Metabolic Syndrome, Physical Activity, and Inflammation: A Cross-Sectional Analysis of 110 Circulating Biomarkers in Japanese Adults

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ABSTRACT

Background: Metabolic syndrome (MetS) is a systemic inflammatory state. Low physical activity (PA) could modify this pathophysiology or act as an independent contributor to inflammation. Previous studies of both conditions have identified altered levels of inflammation- and immune-related proteins based on limited sets of candidate markers.

Methods: We investigated associations of MetS and low PA with circulating inflammation markers in a stratified random sample of Japanese adults ($N = 774$, mean age 60.7 years) within the Japan Public Health Center-based Prospective Study (JPHC) Cohort II. AHA/NHLBI criteria were used to define MetS (19%) and the bottom quartile of PA was considered low. 110 circulating biomarkers, including cytokines, chemokines, and soluble receptors were measured by multiplex bead-based and proximity-extension assays. Associations of MetS and low PA with marker quantiles were adjusted for each other and for age, sex, study site, cigarette smoking, alcohol consumption, and blood sample fasting state by ordinal logistic regression. *P* values were corrected for FDR.

Results: MetS was significantly associated with levels of six markers: IL18R1 [odds ratio 2.37; 95% confidence interval (CI), 1.45–3.87], CRP (2.07; 95% CI, 1.48–2.90), SAP (2.08; 95% CI, 1.47–2.95), CCL19/MIP3β (2.06; 95% CI, 1.48–2.88), CXCL12/SDF1α+β (0.48; 95% CI, 0.32–0.65), and CCL28 (0.44; 95% CI, 0.27–0.71). Low PA had no significant marker associations.

Conclusions: Positively associated markers with MetS are mostly Th1 immune response–related and acute phase proteins, whereas negatively associated markers are generally Th2-related.

Impact: MetS is associated with a broad range of alterations in immune and inflammatory biomarkers that may contribute to risks of various chronic diseases, independent of low PA.

Introduction

Metabolic syndrome (MetS) represents a collection of cardiovascular risk factors associated with visceral adiposity and characterized by a state of chronic low-grade inflammation (1). Adipose tissue secretes numerous cytokines, including TNFα, interleukin (IL6), and monocyte-chemoattractant protein (CCL2/MCP1), that are thought to contribute to the insulin resistance and endothelial dysfunction that underlie MetS (2–4) and stimulate production of C-reactive protein (CRP) in the liver (5). Large cross-sectional epidemiologic studies have consistently linked these markers to MetS (6–8). Furthermore, weight loss of obese patients has been associated with decreases of these molecules. Low physical activity (PA), itself a strong predictor of MetS in prospective studies (9), is also associated with increased levels of inflammatory markers, most notably IL6 and CRP (10–12). The specific functions of these various molecules imply an important role in causing the adverse health consequences of MetS and low PA.

Different sets of inflammatory molecules in circulating blood constitute complex communication networks that may influence or reflect local inflammatory reactions. Multiplex examination of large sets of these markers could reveal their interdependent relationships to pathophysiology (13). However, most previous studies have been conducted in Western populations and investigated only a small set of candidate markers, potentially limiting the detection of novel markers that may be linked to MetS and low PA. Disentangling independent inflammatory signatures of these conditions is complicated by their frequent cooccurrence in source populations. In the present study, we investigated the associations of 110 circulating cytokines, chemokines, receptors, and other inflammation-related markers with MetS and low PA in a representative sample of Japanese adults.

Materials and Methods

Study population

The Japanese Public Health Center-based Prospective Study (JPHC) Cohort II enrolled Japanese citizens between the ages of 40 and 69 ($N =$ 78,825) at six different sites across the country (Niigata, Ibaraki, Osaka, Kochi, Nagasaki, and Okinawa) in 1993. Participants completed a questionnaire assessing medical history and lifestyle factors, including smoking, alcohol use, and PA at baseline. Physical examinations, including blood collection were conducted between 1993–1995, a median 0.4 (maximum 1.2) years after enrollment (14). The present study includes a stratified random sample of 774 participants from

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those providing both questionnaire data and blood samples, frequency matched by age and sex for previously reported case–cohort analyses of several cancer types (15–17).

