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Increased central adiposity is associated with pro-inflammatory immunoglobulin G *N*-glycans

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ABSTRACT

Background: Increased body fat may be associated with an increased risk of developing an underlying pro-inflammatory state, thus leading to greater risk of developing certain chronic conditions. Immunoglobulin G has the ability to exert both anti- and pro-inflammatory effects, and the *N*-glycosylation of the fragment crystallisable portion is involved in mediating this process. Body mass index, a rudimentary yet gold standard indication for body fat, has been shown to be associated with agalactosylated immunoglobulin G *N*-glycans.
Aim: We aimed to determine the association between increased body fat and the immunoglobulin G glycosylation features, comparing body mass index to other measures of body fat distribution.
Methods: We investigated a sample of 637 community-based 45–69 year olds, with mixed phenotypes, residing in Busselton, Western Australia. Body mass index and the waist-to-hip and waist-to-height ratios were calculated using anthropometry, while dual-energy x-ray absorptiometry was performed to gain an accurate measure of total and area specific body fat. Serum immunoglobulin G*N*-glycans were analysed by ultra-performance liquid chromatography.
Results: Twenty-two *N*-glycan peaks were found to be associated with at least one of the fat measures. While the previous association of body mass index to agalactosylated immunoglobulin G was replicated, measures of central adiposity explained the most variation in the immunoglobulin G glycome.
Conclusion: Central adiposity is associated with an increased pro-inflammatory fraction of immunoglobulin G, suggesting that the android/gynoid ratio or waist-to-height ratio instead be considered when controlling for adiposity in immunoglobulin G glycome biomarker studies.

1. Introduction

People who are considered clinically overweight or obese are at an increased risk of developing an array of chronic conditions, including cardiovascular disease, metabolic syndrome and diabetes (Festa et al., 2001; Panagiotakos et al., 2005), as well as inflammatory disorders like rheumatoid arthritis (Crowson et al., 2013) and systemic lupus erythematous (Tedeschi et al. 2017). Although overweight and obesity

Abbreviations: A/G ratio, dual-energy X-ray absorptiometry-measured android/gynoid ratio; BMI, body mass index; CRP, C-reactive protein; DXA, dual-energy X-ray absorptiometry; Fc, fragment crystalisable; FcγR, fragment crystallisable gamma receptor; GP, glycan peak; IgG, immunoglobulin G

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are considered major, modifiable risk factors (Panagiotakos et al., 2005), incidence is on the rise worldwide (Geiss et al., 2014). This is particularly true in developing nations, whereby an increased acceptance of the 'Western lifestyle' may have contributed to the problem (Gupta et al., 2012).

Increased levels of body fat may lead to an increased risk of chronic disease through the presence of chronic, subclinical inflammation (Festa et al., 2001; Alissa et al., 2016). This link is particularly true for central body fat (Fontana et al., 2007; Koster et al., 2010). Koster et al. (2010) found total body mass does not differ between obese people with or without metabolic syndrome, only a body fat distribution with a greater proportion of central or visceral body fat differs (Koster et al., 2010). Indeed, visceral fat is an endocrine organ in its own right that secretes adipokines, such as interleukin-6 (IL-6), adiponectin and leptin (Fontana et al., 2007). In particular, IL-6 measured in the portal vein, which drains visceral fat and is the major source of blood to the liver, correlates with systemic C-reactive protein (CRP), both associated with systemic inflammation, and thus may be a physiological indication of the association between visceral body fat and inflammation (Fontana et al., 2007; Gaens et al., 2015).

Immunoglobulin G (IgG) is an important effector glycoprotein that links the innate and adaptive branches of the immune system. It has the ability to exert both anti-inflammatory and pro-inflammatory responses throughout the body, which are triggered by antigen recognition and are dependent on its affinity for a number of different activating or inhibitory fragment crystallisable receptors (FcRs) and complement factors (Quast et al., 2017; Russell et al., 2018). These immune responses are largely modulated by the fragment crystallisable (Fc) domain of the IgG glycoprotein (Fig. 1).

