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Change in adiposity is associated with change in glycoprotein acetyls but not hsCRP in adolescents with severe obesity

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ABSTRACT

Background: Obesity-associated chronic inflammation mediates the development of adverse cardiometabolic outcomes. There are sparse data on associations between severe obesity and inflammatory biomarkers in adolescence; most are cross-sectional and limited to acute phase reactants. Here, we investigate associations between adiposity measures and inflammatory biomarkers in children and adolescents with severe obesity both cross-sectionally and longitudinally.

Methods: From the Childhood Overweight Biorepository of Australia (COBRA) study, a total of n = 262 participants, mean age 11.5 years (SD 3.5) with obesity had measures of adiposity (body mass index, BMI; % above the 95th BMI-centile, %>95th BMI-centile; waist circumference, WC; waist/height ratio, WtH; % total body fat, %BF; % truncal body fat, %TF) and inflammation biomarkers (glycoprotein acetyls, GlycA; high-sensitivity C-Reactive Protein, hsCRP; white blood cell count, WBC; and neutrophil/lymphocyte ratio, NLR) assessed at baseline. Ninety-eight individuals at mean age of 15.9 years (3.7) participated in a follow-up study 5.6 (2.1) years later. Sixty-two individuals had longitudinal data. Linear regression models, adjusted for age and sex for cross-sectional analyses were applied. To estimate longitudinal associations between change in adiposity measures with inflammation biomarkers, models were adjusted for baseline measures of adiposity and inflammation.

Results: All adiposity measures were cross-sectionally associated with GlycA, hsCRP and WBC at both time points. Change in BMI, %>95th BMI-centile, WC, WtH and %TF were associated with concomitant change in GlycA and WBC, but not in hsCRP and NLR.

Conclusion: GlycA and WBC but not hsCRP and NLR may be useful in assessing adiposity-related severity of chronic inflammation over time.

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Introduction

Obesity in childhood and adolescence is a leading modifiable risk factor for adult morbidity including hypertension, dyslipidaemia and type 2 diabetes mellitus (T2DM), and for premature cardiovascular disease (CVD) [1] and CVD mortality [2,3]. Children and adolescents with more severe obesity also have a higher prevalence of other CVD risk factors [4], including increased blood pressure, type 2 diabetes, and higher levels of apolipoprotein B (apo-B)-containing lipoproteins. Although mechanisms are incompletely understood, stress related to adipose tissue expansion [5] and dietary factors activating peripheral immune cells [6] contribute to chronic inflammation. Acute and chronic inflammatory pathways are well-established drivers for CVD events [7, 8], and many of those pathways are part of an obesity-related metabolic inflammation that links excessive adiposity with obesity-related adverse outcomes [9,10].

High-sensitivity C-reactive protein (hsCRP) [11] is the most widely used inflammatory marker for CVD risk stratification, but there is little evidence for a causal link between hsCRP and atherosclerosis [12,13]. White blood cells (WBC) and neutrophil/lymphocyte ratio (NLR) showed modest improvement in prediction compared to traditional CVD risk factors for 10-year CVD risk [14]. Recently, glycoprotein acetyls (GlycA), a nuclear magnetic resonance (NMR) signal in human blood, has been described as a superior marker of cumulative and chronic inflammation [15,16]. GlycA is a composite measure of circulating plasma proteins (including alpha-1-acid glycoprotein, alpha-1 antitrypsin, alpha-1 antichymotrypsin and haptoglobin) which received N-acetyl-glycosylation on their glycan portions [17]. Glycoproteins contributing to the GlycA signal were first denoted as part of an inflammatory acute-phase response, however GlycA has subsequently been associated with a range of chronic inflammatory conditions including obesity [18], as well as cognitive decline, cancer, and CVD-related [19] and all-cause mortality [20].

