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Effects of regular endurance exercise on GlycA: Combined analysis of 14 exercise interventions

Jacob L. Barber [a], William E. Kraus [b], Timothy S. Church [c], James M. Hagberg [d], Paul D. Thompson [e], David B. Bartlett [b], Michael W. Beets [a], Conrad P. Earnest [f], Kim M. Huffman [b], Rian Q. Landers-Ramos [d], Arthur S. Leon [g], D.C. Rao [h], Richard L. Seip [e], James S. Skinner [i], Cris A. Slentz [b], Kenneth R. Wilund [j], Claude Bouchard [c], Mark A. Sarzynski [a, *]

[a] Department of Exercise Science, University of South Carolina, Columbia, SC, USA
[b] Duke Molecular Physiology Institute, Duke University School of Medicine, Durham, NC, USA
[c] Pennington Biomedical Research Center, Baton Rouge, LA, USA
[d] Department of Kinesiology, University of Maryland, College Park, MD, USA
[e] Cardiology Division, Hartford Hospital, Hartford, CT, USA
[f] Department of Health & Kinesiology, Texas A&M University, College Station, TX, USA
[g] School of Kinesiology, University of Minnesota, Minneapolis, MN, USA
[h] Division of Biostatistics, Washington University School of Medicine, St. Louis, MO, USA
[i] Professor Emeritus of Kinesiology, Indiana University, Bloomington, IN, USA
[j] Department of Kinesiology and Community Health, University of Illinois, Urbana-Champaign, IL, USA

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ABSTRACT

Background and aims: GlycA is a relatively new biomarker for inflammation as well as cardiometabolic disease risk. However, the effect of exercise on GlycA is largely unknown. Therefore, the purpose of this study was to examine the effects of regular exercise on the inflammatory marker GlycA across seven studies and 14 exercise interventions.

Methods: Nuclear magnetic resonance spectroscopy, specifically signal amplitudes originating from the N-acetyl methyl group protons of the N-acetylglucosamine residues on the glycan branches of glycoproteins, was used to quantify GlycA concentrations. GlycA was measured before and after completion of an exercise intervention in 1568 individuals across seven studies and 14 exercise interventions. Random effects inverse variance weighting models were used to pool effects across interventions.

Results: Combined analysis of unadjusted data showed that regular exercise significantly ($p = 2 \times 10^{-6}$) reduced plasma GlycA (-8.26 ± 1.8 μmol/L). This reduction remained significant (-9.12 ± 1.9 μmol/L, $p = 1.22 \times 10^{-6}$) following adjustment for age, sex, race, baseline BMI, and baseline GlycA. Changes in GlycA were correlated with changes in traditional inflammatory markers, C-reactive protein, interleukin-6, and fibrinogen, however, these correlations were relatively weak (range r: 0.21−0.38, $p < 0.0001$).

Conclusions: Regular exercise significantly reduced plasma GlycA across 14 different exercise interventions despite differences in exercise programs and study populations. The current study provides a greater understanding of the use of exercise as a potential therapy for the reduction of systemic inflammation. Further research is needed to understand the mechanisms behind the exercise-related reductions in GlycA.

1. Introduction

Inflammation is an important clinical measure because of its association with increased risk of cardiovascular disease (CVD) and mortality [1,2]. While C-reactive protein (CRP), fibrinogen, and

* Corresponding author. Department of Exercise Science, University of South Carolina, 921 Assembly Street, Room 301, Columbia, SC, 29201, USA.
E-mail address: sarz@mailbox.sc.edu (M.A. Sarzynski).