The IgG-Fc sugar moieties, hereon known as *N*-glycans, affect the affinity of the Fc domain for several different FcRs and complement factors, ultimately initiating different cellular events that lead to an array of inflammatory responses (Pincetic et al., 2014; Dekkers et al., 2017; Quast et al., 2017; Russell et al., 2018). The glycosylation of the IgG-Fc domain is a predesigned outcome of the producing B cell and variation in IgG glycosylation has physiological significance (Pučić et al., 2011; Lauc et al., 2013; Maratha et al., 2016). Indeed, it influenced by both genetic and environmental factors (Lauc et al., 2016). Hundreds of genes are associated with glycan biosynthesis (Krištić et al., 2014a,b; Wahl et al., 2018), and different inflammatory factors may influence B cells during activation and differentiation, modulating the glycosylation of secreted IgG (Wang et al., 2011; Wahl et al., 2018). Furthermore, the IgG glycome is fairly stable over short periods of time, and modifications can result from biological and chronological age (Krištić et al., 2014a,b; Yu et al., 2016; Wang et al., 2016), as well as altered cellular environment and disease status (Vučković et al., 2015; Adua et al., 2017; Russell et al., 2017; Russell et al., 2018).

Aside from ageing and disease presence, factors such as hormone levels (Chen et al., 2012; Engdahl et al., 2017; Ercan et al., 2017), lipid profile parameters (high-density lipoprotein, low-density lipoprotein, total cholesterol, and triglyceride), fasting blood glucose and blood pressure (Wang et al., 2016), among others, are associated with variation to the IgG glycome.

More recently, increases in body fat parameters, such as waist circumference and body mass index (BMI), have been suggested to be associated with the increased pro-inflammatory potential of IgG (Perkovic et al., 2014; Yu et al., 2016; Wang et al., 2016). Perkovic and colleagues (2014) first reported an increase in BMI to be associated with an increase in agalactosylated biantennary IgG *N*-glycans, an IgG glycan profile considered to be more pro-inflammatory (Vučković et al., 2015; Dekkers et al., 2018). Though the result was statistically significant, they found BMI only explained 2% of the variation in the study (Perkovic et al., 2014). Thus, although evidence of the association between body fat and IgG galactosylation exists, BMI may not be the best predictive measure.

We hypothesised that more accurate measures of body fat distribution may be able to explain greater variation in the IgG glycome, and therefore compared the anthropometry measured fat variables BMI, waist-to-hip ratio (WHR) and waist-to-height ratio (WHtR) against various measures taken using dual-energy x-ray absorptiometry (DXA).