Studies in adolescents investigating cross-sectional and longitudinal relationships of adiposity measures with GlycA and other inflammatory biomarkers are scarce. Obesity in childhood strongly tracks into adolescence and adulthood [21]. Better understanding of the inflammatory associations of obesity earlier in life may help guide development and assessment of earlier intervention. Here, we investigated the relationship between adiposity measures (body mass index, BMI; the severity of obesity in percentage above the BMI-centile threshold, %>95th BMI-centile; waist circumference, WC; waist to height ratio, WtH; body fat, %BF; truncal fat, %TF) and inflammatory biomarkers (GlycA, hsCRP, WBC and NLR) in early and late adolescence, and whether longitudinal changes in adiposity measures were reflected in concomitant changes in these inflammatory biomarkers.

Methods

Study population

Participants were enrolled in the Childhood Overweight Biorepository of Australia (COBRA) study. COBRA is comprised of a total of 438 children and adolescents with obesity (BMI ≥95th centile using US Centres for Disease Control (CDC) growth reference charts [22]), recruited at the Royal Children's Hospital (Melbourne, Australia) Weight Management Service between 2009 and 2018 [23]. From COBRA participants, a total of 262 individuals had an initial blood sample collected for the analysis of inflammation biomarkers at baseline. COBRA participants, who consented for recontact for further studies, were asked to participate for a follow-up cardiovascular risk study. From the initial COBRA cohort, a total of 98 adolescents (up to 25 years of age) consented for follow-up (Fig. 1). A total of 62 individuals had data on adiposity and inflammatory biomarkers assessed at both timepoints with a mean interval of 5.6 years. Written informed consent was obtained from the participant aged >18 years or their legally authorised representative if <18 years. Assent was additionally obtained from all participants aged >14 years. The study protocol was in accordance with Helsinki principles and was approved by the Royal Children's Hospital Human Research Ethics Committee (HREC Ref. # 28081Q).

Adiposity and socioeconomic status

At both time points, identical protocols were used for anthropometric measurements: height, weight, BMI, %>95th BMI-centile, WC, WtH, %BF and %TF. Participants wore light clothes and no shoes during these measurements. Weight (kg), %BF and %TF were measured with a four-point bio-impedance device (Tanita Corporation, Tokyo, Japan). Fat percentage measurements have been validated in children aged 5 or older [24], so measurements from any participants <5 years of age were excluded. WC was measured midway between iliac crest and lower end of ribs to the nearest 0.5 cm with a non-stretchable meter. Height (m) was measured using a Harpenden stadiometer (Holtain Ltd., Crymych, Dyfed, UK). WtH ratio was calculated as WC divided by height in centimetres. BMI was calculated as weight divided by height squared. %>95th BMI-centile was derived from CDC reference charts matched for age and sex [22]. Briefly, %>95th BMI-centile is a continuous measure

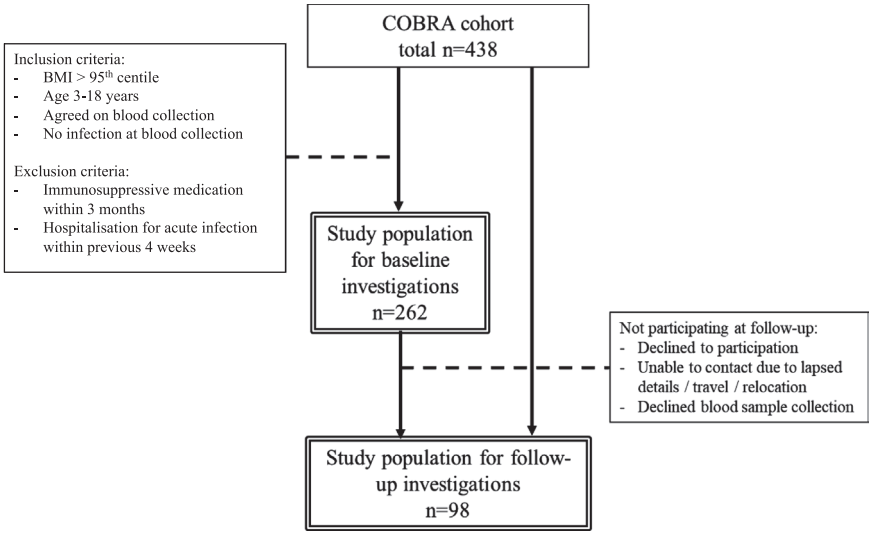

Fig. 1. Flowchart of participants from COBRA cohort that had available inflammation data for this study at each time point (double-bordered boxes).