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interleukin-6 (IL-6) are the primary clinical markers of systemic inflammation, CRP is the favored marker because of its strong relationship with CVD [3]. However CRP has large within-person variability, which makes risk-stratification based on CRP levels difficult [4]. GlycA, a relatively new biomarker for systemic inflammation, is measured via nuclear magnetic resonance (NMR) spectroscopy and reflects the glycosylation states of several acute phase proteins [4], which increase during the inflammatory response to a variety of stimuli [5]. Furthermore, GlycA appears to be an independent marker of inflammation, as it is only moderately correlated with CRP, fibrinogen, and IL-6 [4]. In over 5000 participants from the MESA study, GlycA positively correlated with CRP ($r = 0.56$), fibrinogen ($r = 0.46$), and IL-6 ($r = 0.35$) (all $p < 0.0001$) [4]. Similar to these traditional inflammatory markers, greater GlycA concentrations are associated with increased risk of type 2 diabetes mellitus, CVD, and all-cause mortality [6–8]. GlycA is also higher in subjects with metabolic syndrome and positively correlated with body mass index (BMI) and insulin resistance [9–12]. Additionally, GlycA has reduced within-person variability (CV = 4.3%) compared to CRP (CV = 29.2%) [4] and thus may be a more reliable measurement of inflammation for clinical practice. The quantification of GlycA is inexpensive and a high throughput process, therefore GlycA may also represent a more cost and time efficient marker of inflammation, especially in large samples.

While habitual physical activity and exercise decrease markers of systemic inflammation in a dose-response fashion [13–16], to date only one study has examined the relationship of regular exercise with plasma GlycA. In overweight individuals with prediabetes, a 6-month intervention of endurance exercise alone or exercise combined with diet significantly reduced GlycA levels by 2% [17]. Given the limited knowledge on exercise and GlycA, the purpose of the present study was to examine the effects of regular endurance exercise on plasma GlycA across seven exercise training studies with 14 different exercise interventions. We hypothesized that regular exercise would decrease plasma levels of GlycA across varying endurance exercise interventions.

2. Materials and methods

The effects of standardized, regular endurance exercise on plasma GlycA concentrations were examined across seven exercise training studies and 14 independent exercise interventions: APOE [18], DREW [19], HERITAGE [20], GERS [21], STRRIDE I [22], STRRIDE II [23], and STRRIDE PD [24]. The following studies had only one exercise training group (i.e., prescribed only one dose of exercise): APOE (~13–15 kilocalories per kilogram of body weight per week [KKW]) [18], HERITAGE (~12–14 KKW) [20], and GERS (~10–12 KKW) [21]. The DREW study was a randomized control trial with three different exercise training groups that expended 4, 8, or 12 KKW at 50% VO_2peak for six months [19]. STRRIDE I consisted of a control group and three exercise groups: MILD (14 KKW), low-amount, moderate-intensity exercise (40–55% VO_2peak); MOD (14 KKW), low amount, vigorous-intensity (65–80% VO_2peak); and HIGH (23 KKW), high-amount, vigorous-intensity (65–80% VO_2peak) [22]. Similarly, STRRIDE II consisted of three exercise groups: MOD (14 KKW), low amount, vigorous-intensity (65–80% VO_2peak); MOD plus resistance training (RT), same as MOD plus RT three days/wk, 3 sets/day, 8–12 repetitions/set; and HIGH (23 KKW), high-amount, vigorous-intensity (65–80% VO_2peak) [23]. Finally, STRRIDE-PD participants were randomized to one of four groups: low-amount and moderate intensity (10 KKW at 50% VO_2peak), high amount and moderate intensity (16 KKW at 50% VO_2peak), high amount and vigorous intensity (16 KKW at 75% VO_2peak), and Clinical Lifestyle intervention: low amount moderate intensity intervention plus diet (with weight loss goal of 7%) [24]. The sample, study design, and exercise training protocol of each study have been described elsewhere and are summarized in the Supplemental Methods.

2.1. Measurements

Blood draws: Within each study, all blood draws were taken in the fasted state at both baseline and after completion of exercise training (within 16–72 h of last exercise session). All measures described below were performed on both baseline and post-training samples in all studies.

GlycA measurements: GlycA was assessed by NMR spectroscopy at LipoScience, Inc (now LabCorp, Morrisville, NC) as previously described [4]. Briefly, NMR signal amplitudes originating from the N-acetyl methyl group protons of the N-acetylglucosamine residues on the glycan branches of glycoproteins were used to quantify GlycA concentrations.

Inflammatory markers: CRP was measured in all studies except APOE, STRRIDE II, and STRRIDE-PD. IL-6 was measured in DREW and STRRIDE I and II, while fibrinogen and tumor necrosis factor alpha (TNF-α) were measured in DREW only. All inflammatory markers were measured using standard methods.