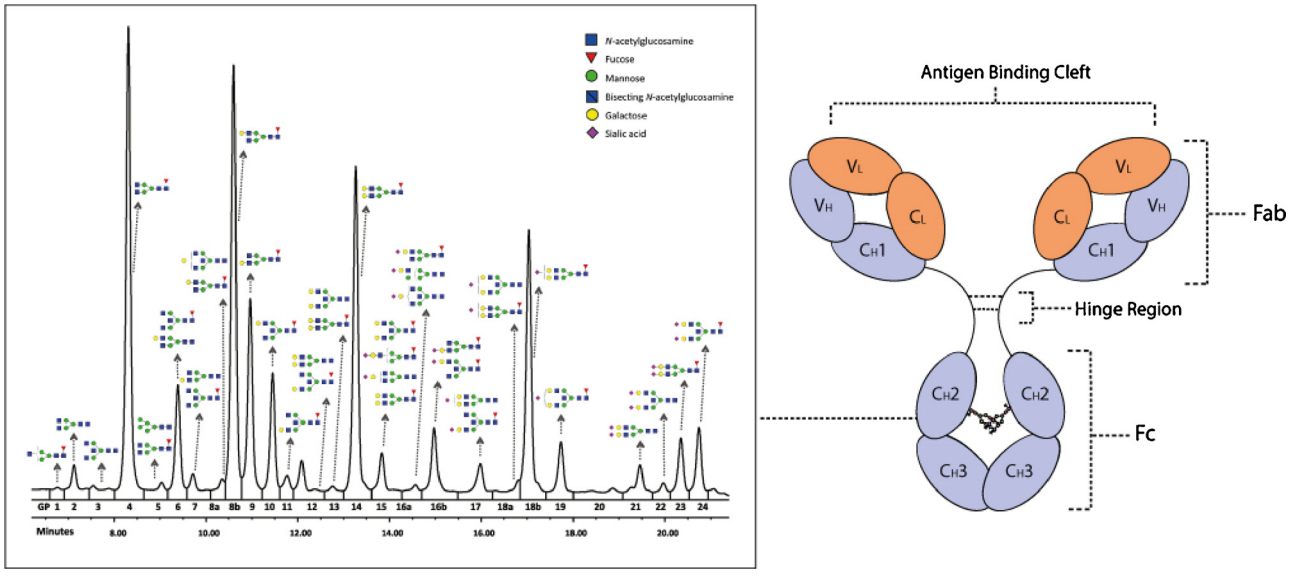

Fig. 1. IgG and the associated *N*-glycan moieties that constitute the IgG glycome chromatogram. Consisting of both heavy chains ('$_H$') and light chains ('$_L$'), the IgG glycoprotein has two domains that infer different properties; the fragment antigen-binding (Fab) and fragment crystallisable (Fc) domains. The Fab and Fc are connected by a hinge containing disulphide bonds, which differ depending on the IgG subclass. The Fab domain is responsible for recognising and binding antigen. The Fc domain contains two glycans attached to conserved regions of the C_H2, and is responsible for effector functions by binding Fc receptors (FcRs) on natural killer and other inflammatory cells. Changes to the attached glycan moieties can significantly alter effector function of the IgG glycoprotein. The different glycan peaks (GPs), side figure, contain different known structures, and properties of these are inferred through population-based studies (figure components reproduced from Lauc et al., 2013 and Russell et al., 2018, with permission).

Table 1
Sample summary data.

Characteristics	Mean (SD)
Female *n (%)*	344 (54%)
Age *years*	57.58 (5.17)
DXA Total Fat *%*	34.99 (8.58)
DXA Android Fat *kg*	2.84 (1.31)
DXA A/G Ratio	0.66 (0.24)
BMI kg/m^2	28.76 (5.02)
WHR	0.91 (0.09)
WHtR	0.55 (0.08)

A/G Ratio: Android/gynoid ratio; BMI: Body mass index; DXA: Dual-Energy X-ray Absorptiometry; WHR: Waist-to-hip ratio; WHtR: Waist-to-height ratio.

2. Methods

2.1. Subjects

In total, the serum samples of 637 participants were utilised in this study. These were a subset of the Busselton Healthy Ageing Study: an ongoing cohort of community-dwelling Baby Boomers (n = 5107) from the Shire of Busselton, Western Australia (James et al., 2013). Participants completed a comprehensive questionnaire as part of the study. Further, they participated in a physical testing session and were given the option to provide a sample of their blood for laboratory-based analyses.

Blood samples were collected by phlebotomists, processed immediately and blood serum separated from whole blood was stored at −70 °C until further analysis. Samples of 100 µL aliquots of blood serum were used for the *N*-glycan analyses in this study.

This study was approved by local ethics committees in Australia, and written informed consent was obtained from all participants. This study conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

2.2. Dual-energy X-ray absorptiometry (DXA)

DXA scans were undertaken (GE Lunar Prodigy Pro densitometer) using encore Version 13 (GE Health) software. Full body densitometry scans are performed to measure regional body bone mineral content and fat mass. The percentage of total body fat, android fat, gynoid fat, and the android/gynoid (A/G) ratio were calculated. All body composition scans are manipulated to define custom regions of interest for specific fat compartmentalisation or distributive analyses (James et al., 2013).

2.3. IgG isolation and N-glycan analysis

IgG was isolated from blood serum using protein G monolithic plates (Pučić et al., 2011) as described previously (Trbojevic-Akmacic et al., 2017). *N*-glycan release and labelling of the samples were performed by the "*in solution*" method, as previously reported (Trbojevic-Akmacic et al., 2017). IgG *N*-glycans were separated by hydrophilic interaction chromatography on a Waters Acquity ultra-performance liquid chromatography (UPLC) instrument (Waters Corporation, Milford, MA, USA) into 24 glycan peaks (GPs) (Pučić et al., 2011).