starting from the 95th BMI-centile, and is a ratio of the individual's BMI divided by the relevant 95th BMI-centile for an age- and sex-matched individual multiplied by 100 %: e.g. the 95th BMI-centile for a male adolescent aged 14 years is 26 kg/m^2, such that if this participant's BMI was 32 kg/m^2, the %>95th BMI-centile is (32/26) x 100 % = 123 %). The %>95th BMI-centile has advantages for tracking longitudinal changes in severity of obesity compared to BMI z-score, particularly in paediatric populations with severe obesity [25]. Severe obesity is defined as ≥120 %>95th BMI-centile [26]. Pubertal development was assessed at baseline and follow-up by an experienced paediatrician using Tanner staging: Tanner 1 was considered pre-pubertal, Tanner 2 or 3 was peri-pubertal, and Tanner 4 or 5 was post-pubertal [27]. Socio-economic status was assessed at baseline using the 2016 Socio-Economic Indexes for Areas (SEIFA) [28] Index of Relative Socioeconomic Disadvantage (IRSD), which is based on residential postcode. A lower IRSD score indicates a greater level of disadvantage.

Inflammatory markers

Blood samples at baseline and follow-up were processed to serum within 2 h and stored at −80 °C. Blood was not collected at baseline or at follow-up if the participant was known to have a current infection based on history and clinical examination. Serum GlycA was quantified using a nuclear magnetic resonance metabolomic platform (Nightingale Health, Helsinki, Finland) as previously described [29]. hsCRP was measured using ELISA (R&D Systems, Minneapolis, Minnesota), according to manufacturer's instructions. Baseline and follow-up measurements of hsCRP were performed with the same assay. Measurements equal to 0 (below the limit of detection) for hsCRP were replaced with values equal to half the lowest non-zero measurement (considered as the lower limit of detection) (n = 5 at baseline and n = 1 at follow-up). Participants with hsCRP greater than 20 mg/L were excluded from the main analyses (n = 8 at baseline, n = 0 at follow-up), as high hsCRP levels suggest acute inflammation, usually infection. Sensitivity analyses including participants with hsCRP >20 mg/L did not alter the findings (data not shown). WBC and differentials were measured in a clinical laboratory prior to blood processing using standard analysis.

Statistical analyses

Descriptive analyses of continuous variables were reported as mean, standard deviation (SD) and minimum-maximum (min-max) range, and categorical variables were reported as absolute numbers and percentage. To ensure representativeness of participants and generalizability of the findings within the COBRA cohort, demographic characteristics (age, sex) and age-standardized measures of adiposity and inflammation biomarkers were compared between i) participants with longitudinal data and participants with only baseline data, ii) participants with longitudinal data and participants with only follow-up data, and iii) between participants with only follow-up data and participants with only baseline data. Inflammation markers were natural log-transformed for correlation and regression analyses. Spearman's correlations (*rho*) were calculated between values of inflammatory marker across both time points. Linear regression modelling was used to investigate associations between adiposity measures (exposure) and inflammatory biomarker (outcome) cross-sectionally, adjusted for age at the relevant timepoint and sex. For the models investigating change between time points, the follow-up adiposity measure was the independent variable of interest, and the follow-up inflammation measure the dependent variable, adjusted for corresponding baseline measures, sex and age at each time point.

Analyses were performed in R (v3.6.1) [30]. Estimated effect sizes are reported in natural units. For % >95th BMI-centile, we reported steps of 5 % units. In figures, WtH units have been multiplied by ×0.01 to facilitate shared axes. In secondary analyses, sex-stratified models, and additional adjustment of models for socioeconomic and pubertal status were evaluated. We also considered adiposity-by-sex and adiposity-by-pubertal status interaction effects on inflammatory outcome measures.