Lipoprotein measurements: A standard lipid panel was measured using standard techniques in all studies. Data for lipoprotein subfractions quantified using Liposcience's LipoProfile-3 algorithm were also available in all studies [25]. Specifically, data for total, large, medium, and small very low-density lipoprotein (VLDL-P) and high-density lipoprotein particles (HDL-P), total, large, and small LDL particles (LDL-P), and intermediate-density lipoprotein particles (IDL-P), as well as weighted average VLDL-P, LDL-P, and HDL-P sizes were available before and after exercise training. Additionally, small and medium HDL-P concentrations were combined into one category and analyzed together (small-medium HDL-P).

Statistical analysis: Only two studies (DREW and STRRIDE I) included control groups, thus our primary analyses focused on the exercise groups only. Each group was analyzed independently because of differences in exercise prescription and training programs. The two MOD and the two HIGH programs from STRRIDE I and II were identical, thus these exercise groups were combined for meta-analysis. Therefore, a total of 14 exercise programs were examined in the combined analysis. Correlations between variables were assessed via Pearson correlation coefficients in SAS 9.4 (Cary, NC) by combining all exercise groups within a study (e.g. DREW correlations were done by grouping the 4, 8, and 12 KKW groups together).

Combined analysis: The effect of regular exercise on plasma GlycA was examined via combined analysis using meta-analytic techniques. The included studies were part of an existing collaboration on lipoprotein responses to exercise training [25]. All of the studies met the following criteria: adult participants (≥17 years) with available pre- and post-training NMR GlycA data, sample size ≥50, and the intervention was supervised, standardized, and lasted at least 12 weeks. Combined analysis on individual level data from each study was performed using Comprehensive Meta-Analysis (v2.2, Englewood, NJ). Unadjusted and adjusted (for age, sex, race, baseline BMI, baseline GlycA) random effects inverse variance weighting models were used to pool effects across interventions. We performed secondary analyses that included combined analysis of the DREW and STRRIDE I studies, as both included control groups. The analysis was performed in the same manner as described above, with the exception that net change in GlycA from baseline to post-training was calculated as the difference of the mean changes between each exercise group and their respective control group.

3. Results

Overall, 1568 (57% Female, 66% White) participants were included in the final combined analysis. Baseline characteristics including mean values for the standard lipid panel and other cardiovascular risk factors across the seven studies are shown in Table 1. The training response of these variables can be found in Supplemental Table 1.

On average, GlycA decreased with regular exercise in 13 of 14 exercise groups, with the adjusted exercise-induced reductions being statistically significant in nine of the 14 groups (Fig. 1). Overall, unadjusted combined analysis found GlycA significantly ($p = 2.38 \times 10^{-6}$) decreased by 8.26 ± 1.8 μmol/L ($1.79 \pm 0.5\%$) following exercise training (Supplemental Figure 1). The exercise-induced decrease in GlycA remained significant (9.12 ± 1.9 μmol/L or $1.76 \pm 0.5\%$) in combined analysis that adjusted for age, sex, race, baseline BMI, and baseline GlycA levels (Fig. 1). In secondary analyses in DREW and STRRIDE I that compared changes in GlycA between the exercise and control groups, there were no differences in mean GlycA change between the groups (adjusted mean change compared to control group: -5.13 ± 3.84 μmol/L, $p = 0.18$). GlycA levels declined in the control groups within STRRIDE I (-1.34 μmol/L, $p = 0.82$) and DREW (-2.29 μmol/L, $p = 0.52$), however, neither reduction was statistically significant.

GlycA positively correlated with CRP at baseline in all five studies with the measure (range: r = 0.29–0.51, $p < 0.0001$–0.046). At baseline, GlycA was positively correlated with IL-6 in the combined exercise groups of DREW (r = 0.22, $p = 0.0002$) and STRRIDE I & II (r = 0.32, $p = 0.009$) and with fibrinogen (r = 0.41, $p < 0.0001$) in DREW. Following training, CRP decreased in two out of four studies that measured it (-0.03 mg/dL in DREW and -0.1 mg/dL in GERS), but these decreases were not statistically significant. There were no significant changes in IL-6, fibrinogen, or TNF-α following training. Exercise-induced changes in GlycA were weakly, positively correlated with changes in CRP in HERITAGE, DREW, and STRRIDE I (range: r = 0.22–0.38, $p < 0.0001$–0.009). Changes in GlycA were also weakly correlated with changes in both IL-6 (r = 0.21, $p = 0.0004$) and fibrinogen (r = 0.36, $p < 0.0001$) in the DREW study only.

