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ORIGINAL ARTICLE

Relative contribution of health-related behaviours and chronic diseases to the socioeconomic patterning of low-grade inflammation

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Abstract
Objectives To test the association of low-grade inflammation with socioeconomic status (SES) and determine the relative contribution of prevalent chronic diseases and health-related behaviours in explaining such association.
Methods Cross-sectional analysis on 19,867 subjects (age ≥35, 48.1% men) recruited within the Moli-sani study from 2005 to 2010 (Italy). A score of low-grade inflammation, including platelet and leukocyte counts, the granulocyte-to-lymphocyte ratio, and C-reactive protein was applied. SES was measured by education, household income, and occupational social class.
Results Low SES was associated with elevated levels of low-grade inflammation. Health behaviours (including adiposity, smoking, physical activity, and Mediterranean diet adherence) explained 53.5, 53.9, and 84.9% of the association between social class, income, and education with low-grade inflammation, respectively. Adiposity and body mass index showed a prominent role, while prevalent chronic diseases and conditions only marginally attenuated SES inequalities in inflammation.
Conclusions Low-grade inflammation was socioeconomically patterned in a large Mediterranean population. Potentially modifiable behavioural factors explained the greatest part of this association with a *leading contribution* of adiposity, body mass index, and physical activity.

Keywords Moli-sani study · Socioeconomic status · Low-grade inflammation · Health-related behaviours · Chronic diseases

Introduction

Low-grade inflammation is a condition linked to increased risk of cardiovascular and neurodegenerative diseases, cancer, and ageing, and is also associated with higher risk of mortality (Danesh et al. 1998; Lind 2003; Coussens and Werb 2002; Samuels 2004; Schnabel et al. 2013; Mendall et al. 2000).

A large body of evidence has suggested that low socioeconomic status (SES) is directly associated with higher inflammatory status (Fraga et al. 2015; Jousilahti et al. 2003), one of the biological pathways through which SES ultimately 'gets under the skin' (Stringhini et al. 2015). More recently, it has been shown that SES differences in inflammation might explain up to one-third of social inequalities in type 2 diabetes incidence (Stringhini et al. 2013).

A number of processes have been proposed to explain the mechanisms through which socioeconomic factors influence inflammatory markers, including the adverse work environment, closely associated with increased stress, which impacts on inflammation (Fraga et al. 2015). In addition, other studies have explored a large panel of health-risk behaviours that are usually socioeconomically patterned and closely associated with inflammation (O'Connor and Irwin 2010; Pampel et al. 2010). Low SES

Moli-sani study Investigators are listed in Acknowledgements.

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subjects are more likely engaged in risky behaviours (Kaplan and Keil 1993), whereas healthy lifestyles associated with lower inflammation (e.g., higher-quality diets, regular physical activity, moderate alcohol consumption, and abstention from smoking) are more prevalent in high SES groups (O'Connor and Irwin 2010; Deverts et al. 2012). Similarly, chronic diseases, highly present in low SES groups, also share a common inflammatory background (Donati 2010). An additional potential mechanism through which SES may influence inflammation is psychological distress, such as depression, which has been associated with elevated inflammatory markers (Empana et al. 2005).

To date, the socioeconomic gradient in low-grade inflammation has been mostly addressed by using a single inflammatory biomarker approach (Jousilahti et al. 2003; Kershaw et al. 2010) or by considering different biomarkers simultaneously (Schnabel et al. 2013; Deverts et al. 2012; Danesh et al. 2000) and far fewer have investigated the contribution of cellular biomarkers of inflammation (Bonaccio et al. 2014). Furthermore, there is lack of evidence on potential SES inequalities in inflammation that may occur within Mediterranean epidemiological settings (Panagiotakos et al. 2004; Fraga et al. 2015).

Using data from a large community-based cohort, the aim of this study was twofold: first to examine the association between a number of SES indicators and low-grade inflammation as measured by a composite score, including plasmatic (C-reactive protein) and cellular (platelet and leukocyte counts and granulocyte-to-lymphocyte ratio) biomarkers, previously tested within the Moli-sani cohort (Pounis et al. 2016); second, to determine the relative contribution of prevalent chronic diseases and health-related behaviours in explaining such association.