Results

At baseline, there were 262 participants, mean age 11.5 years (SD 3.5), BMI 32.7 kg/m^2 (SD 7.4), and at follow-up 98 participants, mean age 15.9 years (SD 3.7), BMI 35.6 kg/m^2 (SD 7.9), with data for at least one adiposity and one inflammatory measure (Table 1). A total of 62 participants had data at both time points (mean interval 5.6 years, SD 2.1, range 1.9–9.1) (Table 1). Participants with data at both time points were younger at baseline than those with only baseline data (mean age 10.6 years, n = 62 vs. 11.7, n = 200), but otherwise did not differ by sex, age-standardised measures of adiposity, or inflammation at baseline. Participants with data at both time points did not differ from those with only follow-up data across any measures used in this study. Participants who had data at follow-up were younger at baseline than those without (mean age 10.4 years, n = 98 vs. 11.7, n = 200), but did not differ by age-standardised characteristics.

At each timepoint (baseline and follow-up), log-transformed inflammatory markers were positively correlated with each other (baseline: Spearman's *rho* 0.23 – 0.39, p = <0.001 – 0.001, Supplementary Table S1; follow-up: Spearman's *rho* 0.25 – 0.44, p = <0.001 – 0.02, Supplementary Table S2). The correlation of inflammation markers longitudinally from baseline to follow-up was highest for WBC (*rho* = 0.49, p = 0.002) and GlycA (*rho* = 0.38, p = 0.003), followed by NLR (*rho* = 0.29, p = 0.09) and hsCRP (*rho* = 0.16, p = 0.22).

At baseline, all adiposity measures (BMI, %>95th BMI-centile, WC, WtH, %BF and %TF) were positively associated with GlycA, hsCRP and WBC in age- and sex-adjusted models (Fig. 2A, Supplementary Table S3). At baseline, only the %> 95 BMI-centile was associated with NLR. At follow-up, all adiposity measures were associated with GlycA, hsCRP and WBC (Fig. 2B, Supplementary Table S3), and the %> 95th BMI-centile, %BF and %TF were associated with NLR.

In models of change in adiposity and inflammation between time points, increases in all adiposity measures were associated with an increase in WBC, and all except %TF were associated with GlycA (Fig. 3, Supplementary Table S3).

In sex-stratified models, generally similar patterns of associations between adiposity and inflammation markers were observed. Cross-sectional associations of BMI and the %> 95th BMI-centile with NLR at baseline appeared to be specific to males. Associations between longitudinal change in adiposity and change in GlycA appeared to be stronger for males for the majority of adiposity measures, while associations of change in adiposity and change in total white blood cell count were generally more evident in females (Supplementary Fig. S1, S2).

Additional adjustment for socioeconomic or pubertal status did not alter the results (data not shown). There was minimal evidence for adiposity-by-sex or adiposity-by-pubertal-status interaction effects on inflammation for any time period (data not shown).

Discussion

In this study of adolescents with severe obesity, we report evidence for cross-sectional associations between higher adiposity and higher inflammation (for GlycA, WBC, hsCRP and NLR) at baseline and at follow-up, and longitudinal associations between change in adiposity and change in inflammation over a mean of 5.6 years (for GlycA and WBC, but not for hsCRP or NLR). These findings suggest that GlycA and WBC, but not hsCRP or NLR, reflect longitudinal change in adiposity-associated inflammation.

Several factors may contribute to the observed differences in the performance of GlycA versus hsCRP with respect to adiposity-related chronic inflammation. First, GlycA represents units of glycoprotein N-acetyl methyl groups, which are attached to the glycan portions of many

Table 1
Characteristics of total cohort at baseline and follow-up and subgroup with longitudinal data.