MetS and PA measures

Total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides (TG), and glucose were measured at 23 laboratories in the cohort area. Samples resubmitted to Osaka Medical Center, a member of the Cholesterol Reference Method Laboratory Network, showed satisfactory precision and accuracy, with mean (SD) within-sample coefficients of variation (CV) between 0.72% (0.32%) and 0.69% (0.30%) and absolute percent bias between 1.30% (0.72%) and 0.66% (0.51%; refs. 18, 19). Blood pressure was measured by trained technicians using standard sphygmomanometers, height was measured in stocking feet, and weight was measured in light clothing. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2).

The components of MetS were defined according to modified AHA/NHLBI criteria as presence of three or more of the following risk factors: (i) hyperglycemia: fasting glucose ≥100 mg/dL, non-fasting glucose ≥140 mg/dL, or use of medication; (ii) hypertension: systolic blood pressure ≥130 mmHg, diastolic blood pressure ≥85 mmHg, or use of medication; (iii) low HDL cholesterol: ≤40 mg/dL for males or ≤50 mg/dL for females, or use of medication; (iv) hypertriglyceridemia: ≥150 mg/dL or use of medication; and (v) obesity: BMI ≥ 25 kg/m^2, which corresponds roughly to the Asia-Pacific criterion of high waist circumference (≥85 cm in males and ≥90 cm in females; refs. 20, 21). 3.1% of participants were missing data on hypertension, 3.1% were missing data on hypertriglyceridemia, 1.6% were missing data on obesity, and 10.2% were missing data on hyperglycemia.

Metabolic equivalents (MET) for self-reported daily PA were calculated as the sum of duration of each activity level (sleeping, sitting, walking, walking quickly, moderate exercise, or strenuous exercise) multiplied by its corresponding MET intensity (0.9, 1.5, 2.0, 3.0, 4.0, and 4.5, respectively), a method that has been validated against gold-standard 24-hour recall ($r = 0.55$–0.80; ref. 22). Low PA was defined as daily METs in the bottom quartile (<31.85), excluding 3.7% of participants with missing data. Considering individuals with complete information about the MetS variables as well as self-reported PA, there were 631 (82%) participants with non-missing data on all exposures of interest.

Missing data were imputed to complete datasets for analysis. Multivariate imputation by chained equations (MICE) was used to impute missing data for PA, MetS components, alcohol consumption (never/less than weekly, <150 g/wk, 150–299 g/wk, or ≥300 g/wk; 3.0% missing), and smoking status (never, past, or current; 0.9% missing; ref. 23). Continuous variables (METs/d, glucose, TG, systolic and diastolic blood pressure, BMI, and alcohol consumption in grams per week) were imputed by predictive mean matching then categorized as previously described, and smoking status was imputed by proportional odds logistic regression. In addition, we performed sensitivity analyses restricted to participants with complete data.

Biomarker measurements

Blood samples collected at the time of health checkups were obtained in vacutainer tubes with heparin and centrifuged within 12 hours of collection to yield plasma and buffy coat layers. Vials were stored at −80° C and had previously undergone a maximum of two freeze-thaw cycles for prior analyses. Levels of 67 immune- and inflammation-related markers were measured using multiplex Milliplex bead-based assays (EMD-Millipore Inc.) and 92 additional markers were measured using Proseek proximity-extension assays (Olink Proteomics). The bead-based assays were performed as previously described, and median batch CV was 13% (15). The proximity-extension markers were analyzed per the manufacturer's protocol using 1 μL samples (24). Briefly, a pair of unique, partially complementary oligo-nucleotide labeled antibodies was bound to each target protein, allowed to hybridize, and measured with real-time qPCR. Inter-batch controls were run on each plate and used to correct for inter-assay variation, and relative expression was reported as Normalized Protein Expression values. A set of 60 masked duplicates were randomly interspersed across plates to assess reproducibility, and inter-batch CVs were all ≤10%.

