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The interplay between birth weight and obesity in determining childhood and adolescent cardiometabolic risk

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Summary

Background Birth weight (BW) is associated with risk of cardiometabolic disease (CMD) in adulthood, which may depend on the state of obesity, in particular if developed at a young age. We hypothesised that BW and a polygenic score (PGS) for BW were associated with cardiometabolic risk and related plasma protein levels in children and adolescents. We aimed to determine the modifying effect of childhood obesity on these associations.

Methods We used data from The cross-sectional HOLBAEK Study with 4263 participants (median [IQR] age, 11.7 [9.2, 14.3] years; 57.1% girls and 42.9% boys; 48.6% from an obesity clinic and 51.4% from a population-based group). We gathered information on BW and gestational age, anthropometrics, cardiometabolic risk factors, calculated a PGS for BW, and measured plasma proteins using Olink Inflammation and Cardiovascular II panels. We employed multiple linear regression to examine the associations with BW as a continuous variable and performed interaction analyses to assess the effect of childhood obesity on cardiometabolic risk and plasma protein levels.

Findings BW and a PGS for BW associated with cardiometabolic risk and plasma protein levels in childhood and adolescence. Childhood obesity modified the associations between BW and measures of insulin resistance, including HOMA-IR (βadj [95% CI per SD] for obesity: −0.12 [−0.15, −0.08]; normal weight: −0.04 [−0.08, 0.00]; Pinteraction = 0.004), c-peptide (obesity: −0.11 [−0.14, −0.08]; normal weight: −0.02 [−0.06, 0.02]; Pinteraction = 5.05E-04), and SBP SDS (obesity: −0.12 [−0.16, −0.08]; normal weight: −0.06 [−0.11, −0.01]; Pinteraction = 0.0479). Childhood obesity also modified the associations between BW and plasma levels of 14 proteins (e.g., IL15RA, MCP1, and XCL1; Pinteraction < 0.05).

Abbreviations: ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; BMI, Body mass index; CI, Confidence interval; CMD, Cardiometabolic disease; CX3CL1, Fractalkine; DBP, Diastolic blood pressure; FGF21, Fibroblast growth factor 21; GDM, Gestational diabetes mellitus; GGT, Gamma-glutamyltransferase; HAOX1, Hydroxyacid oxidase 1; HbA_{1c}, Glycated haemoglobin A1c; HDL-C, High-density lipoprotein cholesterol; HOMA-IR, Homeostasis model assessment of insulin resistance; hs-CRP, High-sensitivity C-reactive protein; IL15RA, Interleukin-15 receptor subunit alpha; IQR, Interquartile range; LEP, Leptin; LDL-C, Low-density lipoprotein cholesterol; LPL, Lipoprotein lipase; MCP1, Monocyte chemoattractant protein 1; OR, Odds ratio; PGS, Polygenic score; SBP, Systolic blood pressure; SDS, Standard deviation score; TC, Total cholesterol; TG, Triglycerides; TWEAK, Tumour necrosis factor ligand superfamily member 12; WBC, White blood cell count; XCL1, Lymphotactin

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Interpretation We identified associations between lower BW and adverse metabolic phenotypes, particularly insulin resistance, blood pressure, and altered plasma protein levels, which were more pronounced in children with obesity. Developing effective prevention and treatment strategies for this group is needed to reduce the risk of future CMD.

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Keywords: Adolescent; Birth weight; Child; Inflammation; Obesity; Polygenic score

Research in context

Evidence before this study

Observational and genetic research points towards prenatal growth conditions, expressed as birth weight, as a key factor in the development of cardiometabolic disease later in life. Associations between birth weight and various health complications, such as low-grade inflammation, dysglycemia, dyslipidemia, hypertension, and altered levels of plasma proteins may be detectable in childhood and modified by obesity. We searched Google Scholar and PubMed from inception to Feb 15, 2024, for references from studies on the interaction between birth weight and childhood obesity on associated cardiometabolic risk factors or plasma protein levels in a large population of children. The search terms we used included "birth weight", "children OR adolescents", "interaction", "overweight OR obesity", "cardiometabolic", "proteomics". A NHANES study found significant interaction between very low birth weight and hypertension, but studies with deep phenotypes were lacking in our search.

Added value of this study

In a Danish cohort consisting of more than 4000 individuals with available birth weight, genotypes, detailed anthropometric measurements, cardiometabolic risk factors, and 149 inflammation- and cardiovascular-related plasma proteins, we identify associations between birth weight and cardiometabolic risk in childhood and adolescence. In addition, we provide evidence that a polygenic score for birth weight has similar directions of effects. Our interaction analyses reveals increased risk of insulin resistance and higher systolic blood pressure in individuals born with a low birth weight who develop obesity in childhood, compared to peers with normal weight. This study also provides new knowledge on how birth weight associates with levels of inflammation- and cardiovascular-related plasma proteins, offering potential mechanisms related to adipose tissue dysfunction.

Implications of all the available evidence

Children who are born with a lower birth weight and later develop obesity may be particularly vulnerable to developing insulin resistance, often indicated by heightened markers of abnormal fat accumulation in non-adipose sites and chronic low-grade inflammation. Our results highlight the need to consider whether prevention and treatment approaches should be tailored specifically for children with obesity who were born with a lower birth weight. Such targeted strategies could potentially reduce their risk of developing obesity-related cardiometabolic complications.

Introduction

Birth weight is a result of fetal growth throughout pregnancy and is a reflection of the intrauterine environment. Early life environmental exposures may have lifelong programming effects on health and disease risk.[1] Epidemiological research have provided consistent evidence that a lower birth weight is associated with increased visceral adipose tissue deposition and an increased risk of cardiometabolic disease (CMD) in adulthood, including type 2 diabetes (T2D),[2] whereas a higher birth weight is associated with a higher body mass index (BMI) in both childhood[3] and adulthood.[4] While previous research has mainly focused on risk of disease in adulthood, markers of CMD may already be present in childhood and adolescence.[5,6] Childhood obesity is a known risk factor for cardiometabolic morbidity and mortality in adulthood.[7] Growth restriction in utero may result in a lifelong failure for adipose tissue expansion, leading to adverse adipose tissue deposition.[8] Hence, the association between birth weight and cardiometabolic risk could be modified by obesity in childhood.[5,6]

Genetic predisposition to birth weight also influences future risk of CMD.[9] Genetic variants that increase birth weight are correlated with anthropometric traits and genetic variants that decrease birth weight are correlated with dysglycemia, including T2D, dyslipidemia, and hypertension in adulthood,[10] suggesting that common genetic variants may have pleiotropic effects, influencing both birth weight and risk of CMD.