	Total Cohort				Subgroup with longitudinal data			
	Baseline		Follow-up (mean 4.4 y difference)		Baseline		Follow-up (mean 5.6 y difference)	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Sex	262		98		62		62	
female		140 (53 %)		47 (48 %)	30	48	30	48
male		122 (47 %)		51 (52 %)	32	52	32	52
Pubertal stage	260		98		60		62	
pre-pubertal		108 (42 %)		8 (8 %)		27 (45 %)		5 (8 %)
peri-pubertal		66 (25 %)		16 (16 %)		16 (27 %)		7 (11 %)
post-pubertal		86 (33 %)		74 (76 %)		17 (28 %)		50 (81 %)
	N	mean (SD)	N	mean (SD)	N	mean (SD)	N	mean (SD)
Age (years)	262	11.5 (3.5)	98	15.9 (3.7)	62	10.6 (3.5)	62	16.2 (3.6)
Height (m)	262	1.5 (0.2)	98	1.7 (0.1)	62	1.5 (0.2)	62	1.7 (0.1)
Weight (kg)	262	79.4 (31.3)	98	101.8 (30.5)	62	73.3 (30.5)	62	105.3 (31.4)
Body mass index (kg/m^2)	262	32.7 (7.4)	98	35.6 (7.9)	62	31.2 (6.6)	62	36.6 (8.1)
% > 95th BMI-centile	262	136.7 (22.4)	98	129.7 (26.1)	62	135.2 (21.2)	62	132.0 (26.7)
Waist circumference (cm)	217	101.4 (20.2)	77	105.2 (16.3)	50	96.0 (18.7)	48	106.8 (17.4)
Waist to height ratio	217	0.7 (0.1)	77	0.6 (0.1)	50	0.6 (0.1)	48	0.6 (0.1)
Body fat (%)	218	42.5 (8.3)	96	40.3 (9.7)	49	41.3 (7.1)	60	41.2 (10.1)
Truncal fat (%)	210	36.5 (8.9)	96	36.3 (9.5)	48	34.6 (7.4)	60	37.4 (9.8)
GlycA (mmol/L)	259	1.32 (0.17)	98	1.11 (0.11)	60	1.33 (0.19)	62	1.11 (0.11)
high-sensitivity CRP (mg/L)	258	3.47 (3.50)	98	1.96 (2.22)	60	2.89 (3.23)	62	2.06 (2.57)
White cell count (10^9/L)	188	7.55 (1.90)	90	7.33 (1.78)	41	7.81 (2.08)	58	7.36 (1.74)
Neutrophiles	191	3.93 (1.46)	90	4.19 (1.31)	41	4.07 (1.73)	58	4.23 (1.24)
Lymphocytes	190	2.84 (0.86)	90	2.43 (0.71)	40	2.99 (0.86)	58	2.43 (0.69)
Neutrophil/Lymphocyte	189	1.47 (0.64)	90	1.82 (0.69)	39	1.45 (0.72)	58	1.84 (0.72)

Participant characteristics of the total cohort at baseline and follow-up in the left column. Participant characteristics of the subgroup with longitudinal data at baseline and follow-up in the right column. Results are provided in mean, standard deviation (SD) for continuous variables and in absolute number of individuals (n) and the proportion in percentage (%). The % > 95th BMI-centile indicates the severity of obesity based on the age- and sex-adjusted 95th BMI-centile (i.e., the threshold for obesity) as described in the methods section. Pubertal status was determined according to Tanner stages: Pre-pubertal: Tanner stage 1; Peri-pubertal: Tanner stage 2 & 3; Post-pubertal: Tanner stage 4 & 5. BMI: body mass index; GlycA: Glycoprotein acetyls.

