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Original Research Article

Association between Moderate-Intensity Physical Activity and Inflammatory Markers in Women With and Without Breast Cancer

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ABSTRACT

Background: Moderate-intensity physical activity has been associated with a lower risk of chronic diseases such as breast cancer. Low-grade chronic inflammation is associated with metabolic disorders and cancer.

Purpose: We evaluated the association between self-reported moderate-intensity physical activity and serum levels of tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6) and C-reactive protein (CRP) in women with and without breast cancer.

Methods: We studied a random subsample of 352 cases and 381 controls obtained from a large population based case-control study. An in-person interview, anthropometric measurements and blood samples were obtained. For the analyses, multiple linear regression models were used.

Results: In controls, there was a negative association between moderate-intensity physical activity and serum levels of IL-6 and CRP (β = -0.0041, 95% CI -0.0079 to -0.0003; β = -0.0088, 95% CI -0.0172 to -0.0005, respectively); no association was found with serum TNF-α levels. In cases, no statistically significant associations were found.

Conclusions: Engaging in moderate-intensity physical activity was independently associated with lower serum concentrations of IL-6 and CRP only in women without breast cancer. Prospective studies are required in order to understand in which moment this association is lost.

Key words: Breast cancer, tumor necrosis factor-α, interleukin-6, C-reactive protein, physical activity.

INTRODUCTION

Physical activity has been associated with a lower risk of non-communicable diseases [1] and several mechanisms have been proposed to explain this risk reduction. [2,3] It has been hypothesized that physical activity impacts on adiposity, sex hormones, insulin resistance, adipokines and inflammatory markers (IM). [2-5] These IM are known for promoting a state known as low-intensity chronic inflammation, a condition characterized by an increase in serum levels of acute phase proteins and cytokines, such as C-reactive protein (CRP), tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6). [6] High levels of these IM have been shown to be positively associated with various adverse health factors, such as endothelial dysfunction, atherosclerosis, insulin resistance, proteolysis, deregulation of normal cell growth and oxidative stress, which in turn are related to various illnesses such as coronary arterial disease, cerebrovascular accident, osteoarthritis, congestive heart failure, diabetes mellitus, and some types of cancer such as breast cancer. [4,5,7,8]

Epidemiological studies have suggested that engaging in physical activity is associated with lower concentrations of certain chronic IM in the adult population. [9-18] However, these studies have been mostly carried out in developed countries and in people with other diseases, such as obesity, [19-21] diabetes, [22-25] metabolic syndrome, [9,26,27] and heart disease. [28-30] To our knowledge, none of these studies have been carried out in women with newly diagnosed breast cancer. In this context, the aim of this study was to determine the association between the times spent in moderate-intensity physical activities during a regular week performed in the past year (h/week), before any symptoms were perceived by those with breast cancer, and serum levels of TNF-α, IL-6 and CRP in women with and without breast cancer.

MATERIALS AND METHODS

Study Design and Population: A random subsample of 352 cases and 381 controls were randomly selected from a population-base case-control study that was carried out between 2004 and 2007 in Mexican women. Detailed methods have been described elsewhere. [31] Briefly, 1,000 breast cancer cases and 1,074 controls aged 35 to 69 and who had lived in Mexico City, Veracruz or Monterrey and surrounding metropolitan areas for the past 5 years, were recruited. The aim of the study was to investigate risk factors for breast cancer. Incident cases were recruited from 12 hospitals from the major health care systems in the country: the Mexican Institute of Social Security (IMSS, Instituto Mexicanodel Seguro Social),the Social Security system for state workers (ISSSTE, Institutode Seguridad y Servicios Sociales de los Trabajadores del Estado) and the Ministry of Health (SS, Secretaría de Salud).Inclusion criteria for cases were having an incident histologically confirmed breast cancer with no previous treatment such as radiotherapy, chemotherapy, or antiestrogens in the last 6 months. Women were excluded if they were pregnant, or were known to be HIV-positive. Women were recruited into the study, on average, on the third day after diagnosis (range of 0 to 6 days). [31] Controls were frequency-matched to the cases, according to 5-year age groups, membership to a health care institution and place of residence.

