Physical exercise is associated with a reduction in inflammatory biomarkers in first-episode psychosis: A pilot study of CRP, SAA, sICAM-1 and sVCAM-1

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Dear Editor,

Individuals with psychotic disorders are at greater risk for cardiovascular morbidity/mortality (Barcones et al., 2018; Laursen et al., 2012) and metabolic syndrome components (Vancampfort et al., 2015). Physical exercise has favorable effects on cardiovascular and metabolic health, including anti-inflammatory properties (Lakka and Laaksonen, 2007; Teixeira-Lemos et al., 2011). Exercise has also been found to improve physical and mental health, including overall wellbeing, in psychotic patients (Firth et al., 2018; Firth et al., 2017; Gorczynski and Faulkner, 2010). To further examine the positive effects of exercise in individuals with psychosis, the FitForLife study was designed and carried out in Stockholm, Sweden (Forsell et al., 2015) following ethical approval by the Regional Ethics Review Board in Stockholm. The pilot phase of the study included young adults with first-episode psychosis (FEP), aged 18–35 years, who completed a 12-week structured physical exercise intervention program consisting of 60 min sessions focusing on cardiovascular fitness and delivered by trained instructors. Following the intervention, FitForLife participants showed better cognitive functioning (Halgren et al., 2019) and a trend for an improvement in measures of patient autonomy (Lambden et al., 2018).

For the purpose of the present study, we collected blood samples from FitForLife participants based on the hypothesis that circulating levels of inflammatory analytes, such as C-reactive protein (CRP), serum amyloid-alpha (SAA), soluble intercellular adhesion molecule-1 (sICAM-1) and soluble vascular cell adhesion molecule-1 (sVCAM-1), may serve as biomarkers for monitoring cardiovascular health. Thus, our specific objectives were to (a) compare plasma levels of these four inflammatory analytes (CRP, SAA, sICAM-1 and sVCAM-1) in FEP subjects versus controls, and (b) examine whether these analytes are affected in FEP subjects by the FitForLife exercise intervention program (see also Sections 1–7 in Supplemental Materials).

The characteristics of all FEP participants who completed the FitForLife study and contributed blood samples both at baseline and follow-up (n = 49) are presented in Supplementary Table S1. The median age of the sample was 28 years (IQR = 24–35), with a majority of males (71.4%) and a median BMI of 25.9 kg/m² (IQR = 23–30). Most of the participants had a diagnosis of un-specified psychosis (55.1%), followed by schizophrenia (20.4%) and schizoaffective disorder (14.3%). About a quarter of participants (22.5%) had a concurrent diagnosis of autism or ADHD. Participants attended a median of 13 exercise sessions during the three-month intervention. Supplementary Table S2 shows the changes in subjects’ metabolic marker levels following the exercise intervention. No significant changes were found for waist circumference, BMI, systolic blood pressure, or levels of cholesterol or Hb1Ac. The control group had a similar age distribution as the FEP participants, although it comprised of more males (42.9% versus 71.4%) and individuals with a lower BMI (median 23.4 versus 25.9 kg/m², Supplementary Table S3).

At baseline, and compared to controls, FEP subjects had elevated levels of CRP (adjusted for gender and BMI) and sICAM-1, as well as a tendency for elevated levels of SAA (adjusted for gender and BMI) and sVCAM-1 (Fig. 1A; note that to correct for multiple tests, the threshold for statistical significance was set at p < 0.013, i.e., 0.05/4 analytes). At follow-up, i.e., after the exercise intervention, FEP individuals had a significant reduction in levels of SAA, sICAM-1 and sVCAM-1, and a tendency for a reduction in levels of CRP (Fig. 1A). Given the known link between obesity and CRP (Aronson et al., 2004), we also examined the effects of exercise on analyte levels by stratifying for obesity (i.e., BMI < 30 kg/m² versus ≥ 30 kg/m²). FEP subjects with a BMI < 30 kg/m² presented with a more pronounced reduction in levels of CRP, including a more significant reduction in levels of sICAM-1 and sVCAM-1 (Fig. 1B).

