-low-density lipoprotein. Differences shown are for females compared with males.



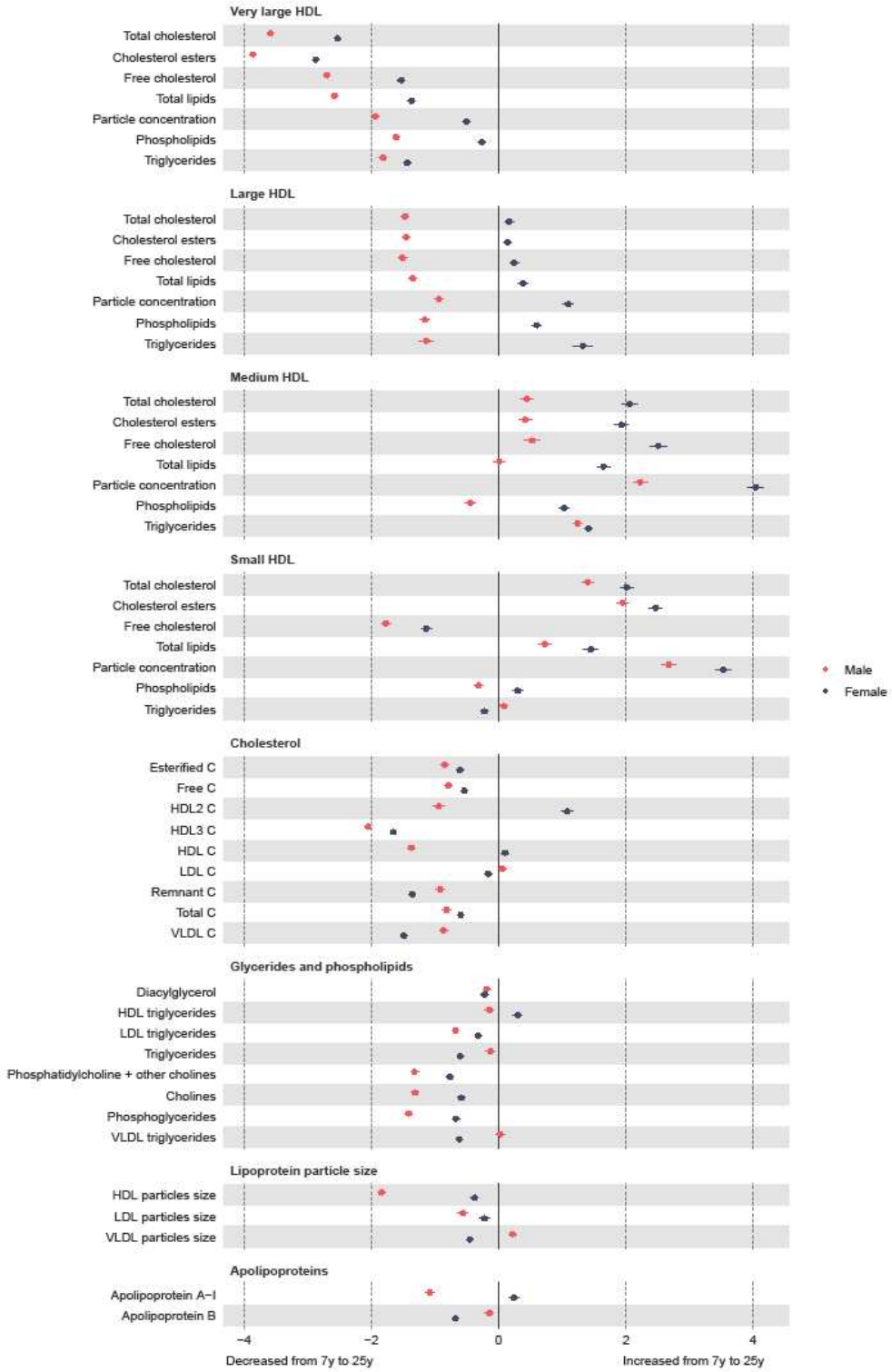
S2 Figure Mean sex difference in lipid concentrations in SD units at 7y and 25y, estimated from multilevel models weighted by the probability of inclusion in analysis. Legend: HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very-low-density lipoprotein. Differences shown are for females compared with males. Note that diacylglycerol is only measured up to 18y.