GlycA levels were also correlated with other CVD risk factors. Baseline BMI and GlycA levels were positively correlated in four of the seven studies (range: r = 0.14–0.44, $p < 0.0001$–0.04), but change in BMI and change in GlycA were only significantly correlated in the HERITAGE and STRRIDE-PD studies (r = 0.11, $p = 0.003$ and r = 0.19, $p = 0.02$, respectively) (Table 2). At baseline, GlycA was weakly correlated with total HDL-P concentration in three of the seven studies: HERITAGE (r = 0.28, $p < 0.0001$), DREW (r = 0.14, $p = 0.02$), and STRRIDE II (r = 0.29, $p < 0.0001$). Exercise-induced changes in GlycA and total HDL-P concentration were significantly correlated in each of these three studies as well as STRRIDE I, with the largest correlation coming from the HERITAGE study (r = 0.34, $p < 0.0001$) (Table 2). At baseline, GlycA and small-medium HDL-P were significantly correlated in HERITAGE, DREW, and STRRIDE I & II (range: r = 0.19–0.33, $p < 0.0001$–0.0006). Changes in GlycA and changes in small-medium HDL-P following training were significantly correlated in the same four studies and STRRIDE-PD (range r = 0.17–0.36, $p < 0.0001$). Changes in GlycA and total LDL-P were significantly correlated in HERITAGE, GERS, and STRRIDE I (range: r = 0.26–0.34, $p < 0.0001$) (Table 2).

4. Discussion

Combined analysis using meta-analytic techniques showed that regular exercise decreased plasma GlycA levels in previously sedentary adults across various exercise interventions. These findings remained significant after taking into account differences in study populations (i.e., age, sex, race, BMI, and baseline GlycA levels). There was no clear pattern of dose-response across the groups ranging in weekly energy expenditure from 4 KKW to 23 KKW, as groups from both the low and high exercise doses showed significant mean reductions in GlycA. However, it should be noted that when compared to the limited control group data available, there was no significant effect of exercise on GlycA. Compared to more traditional inflammatory markers, exercise associated changes in plasma GlycA levels were correlated with changes in CRP, IL-6, and fibrinogen, but the relationships were not particularly strong indicating that GlycA levels may be partially independent.

Chronic systemic inflammation is linked to CVD risk and the pathogenesis of several chronic diseases [3,26–28]. Therefore strategies to lower chronic inflammation are of great public health importance. Regular endurance exercise represents one potential strategy, as it has been shown to decrease the risk of chronic disease and may improve inflammatory profiles. However, to date the effects of exercise on inflammation have been inconclusive. The effect of regular endurance exercise on traditional inflammatory markers such as CRP is still largely unclear [29], but large observational cohort studies have shown inverse relationships between inflammatory markers and physical activity or physical fitness [30]. The current analysis showed that on average long-term endurance-based exercise interventions reduce plasma GlycA levels and therefore likely reduce systemic inflammation. The novelty and

Table 1
Baseline characteristics of the combined exercise groups within each study, given as means (standard deviation).