Methods

Study population

Cross-sectional analyses were conducted in the framework of the Moli-sani cohort, a prospective study that randomly enrolled 24,325 men and women aged ≥35 from the general population of a Southern Italian region (Di Castelnuovo et al. 2012), from March 2005 to April 2010. For the purpose of this study, individuals with unreliable medical (1%) or dietary questionnaires (3.9%) or with missing values for main SES indicators (0.3%), low-grade inflammation (3.3%), and those for whom no information was available for health-related behaviours of interest (0.6%) were not included in the analyses. To avoid introducing confounding due to an acute inflammatory condition, we also excluded subjects with hepatitis B or C (2.9%), any haematological disease (2.2%), those with C-reactive protein ≥10 mg/l (4%) or included in the percentiles of either highest (1%) or lowest (99%) values for platelet (1.9%) or WBC counts (1.9%).The final sample was of 19,867 subjects. Participants excluded from the analyses (n = 4458) were comparable to the study sample in terms of sex (prevalence of men = 48.1% in both groups, p value = 0.96), whereas the mean age of the study sample was slightly lower (55.1 ± 11.6 vs 59.1 ± 12.8, p value <0.0001) and the study sample had a lower prevalence of some chronic diseases (CVD = 4.9 vs 7.7%; cancer = 2.9 vs 4.8%; diabetes = 9 vs 12.4%; all p values <0.05 analysis controlled for age and sex) with the exception of hypertension (55.1 vs 63.4%, p value = 0.15).

The Moli-sani study complies with the Declaration of Helsinki and was approved by the Ethics Committee of the Catholic University of Rome, Italy. All participants provided written informed consent.

Ascertainment of chronic diseases and conditions

History of cardiovascular disease included documented angina, myocardial infarction, revascularisation procedures, and stroke. History of cancer included self-reported diagnosis of cancer. Hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or treatment for hypertension. Hypercholesterolemia was defined as total cholesterol ≥240 mg/dl or by use of medication. Diabetes was defined as blood glucose ≥126 mg/dl or by use of pharmacological treatment. Depression (no/yes/unascertained) was defined by the use of anti-depressive drugs.

Socioeconomic indicators

Socioeconomic information was self-reported and collected by a structured questionnaire administered by trained personnel. Education was based on the highest qualification attained and was categorized as up to middle school (≤8 years of study), secondary school (8–13), and university or higher (>13).

Household income, expressed as earned Euros per year, was a six-level variable (<10,000; 10,000–25,000; 25,000–40,000; 40,000–60,000, and >60,000) with missing values collapsed into a non-respondent category.

Occupational social class was based on the Registrar General's occupation based classification scheme (McFadden et al. 2008), but, differently from the original UK classification, the social class for women was obtained as done for men. Social class was coded using current occupation at the time of survey except when subjects were unemployed in which case their partner's social class was used. Last employment was used for subjects who were

retired. Unemployed subjects without partners were unclassified as well as those for whom no information on social class was available or for those indicating "other" during recruitment. Social class for housewives was based on their last employment otherwise on their partner's social class except when the partner's social class was unclassified, missing, or they had no partner. Finally, occupational class was categorized as professional/managerial, skilled non-manual, skilled manual, semi-skilled/unskilled, and unclassified subjects.

Marital status was considered as a measure of social support and networks (Khang et al. 2009) and was considered as married, cohabiting, divorced, separated, single, or widowed.

Health-related behaviours assessment

Food intake during the year before enrolment was assessed by the validated Italian EPIC food frequency questionnaire (Pisani et al. 1997). Adherence to the Mediterranean diet (MD) was used as marker of diet quality and defined according to the Mediterranean Diet Score (Trichopoulou et al. 2003) scoring 0–9 and then collapsed into four categories of adherence.