2.4. Statistical analysis

UPLC measured *N*-glycans are subjected to experimental variability, resulting in non-biological, technical variability in the data. This can be controlled with normalisation methods and batch correction, which adjusts individual measurements to balance them across all samples and make them comparable. Raw *N*-glycan intensities were therefore normalised by total area: peak area of every GP in each sample was divided by the total chromatographic area of all GPs. Resulting GP values were relative abundances, with all GPs within each sample summing to a 100. Batch correction was performed using the ComBat method (R package "sva"; https://bioconductor.org/packages/sva/), in which the technical source of variation (which sample was analysed on which plate) was modelled as a batch coefficient. The estimated batch effects were subtracted from the measurements to correct for measurement error.

From 24 directly measured GPs, an additional 57 derived traits were calculated (**Supplementary** Table 1). These derived traits average particular glycosylation features (galactosylation, core fucosylation, sialylation, bisection) across different individual glycan structures, and consequently they are more closely related to individual enzymatic activities and underlying genetic polymorphisms. As derived traits represent ratios and sums of initial glycans, they were calculated using normalised and batch-corrected *N*-glycan measurements after transformation to the proportions (exponential transformation of batch-corrected measurements).

The association between glycan variables and the body fat parameters were explored using Spearman's correlation coefficient. Tests of equality for dependent variables were performed using a standard method (Steiger, 1980). The false discovery rate was controlled using the Benjamini-Hochberg procedure (Benjamini and Hochberg, 1995), thus adjusted *P*-values are shown throughout.

3. Results

In total, 637 participants had complete demographic, fat and IgG *N*-glycan data for this study (Table 1).

3.1. The association between different GPs and the fat distribution measures

In total, 22 GPs were found to be associated with at least one of the fat measures, with measures of central adiposity explaining the most variation in the IgG GPs. In total, 17 GPs were significantly associated with the A/G ratio, 14 with WHtR, 13 with android fat (central fat), 12 with BMI, and 9 with both DXA total body fat percentage and WHR (Table 2).

The A/G ratio and WHtR were associated with the most change to the total glycan composition, in terms of magnitude of association and number of significantly associated GPs to the fat measures. There was an overall trend for more pro-inflammatory glycan moieties (increased GP1 to GP6; Table 2) with an increase in the A/G ratio or WHtR. Out of all the fat distribution measures, the A/G ratio tended to explain the most variation in more glycosylation features when compared with the other fat measures (Table 3).

3.2. Galactosylation

The WHtR and the A/G ratio explained 3.87% and 3.61% of the variation in agalactosylation (G0n; Table 3), respectively. This was greater than the previously reported 2% explained variation by BMI (Perkovic et al., 2014), which was replicated in this study (1.86%; Table 3). The WHR explained the least amount of variation in agalactosylation (1.21%). Similar effect sizes for mono- (G1n) and digalactosylation (G2n) were shown (Table 3). The WHtR explained fractionally more variation in galactosylation than the A/G ratio, though this was not significant when tested using Fisher's r-to-z transformation; for G0n, $\rho_1 = 0.1900$,

$\rho_2 = 0.1967$, $\rho_3 = 0.5723$, n = 637, z = -0.187, $P = 0.8519$, where ρ_1, ρ_2, and ρ_3 are the correlations between the A/G ratio and G0n, the WHtR and G0n, and the A/G ratio and the WHtR, respectively.

Table 2
Spearman's correlations between glycan peaks (GPs) and different body fat measurements, adjusted for false discovery rate.