	HERITAGE (n = 700)	DREW (n = 292)	GERS (n = 78)	APOE (n = 103)	STRRIDE I (n = 132)	STRRIDE II (n = 102)	STRRIDE PD (n = 161)
Age (years)	35.1 (13.7)	57.3 (6.5)	58.0 (5.8)	39.1 (10.9)	52.3 (6.0)	48.5 (9.6)	59.3 (7.6)
BMI (kg/m^2)	26.4 (5.3)	31.8 (3.7)	27.9 (4.1)	27.6 (4.9)	29.9 (2.9)	30.5 (3.3)	30.9 (5.7)
VO_2 max (L/min)	2.3 (0.7)	1.3 (0.3)	2.0 (0.5)	2.6 (0.8)	2.5 (0.7)	2.5 (0.6)	2.2 (0.6)
HDL-C (mg/dL)	40.7 (10.6)	57.3 (14.3)	46.1 (13.4)	50.5 (15.9)	53.1 (16.8)	51.0 (13.2)	44.2 (14.9)
LDL-C (mg/dL)	113.9 (30.9)	117.7 (26.5)	130.9 (28.1)	131.5 (31.8)	144.9 (31.2)	144.1 (21.5)	111.8 (26.1)
TC (mg/dL)	170.8 (35.9)	200.7 (30.1)	209.9 (32.4)	204.5 (37.8)	233.1 (28.8)	224.7 (28.1)	182.8 (31.7)
TG (mg/dL)	112.5 (67.5)	129.4 (63.4)	163.7 (86.8)	137.9 (91.0)	168.66 (104.3)	149.9 (73.1)	133.2 (71.2)
CRP (mg/dL)	2.7 (4.8)	5.5 (5.3)	3.2 (3.3)	N/A	3.4 (3.1)	N/A	N/A
SBP (mmHg)	118.7 (11.9)	138.8 (13.0)	129.6 (16.6)	N/A	130.1 (14.4)	118.9 (13.6)	N/A
DBP (mmHg)	68.3 (8.9)	80.8 (8.9)	83.3 (10.8)	N/A	84.3 (8.0)	78.2 (8.7)	N/A
Glucose (mg/dL)	91.6 (11.2)	94.6 (8.7)	91.1 (9.2)	N/A	94.5 (9.7)	94.6 (11.8)	105.6 (9.8)
Waist (cm)	90.2 (14.8)	100.6 (11.6)	90.9 (13.0)	89.6 (14.8)	95.7 (10.3)	96.9 (9.5)	99.0 (8.6)
Percent fat	27.6 (10.2)	28.3 (4.5)	35.7 (9.3)	22.7 (6.2)	N/A	N/A	40.9 (7.8)
GlycA (μmol/L)	324.7 (56.5)	364.9 (47.8)	405.718 (64.9)	422.5 (70.6)	325.2 (314.0)	362.6 (65.4)	347.1 (49.5)

BMI: body mass index, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, TC: total cholesterol, TG: triglycerides, CRP: C-reactive protein, SBP: systolic blood pressure, DBP: diastolic blood pressure, N/A: data not available.