Sport activity was expressed as hours of sport practiced during the week (h/week) and categorized as none, <2 or ≥ 2. Leisure-time physical activity (PA) was expressed as daily energy expenditure in metabolic equivalent task-hours (MET-h/d) for walking, gardening, repairs job, walking to work, shopping, cleaning, babysitting, and climbing stairs, and used as a categorical variable below and above the median ($\leq$ or >3.55) of the study population.

Body mass index (BMI) was calculated as kg/m^2 and then grouped into three categories as normal (≤ 25), overweight ($> 25 < 30$) or obese (≥ 30). Abdominal obesity was defined as waist-to-hip ratio ≥ 0.85 or ≥ 0.90 for women and men, respectively (WHO 2008). Both BMI and waist-to-hip ratio were used as measures of relative weight and body fat distribution, respectively, and, therefore, as a proxy for eating behaviour.

Subjects were classified as never-smokers, current smokers, or ex-smokers (quitting from at least 1 year).

Inflammatory biomarkers and INFLA score

Blood samples were obtained from participants who had fasted overnight and had refrained from smoking for at least 6 h. A full description of biomarkers measurement is provided elsewhere (Santimone et al. 2011).

Low-grade inflammation was assessed by an INFLA score already used within the Moli-sani cohort (Pounis et al. 2016) and including 10 tiles of C-reactive protein (CRP, mg/l), leukocyte (WBC, $\times 10^9$/L) and platelet counts ($\times 10^9$/L), and the granulocyte-to-lymphocyte ratio (G/L ratio). For all four components, being in the highest deciles (7–10) scored increasingly from 1 to 4, while being in the lowest deciles (1–4) was negatively scored from -4 to -1. Being in the deciles 5 or 6 got zero point. The INFLA score ranged between -16 and 16, and came up as the sum of the four components. An increase in the score represented an increase in low-grade inflammation intensity. For analysis purposes, the INFLA score was rescaled to have a mean of zero and a standard deviation of one.

Statistical analysis

Characteristics of the study population were presented as numbers and percentages, or mean values and standard deviation for continuous variables. Differences in Table 1 were calculated using the analysis of variance adjusted for age and sex.

Beta-coefficients ($\pm$SE) from multivariable linear regression analysis were used to estimate the association of the INFLA score (used as dependent variable) with health-related behaviours and chronic diseases and conditions (Table 2), while beta-coefficients with 95% confidence intervals (95% CI) were calculated for the association with indicators of SES (Tables 3, 4). Beta-coefficients represent the change in INFLA score for each level of the independent variable in comparison with the reference level. For the association of INFLA score with SES four models were fitted: the first one adjusted for age, sex, and marital status (Model 1), the second as in model 1 further adjusted for major chronic disease (cardiovascular disease, cancer, and diabetes), health conditions (hypertension and hypercholesterolemia), and depression, the third as in model 1 further controlled for health-related behaviours (smoking habit, Mediterranean diet, energy intake, leisure-time physical activity, sport activity, BMI, and waist-to-hip ratio). Finally, the fourth model included all the previous ones.

Associations of SES indicators with diseases and health behaviours were obtained by general linear models (PROC GENMOD in SAS) adjusted for age and sex (supplemental tables).

Because the inclusion of strongly correlated variables in the same regression model introduces collinearity problems, we tested multi-collinearity by measuring the variance inflation factor for each regressor and the condition index for the full model. A regressor whose variance inflation factor values are greater than 10 indicates that the presence of collinearity, as well as a large condition index, 10 or more, is an indication of the global instability of the

Table 1 Characteristics of the study population, low-grade inflammation, and inflammatory biomarkers by indicators of socioeconomic status (Moli-sani study, 2005–2010, Italy)