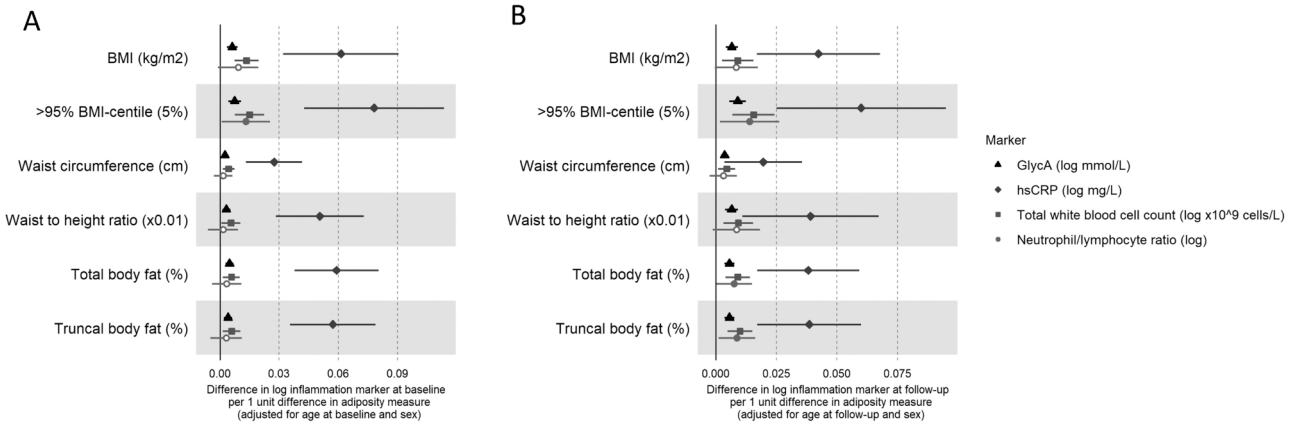

Fig. 2. Cross-sectional associations between adiposity measures and inflammation markers at baseline (**A**) and follow-up (**B**). Estimates are log unit change in inflammation marker per unit change in adiposity measure, adjusted for age and sex. Note that WtH has been scaled to x0.01 units for this figure. Closed points represent $p < 0.05$, open points are $p > 0.05$. Error bars are 95 % confidence intervals.

acute phase proteins during the process of glycosylation. The main purpose of glycosylation is to increase protein stability by protecting from degradation over a longer period [31]. In contrast, the plasma half-life of hsCRP is approximately 19 h, and its levels are largely determined by rate of synthesis [32], which in turn is driven by the intensity of the inflammatory response to the underlying, acute, pathological process [33].

Secondly, GlycA is a composite measure of a number of glycosylated acute phase proteins, thereby cumulatively reflecting many aspects of innate humoral immune pathways [34]. The most abundant of these acute phase proteins include alpha-1-acid glycoprotein, alpha-1 antitrypsin and haptoglobin [19]. Levels of serum amyloid A, hsCRP (as in this study) and tumor necrosis factor alpha [35] may also contribute to the GlycA level, but the degree of glycosylation of these proteins is low and their concentrations are much lower compared to levels of alpha-1-acid glycoprotein, alpha-1 antitrypsin and haptoglobin, so their contribution to the GlycA signal is considered neglibile [35].

Thirdly, levels of hsCRP are predominantly induced by measures interleukin-6 on hepatocytes [36], whereas acute phase proteins contributing to the GlycA signal are produced by the liver and neutrophils [19,37].

GlycA and hsCRP have clinical utility in risk stratification for CVD and mortality [15,20] and each are independently associated with later CVD after mutual adjustment [38], suggesting they capture different, albeit overlapping inflammatory pathways. Here, adiposity measures were cross-sectionally associated with both GlycA and hsCRP, whereas an increase or decrease in adiposity over a mean interval of 5.6 years was only associated with a concomitant change in GlycA. Longitudinal

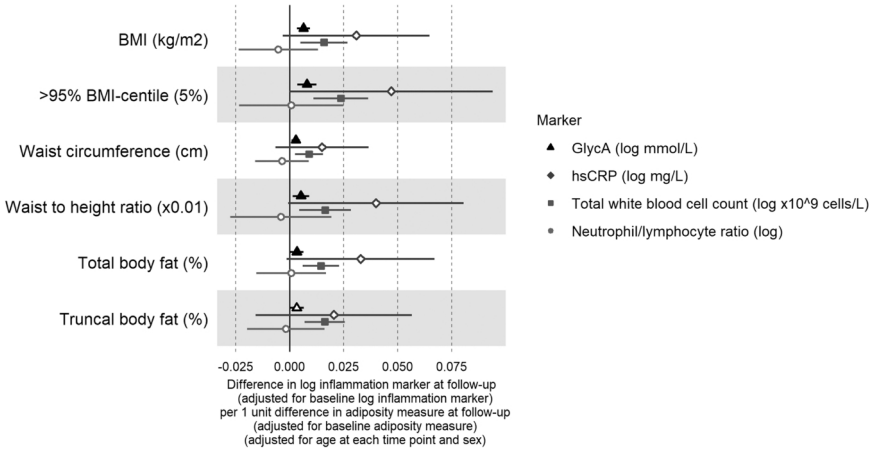

Fig. 3. Associations between change in adiposity (follow-up adiposity adjusted for baseline adiposity) and change in inflammation (follow-up adjusted for baseline) between time points, adjusted for age and sex. Note that WtH has been scaled to x0.01 units for this figure. Closed points represent $p < 0.05$, open points are $p > 0.05$. Error bars are 95 % confidence intervals.