During fetal development, insulin is a growth factor that may account for up to 50% of the variation in birth weight.[11] The fetal insulin hypothesis proposes that genetic variants related to insulin secretion and insulin action may regulate both prenatal growth *and* affect the risk of T2D later in life.[12] Therefore, genetic variants decreasing insulin sensitivity may result in growth restriction in utero and increase the risk of insulin resistance or insulin deficiency later in life.

Utilising data from The HOLBAEK Study, we aimed to examine whether birth weight and genetic liability for birth weight were associated with cardiometabolic risk factors and plasma protein levels in childhood and adolescence. We hypothesised that lower birth weight would be associated with an adverse adipose tissue deposition, worsened cardiometabolic risk factors, and low-grade inflammation, and that these associations would be more pronounced in children and adolescents with obesity.

Methods

Study design and participants

In the present cross-sectional study, we used data from The HOLBAEK Study. Patients were recruited from the Children's Obesity Clinic, accredited Centre for Obesity Management, offering the multidisciplinary childhood obesity management program at Copenhagen University Hospital Holbæk[13] Participants were also recruited from the general population from schools across the region of Zealand, Denmark.[14] All individuals were enrolled between January 2009 and April 2019.

Inclusion and exclusion criteria

Inclusion criteria was age four to 20 years for all study participants and a BMI standard deviation score (SDS) above the 90th percentile (BMI SDS $\geq$ 1.28) according to Danish reference values[15] for patients in the obesity clinic group.

Exclusion criteria applied to all study participants were: 1) gestational age <37 and >42 weeks (n = 376); 2) diagnosed type 1 diabetes (n = 10); 3) diagnosed T2D (n = 1); 4) treatment with medications including insulin, liraglutide, metformin, and/or statins (n = 4); 5) meeting T2D criteria[16] based on the blood sample taken for this study (fasting plasma glucose >7.0 mmol/L and/or haemoglobin A1c (HbA1c) > 48 mmol/mol (n = 8) (see flowchart, Supplementary Fig. S1).

Ethics

The study protocol was approved by the ethics committee for the Region Zealand (protocol no. SJ-104) and is registered at the Danish Data Protection Agency (REG- 043-2013). The HOLBAEK Study including the obesity clinic group and the population-based group are also registered at ClinicalTrials.gov (NCT00928473). The study was conducted according to the principles of the Declaration of Helsinki. Oral and written informed consents were given by the study participants of 18 years of age or older, and by their parent(s)/legal guardian(s) if younger than 18 years. Additionally, all participants younger than 18 years of age gave oral assents.

Birth anthropometrics

Birth weight and gestational age were extracted from the Danish Medical Birth Register and obtained via the nationwide Danish Neonatal Screening Biobank.[17] In brief, birth weight was measured at birth by trained medical professionals at the birth ward, and gestational age was assessed at the translucency scan at the end of first trimester of pregnancy and registered at time of birth.

Self-reported information on socioeconomic status, preeclampsia (yes/no), gestational diabetes mellitus (GDM, yes/no), maternal smoking during pregnancy (yes/no), and duration of breastfeeding (reported in whole months) were obtained through structured family interviews. Socioeconomic status was categorised into five groups (Grade 1–5; with Grade 1 representing the highest level) depending on parental occupation, based on a national classification system.[18]

Tanner stage was evaluated by trained medical professionals for individuals recruited at the obesity clinic and self-reported using a questionnaire with picture pattern recognition for individuals in the population-based group.

Anthropometrics

Anthropometrics (height, weight, waist circumference, and hip circumference) were obtained by trained medical professionals. BMI SDS was calculated according to a Danish reference[15] and waist circumference and waist-hip ratio SDS were calculated according to an international age- and sex-specific reference.[19]

Cardiometabolic risk factors

Whole-body dual-energy x-ray absorptiometry and body fat percentage was quantified in a subset of the study population using a GE Lunar Prodigy (DF + 10031, GE Healthcare, Madison, Wisconsin, USA) until October 2009 and thereafter on a GE Lunar iDXA (ME + 200179, GE Healthcare). Liver fat percentage was quantified in a subset of individuals by proton magnetic resonance spectroscopy (3T Achieva MR imaging system, Philips Medical Systems, Best, Netherlands).

Venous blood samples were collected following an overnight fast of at least 8 h. Biochemical measurements include serum leptin (R&D Systems, Cat#DY398, RRID:AB_2861156) and serum adiponectin (R&D Systems, Cat#DY1065, RRID:AB_2861158), plasma alanine transaminase (ALT), plasma aspartate aminotransferase (AST), plasma gamma-glutamyltransferase (GGT) (Roche, Cobas®6000 and Siemens, Dimension Vista®1500), serum high-sensitivity C-reactive protein (hs-CRP, Brahms, ultra-sensitive CRP immunofluorescent assay, Kryptor analyser), white blood cell count (WBC, Sysmex XN), serum insulin, serum C-peptide (Roche, Cobas®6000), plasma glucose (Siemens, Dimension Vista®1500), whole blood HbA1c (Tosoh high-performance liquid chromatography G8), plasma glucagon (Mercodia, Cat#10-1271-01, RRID: AB_2737304), and plasma total glucagon-like peptide-1 (GLP-1; Mercodia, Cat#10-1278-01, RRID: AB_2892202), plasma total cholesterol (TC), plasma high-density lipoprotein cholesterol (HDL-C), plasma low-density lipoprotein cholesterol (LDL-C), and plasma triglycerides (TG) (Roche, Cobas®6000 and Siemens, Dimension Vista®1500). Homeostasis model assessment of insulin resistance (HOMA-IR) and TG/HDL-C ratio were calculated.