All 774 participants were screened by bead-based panels, and a randomly selected subset ($N = 410$ participants) were assessed by the proximity-extension panel. Subject characteristics of those included in proximity extension testing was comparable with that of the overall population. Three markers were measured using both conventional and high-sensitivity assays in separate bead-based panels and the assay yielding fewer missing results was used for analysis (high sensitivity: IL7, conventional: CXCL8/IL8 and CCL20/MIP3α). Twenty-two markers [Milliplex: interleukin 3 (IL3) and tumor necrosis factor beta (TNFβ); Proseek: artemin, brain-derived neurotrophic factor, fibroblast growth factor 5, glial cell line–derived neurotrophic factor, interferon gamma, IL1A, IL15RA, IL20, IL20RA, IL22RA1, IL24, IL2RB, IL13, IL2, IL33, IL4, leukemia inhibitory factor, neurturin, TNF, and thymic stromal lymphopoietin] detectable in less than 10% of samples were excluded from analysis, as were 24 Proseek markers that duplicated Milliplex assays (CCL19/MIP3β, CCL20/MIP3α, CCL2/MCP1, CXCL6/GCP2, IL17α, CXCL9/MIG, CCL8/MCP2, IL6, TGFα, CCL3/MIP1α, CCL4/MIP1β, CXCL10/IP10, IL5, IL8, CCL13/MCP4, CCL11/EOTAXIN, IL7, IL10, SCF, CX3CL1/FRACTALKINE, CXCL1/GRO, TRAIL, CXCL11/ITAC, CXCL5/ENA78).

Statistical analyses

Markers were analyzed as quantiles to detect potential nonlinear relationships, as previously described (15). Markers with 75%–90% of individuals measured below the lower limit of detection (LLOD) were categorized as detectable and undetectable ($N = 5$ markers), markers with 50%–75% of individuals below the LLOD were categorized as less than LLOD and below or above the median of detectable marker values ($N = 4$ markers), markers with 25%–50% of individuals below LLOD were categorized as less than LLOD and tertiles of detectable levels ($N = 9$ markers), and markers with <25% of individuals below the LLOD were categorized as quartiles ($N = 92$ markers). A complete list (full names and abbreviations) of the markers included in analyses, along with quantile classifications, is shown in Supplementary Table S1.

Ordinal logistic regressions were used to calculate odds ratios (OR) and 95% confidence intervals (CI) for the association of each marker's quantiles as dependent variables with: (i) MetS, (ii) low PA, (iii) obesity, (iv) hypertension, (v) hyperglycemia, (vi) hypertriglyceridemia, and (vii) low HDL. The base model was adjusted for age, sex, and study area, and the fully adjusted model also included smoking status, weekly alcohol consumption, fasting status at blood draw (<8 hours or ≥8 hours), MetS, and low PA.

FDR P values were calculated to account for multiple comparisons. To assess relationships among markers, continuous measures of markers measured with bead-based assays were log transformed to approximate normal distributions and facilitate comparison with the relative scale of markers measured in proximity extension assays. Pairwise correlations amongst markers were assessed by Pearson

Table 1. Baseline characteristics of JPHC Cohort II study sample.