We also asked which baseline FEP characteristics associated with the baseline levels of the inflammatory analytes. To this end, we first computed the bivariate correlations between baseline FEP characteristics and inflammatory analytes (Supplementary Table S4, left columns). There was a significant positive correlation between baseline BMI and CRP levels. A second significant positive correlation was observed for baseline CRP and SAA levels. Next, we examined the effect of clinical...
Fig. 1. Levels of inflammatory markers at baseline in controls and FEP participants, as well as the change of inflammatory marker levels from baseline to follow-up of the physical exercise intervention (A) in all FEP participants; (B) in the FEP individuals with a BMI below 30 kg/m². The y-axes represent the unadjusted and untransformed levels of the analytes. Differences between controls and FEP participants at baseline were tested using linear regression on the natural logarithm (ln) of the analyte levels adjusting for covariates. Covariates for CRP and SAA were sex and BMI. For sICAM-1 and sVCAM-1 no covariate was adjusted for. Effect sizes of the group variable (adjusted partial $R^2$) and fitness of the model (adjusted $R^2$) were estimated for each analyte (for sICAM-1 and sVCAM-1 partial $R^2 = R^2$) and were as follows: in A) partial $R^2_{CRP} = 0.12$, $R^2_{CRP}= 0.35$; partial $R^2_{SAA} = 0.05$, $R^2_{SAA}= 0.23$; $R^2_{sICAM-1} = 0.06$; $R^2_{sVCAM-1} = 0.02$, and in B) partial $R^2_{CRP} = 0.17$, $R^2_{CRP}= 0.34$; partial $R^2_{SAA} = 0.06$, $R^2_{SAA}= 0.18$; $R^2_{sICAM-1} = 0.05$; $R^2_{sVCAM-1} = 0.02$. Differences of change in levels between baseline and follow-up were tested using paired t-tests on the natural logarithm of the analyte levels. Effect sizes (Cohen's d) were in A) $d_{CRP} = 0.15$, $d_{SAA} = 0.34$, $d_{sICAM-1} = 0.40$, $d_{sVCAM-1} = 0.51$, and in B) $d_{CRP} = 0.30$, $d_{SAA} = 0.39$, $d_{sICAM-1} = 0.54$, $d_{sVCAM-1} = 0.69$. (C–F) The effect of baseline clinical characteristics, as independent variables, on the follow-up analyte levels adjusted for baseline analyte levels for CRP, SAA and sICAM-1 were estimated using linear regression models (stepwise forward selection), and confirmed using quantile regression (see also Supplementary Table S6 Model 1). (C) A diagnosis of ADHD or autism associated with a stronger post-exercise reduction in CRP and SAA levels, here SAA is shown (effect size: partial $R^2_{SAA} = 0.16$). (D–E) Alcohol use associated with a weaker post-exercise reduction in CRP, SAA and sICAM-1 levels, here (D) SAA and (E) sICAM-1 are shown ($R^2_{SA} = 0.16$ and $R^2_{sCAM-1} = 0.12$). (F–G) Higher baseline BMI associated with a weaker post-exercise CRP, SAA and sICAM-1 levels, here (F) SAA and (G) sICAM-1 are shown ($R^2_{SA} = 0.30$ and $R^2_{sCAM-1} = 0.13$). (CRP = C-reactive protein, SAA = serum amyloid A, sICAM-1 = soluble intercellular adhesion molecule-1, sVCAM-1 = soluble vascular cell adhesion molecule-1, ADHD = attention-deficit hyperactivity disorder, BMI = Body mass index [kg/m²]).
characteristics on baseline inflammatory analyte levels using two linear regression models (one based on predictor selection criteria using the computed correlations and one including all variables available; see also Section 7 in Supplemental Materials). Both regression models revealed again a significant association between higher baseline BMI and higher baseline CRP levels (Supplementary Table S5). Moreover, the regressions revealed an association between higher baseline BMI and higher baseline SAA levels, including an association between lower baseline systolic blood pressure and higher baseline CRP and SAA levels.

Next, we asked which baseline FEP characteristics associated with the post-exercise change in inflammatory analytes (Δ: follow-up minus baseline). To this end, we computed the bivariate correlations between baseline FEP characteristics and the change in analyte levels (Δ). Defined as the follow-up analyte level variance that was not explained by the baseline level of the corresponding inflammatory analyte (Supplementary Table S4, right columns). There was a significant positive correlation between higher baseline BMI and higher follow-up CRP and SAA levels, adjusted for the corresponding baseline analyte levels (ΔCRP and ΔSAA). Significant positive correlations were also found for ΔCRP and ΔsVCAM-1 to the post-exercise change in all other analytes. Next, we examined the effect of clinical characteristics on the post-exercise change in inflammatory analytes using the two linear regression models. As shown in Fig. 1C–G, and in Supplementary Table S6, the presence of an autism or ADHD diagnosis was significantly associated with a stronger post-exercise reduction in both CRP and SAA levels. Moreover, alcohol use and higher baseline BMI associated with a lower post-exercise reduction in CRP, SAA and sICAM-1 levels.

The present study provides pilot data to support the use of exercise for decreasing the systemic pro-inflammatory state that is often found in patients with psychosis (see also Section 8 in Supplemental Materials for a discussion on the study’s findings in relation to previous literature). The data also suggest that both high BMI and alcohol use may dampen the anti-inflammatory effects of exercise. However, given the limitations inherent to this pilot study (see Section 9 in Supplemental Materials), the present data should be considered preliminary in nature and larger randomized studies are warranted to test the robustness of these findings.

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Credit authorship contribution statement
YF, MSk and CL conceptualized the study. YF, MSk, MST, PK and CL performed the study and acquired data. MST and DY conducted statistical analyses. CL, MS, PAM, YF analyzed and interpreted the data. PAM drafted the manuscript. CL, MS, PAM, YF critically revised the manuscript. CL, YF received grants. All authors approved the final manuscript.

Declaration of competing interest
The authors declare no conflict of interest.

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Appendix A. Supplementary materials, methods, discussion, limitations and tables
Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2020.12.021.

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