Oscillometric blood pressure (Omron 705IT, Omron Healthcare Co., Ltd., Kyoto, Japan) was measured three times. The mean value of the last two measurements was calculated and converted to systolic and diastolic blood pressure SDS (SBP SDS and DBP SDS) based on age-, sex-, and height-specific reference values from the American Academy of Pediatrics.[20]

Polygenic score

Participants in this study were genotyped in three batches on the Infinium HumancoreExome12 v1.0 and HumancoreExome24 v1.1 Beadchips (Illumina, San Diego). Genotypes were called using the Genotype module (version 1.9.4) of the GenomeStudio (Illumina). Before imputation, datasets from the three different batches were merged after quality control (only variants present on both chip versions were kept), and monomorphic variants as well as batch-associated variants were removed (Fishers exact test, $P < 1E\text{-}07$). The Sanger imputation server was used to phase the genotype data using EAGLE2 (v2.0.5) and imputed using PBWT with the HRC1.1 panel (GRCh37). We excluded individuals with more than five percent missing genotypes, with too high or too low heterozygosity (inbreeding coefficient abs(F) > 0.2), duplicated measurements (keeping the one with higher quality), related individuals (identity by descent, phihat > 0.1875), and non-European individuals determined using principal component analysis based on ancestry informative markers.

A polygenic score (PGS) for birth weight including 827,714 single nucleotide polymorphisms (SNPs) was calculated from a published score.[21] A genetic risk score (GRS) consisting of 71 autosomal SNPs with genome-wide significant associations with offspring birth weight[10] was also calculated and presented in the Supplementary.

Targeted plasma proteomics

Proximity extension assay was performed to quantify plasma protein levels using the Target 96 Inflammation and Cardiovascular II panels from Olink Proteomics AB (Uppsala, Sweden) using EDTA plasma stored at −80 °C. Two Olink batches were randomised, bridged, and normalised using 16 controls using the "OlinkAnalyze" R package (https://cran.r-project.org/web/packages/OlinkAnalyze/index.html). Individual proteins were included if > 80% of individuals were above the limit of detection, leaving a total of 149 unique proteins.

Statistics

Statistical analysis was performed in R, version 4.3.2.[22] Normality of parameter distributions were evaluated. Continuous variables were presented as mean with standard deviation (SD) or median with interquartile range (IQR). Categorical variables were presented as frequencies and percentages. The two groups were compared using paired t-tests and Wilcoxon rank sum tests for continuous variables and χ^2 tests for categorical variables. Statistical significance was set at false discovery rate (FDR, Benjamini-Hochberg) $P < 0.05$.

The associations between birth weight and birth weight PGS (as continuous traits) on cardiometabolic risk factors and plasma proteins were estimated using multiple linear regression models (checking for linearity), pooling the obesity clinic and population-based groups. Non-normally distributed (right-skewed) cardiometabolic risk factors were log-transformed and plasma proteins were inverse normally transformed. Estimated β-effect sizes and 95% confidence intervals (CI) were reported as the SD change in outcome per 1 SD unit exposure to facilitate direct comparisons of the strength of associations. Covariates in Model 1 include gestational age (weeks), sex, age, childhood BMI SDS (not used for anthropometric outcomes), year of blood sample collection (used for the plasma proteins as outcomes), and three genotype batches and the first five genetic principle components (used for the birth weight PGS as exposure). In Model 2, a subgroup analysis (restricted to individuals with all available data), included further adjustments for socioeconomic status (Grade: 1–5, ordinal), preeclampsia (yes/no), gestational diabetes (yes/no), maternal smoking during pregnancy (yes/no), duration of breastfeeding (months), and puberty stage (pre-puberty = Tanner stage 1, puberty = Tanner stage 2–5). Associations with birth weight and birth weight PGS (as exposures) were assessed in both Model 1 and 2.

Stratified analyses were also carried out in the obesity clinic group and population-based group separately in a non-BMI SDS and BMI SDS adjusted model and are presented in the Supplementary.

Multiple interaction models were conducted to examine the effect of overweight/obesity (herein referred to as obesity, BMI SDS ≥ 1.28) versus normal weight (BMI SDS > −1.28 and <1.28) on the associations between birth weight and outcomes. BMI SDS was assessed across the whole study population, as the population-based group included individuals with obesity. To distinguish between the effects of obesity and normal weight, we excluded individuals from the population with underweight from the interaction analyses (n = 118).

Additional, stratified analyses according to puberty stage were performed and presented in the Supplementary.

Role of funders

Novo Nordisk Foundation (NNF15OC0016692, NNF15OC0016544, NNF0064142 to T.H., NNF15OC0016692 to T.H. and A.K., NNF18CC0033668 to S.E.S, NNF18SA0034956 to C.E.F., NNF20SA0067242 to DCA, NNF18CC0034900 to NNF CBMR), The Innovation Fund Denmark (0603-00484B to T.H.), The Danish Cardiovascular Academy (DCA) and the Danish Heart Foundation (HF) (PhD2021007-DCA to P.K.R, 18-R125-A8447-22088 (HF) and 21-R149-A10071-22193 (HF) to M.A.V.L., PhD2023009-HF to L.A.H), EU Horizon (668031, 847989, 825694, 964590 to A.K.), Innovative Health Initiative (101132901 for A.K.), A.P. Møller Foundation (19-L-0366 to T.H.), The Danish National Research Foundation, Steno Diabetes Centre Sjælland, and The Region Zealand and Southern Denmark Health Scientific Research Foundation. The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Population characteristics

We obtained data on birth weight and gestational age from 4263 children and adolescents, 2073 from an obesity clinic and 2190 from the general population (Supplementary Fig. S1). Patients from the obesity clinic had a higher birth weight with a shorter gestational age, lower self-reported socioeconomic status, a higher proportion of preeclampsia, GDM, maternal smoking during pregnancy, and a shorter duration of breast-feeding than individuals from the population (Table 1). Age was comparable between groups and there was a smaller proportion of girls in the obesity clinic. A higher