	N (%) or mean (SD)				
	Total (*N* = 774)	**MetS (*N* = 152)**	***P***	**Low PA (*N* = 160)**	***P***
Male	413 (53.4)	68 (44.7)	0.017	99 (61.9)	0.024
Age at enrollment (y)	60.7 (7.6)	61.8 (6.2)	0.045	60.7 (8.5)	0.834
Energy consumption (kcal/d)	1,437 (547.4)	1,298 (474.7)	<0.001	1,437 (455.8)	0.883
BMI (kg/m^2)	23.5 (3.0)	25.8 (2.6)	<0.001	23.5 (3.1)	0.361
PA (METs/d)			0.184		—
Q1 (<31.85)	160 (21.5)	38 (25.9)		160 (100)	
Q2–Q4 (≥31.85)	585 (75.6)	109 (71.7)		0 (0)	
Alcohol consumption			0.001		0.001
Never/less than weekly	424 (56.5)	105 (71.4)		84 (53.5)	
<150 g/wk	159 (21.2)	20 (13.6)		31 (19.7)	
150–299 g/wk	95 (12.6)	10 (6.8)		34 (21.7)	
≥300 g/wk	73 (9.7)	12 (8.2)		8 (5.1)	
Smoking status			0.117		0.010
Never	452 (58.9)	99 (66.0)		78 (49.1)	
Past	134 (17.5)	24 (16.0)		39 (24.5)	
Current	181 (23.6)	27 (18.0)		42 (26.4)	
MetS components					
Hypertension (BP ≥130/85 mmHg, medication use)	443 (59.1)	134 (88.2)	0.022	97 (64.2)	0.184
Hyperglycemia (FPG ≥100, non-fasting ≥140, medication use)	161 (23.2)	71 (50.7)	<0.001	33 (22.9)	0.995
Low HDL [HDL <50 mg/dL (female) or <40 mg/dL (male)]	193 (24.9)	95 (62.5)	<0.001	46 (28.7)	0.199
High TG (TG ≥150 mg/dL, medication use)	182 (24.3)	111 (73.0)	<0.001	47 (30.9)	0.040
Obesity (BMI ≥25 kg/m^2)	218 (28.6)	102 (67.5)	<0.001	38 (24.1)	0.187

Note: *P* values compare MetS with non-MetS and low PA with non–low PA, respectively.
Abbreviations: BP, blood pressure; FPG, fasting plasma glucose; MET, metabolic equivalent of task.

statistics. Principal component analysis (PCA) was conducted for potential dimensionality reduction.

Tests of statistical significance were based on two-sided *P* values, with unadjusted $P < 0.05$ considered nominally significant and FDR-adjusted $P < 0.05$ considered statistically significant. All analyses were carried out in R, version 3.6.0. (25). Multiple imputation was conducted using R package "mice" (23). Ordinal logistic regressions were run using the polr function from the MASS package (26), proportional odds assumptions were tested using the Brant test provided in the brant package (27), PCA was conducted using the PCA function in the FactoMineR package (28), and graphs were generated in ggplot2 (29) and corrplot (30). R package "polycor" was used to calculate polychoric correlation between MetS and low PA (31). A bootstrapped power analysis was conducted by simulating 1,000 sets of 110 trials at the two given sample sizes (bead-based: $N = 774$, proximity extension: $N = 410$), and applying the FDR correction to each generated set of associations.

Results

Baseline characteristics of the subjects are shown in **Table 1**. The median interval between the questionnaire completion and blood sample/physical assessment was 0.4 years (maximum 1.2 years). The prevalence of MetS was 19.6%. Compared with participants without MetS, participants with MetS were older, more likely to be female, and less likely to drink alcohol. Participants with low PA were more likely to be male, smoke, drink moderately, and have hypertriglyceridemia than those in the top three PA quartiles. Low PA was not correlated with MetS in study participants ($\rho = 0.05$, $P = 0.15$).

Figure 1A depicts the 22 nominally significant associations between MetS and biomarkers in fully adjusted models. Six of these markers survived FDR correction, including increased levels of CCL19/MIP3β, CRP, SAP, and IL18R1 and decreased levels of CXCL12/SDF1α+β and CCL28. Low PA was nominally associated with thirteen markers, none of which remained significant after FDR correction (**Fig. 1B**). Crude and adjusted associations of MetS and low PA with all 110 markers are shown in Supplementary Tables S2 and S3. All adjusted associations for these markers differed by <10% from crude associations. Four markers were at least nominally associated with both MetS and low PA (CCL19/MIP3β, CD5, CCL27/CTACK, and SCF). In fully adjusted models restricted to the 82% of participants with complete exposure data, the same six markers were associated with MetS (after FDR correction), whereas one new marker (IL12B) was associated with low PA (FDR *P* value changing from 0.08 to 0.04). The ORs in the sensitivity analyses for all seven markers were within 10% of the estimates from the main analyses.