All participants signed an informed consent form. A nurse carried out an interview to obtain socio-demographic information, as well as data on physical activity, diet and health. Additionally, blood samples were taken for biochemical determinations as well as anthropometric measurements (weight, height and waist circumference).Response rate for cases was 94.4% for Monterrey, 95.5% for Mexico City, and 97.4% for Veracruz; for controls it was 90.1%, 87.4%, and 97.6%, respectively. The study was approved by the research, ethics and bio security committees of the National Institute of Public Health, as well as by the respective committees from each of the participating hospitals.

Recruitment

Nurses were based, from Monday to Friday, at each hospital, where they interviewed cases and obtained fasting blood samples. Controls were interviewed at their home and an appointment was scheduled for each woman to attend the hospital for anthropometric measurements and blood samples. No more than one hour later, the samples were centrifuged and serum was obtained and stored between -20 and-70 °C, in the hospitals. Within a period of less than four weeks, these samples were transported to the National Institute of Public Health where they were stored at -70°C until the IM were determined.

Inflammatory Markers

Serum concentrations of IM were determined in duplicate. TNF-α and IL-6 were determined at the Quest Diagnostics Nichols Institute (San Juan Capistrano, CA, USA) using the Quantikine Elisa Kit (R & D Systems, Inc. Minneapolis, MN, USA). The inter- and intra-assay variation coefficients were below 20% for both cytokines. CRP concentrations were determined at the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán (Mexico City, Mexico) using the Tina quant CRP high sensitivity immunoturbidimetric method (Roche Diagnostics, Mannheim, Germany). Both variation coefficients were below 9%. The labeling on the samples did not allow the identification of the case-control status. The IM determinations showed values within the detectable ranges, except for TNF-α which in less than 11% of the samples the values were found below the detection level (less than 1 pg/dL). In these situations, a random value between 0.1 and 0.9pg/dL was assigned.

Physical Activity

A semi-structured interview was performed in order to determine the time spent in physical activities during a regular week, within the last 12 months, in controls, and before the appearance of any symptoms in cases, in order to reduce the possibility of reverse causation bias. The questionnaire was designed based on the 7 day recall questionnaire proposed by Sallis et al. [32] Depending on the intensity, physical activity was divided into three categories based on the Compendium of Physical Activities by Ainsworth et al.:1) Light-intensity physical activities, which require light physical effort and correspond to a consumption of 1.1 to 2.9 metabolic equivalents of energy expenditure (METs) (e.g., office work, watching TV, listening to the radio, reading a book, or driving a car); 2) Moderate-intensity physical activities, which make people feel tired but do not make a person to become out of breath and require an energy consumption of 3.0 to 5.9 METs (e.g. painting walls, washing and dressing children, light sports, dancing slowly, or washing a car); and 3) Vigorous-intensity physical activities, which make people sweat, increase their heart rate and become breathless, require 6.0 or more METs of energy consumption (i.e. climbing the stairs carrying heavy bags, chopping wood, running, playing tennis or basketball). [33]

Covariates

To obtain information about diet, we used Willet's semi-quantitative Food Frequency Questionnaire [34] adapted to the Mexican population and previously validated in Mexico City. [35] We estimated total fiber intake (g/day), fat intake (g/day), and total calorie intake (kcal/day). By means of a questionnaire, during the interview, we collected information on age (years), state (Mexico City, Veracruz and Monterrey), health institution (IMSS, ISSSTE, and SS), menopausal status (pre-/post-menopause), and alcohol consumption during the last year (yes/no), and history of chronic diseases: diabetes, hypertension, hypercholesterolemia, arthritis, other cancers, and gastric ulcer (yes/no). A socioeconomic status (SES) index was constructed using principal components (low, middle, high), [36] and then categorized into tertiles based on the controls distribution. Body mass index (BMI) was estimated by dividing weight in kilograms by height in squared meters (kg/m^2) and waist circumference was measured in centimeters.

Statistical analysis: We analyzed cases and controls separately. Characteristics are presented by case-control status. We estimated means and standard deviations or medians and interquartile ranges for continuous variables and relative frequencies for the qualitative variables. The Shapiro-Wilk test was used to analyze the normality of the variables, and the Spearman correlation coefficient was used to determine the correlation between chronic IM and other variables of interest.