Characteristic	n	Obesity clinic	n	Population-based	P
Birth weight (g) [median, IQR]	2073	3600 (3250–3950)	2190	3520 (3200–3870)	<0.001
Gestational age (weeks) [mean, sd]	2073	39.8 (1.36)	2190	40.0 (1.36)	<0.001
Socioeconomic status, n (%)	1823		1984		<0.001
1 (highest)		162 (8.9%)		793 (40.0%)	
2		415 (22.8%)		600 (30.2%)	
3		577 (31.7%)		445 (22.4%)	
4		437 (24.0%)		112 (5.6%)	
5 (lowest)		232 (12.7%)		34 (1.7%)	
Preeclampsia, yes (%)	910	40 (4.4%)	1190	14 (1.2%)	<0.001
GDM, yes (%)	910	38 (4.2%)	1190	2 (0.2%)	<0.001
Smoking during pregnancy, yes (%)	1036	349 (33.7%)	1412	155 (11.0%)	<0.001
Breastfeeding (months) [median, IQR]	1501	4 (2–6)	1298	5 (4–6)	<0.001
Age (years) [median, IQR]	2073	11.7 (9.4–13.9)	2190	11.6 (9.0–14.6)	0.430
Sex, n (%)	2073		2190		<0.001
Girls		1107 (53.4%)		1326 (60.5%)	
Boys		966 (46.6%)		864 (39.5%)	
Puberty stage, pre-puberty, n (%)	1656	696 (42.0%)	1549	475 (30.7%)	<0.001
BMI SDS, [median, IQR]	2073	2.91 (2.48–3.36)	2190	0.28 (−0.40 to 1.00)	<0.001
Waist circumference SDS [median, IQR]	1441	2.41 (2.03–2.70)	1612	−0.02 (−0.69 to 0.66)	<0.001
Waist-hip ratio SDS	1439	1.88 (1.38–2.27)	1612	−0.04 (−0.76 to 0.65)	<0.001
Body fat (%) [median, IQR]	1853	43.7 (40.2–47.1)	277	26.6 (21.9–32.4)	<0.001
Liver fat (%) [median, IQR]	526	1.0 (0.5–2.4)	138	0.5 (0.5–0.5)	<0.001

Continuous values are shown as mean (SD) and medians (IQR) for non-normally distributed variables, categorical variables are presented as frequencies, n (%). Puberty stage is defined as pre-pubertal (Tanner stage 1) versus pubertal/post-pubertal (Tanner stage 2–5). Statistical analysis was performed using paired t-tests, Wilcoxon rank sum tests, or χ^2 tests. Abbreviations: BMI = body mass index, IQR = interquartile range, SDS = standard deviation score.

Table 1: **Characteristics of the children and adolescents from the obesity clinic and population-based groups.**

proportion of individuals from the obesity clinic were in the pre-puberty stage compared to peers from the population. Individuals in the obesity clinic had higher BMI SDS, waist circumference SDS, waist-hip ratio SDS, total body fat, and liver fat percentage.

Birth weight associates with cardiometabolic risk factors

For crude adjustments through pooled Model 1, birth weight was positively associated with BMI SDS, waist circumference SDS, waist-hip ratio SDS, and total body fat percentage (FDR $P < 0.05$; Fig. 1a, Supplementary Table S1). Birthweight was also positively associated with adiponectin, but negatively associated with leptin, liver fat percentage, ALT, AST, hs-CRP, WBC, HOMA-IR, c-peptide, HbA1c, glucagon, total GLP-1, TG/HDL-C, TC, LDL-C, SBP SDS, and DBP SDS. No significant association was observed for GGT. Through pooled Model 2, results remained consistent after the additional adjustments, except for adiponectin, liver fat percentage, WBC, HbA1c, total GLP-1, TG/HDL-C, and LDL-C which no longer reached nominal significance ($P \geq 0.05$, Supplementary Table S1).

When stratified by the obesity clinic and population-based groups, associations between birth weight and cardiometabolic risk factors displayed similar tendencies, with seemingly stronger effect sizes of birth weight on certain cardiometabolic risk factors in the obesity clinic compared to the population (Supplementary Fig. S2 and Table S2).

The association between birth weight and cardiometabolic risk factors is modified by obesity

Through Model 1, the association between birth weight and GGT, HOMA-IR, c-peptide, and SBP SDS were significantly modified by obesity, with clear negative associations in patients with obesity, whereas effects were weaker or non-significant in participants with normal weight (P for interaction < 0.05; Fig. 1b–d; Supplementary Table S3). There were no significant interactions for the remaining cardiometabolic risk factors (Supplementary Table S3). Through Model 2, the