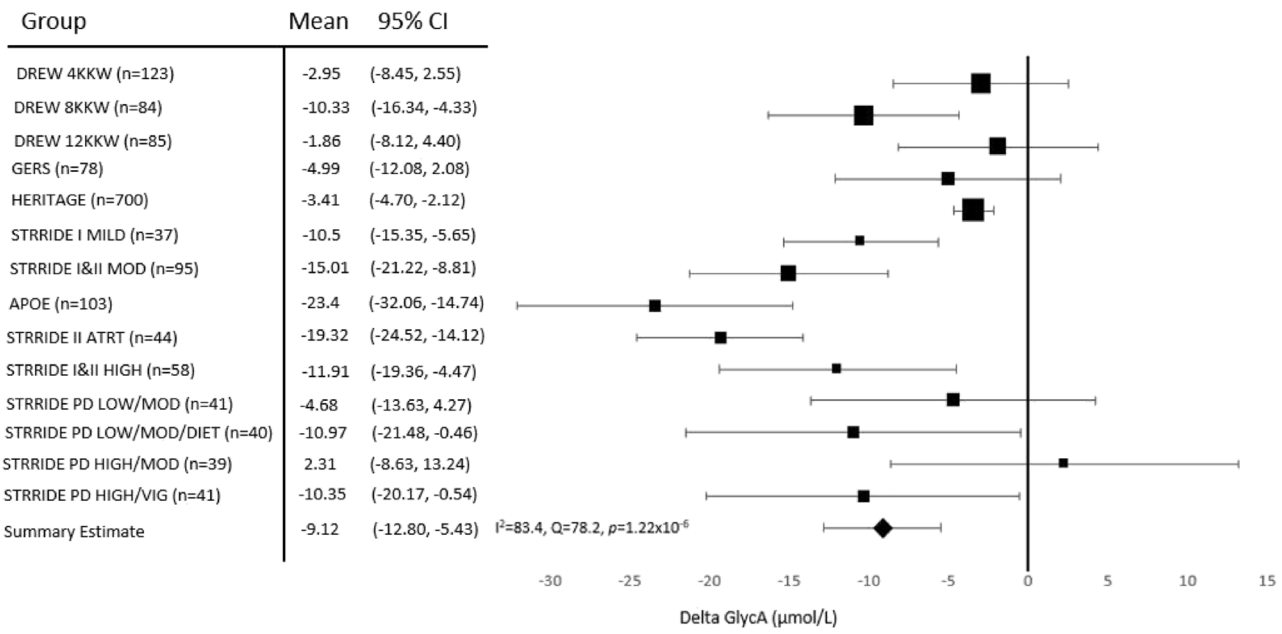

Fig. 1. Adjusted meta-analysis results for change in GlycA following various exercise interventions.
Adjusted mean change with 95% confidence intervals (CI) are shown. Mean values were adjusted for age, sex, race, baseline BMI, and baseline GlycA. Summary estimate = −9.12 μmol/L, I [2] = 83.4, Q = 78.2, $p = 1.22 \times 10\text{-}6$. Size of the marker for the mean value of each exercise group represents the relative weight of the study in the combined analysis. KKW, kilocalories per kilogram of body weight per week.

Table 2
Correlation between change in GlycA (μmol/L) and concomitant change in select cardiometabolic traits in the seven different studies.

	HERITAGE	DREW	GERS	APOE	STRRIDE I	STRRIDE II	STRRIDE PD
Age (years)	NS	NS	NS	NS	NS	NS	NS
BMI (kg/m^2)	0.11	NS	NS	NS	NS	NS	0.19
VO_2 max (L/min)	NS	NS	NS	NS	0.18	NS	NS
Total LDL-P (nmol/L)	0.26	NS	0.34	NS	0.26	NS	NS
Small LDL-P (nmol/L)	0.22	0.15	NS	NS	0.28	NS	NS
Total HDL-P (μmol/L)	0.34	0.20	NS	NS	0.26	0.33	NS
Small-medium HDL-P (μmol/L)	0.36	0.25	NS	NS	0.29	0.25	0.17
HDL-C (mg/dL)	NS	NS	NS	NS	NS	0.31	NS
LDL-C (mg/dL)	NS	NS	NS	NS	NS	NS	NS
Insulin (pmol/L)	0.08	0.2	NS	NS	NS	NS	NS
CRP (mg/dL)	0.22	0.38	NS	NS	0.25	NS	NS
IL-6 (pg/mL)	NS	0.21	NS	NS	NS	NS	NS
Fibrinogen (mg/dL)	NS	0.36	NS	NS	NS	NS	NS

BMI: body mass index, LDL-P: low-density lipoprotein particles, HDL-P: high-density lipoprotein particles, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, CRP: C-reactive protein, IL-6: interleukin-6.
All correlations listed were $p < 0.05$. NS, not significant ($p > 0.05$). In studies with multiple exercise groups, the exercise groups were combined for the correlation analyses.

partial independence of GlycA from other traditional inflammatory markers may explain why the present results differ from previous exercise training studies of inflammatory markers. Thus, improvements in GlycA levels with exercise may represent a potential novel pathway contributing to the decreased risk of chronic disease associated with regular exercise.

Elevated concentrations of GlycA are associated with increased mortality and incidence of diabetes, arthritis, CVD, and colorectal cancer [6,31–33]. Additionally, several studies [31,32] have shown that even small differences in plasma GlycA are associated with large differences in disease risk. A prospective study examining GlycA and colorectal cancer risk showed that compared to plasma GlycA quartile 1 (≤326 μmol/L), quartile 2 (327–369 μmol/L) was associated with an approximately 20% increase in colorectal cancer incidence, and for colorectal incidence and mortality the hazard ratio per standard deviation of GlycA was 1.26 [32]. GlycA levels are also associated with atherosclerosis, as each increasing quartile of GlycA is associated with 48% increased odds of having coronary artery calcium, a marker of atherosclerosis [31]. These results demonstrate the clear adverse associations of elevated GlycA concentrations on health outcomes, and therefore strategies for reducing plasma GlycA even slightly may have potential clinical relevance. The observed mean changes in GlycA were rather small (−9.12 μmol/L or about −2%), however each cohort started at differing baseline concentrations of GlycA, thus the reduction will have differing clinical significance based on the starting point. Furthermore, there was large inter-individual variation in GlycA responsiveness to exercise training across the studies (range: −315 to +189 μmol/L). Thus, these results suggest that although regular exercise is effective in reducing plasma GlycA levels in most individuals, these reductions may only be clinically relevant in certain individuals.