The analysis of the association between moderate-intensity physical activity and each of the IM was carried out through multiple linear regression models, where the dependent variables corresponded to the natural logarithm of each of the three IM and the independent variable was the time in hours per week dedicated to moderate-intensity physical activity. Multiple linear regression models were used in order to determine a unit of change of IM per increased hour of physical activity. Potential confounders were considered in each the models. For cases, we also adjusted for clinical stage of the tumor, since there have been reports that show that the cancer per se is capable of inducing local production of these IM. [37] For CRP, we only present information from premenopausal women, since we did not have this marker from the post-menopausal women due to insufficient resources. We used the mean plus three standard deviations to eliminate IM extreme values, [38] and since they were not normally distributed we used a logarithmic transformation. For the interpretation of the beta coefficients and the confidence intervals from the linear regressions, we used the following formula : $(\beta_1) * 100$. [39] A p value below 0.05 was considered to be statistically significant. All of the statistical analyses were carried out using STATA v. 11.2 (Stata Corporation, College Station, TX, USA 2009).

RESULTS

Table 1 summarizes the general characteristics of each group of participants. The mean age of cases was 52.2 years (SD 10.0) and for controls 52.3 years (SD 9.0), the median time spent doing moderate-intensity physical activity was lower in cases (6 h/week; interquartile range [IQR] 2.5-15.0) than in controls (13.5 h/week; IQR 3.0-24.0). Cases had higher concentrations of IM than controls. The medians for TNF-α corresponded to 2.30 vs. 2.00pg/mL ($p<0.01$), 2.77 vs. 2.36pg/mL ($p<0.001$) for IL-6 and 3.98 vs. 3.36 mg/dL ($p<0.04$) for CRP, respectively.

Table 2 shows serum IM by TNM classification. Although in advanced stages women had higher concentrations of TNF-α, IL-6 and CRP, p trend analyses were not significant. Regarding the IM correlations, Table 3 shows that IL-6 was positively correlated with both TNF-α and CRP in controls (rho 0.35, $p <0.001$; rho = 0.54; $p <0.001$, respectively) and in cases (rho 0.20, $p <0.001$; rho = 0.63; $p <0.001$, respectively). No significant correlation was observed between TNF-α and CRP. In both groups, IL-6 and CRP showed a positive correlation with BMI and waist circumference (Table 3).

In controls, after adjusting only for age, a statistically significant negative association between moderate-intensity physical activity and serum levels of IL-6 and CRP (β = -0.0041, 95% CI -0.0077 to -0.0005; β = -0.0096, 95% CI -0.0172 to -0.0020, respectively) was observed (Table 4).After adjusting for all variables shown in Table 4, the association was maintained, observing that for every extra hour per week of moderate-intensity physical activity, there was an IL-6 serum levels reduction of approximately 0.4% and of 0.9% in the serum levels of CRP (β = -0.0041, 95% CI -0.0079 to -0.0003; β = -0.0088, 95% CI -0.0172 to -0.0005, respectively). No associations were found between moderate-intensity physical activity and TNF-α.

Table 1: Characteristics of Mexican women by case-control status, 2004-2007

	Controls (381)		Cases (352)		
	Mean, Median,%	**SD or IQR**	**Mean, Median, %**	**SD or IQR**	**p value**
Age (years)*	52.3	9.0	52.2	10.0	0.86
Socioeconomic status %					
Low	34.4		33.8		
Middle	32.8		26.7		
High	32.8		39.5		0.10
Body mass index (kg/m^2)*	30.5	5.0	29.2	5.2	<0.001
Waistcircumference (cm)*	99.9	11.8	95.5	11.9	<0.001
Post-menopause %	56.6		56.2		0.90
Auto-report of diabetes %	18.7		20.1		0.66
Smoking %	18.6		21.3		0.36
Alcohol consumption during the last year %	9.2		20.6		<0.001
Moderate-intensity physical activity (hours per week)*	13.5	(3.0 - 24.0)	6.0	(2.5 - 15.0)	<0.001
Total physical activity (METs-hour per week)**	270.0	(246.0 - 302.3)	261.8	(240.2 - 289.2)	<0.001
Inflammatorybiomarkers					
Tumor necrosis factor-α (pg/mL)**	2.00	(1.20 - 3.70)	2.30	(1.50 - 4.00)	<0.01
Interleukin-6 (pg/mL)**	2.36	(1.69 - 3.34)	2.77	(1.72 - 5.13)	<0.001
C-reactive protein (mg/dL)**	3.36	(1.72 - 5.07)	3.98	(1.41 – 8.85)	0.04

The continuous variables are represented on the table as *mean and standard deviation or **median and interquartile range.