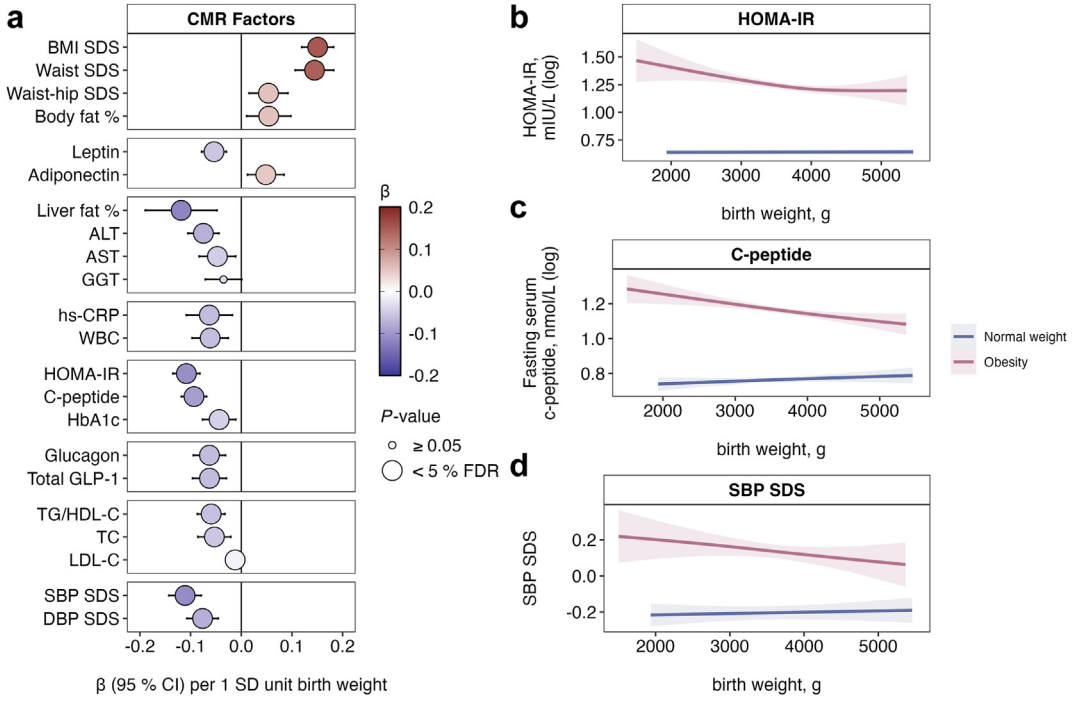

Fig. 1: (a) Estimated regression β-effects (95% CI:s) for associations of birth weight (SD units) on CMR factors (SD units), pooling the obesity clinic and population-based groups, adjusted for gestational age (weeks), sex, age (for anthropometric traits), and childhood BMI SDS (for remaining CMR factors). Right-skewed risk factors were log-transformed, affecting all but BMI SDS, waist circumference SDS, waist-hip SDS, SBP SDS, and DBP SDS. (b–d) Top interactions between birth weight and obesity (pink) or normal weight (blue) on HOMA-IR, c-peptide, and TG/HDL-C. Sample sizes are specified in Supplementary Tables S1 and S3. Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, CMR = cardiometabolic risk, DBP = diastolic blood pressure, GGT = gamma-glutamyltransferase, GLP-1 = glucagon-like peptide-1, HbA1c = haemoglobin A1c, HOMA-IR = homeostasis model assessment of insulin resistance, hs-CRP = high-sensitivity C-reactive protein, LDL-C = low-density lipoprotein cholesterol, SBP = systolic blood pressure, SDS = standard deviation score; TC = total cholesterol, TG/HDL-C = triglyceride to high-density lipoprotein cholesterol ratio, WBC = white blood cell count.

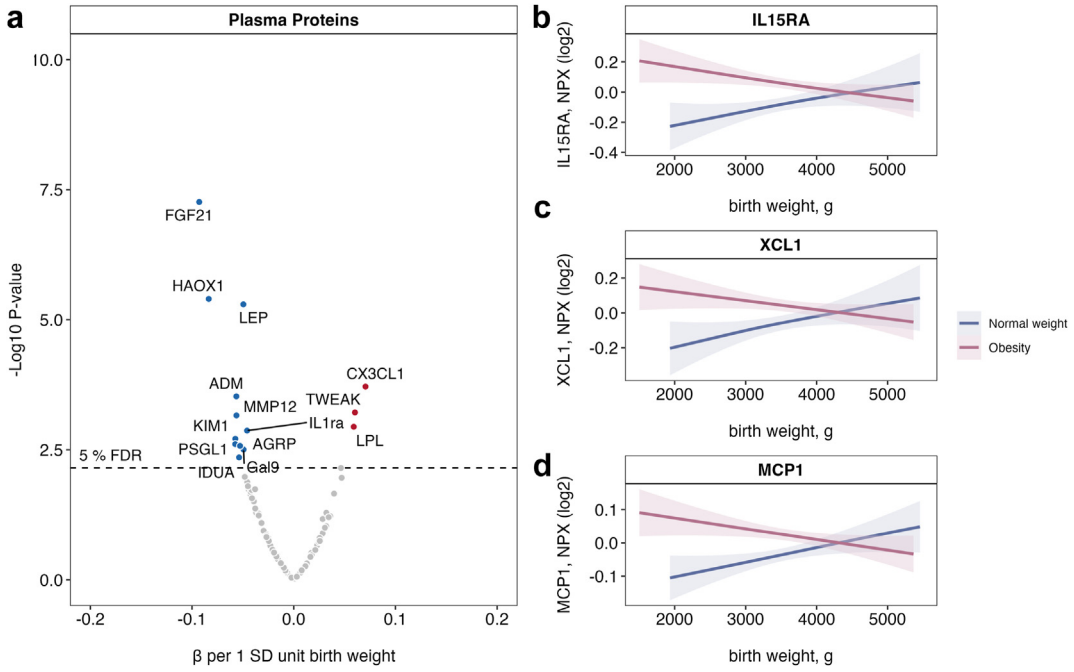

Fig. 2: (a) Estimated regression β-effects for associations of birth weight (SD units) on plasma protein levels (SD units), pooling the obesity clinic and population-based groups, adjusted for gestational age, sex, age, childhood BMI SDS, and blood sample storage time. Plasma proteins (non-normal distribution) were inverse-normal transformed. FDR-corrected $P < 0.05$ (blue = negative, red = positive), FDR-corrected $P \geq 0.05$ (grey). Labelled proteins are FDR-corrected. (b–d) Top interactions between birth weight and obesity (pink) or normal weight (blue) on IL15RA, XCL1, and MCP1. Sample sizes are specified in Supplementary Tables S5 and S7. Abbreviations: IL15RA = interleukin-15 receptor subunit alpha, MCP1 = monocyte chemoattractant protein 1 or C–C motif chemokine 2; XCL1 = lymphotactin.

interaction remained consistent for GGT, HOMA-IR, and c-peptide, while SBP SDS was attenuated (P for interaction = 0.206; Supplementary Table S3).

When further stratified by puberty stage, the interaction between obesity and birth weight on HOMA-IR and c-peptide was significant in pubertal/post-pubertal (P for interaction = 0.008; 0.001), but not in pre-pubertal (P for interaction = 0.148; 0.111) children (Supplementary Table S4).

Birth weight associates with plasma protein levels

A total of 3342 individuals had plasma proteomics available. Out of 149 proteins through pooled Model 1, birth weight was positively associated with 3 plasma proteins and negatively associated with 10 (FDR $P < 0.05$; Fig. 2a; Supplementary Table S5). Of these, birth weight was positively associated with CX3CL1 (or fractalkine), TWEAK (tumour necrosis factor ligand superfamily member 12, or TNFSF12), and LPL (lipoprotein lipase). Most notably, birth weight was negatively associated with FGF-21 (fibroblast growth factor 21), HAOX1 (hydroxyacid oxidase 1), and LEP (leptin). Through Model 2, consistent direction of effects were observed, with significant negative associations for HAOX1 and LEP, yet CX3CL1, TWEAK, LPL, and FGF21 were attenuated (FDR $P \geq 0.05$; Supplementary Table S5).