As presented in **Table 2**, after FDR correction in Model 2, obesity was associated with 8 markers, hyperglycemia was associated with 2 markers, low HDL was associated with 13 markers, hypertriglyceridemia was associated with 25 markers, and hypertension was associated with 1 marker, representing a total of 38 unique markers. Thirty of these component markers were positively associated (ADA, CCL7/MCP3, CCL19/MIP3β, CCL20/MIP3α, CCL2/MCP1, CD5, CD6, CRP, CXCL13/BCA1, CXCL6/GCP2, CXCL9/MIG, ENRAGE, FLT3L, HGF, IL10Rβ, IL18, IL18R1, IL4, NT3, SAA, SAP, SCF, sIL6R, sTNFR1, sTNFR2, sVEGFR3, TNFRSF9, TRAIL, TRANCE, and VEGFα) and eight were negatively associated (CCL28, IL1β, IL13, IL17α, IL5, OSM, CCL17/TARC, and CXCL12/SDF1α+β). Supplementary Tables S4–S8 depict crude and adjusted associations between MetS components and all 110 candidate markers. Of the markers associated with more than one component of MetS, two were associated with obesity,

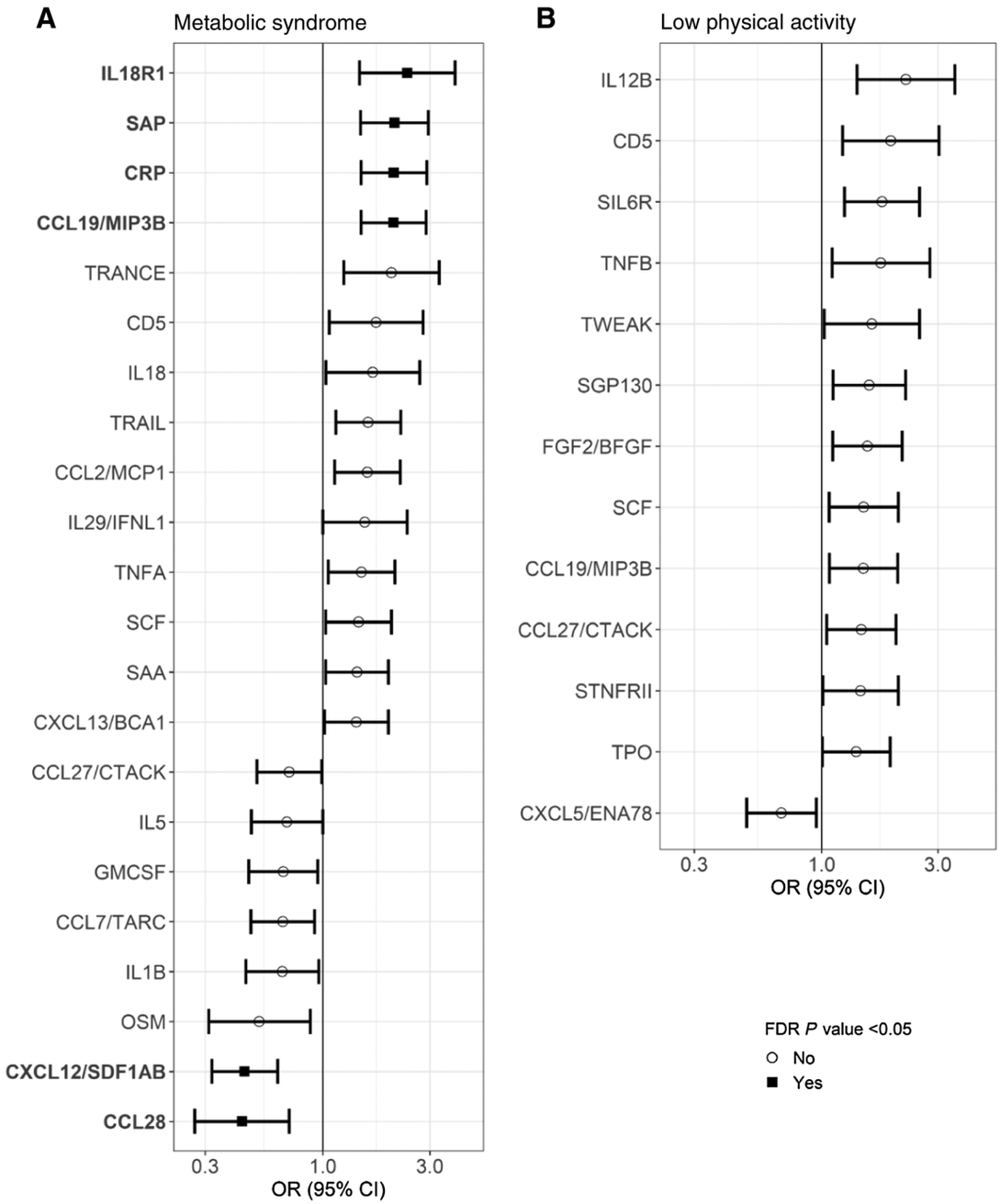

Figure 1.

Nominally significant results of ordinal logistic regressions estimating inflammatory marker quantile according to AHA/NHLBI metabolic syndrome (**A**) and low PA (**B**) in the JPHC Cohort II. Odds ratios (OR) and 