	No of subjects, %	Low-grade inflammation (score)	CRP* (mg/L)	WBC ($\times 10^9$/L)	Platelets ($\times 10^9$/L)	G/L ratio
All	19,867	0.00 (1.00)	1.38 (1.36–1.40)	6.14 (1.42)	248.3 (55.7)	1.97 (0.87)
Age, years						
<50	7698 (38.8)	0.02 (1.00)	1.11 (1.08–1.13)	6.22 (1.44)	256.5 (56.1)	2.02 (1.01)
50–65	7874 (39.6)	−0.05 (1.00)	1.49 (1.46–1.52)	6.13 (1.44)	246.6 (54.2)	1.87 (0.73)
>65	4295 (21.6)	0.04 (0.99)	1.79 (1.74–1.84)	6.06 (1.36)	234.8 (54.3)	2.07 (0.81)
P value		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Sex						
Women	10,311 (51.9)	0.02 (1.01)	1.41 (1.39–1.44)	5.89 (1.37)	258.3 (56.0)	1.97 (0.96)
Men	9556 (48.1)	−0.03 (0.98)	1.35 (1.33–1.38)	6.41 (1.43)	237.5 (52.2)	1.97 (0.75)
P value		0.0003	0.0013	<0.0001	<0.0001	0.53
Education						
University or higher	2564 (12.9)	−0.08 (0.99)	1.19 (1.15–1.23)	6.07 (1.38)	247.9 (55.3)	2.00 (0.87)
Secondary school	6920 (34.8)	−0.05 (1.00)	1.29 (1.26–1.32)	6.09 (1.42)	247.4 (55.4)	1.98 (1.05)
Up to middle school	10,383 (52.3)	0.05 (1.00)	1.50 (1.47–1.53)	6.21 (1.43)	248.3 (55.6)	1.96 (0.72)
P value		<0.0001	<0.0001	<0.0001	0.56	0.072
Household income, EUR/year						
>60,000	786 (4.0)	−0.13 (0.99)	1.18 (1.11–1.26)	5.97 (1.39)	246.7 (55.1)	1.98 (0.73)
40,000–60,000	1550 (7.8)	−0.10 (1.01)	1.26 (1.20–1.31)	6.06 (1.43)	246.3 (57.2)	1.96 (0.91)
25,000–40,000	4098 (20.6)	−0.04 (0.99)	1.35 (1.31–1.38)	6.14 (1.44)	245.2 (54.4)	1.97 (1.22)
10,000–25,000	6097 (30.7)	0.01 (1.00)	1.45 (1.42–1.48)	6.16 (1.41)	247.8 (55.5)	1.94 (0.70)
<10,000	1089 (5.5)	0.04 (1.04)	1.46 (1.38–1.54)	6.21 (1.45)	248.8 (57.9)	1.95 (0.71)
Non respondents	6247 (31.4)	0.05 (1.00)	1.39 (1.36–1.42)	6.18 (1.42)	250.1 (55.9)	2.00 (0.76)
P value		<0.0001	<0.0001	0.0001	0.0005	0.0019
Occupational class						
Professional and managerial	4054 (20.4)	−0.07 (0.99)	1.29 (1.25–1.33)	6.10 (1.40)	246.9 (55.3)	1.95 (1.22)
Skilled non-manual	7163 (36.0)	−0.02 (1.00)	1.33 (1.30–1.36)	6.12 (1.44)	248.0 (55.8)	1.98 (0.78)
Skilled manual	3641 (18.3)	0.02 (1.01)	1.43 (1.39–1.47)	6.18 (1.44)	247.7 (55.1)	1.97 (0.72)
Semi-skilled/unskilled	3826 (19.3)	0.07 (0.99)	1.50 (1.46–1.55)	6.19 (1.42)	248.8 (56.0)	1.99 (0.73)
Unclassified	1183 (6.0)	0.06 (1.00)	1.50 (1.42–1.58)	6.25 (1.38)	248.5 (56.6)	1.94 (0.72)
P value		<0.0001	<0.0001	0.0019	0.57	0.28

Means and *p* values adjusted for age (continuous) and sex

Analyses for age were controlled for sex and vice versa. All other associations were adjusted for age and sex. Analyses with platelet count were further controlled for haematocrit

CRP C-reactive protein, *WBC* white blood cell count, *G/L ratio* granulocyte-to-lymphocyte ratio

*Geometric hs-CRP means with corresponding 95% confidence intervals, adjusted for age (continuous) and sex

regression coefficients. Test for collinearity, performed for each regression model, provided a variance inflation factor <6.2 for each regressor. Moreover, the condition index was 3.73, 7.03, and 3.64 for analysis with education, household income, and occupation, respectively; such findings thus overcome possible problems of collinearity of the models.