When stratified by obesity clinic and population-based, birth weight was negatively associated with MMP12 and FGF21 in the obesity clinic group, with no significant associations in the population-based group following correction for multiple testing (FDR $P \geq 0.05$; Supplementary Fig. S3 and Table S6).

The association between birth weight and plasma protein levels is modified by obesity

Through model 1, the associations between birth weight and plasma levels of 14 plasma proteins were modified by obesity (P for interaction < 0.05; Supplementary Table S7). Most notably, the effect of birth weight on plasma levels of IL15RA (interleukin-15 receptor subunit alpha), XCL1 (lymphotactin), and MCP1 (monocyte chemoattractant protein 1 or C–C motif chemokine 2) were stronger in children and adolescents with obesity compared to peers with normal weight (Fig. 2b–d). FGF21 (P for interaction = 0.077) displayed a marginal interaction and MMP12 (P for interaction = 0.017) was significant, with larger negative effect sizes in obesity compared to normal weight (Supplementary Table S7). Results for XCL1 and MCP1 remained consistent when

additionally adjusting for further covariates included in Model 2 (Supplementary Table S7). Results for IL15RA were pattern-wise similar but attenuated (P for interaction = 0.12; Supplementary Table S7).

Polygenic score for birth weight associates with cardiometabolic risk factors

A total of 3178 individuals had genotypes available. The birth weight PGS explained 6.04% of the variation in birth weight. Through Model 1, the birth weight PGS was positively associated with BMI SDS and waist circumference SDS, but not waist-hip ratio SDS and total body fat percentage (FDR $P < 0.05$; Fig. 3a; Supplementary Table S8). Whereas the birth weight PGS was negatively associated with GGT, HOMA-IR, serum c-peptide, plasma glucagon, and SBP and DBP SDS. The birth weight PGS was not significantly associated with adipokines (leptin and adiponectin), inflammation-related traits (hs-CRP and WBC), glycemic traits (HbA1c), total GLP-1, and lipid traits (TG/HDL-C, TC, and LDL-C). Results remained consistent with further adjustments in Model 2, except for hs-CRP which became significantly negatively associated (FDR $P = 0.0128$), and glucagon and DBP SDS which displayed similar direction of effects but were weakly attenuated (FDR $P \geq 0.05$; Supplementary Table S8).

The birth weight GRS explained 3.69% of the variation in birth weight. Consistent associations between a GRS for birth weight and cardiometabolic risk factors were observed compared to PGS (Supplementary Fig. S4).

Stratified analysis of the associations between birth weight PGS and cardiometabolic risk factors in the obesity clinic group and population-based group showed similar tendencies, with the exception of waist SDS, body fat percentage, GGT, and c-peptide which were

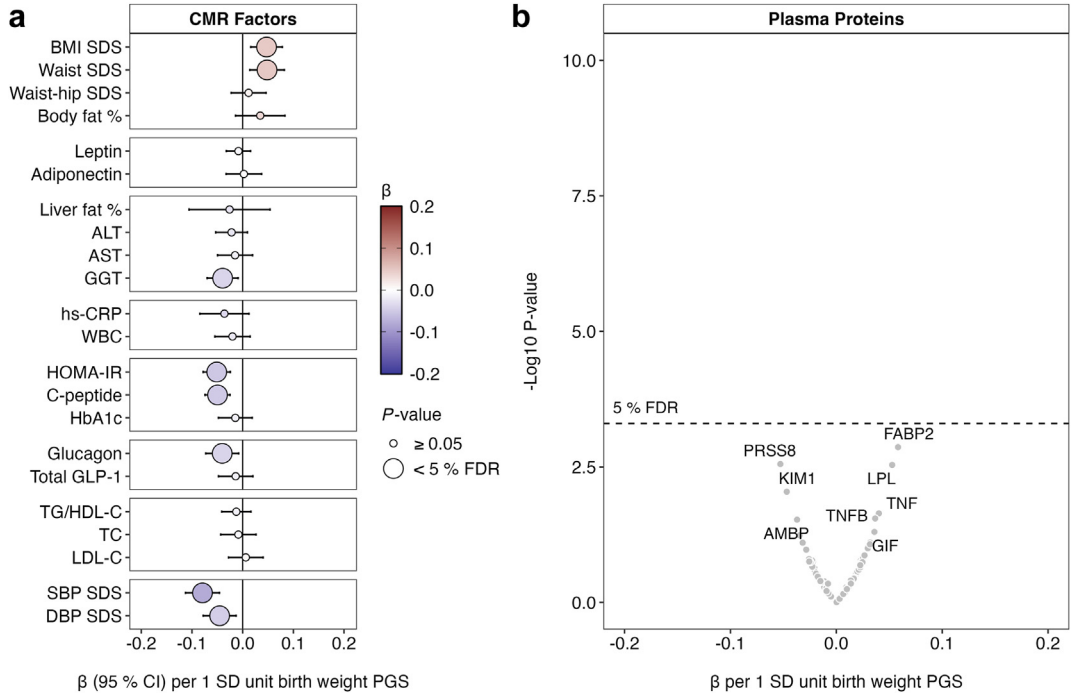

Fig. 3: (a) Estimated regression β-effects (95% CI:s) for associations of birth weight PGS (SD units) on CMR factors (SD units), pooling the obesity clinic and population-based groups, adjusted for gestational age, sex, age (for anthropometric traits), childhood BMI SDS (for remaining CMR factors), genotype batch, and the first five genetic PCs. Right-skewed CMR factors were log-transformed, affecting all but BMI SDS, waist SDS, waist-hip SDS, SBP SDS, and DBP SDS. (b) Estimated regression β-effects for associations of birth weight PGS (SD units) on plasma protein levels (SD units), pooling obesity clinic and population, adjusted for gestational age, sex, age, childhood BMI SDS, blood sample storage time, genotype batch, and the first five genetic PCs. Plasma proteins (non-normal distribution) were inverse-normal transformed. FDR-corrected $P \geq 0.05$ (grey). Sample sizes are specified in Supplementary Tables S8 and S10. Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, CMR = cardiometabolic risk, DBP = diastolic blood pressure, FABP2 = fatty acid binding protein 2, GGT = gamma-glutamyltransferase, GLP-1 = glucagon-like peptide-1, HbA1c = haemoglobin A1c, HDL-C = high-density lipoprotein cholesterol, HOMA-IR = homeostasis model assessment of insulin resistance, hs-CRP = high-sensitivity C-reactive protein, LDL-C = low-density lipoprotein cholesterol, LPL = lipoprotein lipase, PC = principal component, PGS = polygenic score, PRSS8 = prostasin, SBP = systolic blood pressure, SDS = SD score, TC = total cholesterol, TG = triglycerides, WBC = white blood cell count.

significant only in the obesity clinic group and HOMA-IR, glucagon, and DBP SDS only in population-based. BMI SDS were not significant in either group, while previously significant in the pooled model (Supplementary Fig. S5 and Table S9).