95% confidence intervals (95% CI) were adjusted for age (years), sex, study site, smoking status (never, past, and current), alcohol use (never or less than weekly, <150 g/wk, 150–299 g/wk, ≥300 g/wk), fasting status at blood draw (<8 hours, ≥8 hours), metabolic syndrome, and PA (bottom quartile or top 3 quartiles).

hypertriglyceridemia, and low HDL (CCL19/MIP3β, and CRP); one was associated with obesity, hypertriglyceridemia, and hyperglycemia (IL18R1); four were associated with hypertriglyceridemia and low HDL (CCL2/MCP1, CD5, CXCL12/SDF1α+β, and SCF); and one was associated with obesity and hypertriglyceridemia (TRAIL). Considering associations that were at least nominally significant, all markers of MetS except IL29/IFNL1 and five markers of low PA (CCL19/MIP3β, SCF, sIL6R, sTNFR2, and CD5) were also associated with one or more MetS components.

Most correlations among markers associated either with MetS or low PA were weak ($|r| \leq 0.3$), although strong correlations, all with $P < 0.001$, were observed between SCF and TPO ($r = 0.70$), CRP and SAA

Table 2. ORs and 95% CIs of 38 markers significantly associated with components of MetS after FDR correction in fully adjusted ordinal logistic regression models.