The molecular mechanisms responsible for the exercise related reductions in GlycA are still not understood. One potential

mechanism for the exercise-mediated decrease in plasma GlycA is through an interaction with lipoproteins. A previous study found an interaction between GlycA and small and medium HDL subclasses, with greater GlycA concentrations mitigating the reduced mortality risk associated with smaller HDL subclasses [34]. One of the beneficial actions of HDL that likely contributes to this protective effect is the inhibition of inflammatory endothelial cell adhesion molecule expression [35]. By inhibiting these molecules, HDL reduces systemic inflammation. Given that GlycA is a marker of systemic inflammation, there may be an interaction between plasma GlycA levels and HDL. The current study showed that changes in plasma GlycA were significantly correlated with changes in the concentration of total HDL-P, small-medium HDL-P, and even total LDL-P. Most notably, changes in GlycA were significantly correlated with changes in small-medium HDL-P in five of the seven studies, which were made up of 14 different exercise interventions. The correlations observed were mostly weak, therefore it is difficult to conclude that GlycA and lipoprotein subfractions are changing in concert with regular exercise, however the current study may provide some evidence of such an interaction.

Combined analysis comparing the exercise and control groups in DREW and STRRIDE I showed no significant effect of exercise compared to controls on plasma GlycA ($p = 0.18$). The lack of a significant effect of regular endurance exercise compared to control may be due to the lack of power, as only the DREW and STRRIDE I studies included control groups. Additionally, while combined analysis did not show a dose-dependent relationship between endurance exercise training and changes in plasma GlycA, DREW had the lowest intensity exercise program (50% VO_2peak). The lower intensity of DREW, along with the uniqueness of the study population (post-menopausal, overweight/obese women with elevated blood pressure) may have played a role in the lack of a training effect compared to controls. Finally, in both control groups we saw nominal reductions in GlycA levels. While not significant, the reductions in GlycA in the control groups suggests that the participants may have changed some behaviors, despite not actively being in an intervention group. These reductions may have blunted the ability to detect differences in change in GlycA between the exercise and control groups after the intervention in these studies. Further randomized controlled trials are needed to clarify the effects of regular endurance exercise on plasma GlycA.

Our study benefitted from a large, diverse sample size and the fact that plasma GlycA was measured using the same methods in the same laboratory across all studies, which minimized the potential for measurement error and variability. The current study was limited by the lack of control groups in almost every study. Therefore, changes in GlycA could only be compared to an individual's baseline levels. We were also unable to clearly elucidate the driver of the change in GlycA, since the signal measures more than one acute phase protein and the current study did not measure individual acute phase protein responses.

The current study demonstrates that regular endurance exercise may reduce plasma GlycA levels and therefore may contribute to reductions in systemic inflammation. However, the lack of a significant effect of exercise on plasma GlycA compared to controls highlights the need for further research on the effects of exercise on this novel biomarker of inflammation. The current study provides insight into the beneficial effects of exercise and in particular the use of exercise as a potential therapy for the reduction of systemic inflammation.

Conflicts of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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Author contributions

JLB and MAS conceived and designed the study and wrote the manuscript. WEK, TSC, JMH, PTD, CPE, KMH, RQLR, ASL, DCR, RLS, JSS, CAS, KRW, and CB conceived and designed and/or contributed to the data for the various exercise training studies. JLB, MWB, and MAS analyzed and interpreted the data. All authors read, critically revised, and approved the manuscript.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.atherosclerosis.2018.07.029.

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