GP	DXA Total Fat %		DXA Android Fat (kg)		DXA A/G Ratio		WHR		BMI		WHtR	
	ρ	p-value	ρ	p-value	ρ	p-value	ρ	p-value	ρ	p-value	ρ	p-value
GP1	−0.0516	0.2532	−0.0022	0.9557	0.1051	**0.0194**	0.0868	0.0537	−0.0313	0.5086	0.0221	0.6401
GP2	0.0570	0.2055	0.0040	0.9258	−0.0251	0.6119	−0.0067	0.8778	−0.0081	0.8566	0.0199	0.6679
GP3	0.0893	**0.0498**	0.1261	**0.0058**	0.1612	**0.0004**	0.1226	**0.0065**	0.1017	**0.0216**	0.1668	**0.0002**
GP4	0.1256	**0.0060**	0.1819	**0.0001**	0.2103	**0.0000**	0.1211	**0.0069**	0.1451	**0.0011**	0.1982	**0.0000**
GP5	−0.0099	0.8374	−0.0987	**0.0272**	−0.0705	0.1170	−0.0537	0.2287	−0.1037	**0.0198**	−0.0825	0.0623
GP6	0.1652	**0.0003**	0.1067	**0.0179**	0.0795	0.0759	0.0586	0.1903	0.0732	0.1003	0.1354	**0.0027**
GP7	−0.0153	0.7483	−0.1216	**0.0069**	−0.1495	**0.0010**	−0.0850	0.0580	−0.1098	**0.0141**	−0.1026	**0.0206**
GP8	−0.0315	0.5086	−0.0685	0.1264	−0.1008	**0.0244**	−0.0687	0.1228	−0.0640	0.1505	−0.1143	**0.0106**
GP9	−0.0987	**0.0272**	0.0097	0.8374	0.1100	**0.0146**	0.0830	0.0616	0.0306	0.5152	0.0242	0.6145
GP10	0.1274	**0.0053**	0.0366	0.4356	−0.0597	0.1865	−0.0485	0.2780	0.0346	0.4603	0.0245	0.6141
GP11	0.1184	**0.0085**	0.0878	0.0531	0.0543	0.2287	0.0237	0.6146	0.0864	0.0539	0.1141	**0.0106**
GP12	−0.0835	0.0616	−0.1664	**0.0002**	−0.2037	**0.0000**	−0.1047	**0.0193**	−0.1277	**0.0048**	−0.1505	**0.0008**
GP13	−0.0667	0.1360	−0.1773	**0.0001**	−0.2115	**0.0000**	−0.1459	**0.0011**	−0.1683	**0.0002**	−0.1920	**0.0000**
GP14	−0.1484	**0.0011**	−0.1516	**0.0008**	−0.1584	**0.0005**	−0.0819	0.0640	−0.1117	**0.0126**	−0.1724	**0.0002**
GP15	−0.0620	0.1678	−0.1212	**0.0069**	−0.1697	**0.0002**	−0.0830	0.0616	−0.0899	**0.0460**	−0.1203	**0.0069**
GP16	−0.0785	0.0785	0.0086	0.8527	0.0637	0.1555	0.0477	0.2854	0.0240	0.6145	0.0210	0.6511
GP17	−0.0850	0.0590	−0.1769	**0.0001**	−0.2144	**0.0000**	−0.1240	**0.0060**	−0.1554	**0.0005**	−0.1663	**0.0002**
GP18	−0.1546	**0.0007**	−0.1475	**0.0011**	−0.1474	**0.0011**	−0.0785	0.0768	−0.1030	**0.0203**	−0.1576	**0.0005**
GP19	0.0123	0.7965	−0.0720	0.1087	−0.1246	**0.0060**	−0.1036	**0.0199**	−0.0696	0.1173	−0.0852	0.0578
GP20	−0.0836	0.0616	−0.1341	**0.0033**	−0.1274	**0.0053**	−0.1059	**0.0179**	−0.1389	**0.0020**	−0.1673	**0.0002**
GP21	−0.0260	0.5989	−0.0751	0.0945	−0.1169	**0.0094**	−0.0434	0.3347	−0.0716	0.1087	−0.0875	0.0525
GP22	−0.0220	0.6413	−0.1218	**0.0069**	−0.1835	**0.0001**	−0.0986	**0.0265**	−0.1058	**0.0179**	−0.1262	**0.0053**
GP23	−0.1296	**0.0048**	−0.0565	0.2082	−0.0182	0.6975	−0.0140	0.7670	−0.0487	0.2773	−0.0848	0.0580
GP24	0.0584	0.1947	−0.0439	0.3347	−0.1215	**0.0069**	−0.1095	**0.0144**	−0.0504	0.2603	−0.0671	0.1307

GPx: glycan GP: Glycan peak with 'x' corresponding to number A/G Ratio: Android/gynoid ratio; BMI: Body mass index; DXA: Dual-Energy X-ray Absorptiometry; WHR: Waist-to-hip ratio; WHtR: Waist-to-height ratio Bold text indicates a statistically significant difference, with a p-value less than 0.05.