Table 2: Serum levels of TNF-α, IL6 and CRP in different stages of breast cancer according to TNM classification

		Tumor necrosis factor-α (pg/mL)	Interleukin-6 (pg/mL)	C-reactive protein (mg/dL)
		Median, IQR	**Median, IQR**	**Median, IQR**
	n			
Stage 0	7	1.8 (1.8 - 2.3)	1.0 (0.7 - 5.5)	2.2 (0.4 - 4.6)
Stage I	33	2.2 (1.6 - 4.4)	2.7 (2.0 - 3.9)	3.4 (1.1 - 9.6)
Stage II A	72	2.8 (1.5 - 5.7)	3.3 (2.1 - 6.2)	4.2 (1.7 - 8.3)
Stage II B	76	2.5 (1.6 - 3.9)	3.3 (2.0 - 5.9)	4.2 (1.6 - 10.4)
Stage III A	33	1.9 (1.3 - 3.4)	2.4 (1.6 - 3.5)	4.0 (2.7 - 15.1)
Stage III B	48	2.6 (1.5 - 3.8)	2.7 (1.6 - 5.2)	3.4 (1.4 - 12.2)
Stage III C	2	2.5 (2.5 - 2.6)	3.6 (1.3 - 5.9)	No data
Stage IV	6	2.5 (2.2 - 3.0)	5.4 (3.7 - 7.4)	16.9 (4.9 - 26.3)
No classifiable	8	1.6 (1.1 - 4.2)	2.5 (1.8 - 2.9)	3.9 (2.0 - 7.8)
No Data	67	2.2 (1.3 - 3.6)	2.7 (1.7 - 5.0)	4.2 (2.6 - 12.5)
	352	p trend 0.75	p trend 0.56	p trend 0.12

The continuous variables are represented on the table as medians and their interquartile ranges. An extension of the Wilcox on rank-sum test for trend across ordered groups were performed. No classifiable tumors were not included in the p for trend analysis.

Table 3: Spearman correlations between tumor necrosis factor-α, interleukin-6, C-reactive protein and variables of interest in cases and controls, 2004-2007

	TNF-α		IL-6		CRP		Age		BMI		WC		MPA		TPA
Controls															
TNF-α	1														
IL-6	0.35	***	1												
CRP	-0.01		0.54	***	1										
Age	0.12	**	0.06		-0.01		1								
BMI	0.02		0.31	***	0.40	***	0.02		1						
WC	-0.01		0.32	***	0.33	***	0.12	**	0.80	***	1				
MPA	0.14	**	-0.10	*	-0.16		-0.01		-0.08		-0.11	*	1		
TPA	0.09		-0.09		-0.17	*	-0.15	**	-0.09		-0.13	**	0.77	***	1
Cases															
TNF-α	1														
IL-6	0.20	***	1												
CRP	0.08		0.63	***	1										
Age	0.02		0.07		0.19	*	1								
BMI	-0.08		0.24	***	0.34	***	0.16	**	1						
WC	0.01		0.21	***	0.29	***	0.24	***	0.72	***	1				
MPA	0.06		0.05		0.06		-0.20	***	-0.01		-0.05		1		
TPA	0.00		-0.08		-0.06		-0.23	***	-0.05		-0.06		0.70	***	1
WC, waist circumference; MPA, moderate-intensity physical activity (hours per week); TPA, total physical activity (METs-hour per week).															
p < 0.05 = *															
p < 0.01 = **															
p < 0.001 = ***															

Table 4: Multiple linear regression models with the natural logarithm of tumor necrosis factor-α, interleukin-6 and C-reactive protein as dependent variables incases and controls, 2004-2007