To address and quantify the contribution of prevalent diseases and health-related behaviours in explaining the possible SES inequalities in low-grade inflammation, we compared the percentage change in regression coefficients of each enlarged model as compared to the reference model. The percentage change was calculated using the formula: (regression coefficient$_{\text{reference model}}$ − regression coefficient$_{\text{explanatory models}}$)/(regression coefficient$_{\text{reference model}}$). Model 1 was the reference model used to estimate the contribution of health behaviours and diseases (as a whole) in low-grade inflammation inequalities (Table 3), whereas model 2 was the reference model used to estimate the role of specific dietary and lifestyle factors (Table 4).

Table 2 Association of low-grade inflammation with health-related behaviours and chronic diseases (Moli-sani study, 2005–2010, Italy)

	%	Low-grade inflammation (score)*	Age/sex adjusted model		Multivariable model	
			Regression coefficient (SE)	*P* value	Regression coefficient (SE)	*P* value
Mediterranean diet**						
Low (0–2)	13.3	0.07 (0.02)	Reference		Reference	
Medium (3–4)	40.0	0.02 (0.01)	−0.056 (0.022)	0.013	−0.064 (0.022)	0.0034
Good (5–6)	36.7	−0.03 (0.01)	−0.102 (0.023)	<0.0001	−0.111 (0.022)	<0.0001
Very good (7–9)	10.0	−0.08 (0.02)	−0.157 (0.030)	<0.0001	−0.153 (0.029)	<0.0001
Leisure-time PA						
Below median	49.5	0.04 (0.01)	Reference		Reference	
Above median	50.5	−0.04 (0.01)	−0.086 (0.014)	<0.0001	−0.051 (0.014)	0.0002
Sport						
None	82.0	0.37 (0.01)	Reference		Reference	
≤2 h/week	12.4	−0.14 (0.02)	−0.180 (0.022)	<0.0001	−0.137 (0.031)	<0.0001
>2 h/week	5.6	−0.24 (0.03)	−0.281 (0.031)	<0.0001	−0.110 (0.021)	<0.0001
Abdominal obesity						
No	27.2	−0.19 (0.01)	Reference		Reference	
Yes	72.8	0.07 (0.01)	0.264 (0.016)	<0.0001	0.110 (0.017)	<0.0001
BMI						
Normal	27.6	−0.26 (0.01)	Reference		Reference	
Overweight	43.1	−0.01 (0.01)	0.256 (0.017)	<0.0001	0.209 (0.018)	<0.0001
Obese	29.3	0.25 (0.01)	0.513 (0.019)	<0.0001	0.422 (0.020)	<0.0001
Smoking						
No	49.7	−0.09 (0.01)	Reference		Reference	
Current	22.9	0.23 (0.01)	0.311 (0.018)	<0.0001	0.339 (0.018)	<0.0001
Former	27.4	−0.04 (0.01)	0.047 (0.018)	0.0091	0.045 (0.017)	0.010
CVD						
No	93.6	−0.01 (0.01)	Reference		Reference	
Yes	4.9	0.08 (0.03)	0.084 (0.034)	0.013	0.062 (0.033)	0.062
Not ascertained	1.5	−0.01 (0.06)	−0.003 (0.059)	0.96	−0.028 (0.057)	0.62
Cancer						
No	96.8	0.001 (0.01)	Reference		Reference	
Yes	2.8	−0.07 (0.04)	−0.066 (0.043)	0.12	−0.065 (0.041)	0.11
Not ascertained	0.4	0.11 (0.12)	0.112 (0.116)	0.33	0.106 (0.112)	0.34
Diabetes						
No	78.6	−0.04 (0.01)	Reference		Reference	
Prediabetes	11.5	0.12 (0.02)	0.164 (0.023)	<0.0001	0.066 (0.022)	0.0030
Yes	9.0	0.18 (0.02)	0.222 (0.026)	<0.0001	0.103 (0.025)	<0.0001
Not ascertained	0.9	0.20 (0.07)	0.245 (0.075)	0.0011	0.219 (0.074)	0.0031
Hypertension						
No	28.7	−0.19 (0.01)	Reference		Reference	
Prehypertension	15.5	−0.03 (0.02)	0.156 (0.023)	<0.0001	0.096 (0.022)	<0.0001
Yes	55.1	0.10 (0.01)	0.290 (0.019)	<0.0001	0.178 (0.019)	<0.0001
Not ascertained	0.7	0.05 (0.08)	0.236 (0.085)	0.0054	0.091 (0.084)	0.28
Hypercholesterolemia						
No	32.9	−0.05 (0.01)	Reference		Reference	
Pre-hypercholesterolemia	34.2	0.002 (0.01)	0.051 (0.017)	0.0030	0.012 (0.017)	0.49
Yes	31.6	0.05 (0.01)	0.097 (0.018)	<0.0001	0.013 (0.018)	0.48
Not ascertained	1.3	−0.01 (0.06)	0.039 (0.063)	0.54	0.010 (0.062)	0.87