3.3. Sialylation

The percentage of sialylation among all fucosylated GPs (FGS/F + FG + FGS; Table 3) was negatively associated with the fat distribution measures, with the WHtR and the DXA variables explaining the most variation (2.02%–2.32%) compared with BMI (1.14%) and the WHtR (0.69%).

3.4. Core fucosylation

The DXA variables, A/G ratio and body fat % were associated with the most fucosylation traits (Table 3), each explaining variation in 6 derived traits. They were positively associated with different traits; body fat % with the relative abundance of bisected fucosylated GPs, and the A/G ratio with total fucosylation traits (Table 3).

3.5. Bisecting N-acetylglucosamine

In line with the aforementioned bisection traits, DXA body fat % was positively associated with the bisecting *N*-acetylglucosamine variables (Table 3). However, the A/G ratio was negatively associated with the percentage of bisection of fucosylated disialylated GPs among all fucosylated disialylated GPs (FBS2/(FS2 + FBS2); Table 3).

3.6. Increased pro-inflammatory fraction of IgG glycans with increased central adiposity

The relative abundance of agalactosylated IgG glycans tended to increase as the body fat measures increased, but more markedly for visceral fat, A/G ratio and WHtR (Table 3). Additionally, the relative abundance of individual (GP16 to GP24; see Table 2) and derived (FGS/(F + FG + FGS)); Table 3) sialylated IgG glycans tended to decrease, though also for DXA body fat %. These results suggest an association between body fat, and especially central adiposity, and an increased proportion of IgG in a pro-inflammatory state.

4. Discussion

Although a previous study analysed the association between BMI and IgG *N*-glycans (Perkovic et al., 2014), this was the first study, to our knowledge, that compared the effects of different measures of the distribution of body adiposity on IgG glycosylation. It was hypothesised that accurate measures of body fat distribution would be able to explain more variation in the IgG glycome, measured by the percentage of variation explained as well as the number of IgG glycosylation features (individual GPs and derived traits) with significant associations. Specifically, we wished to compare measures of body fat more commonly used in population studies (BMI and WHR) against lesser used and newer measures (various DXA variables and WHtR).

Overall, it was evident that higher levels of central fat when compared with hip fat (A/G ratio) or height (WHtR) were positively associated with pro-inflammatory IgG *N*-glycans. This may have physiological importance as increases in pro-inflammatory IgG *N*-glycans are associated with a number of chronic and immunological conditions, including: rheumatoid arthritis (Malhotra et al., 1995; Sebastian et al., 2016), type 2 diabetes (Lemmers et al., 2017), hypertension (Wang et al., 2016, Liu et al., 2018b, Dolikun et al. 2018), Parkinson's disease (Russell et al., 2017), Alzheimer's disease (Lundström et al., 2013), ischaemic stroke (Liu et al., 2018a), haematological cancers (Lauc et al., 2013), and lung cancer (Chen et al., 2013). Further, the selection of the A/G ratio and WHtR as the fat variables explaining the most variation has biological importance since central fat is associated with disorders such as metabolic syndrome (Koster et al., 2010), cardiovascular disease (Shen et al., 2017) and Alzheimer's disease (Whitmer et al., 2008).

The cross-sectional design of this study does not explain whether increases in central body fat are causing changes to the IgG *N*-glycan profile, or whether it is reverse causation or bidirectional. However, there are reports that visceral body fat produces IL-6, more so than subcutaneous fat (Panagiotakos et al., 2005), and visceral body fat is associated with increased levels of an array of systemic inflammatory markers (Hsieh et al., 2014; Gaens et al., 2015), including C-reactive protein (Fontana et al., 2007). Further, chronic, subclinical inflammation has been linked to obesity (Festa et al., 2001; Alissa et al., 2016).