	Tumor necrosis factor-α				Interleukin-6				C-reactive protein			
	n	β	R^2	IC 95%	n	β	R^2	IC 95%	n	β	R^2	IC 95%
Bivariate models[a]												
Controls												
Moderate-intensity physical activity (h/wk)	369	0.0082	0.03	(0.0021, 0.0144)	378	-0.0041	0.02	(-0.0077, -0.0005)	150	-0.0096	0.04	(-0.0172, -0.0020)
Cases												
Moderate-intensity physical activity (h/wk)	338	0.0043	0.01	(-0.0026, 0.0112)	347	0.0045	0.01	(-0.0016, 0.0106)	136	0.0021	0.04	(-0.0116, 0.0158)
Multivariable models[b]												
Controls												
Moderate-intensity physical activity (h/wk)	316	0.0059	0.13	(-0.0010, 0.0127)	325	-0.0041	0.18	(-0.0079, -0.0003)	130	-0.0088	0.37	(-0.0172, -0.0005)
Cases												
Moderate-intensity physical activity (h/wk)	236	0.0037	0.12	(-0.0042, 0.0117)	243	-0.0016	0.26	(-0.0084, 0.0051)	102	-0.0041	0.42	(-0.0184, 0.0101)

a Bivariate models adjusted for age (years)

b Multivariable models in controls were adjusted for age (years); state (Mexico City, Veracruz and Monterrey); health institution (IMSS, ISSSTE, and SS); SES (low, middle, high); menopausal status (pre-/post-); BMI (kg/m2); alcohol consumption during the last year (yes/no); consumption of fiber (g/day), fat (g/day) and total calories (kcal/day); and history of chronic illnesses (diabetes (yes/no), hypertension (yes/no), hypercholesterolemia (yes/no), arthritis (yes/no), gastric ulcer (yes/no).

Multivariable models in cases were adjusted for age (years); state (Mexico City, Veracruz and Monterrey); health institution (IMSS, ISSSTE, and SS); SES (low, middle, high); menopausal status (pre-/post-); BMI (kg/m2); alcohol consumption during the last year (yes/no); consumption of fiber (g/day), fat (g/day) and total calories (kcal/day); and history of chronic illnesses (diabetes (yes/no), hypertension (yes/no), hypercholesterolemia (yes/no), arthritis (yes/no), gastric ulcer (yes/no) and clinical stage of cancer (TNM).

In all of the models, the dependent variable corresponds to the natural logarithm of the corresponding biomarker. For the interpretation of the beta coefficients and the confidence intervals, we used the next formula (eβ1-1)*100

In cases, after adjusting only for age, there was no statistically significant association between moderate-intensity physical activity and serum levels of IL-6 and CRP (β = 0.0045, 95% CI -0.0016 to 0.0106; β = 0.0021, 95% CI -0.0116 to 0.0158, respectively). After adjusting for all potential confounders and clinical stage no statistically significant reductions were observed in serum levels of IL-6 and CRP for every hour of moderate-intensity physical activity increment (β = -0.0016, 95% CI -0.0084 to 0.0051; β = -0.0041, 95% CI -0.0184 to 0.0101, respectively). No associations were found between moderate-intensity physical activity and TNF-α (Table-4).

DISCUSSION

The results from this study showed, in controls, an inverse association between moderate-intensity physical activity time and serum concentrations of IL-6 and CRP, after adjusting for age, location (state), health institution, menopausal status, SES, BMI, alcohol consumption, dietary indicators, and history of chronic illnesses. No statistically significant associations were observed in cases and no statistically significant associations were found between moderate-intensity physical activity time and serum levels of TNF-α in either group.

It has been shown that the effect of physical activity on serum concentrations of TNF-α is very low and [9] in some cases null. [25] This was shown by Pitsavos et al., [9] who analyzed two groups, one of apparently healthy adult population and another one with metabolic syndrome. In this study, the results from both groups showed that of the six IM analyzed (TNF-α, IL-6, CRP, fibrinogen, serum amyloid A and white cell count), TNF-α was the least associated with physical activity. In another study that examined the association between walking and IM, Yates et al., [25] found a negative association between walking and TNF-α after adjusting for age, ethnicity, sex, social deficits, tobacco consumption, as well as for METs from other physical activities; however, when adjusting for waist circumference, the statistical significance was lost. In the same manner, Colbert et al., [11] carried out an analysis measuring serum levels of TNF-α by quartiles of physical activity different from exercise and found no differences after adjusting for age, sex and race (Geometric Mean [GM] = 3.35, 3.19, 3.13, 3.19pg/mL; p-trend = 0.14). When adjusting for other diseases and alcohol and tobacco consumption, this association was reduced (GM = 3.35, 3.16, 3.13, 3.22pg/mL; p-trend = 0.29) and after incorporating variables such as body and visceral fat, this association was reduced even more (GM = 3.35, 3.16, 3.13, 3.22pg/mL; p-trend= 0.36).