Polygenic score for birth weight does not associate significantly with plasma protein levels

A total of 2849 individuals had both genotypes and proteomics available. Through Model 1, there was a tendency towards a positive association between birth weight PGS and plasma levels of 5 proteins FABP2 (fatty acid-binding protein, intestinal), LPL, TNF (tumour necrosis factor), TNFB (TNF beta), GIF (gastric intrinsic factor) and a negative association with 3 proteins PRSS8 (prostasin), KIM1 (hepatitis A virus cellular receptor 1), and AMBP (protein AMBP), which were nominally significant ($P < 0.05$) (Fig. 3b; Supplementary Table S10). After correction for multiple testing (FDR $P \geq 0.05$) the birth weight PGS was not significantly associated with any plasma protein levels. Through model 2, FABP2, LPL, PRSS8 remained consistent, TNF, TNFB, GIF, KIM1, and AMBP were attenuated ($P \geq 0.05$), and FGF-21 became nominally significant ($P < 0.05$).

Stratified analysis of the associations between birth weight PGS and plasma proteins revealed nominal positive associations with FABP2, TNF, and SLAMF1 (signalling lymphocytic activation molecule) and negative associations with KIM1, HAOX1, CTRC (chymotrypsin-c) in the obesity clinic and nominal positive associations with LPL and negative associations with PRSS8 in the population-based group ($P < 0.05$; Supplementary Fig. S6 and Table S11).

Discussion

In this study of over 4000 deeply phenotyped children and adolescents, we confirm our hypothesis that birth weight is associated with cardiometabolic risk before adulthood, and that individuals born with a lower birth weight might be more vulnerable to the adverse cardiometabolic effects of obesity in childhood and adolescence.

The programming effects of fetal growth restriction, resulting in lower birth weight, may cause visceral adipose tissue deposition, due to a failure in the capacity of the subcutaneous adipose tissue to expand.[8] Accumulation of visceral adipose tissue impacts cardiometabolic health, by promoting low-grade inflammation, impairments in glucose metabolism, dyslipidemia, and hypertension.

The present study demonstrated that birth weight was positively associated with BMI SDS and related anthropometric traits (Fig. 1a) in alignment with recent literature.[3] A recent study found that newly diagnosed T2D patients born with low birth weight (<3000 g) had a lower BMI at time of diagnosis.[2] Likewise, men born with low birth weight have higher liver fat percentage even with an adult BMI below 30.[23] A higher prevalence of low birth weight has also been reported in a paediatric population with metabolic dysfunction-associated steatotic liver disease (MASLD).[24] Adding to this, we showed that lower birth weight was associated with higher liver fat percentage. The observed associations between increased liver fat percentage and consequently, altered lipid and glucose metabolism,[23] points towards the adipose tissue expandability theory.[25] This suggests that low birth weight individuals may be more sensitive to deleterious effects of obesity in childhood due to a failure in the capacity to expand subcutaneous adipose tissue.

Further supporting this theory, we found that lower birth weight was positively associated with lower concentrations of adiponectin and higher leptin, as seen previously in adults.[23] These findings also reflect a metabolically adverse phenotype, as these hormones have been linked to obesity, visceral adipose tissue deposition, and insulin resistance.[26,27]

Notably, lower birth weight was associated with higher blood pressure (both SBP and DBP SDS), consistent with previous findings in children.[5] These associations may be a consequence of a lower nephron count in prenatal growth restricted individuals which increases the risk of hypertension.[28]

Few studies have examined associations between birth weight with a broad range of cardiometabolic risk factors with interactions with paediatric obesity. A study of 68 children with overweight or obesity demonstrated that measures of insulin resistance, lipids, blood pressure, and apolipoprotein levels were significantly elevated in those born with low birth weight compared to normal birth weight.[6] Another study of 14615 children and adolescents from NHANES, found a significant interaction of overweight or obesity in the association between very low birth weight and hypertension.[5] Our findings in a deeply phenotyped study population revealed significant interactions of obesity on the association between birth weight and HOMA-IR, C-peptide, and SBP SDS (Fig. 1b–d). This indicates that the adverse effects of being born with a low birth weight observed in childhood and adolescence could be dependent on the degree of childhood obesity and may emerge during puberty, in the case of insulin resistance.

We demonstrated significant associations between birth weight and plasma levels of 13 out of 149 plasma proteins measured in childhood and adolescence (Fig. 2a), which is in line with recent findings in adults.[29] Birth weight was negatively associated with 13 plasma proteins with the largest estimated effects for FGF21, HAOX1, and LEP. FGF21 has previously been shown to be elevated in individuals with obesity, MASLD, and T2D,[30] and studies in newborn infants suggest that FGF21 is involved in early growth and development.[31] HAOX1 is a liver-specific peroxisomal enzyme, and

emerging evidence has linked it to chronic liver disease.[32] Leptin is a key player in fat mass regulation and appetite control, and it has been implicated in the regulation of early adiposity.[26] Higher birth weight was associated with higher levels of three plasma proteins, CX3CL1, TWEAK, and LPL. CX3CL1 is a chemokine with anorexigenic actions shown to suppress high fat diet-induced hypothalamic inflammation in mice.[33] TWEAK plays a role in cellular events including proliferation, migration, differentiation, apoptosis, angiogenesis, and inflammation.[34] LPL is a key enzyme in triglyceride metabolism and is involved in lipid clearance from the bloodstream, lipid utilisation, and lipid storage.[35]