Table 3
Spearman's correlations between derived traits and the different body fat measurements, adjusted for false discovery rate.

Glycan Variables	DXA Total Fat %		DXA Android Fat (kg)		DXA A/G Ratio		WHR		BMI		WHtR	
	ρ	p-value	ρ	p-value	ρ	p-value	ρ	p-value	ρ	p-value	ρ	p-value
Total IgG Glycans (neutral + charged)												
Sialylation												
FGS/(FG + FGS)	−0.1018	**0.0442**	−0.0726	0.1893	−0.0573	0.3260	−0.0336	0.6007	−0.0462	0.4461	−0.0688	0.2139
FBGS/(FBG + FBGS)	−0.0407	0.5048	−0.0465	0.4461	−0.0359	0.5714	−0.0472	0.4406	−0.0519	0.3846	−0.0573	0.3236
FGS/(F + FG + FGS)	−0.1447	**0.0039**	−0.1456	**0.0038**	−0.1421	**0.0043**	−0.0832	0.1128	−0.1068	**0.0338**	−0.1524	**0.0019**
FBGS/(FB + FBG + FBGS)	−0.0719	0.1935	−0.0836	0.1128	−0.0937	0.0705	−0.0912	0.0779	−0.0743	0.1729	−0.1084	**0.0309**
FG1S1/(FG1 + FG1S1)	−0.0408	0.5048	0.0235	0.7103	0.0640	0.2629	0.0443	0.4659	0.0321	0.6070	0.0480	0.4318
FG2S1/(FG2 + FG2S1 + FG2S2)	0.0282	0.6679	0.0242	0.7075	0.0006	0.9886	−0.0101	0.9059	0.0316	0.6070	0.0325	0.6070
FG2S2/(FG2 + FG2S1 + FG2S2)	0.0023	0.9807	0.0788	0.1421	0.1219	**0.0145**	0.0674	0.2263	0.0528	0.3729	0.0744	0.1729
FBG2S1/(FBG2 + FBG2S1 + FBG2S2)	0.0036	0.9663	0.0170	0.7963	0.0424	0.5000	0.0045	0.9660	0.0017	0.9849	0.0083	0.9199
FBG2S2/(FBG2 + FBG2S1 + FBG2S2)	0.0912	0.0793	0.0482	0.4322	0.0106	0.9059	−0.0339	0.6004	0.0240	0.7075	0.0269	0.6780
FtotalS1/FtotalS2	−0.0671	0.2318	−0.0513	0.3941	−0.0463	0.4468	0.0007	0.9886	−0.0090	0.9118	−0.0310	0.6082
FS1/FS2	0.0385	0.5331	−0.0414	0.5048	−0.0947	0.0675	−0.0550	0.3504	−0.0106	0.9059	−0.0239	0.7075
FBS1/FBS2	−0.0717	0.1935	−0.0217	0.7443	0.0278	0.6679	0.0409	0.5048	−0.0089	0.9118	−0.0037	0.9663
Bisecting N-GlcNAc												
FBStotal/FStotal	0.1401	**0.0048**	0.0327	0.6070	−0.0256	0.6965	−0.0505	0.3960	−0.0026	0.9807	0.0249	0.6995
FBS1/(FS1 + FBS1)	0.1019	**0.0442**	0.0260	0.6925	−0.0071	0.9273	−0.0315	0.6070	−0.0065	0.9286	0.0180	0.7766
FBS2/(FS2 + FBS2)	0.2044	**0.0000**	0.0133	0.8618	−0.1236	**0.0132**	−0.1137	**0.0227**	0.0041	0.9660	0.0182	0.7766
Neutral IgG Glycans												
Galactosylation												
G0n	0.1425	**0.0043**	0.1733	**0.0004**	0.1900	**0.0001**	0.1101	**0.0280**	0.1365	**0.0056**	0.1967	**0.0000**
G1n	−0.0885	0.0911	−0.1129	**0.0247**	−0.1318	**0.0084**	−0.0786	0.1409	−0.1011	**0.0442**	−0.1484	**0.0029**
G2n	−0.1553	**0.0019**	−0.1699	**0.0005**	−0.1797	**0.0002**	−0.0900	0.0808	−0.1284	**0.0095**	−0.1846	**0.0001**
Core Fucosylation & Bisecting N-GlcNAc												
Fn total	0.0250	0.6995	0.1231	**0.0132**	0.1682	**0.0005**	0.0968	0.0588	0.1024	**0.0433**	0.1063	**0.0347**