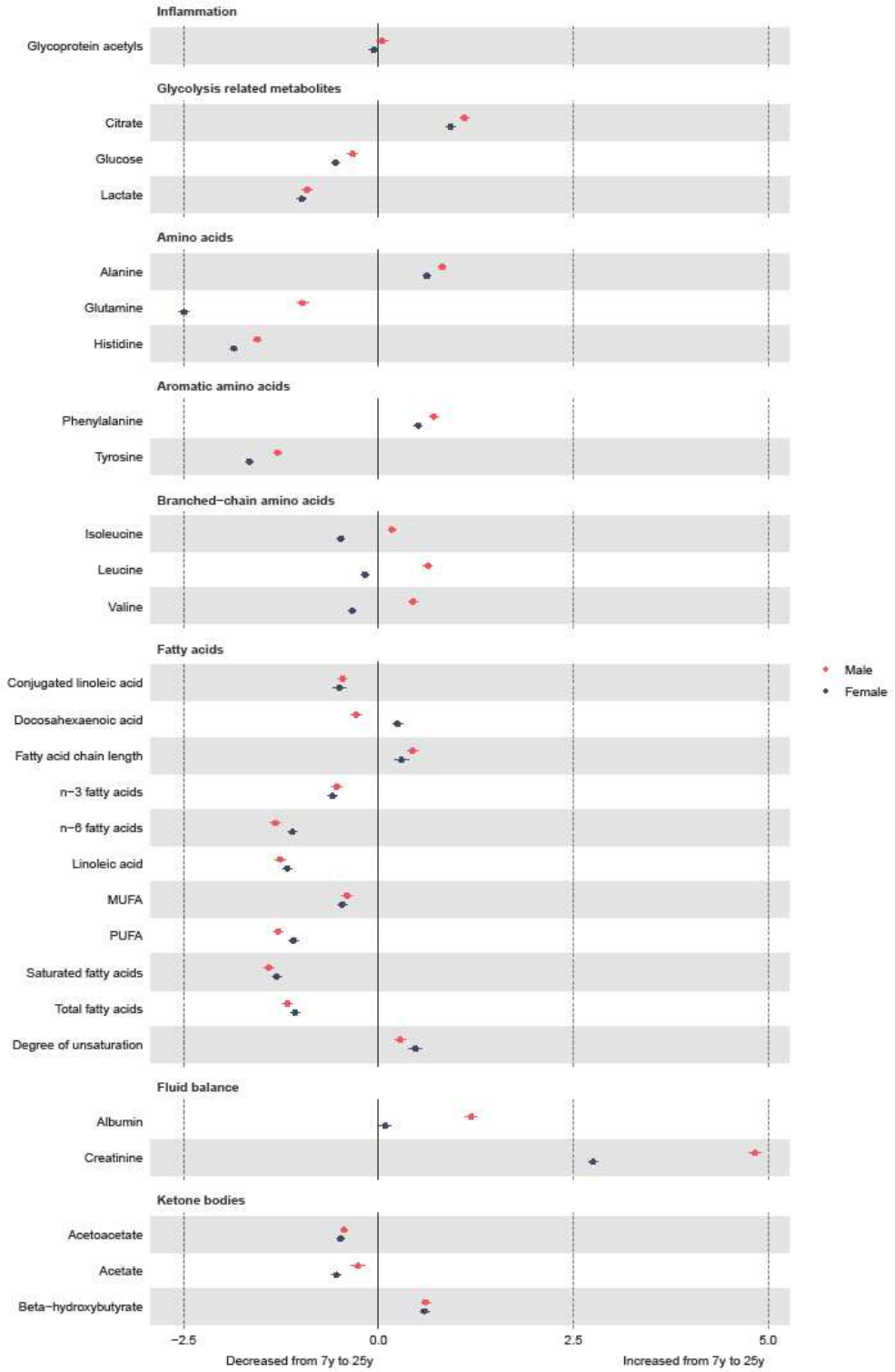
S3 Figure Mean sex difference in other trait concentrations in SD units at 7y and 25y, estimated from multilevel models weighted by the probability of inclusion in analysis. Legend: MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids. Differences shown are for females compared with males. Note that conjugated linoleic acid, fatty acid chain length and estimated degree of unsaturation are only measured up to 18y.



S4 Figure Mean sex-specific change in VLDL and LDL lipoprotein concentrations in SD units (standardised using sex-specific SDs) from 7y to 25y, estimated from multilevel models. Legend: LDL, low-density lipoprotein; VLDL, very-low-density lipoprotein.



S5 Figure Mean sex-specific change in lipid concentrations in SD units (standardised using sex-specific SDs) from 7y to 25y, estimated from multilevel models. Legend: HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very-low-density lipoprotein. Note that diacylglycerol is only measured up to 18y.



S6 Figure Mean sex-specific change in other trait concentrations in SD units (standardised using sex-specific SDs) from 7y to 25y, estimated from multilevel models. Legend: MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids. Note that conjugated linoleic acid, fatty acid chain length and estimated degree of unsaturation are only measured up to 18y.

References

1. Hughes DA, Taylor KA, McBride N, et al. metaboprep: an R package for pre-analysis data description and processing. 2021