We found significant interactions between birth weight and obesity on the associations with 14 plasma proteins. Notably, the associations between birth weight and plasma levels of IL15RA, XCL1, and MCP1 were negatively associated in individuals with obesity, with opposite direction of effects in those with normal weight (Fig. 2b–d). IL15RA is the receptor of interleukin 15, expressed in the adipose tissue. IL15RA knockout mice are leaner than wildtype mice, have enhanced fatigue resistance, and increased exercise capacity.[36] XCL1 is a cytokine with chemotactic activity for lymphocytes, and studies have shown that individuals with obesity exhibit higher levels of XCL1 in subcutaneous adipose tissue.[37] MCP1 (or CCL2) is a chemokine expressed in adipose tissue, where the abundance is higher in obesity, MCP1 is a known marker of perturbed white adipocyte function.[38] In summary, these findings reveal intriguing interactions between birth weight and obesity, particularly in their associations with specific plasma proteins such as IL15RA, XCL1, and MCP1, shedding light on potential mechanisms driving adipocyte dysfunction in children with low birth weight.

Several studies have provided evidence that associations between lower birth weight and increased risk of cardiometabolic disease in adulthood is partly due to shared genetic effects.[9,10] In our study we found that a PGS for birth weight was inversely associated with GGT, glycemic traits, glucagon, and blood pressure (Fig. 3a). This indicates that increased risk of cardiometabolic disease due to the genetic pleiotropy of birth weight may be detectable already in childhood. Conversely, the PGS for birth weight was positively associated with BMI SDS and waist SDS, which is in line with previous findings of shared genetic loci between birth weight and childhood obesity.[39] A study in adults found that birth weight increasing variants were associated with increased adiposity in adulthood, but favourable metabolic outcomes.[39] The PGS for birth weight was not associated with lipid related traits in the present study, in line with previous studies,[10] suggesting that the association between lower birth weight and an unfavourable lipid metabolism later in life may mainly be due to fetal programming effects, as opposed to genetic effects.

The large study group of children and adolescents with obesity in comparison with previous studies is considered a strength of the present study. The obesity clinic and population-based groups are both deeply phenotyped, with thorough clinical examinations and biochemical analyses as well as genotypes in a subset of individuals. In addition, birth weight was obtained through medical records, as opposed to a potentially biased parent/guardian recall. Many previous studies in adults have used self-reported obesity in childhood which is also subject to bias. Linearity of the models was assessed and spline models were performed, with no significant differences when compared to the linear models, data not shown. Access to case records on diagnoses and medications allowed for exclusion of relevant diseases.

Limitations include the cross-sectional design of the study. A longitudinal approach could enable an investigation of the temporality implied in the mechanisms underlying the associations between birth weight, birth weight genetics, postnatal growth patterns, childhood obesity, and the subsequent risk of developing CMD in adulthood, which would require longer follow-up. Also, information on maternal and paternal BMI and mode of delivery were not available. The difference in Tanner stage assessment between the two groups is considered a limitation, as it was assessed by a paediatrician in the obesity clinic group this might have introduced selection bias, reflected in a higher mean age of individuals with missing data in the obesity clinic group compared to the population-based group. This could explain why there is a higher percentage of prepubertal children in the obesity clinic group. While it is a strength of the study that we were able to include information on pregnancy complications (preeclampsia and GDM) this information is self-reported and might be underestimated as illustrated by the very few cases of especially GDM in the population-based group.

Our findings indicate that early life programming and genetic determinants of birth weight associaste with cardiometabolic disease risk in childhood and that the associations are more pronounced in children with obesity. Thus, supporting the theory that low birth weight individuals exhibit a distinct phenotype that may be more vulnerable to health hazards – such as excess weight gain – throughout the course of life. This study underlines the importance of early intervention and prevention in the effort to combat the pandemic of obesity and cardiometabolic disease.

Contributors

S.E.S. contributed to the conceptualization, statistical layout and design of the study, performed analysis of the data, drafted the initial manuscript, and revised the final manuscript. P.K.R. contributed to the conceptualization, statistical layout and design of the study, drafted the initial manuscript and revised the final manuscript. M.A.V.L. recruited participants, collected and prepared clinical data, and revised the final manuscript. U.L.T. was involved in collecting data and revised the final

manuscript. L.A.H. and C.E.F. recruited participants, collected data, and revised the final manuscript. Y.H. was involved in analysis of the data and revised the final manuscript. C.B., A.V., M.T., and A.K. were involved in interpretation and revised the final manuscript. N.G. was involved in the generation of genetic data and revised the final manuscript. O.P. was involved in conceptualization and revised the final manuscript. M.C. was involved in generation of biochemical data and conceptualization. L.A. and T.I.A.S. were involved in statistical analysis and revised the final manuscript. J.C.H. and T.H. were involved in conceptualization, design of the studies, obtaining funding, supervision, and revised the first and final manuscript. All authors reviewed and revised the final manuscript. S.E.S. and P.K.R. had full access to all the data and had final responsibility for the decision to submit for publication.

Data sharing statement

The data presented in this study are not publicly available due to ethical restrictions because they relate to information that could compromise research participant privacy or consent. Permission to access and analyse data can be obtained following approval from The Danish Data Protection Agency and the ethics committee for the Region Zealand, Denmark. All analysis results are available as Supplementary Tables.

Declaration of interests

C.E.F. has received speaker honoria from The Danish Society for General Practice, Novo Nordisk, Nestlé and payment for manuscript writing from The Danish Health Authority. C.B. and T.H. have stocks in Novo Nordisk. A.K. receives royalties from Gyldendal, payment for lectures from Norgine, Siemens, Nordic Bioscience, Novo Nordisk. A.K. has two patents planned/pending, participates on an advisory board for Norgine, Siemens, Novo Nordisk, B&I. A.K. has a leadership role as the Secretary General European Association for the Study of The Liver (EASL) 2023–2025. A.K. has received equipment, materials, and drugs from Norgine (Rifaximin), Siemens (ELF Test), Echosence (FibroScan), and Nordic Bioscience (ECM markers). A.K. has finical interest as the Board member and co-founder Evido. J-C.H. has received payment for expert testimony from Novo Nordisk and support for meetings and travel from Rhytm, provides training and treatment of obesity. We declare no other competing interests from remaining coauthors.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ebiom.2024.105205.

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