In accordance with our results, the majority of the studies that have evaluated the association between physical activity and serum levels of IL-6, have found that they are inversely associated. [12,13,15] Yates et al., [25] found lower concentrations of IL-6 (~30%, p = 0.004) in a group of subjects that reported walking 30 or more minutes at least five times a week (3.3 vs 35.8 METs-hour/week) when adjusting for age, ethnicity, sex, social deficits, tobacco consumption and waist circumference, as well as METs from other activities. In the Whitehall II cohort, Hamer et al. [40] recommended to a group of subjects to carry out physical activity in order to improve their cardiovascular health; these subjects were evaluated 11 years later. Approximately half of them followed these suggestions, and they showed lower concentrations of serum IL-6 compared to the other half (β = -0.07; 95% IC -0.10 to -0.03).

Similarly to our results, a number of cross-sectional studies have found a negative association between physical activity and serum levels of CRP. [12,40-43] Results from the NHANES 2003-2006 showed a negative relationship with total physical activity as well as with moderate- to vigorous-intensity physical activity in adults (β = -0.230 and -0.712; respectively). [41] In the NHANES of previous years, Abramson et al. [42] reported this relationship in subjects over 40 years of age by comparing a group that did more physical activity versus one that did less activity (OR = 0.63; 95% CI 0.43 to 0.93). Furthermore, in the cohort studied by Hamer et al., the subjects who followed the recommendation to increase their physical activity had lower CRP concentrations compared to those who did not follow the recommendation (β-0.07; 95% CI, -0.12 to -0.02). [40]

In cases, although the clinical stage is considered to be the degree of progression and/or severity of the lesion, and has been related to the increase production of IM, [37] it did not confound our results (Table 4).

Many studies have suggested mechanisms by which greater physical activity could be associated with lower serum concentrations of IM. One of these postulates that while carrying out moderate- to vigorous-intensity physical activity, the muscle is capable of producing cytokines, including IL-6. [44] Depending on the duration and intensity of the activity, serum concentration levels of IL-6 can increase up to 100 times, [10] which in turn induce the production of anti-inflammatory cytokines and cortisol. [45] One hour after the conclusion of the activity, IL-6 returns to its basal concentration. The anti-inflammatory cytokines produced can reduce the adaptive immune response. [46] It is thought that the actions of these cytokines are due, in part, to the reduction in expression of certain molecules, such as the major histocompatibility complex (MHC), intercellular adhesion molecule 1 (ICAM-1), as well as a reduction in the expression of co-stimulatory molecules in antigen presenting cells (CD80 and CD86). All of the above makes the T cells incapable of maintaining an inflammatory response. [3,46]

Our study has several strengths. Health professionals were trained and standardized to carry out interviews in order to obtain socio-demographic information, as well as data on physical activity, diet and health. Additionally, standardized personnel obtained anthropometric measurements. One of the limitations in our study was that we did not measure CRP in postmenopausal women; however, no menopause-related differences in serum CRP have been observed in other studies. [47] Moderate-intensity physical activity was estimated using a 7-day recall questionnaire, based on a physical activity questionnaire previously validated in the general population, [32,48] and reproducibility results were similar to other studies. [49,50] For this study, we only took into consideration the time assigned to moderate-intensity physical activity, since very few women reported doing vigorous-intensity physical activity [31] and it has previously been reported that Mexican women spend very little time on these types of activities. [51] Serum measurements of TNF-α and IL-6 had variation coefficients below 20% which are acceptable. [52] The study design does not allow us to determine causality, although it is important to consider our results for the planning of future experimental studies.

CONCLUSION

In women without breast cancer, the time dedicated to moderate-intensity physical activity was associated with lower serum levels of IL-6 and CRP. Prospective studies are required in order to understand in which moment this association is lost.

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