	Obesity	High TG	Low HDL	Hyperglycemia	Hypertension
ADA				2.22 (1.40–3.54)	
CCL7/MCP3	2.10 (1.38–3.19)				
CCL17/TARC		0.58 (0.43–0.79)			
CCL19/MIP3B	1.91 (1.42–2.57)	1.88 (1.38–2.56)	1.83 (1.34–2.49)		
CCL20/MIP3A			1.60 (1.17–2.18)		
CCL2/MCP1		1.62 (1.19–2.21)	1.77 (1.29–2.43)		
CCL28	0.47 (0.31–0.72)				
CD5		2.21 (1.42–3.44)	1.93 (1.25–2.97)		
CD6		1.79 (1.14–2.81)			
CRP	2.16 (1.61–2.90)	1.75 (1.29–2.39)	2.14 (1.56–2.93)		
CXCL12/SDF1AB		0.42 (0.31–0.57)	0.48 (0.35–0.66)		
CXCL13/BCA1			1.59 (1.16–2.17)		
CXCL6/GCP2			1.78 (1.30–2.43)		
CXCL9/MIG			1.76 (1.28–2.41)		
ENRAGE		1.84 (1.17–2.90)			
FLT3L	2.05 (1.32–3.18)				
HGF		2.13 (1.34–3.37)			
IL10RB		2.07 (1.31–3.27)			
IL17A		0.63 (0.45–0.88)			
IL18			2.13 (1.36–3.32)		
IL18R1	2.34 (1.54–3.54)	2.14 (1.36–3.36)		2.63 (1.65–4.19)	
IL1B		0.60 (0.42–0.86)			
IL13		0.60 (0.43–0.85)			
IL4			2.09 (1.31–3.34)		
IL5		0.56 (0.39–0.78)			
NT3		2.21 (1.38–3.53)			
OSM					0.45 (0.30–0.68)
SAA	1.64 (1.22–2.20)				
SAP		2.39 (1.73–3.29)			
SCF		1.55 (1.13–2.11)	1.64 (1.20–2.24)		
SIL6R		1.71 (1.22–2.38)			
STNFRI		1.57 (1.13–2.19)			
STNFRII			1.73 (1.22–2.44)		
SVEGFR3		1.80 (1.29–2.52)			
TNFRSF9		1.95 (1.24–3.09)			
TRAIL	1.80 (1.34–2.42)	1.78 (1.31–2.42)			
TRANCE		3.38 (2.14–5.35)			
VEGFA		1.99 (1.28–3.08)			

Note: Models are adjusted for age, sex, study site, smoking status (never, past, current), alcohol use (never/less than weekly, <150 g/wk, 150–299 g/wk, ≥300 g/wk), fasting status at blood draw, and PA (bottom quartile, top 3 quartiles).

($r = 0.61$), GMCSF and IL1β ($r = 0.58$), SCF and IL29/IFNL1 ($r = 0.53$), and OSM and TNFα ($r = 0.50$; Supplementary Fig. S1). In PCA of all 110 markers, 32 PCs with eigenvalues ≥1.0 were identified. Taken together, these explained 68% of the variance in marker levels.

Discussion

Using one of the largest sets of circulating inflammatory biomarkers assessed to date, we identified 6 markers associated with MetS and another 32 markers associated with MetS components. No markers were significantly associated with low PA. These findings support a broad association between MetS and inflammation and suggest that the adverse health effects of low PA may not involve inflammation. The PCA results indicate these perturbations are complex and not readily amenable to data reduction.

Four of the markers associated with MetS were cytokines or cytokine receptors, including 3 chemokines (CCL19/MIP3β, CCL28, and SDF1α+β/CXCL12), and an interleukin receptor (IL18R1). Cytokines are a heterogenous set of signaling proteins involved in immune cell differentiation, adhesion, and chemotaxis (32). Though generally implicated in more than one type of immune signaling, cytokines can be roughly categorized according to the primary immune cell type of production and/or effect [T-helper cell 1 (Th1), 2 (Th2), 17 (Th17), etc.; ref. 33].

The metabolic dysfunction accompanying obesity is thought to disrupt the balance among these immune responses, skewing in favor of Th1 and Th17 pathways over Th2 and T-regulatory (Treg) pathways (34–36). Our results are consistent with this hypothesis, as we found that MetS was associated with increased Th1-associated CCL19/MIP3β and IL18R1 and decreased Th2-associated SDF1α+β/CXCL12 and CCL28. CCL19/MIP3β primes dendritic cells toward a Th1 fate (37), and activation of IL18R1 by IL18 can enhance production of IFNγ, a Th1 cytokine (38). Conversely, SDF1α+β/CXCL12 stimulates production of IL10 (39, 40), a Th2 cytokine that is involved in Th1 inhibition, and CCL28 is a chemoattractant for IL10-producing Treg cells (41). Previous epidemiologic studies have reported positive

associations of MetS with IL18R1 (42) and obesity with CCL19/MIP3β levels (43), and a negative association of waist circumference with SDF1α+β/CXCL12 levels (44). To our knowledge, an association between MetS and CCL28 has not been previously documented.