associations between change in adiposity and change in hsCRP were not evident. Together with increasing evidence for associations between GlycA and obesity-related adverse cardiometabolic outcomes [16,20], and the evidence provided in this population that change in obesity parallels change in GlycA, we hypothesize that GlycA may be a superior clinical inflammatory marker for risk stratification. However, further studies in different populations with larger sample size and longer follow-up are needed to support this hypothesis.

Both WBC and NLR have been associated with CVD and metabolic risk factors [39,40], and WBC is reduced following bariatric surgery [41]. Here, adiposity measures were strongly associated with WBC cross-sectionally and longitudinally. In contrast, we only found cross-sectional associations between adiposity measures and NLR, with no evidence for longitudinal associations, consistent with adult data [42]. These findings suggest that in adolescents with obesity, NLR may have less clinical utility as an inflammatory biomarker than GlycA or WBC.

A positive correlation between BMI and WBC particularly in women with obesity has been reported [43], in line with our results for associations between change in adiposity and change in WBC predominantly in adolescent females. In a study investigating 7997 adolescents (3738 females) aged 10–18 years, individuals with obesity had higher levels of WBC compared to individuals with overweight or normal weight [44]. In addition to WBC, absolute neutrophil and lymphocyte counts are also increased with higher BMI in women, with a larger effect size reported for neutrophils than lymphocytes [45].

The strengths of our study are the assessment of several adiposity measures and inflammatory biomarkers in a unique longitudinal adolescent cohort with severe obesity. Our findings are relevant to the increasing number of children and adolescents living with obesity, which often persists into adulthood [46]. Limitations include firstly a lack of a comparison group with normal weight. Second, the number of participants with complete data at both time points was relatively modest, limiting statistical power. This attrition reflects the inherent difficulties in retention of adolescents in longitudinal studies [47]. The lack of race/ethnic diversity and sample size also limits the generalisability of our findings and replication in other settings – particularly studies including ethnic minorities – is warranted. However, sensitivity analyses did not show differences in measures for adiposity or inflammation biomarkers between subpopulations investigated at baseline, at follow-up, nor in longitudinal analyses. Lastly, the study design does not allow for causal inference between adiposity and inflammation. However, there is growing evidence for change in adiposity preceding concomitant change in inflammation, as shown in studies using Mendelian randomisation to assess effects of adiposity on GlycA [18] and as reported for concordant reductions in GlycA after weight loss related to bariatric surgery [48].

Conclusion

In adjusted models, all adiposity measures were associated with cross-sectional measures of GlycA, hsCRP, WBC and NLR in both early and later adolescence. Changes in adiposity measures were most evident with concomitant changes in GlycA and WBC (but not for the widely used hsCRP), suggesting that reduction in adiposity severity may be associated with less inflammation, and plausibly with lower subsequent risk of obesity-related CVD. Replication in longitudinal studies involving clinical CVD endpoints is warranted.

CRediT authorship contribution statement

TM, SB, DB and CS conceptualised and developed the study. MAS and RS established the cohort, supervised the data collection and critically revised the manuscript. BEH, ZM, KTK and AV collected data and critically revised the manuscript. TM undertook statistical analysis. CGM assisted with the statistical analysis plan and provided support in interpreting the results. TM, SB, DL, DB and CS drafted the manuscript. MJ and RS revised the manuscript for important intellectual content. All authors provided expert advice and critical review of the manuscript, approved the final version and agreed on accountability for all aspects of the work related to accuracy and integrity.

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Declaration of Competing Interest

The authors declare no conflict of interest.

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Disclosure summary

The authors have nothing to disclose.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.orcp.2023.08.003.

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