FG0n total/G0n	−0.0015	0.9855	0.0738	0.1817	0.1173	**0.0193**	0.0664	0.2318	0.0632	0.2629	0.0630	0.2629
FG1n total/G1n	0.0103	0.9059	0.1140	**0.0232**	0.1417	**0.0043**	0.0820	0.1180	0.1041	**0.0396**	0.0939	0.0675
FG2n total/G2n	0.0073	0.9273	0.0917	0.0779	0.1282	**0.0104**	0.0675	0.2263	0.0836	0.1115	0.0725	0.1866
Fn	−0.0961	0.0634	0.0150	0.8346	0.0879	0.0918	0.0531	0.3729	0.0236	0.7091	0.0010	0.9886
FG0n/G0n	−0.0586	0.3175	0.0617	0.2819	0.1349	**0.0067**	0.0876	0.0911	0.0574	0.3236	0.0551	0.3504
FG1n/G1n	−0.1199	**0.0166**	−0.0204	0.7554	0.0602	0.2970	0.0433	0.4807	−0.0119	0.8865	−0.0277	0.6679
FG2n/G2n	−0.0603	0.2970	0.0195	0.7691	0.0708	0.2005	0.0405	0.5048	0.0346	0.5876	0.0022	0.9807
FBn	0.1314	**0.0084**	0.0314	0.6082	−0.0385	0.5331	−0.0315	0.6070	0.0190	0.7728	0.0410	0.5048
FBG0n/G0n	0.0643	0.2625	−0.0543	0.3637	−0.1194	**0.0168**	−0.0800	0.1320	−0.0491	0.4147	−0.0469	0.4406
FBG1n/G1n	0.1356	**0.0065**	0.0455	0.4570	−0.0384	0.5331	−0.0404	0.5048	0.0386	0.5331	0.0445	0.4659
FBG2n/G2n	0.1492	**0.0029**	0.0854	0.1055	0.0214	0.7470	0.0071	0.9273	0.0628	0.2629	0.1024	**0.0433**
FBn/Fn	0.1254	**0.0122**	0.0206	0.7552	−0.0512	0.3941	−0.0367	0.5536	0.0092	0.9118	0.0317	0.6070
FBn/Fn total	0.1254	**0.0122**	0.0206	0.7552	−0.0512	0.3941	−0.0367	0.5536	0.0092	0.9118	0.0317	0.6070

B, bisecting GlcNAc; F, core fucose; G, galactose; S, sialic acid A/G Ratio: Android/gynoid ratio; BMI: Body mass index; DXA: Dual-Energy X-ray Absorptiometry; WHR: Waist-to-hip ratio; WHtR: Waist-to-height ratio Bold text indicates a statistically significant difference, with a p-value less than 0.05.

Central body fat is also more detrimental than total body fat %; obese individuals (according to BMI guidelines) with low A/G ratios are less likely to develop metabolic syndrome (Koster et al., 2010). Indeed, it may be that glycan biosynthesis is altered due to an immunological response to central body fat, though this remains to be determined with a study in longitudinal design.

Importantly, this study replicated a previous investigation comparing BMI to agalactosylated IgG glycans (Perkovic et al., 2014). We also demonstrated a modest improvement in the explained variation of the IgG glycome when using measures of central adiposity rather than BMI, and suggested that the A/G ratio or WHtR, rather than BMI, be considered when controlling for adiposity in IgG glycome biomarker studies.

Conflicts of interest

GL is the founder and owner, and ITA and IU are employees of Genos Ltd., which offers commercial service of glycome analysis.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.imbio.2018.10.002.

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