The remaining two markers positively associated with MetS were acute phase proteins. These types of proteins are secreted by hepatocytes in response to infection, injury, and other immunologic challenges. Acute phase proteins are primarily induced by Th1-associated cytokines such as TNFα or IL1β as well as by IL6, and are implicated in monocyte recruitment, adhesion, and chemotaxis, as well as regulation of other proinflammatory cytokines (45). MetS and obesity are consistently associated with elevated CRP in large cross-sectional epidemiologic studies (6, 46–48) and meta-analyses (49), though the causal direction of this relationship is debated (50–53). Also consistent with our findings, two small studies showed elevated circulating SAP in the blood of obese adolescents (54, 55).

No markers were significantly associated with low PA, and most nominally associated markers of low PA were distinct from those of MetS. Previous studies linking low PA to inflammation have been conducted primarily in populations where low PA and MetS were found to be highly correlated (9), and observed associations between PA and inflammatory markers were often substantially attenuated after adjustments for BMI or MetS (43, 56). Together, these findings suggest that the association between low PA and inflammation may be confounded by MetS. Our unique study population in which low PA and MetS were uncorrelated minimized potential for residual confounding and demonstrated a null association of low PA with inflammation.

In several instances, we failed to confirm previously reported positive associations, notably for TNFα and IL18 (8, 57). The lack of association in our study may be partially due to adjustment for multiple comparisons, as both these markers were nominally associated with MetS. Furthermore, although IL6 has previously been reported to be positively associated with MetS, we found a nonsignificant inverse association. However, previous studies demonstrating a positive association between MetS or obesity and IL6 have generally been conducted in Western populations (58, 59), and circulating levels of IL6 are lower in Japanese adults than age-matched Caucasians or African Americans (60). Interestingly, previous studies comparing Japanese and Caucasian adults have found that IL6 levels were related to the development of insulin resistance in Caucasian participants but not Japanese participants (61, 62).

The strengths of our study include the large community-based sample, comprehensive set of biomarkers, and reproducible assay methodology (63). Nonetheless, there were several limitations. We used both fasting and non-fasting blood samples, which may have inflated the prevalence of hypertriglyceridemia, and our definition of obesity was based on BMI rather than waist circumference, which could result in misclassification of participants with high lean body mass. Second, all measures, including blood samples and assessment of MetS components, were assessed at a single point in time and may not be representative of a given participant's general physical status. Third, our study was cross-sectional, so we could not establish temporal relationships among the components of MetS, PA, and biomarkers. Finally, although the distribution of MetS and low PA in this sample allowed for detection of distinct sets of markers for each condition, the lack of overlap may limit generalizability to populations in which these two conditions are correlated.

This cross-sectional study indicates that MetS is associated with a wide range of inflammation markers that are not indicative of low PA. Conversely, low PA may contribute to adverse health effects in pathways independent of inflammation.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: C.S. Rabkin, M.C. Camargo, S. Tsugane, M. Song
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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): N. Sawada, T. Shimazu, H. Charvat, T. Yamaji, M. Inoue, L.A. Pinto, S. Tsugane
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): S.C. Van Alsten, C.S. Rabkin, M.C. Camargo, M. Song
Writing, review, and/or revision of the manuscript: S.C. Van Alsten, C.S. Rabkin, T. Shimazu, H. Charvat, T. Yamaji, M. Inoue, T.J. Kemp, M.C. Camargo, S. Tsugane, M. Song
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): C.S. Rabkin, S. Tsugane
Study supervision: C.S. Rabkin, S. Tsugane, M. Song

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