Table 2 continued

	%	Low-grade inflammation (score)*	Age/sex adjusted model		Multivariable model	
			Regression coefficient (SE)	*P* value	Regression coefficient (SE)	*P* value
Depression						
No	92.1	−0.004 (0.01)	Reference		Reference	
Yes	2.9	0.08 (0.04)	0.085 (0.042)	0.045	0.029 (0.041)	0.48
Not ascertained	5.0	0.01 (0.03)	0.010 (0.033)	0.76	−0.009 (0.032)	0.76

Multivariable model included all the listed variables and was further controlled for energy intake

PA physical activity

*Means ±SE adjusted for age and sex

**Analysis for Mediterranean diet were further controlled for energy intake

Dummies variables for missing values were created. Two-sided *P* value <0.05 was considered as statistically significant.

The data analysis was generated using the SAS/STAT software, Version 9.1.3 of the SAS System for Windows©2009. SAS Institute Inc. and SAS are registered trademarks of SAS Institute Inc., Cary, NC, USA.

Results

Characteristics of the study sample are reported in Table 1. Higher INFLA score was found for aged people and women, and a clear gradient was recorded for all SES indicators, with subjects in the lower SES groups reporting the highest values of low-grade inflammation (Table 1 and Model 1 in Table 3) and generally of each inflammatory biomarker.

The association of health behaviours and diseases with low-grade inflammation is shown in Table 2. Higher adherence to the MD, increased leisure-time PA, and sport activity were all associated with reduced low-grade inflammation as compared to the reference groups. Overweight and obese subjects and those with abdominal obesity reported higher low-grade inflammation than the counterparts with normal BMI or without abdominal obesity, along with smokers who were more likely to have higher low-grade inflammation than non-smokers (Table 2).

Individuals with cardiovascular disease, diabetes, or hypertension had raised INFLA score as compared to those free from the disease.

Health behaviours and diseases were socioeconomically patterned (supplementary Tables 1 and 2) with lower SES groups generally reporting higher prevalence of health-risk behaviours and undesirable health status.

Explanatory models

SES inequalities in low-grade inflammation were differently explained by several explanatory models here considered.

Differences in low-grade inflammation for the lowest category of education as compared to the highest were attenuated by 24.2% when prevalent diseases were entered into the model (Table 3; Model 2 and Fig. 1), and by 84.9%, when the whole set of health behaviours was entered (Table 3; Model 3 and Fig. 1).

A different distribution of diseases across income groups contributed to the low-grade inflammation inequalities for 11.4% (<10,000 v*s* >60,000 Euros/year; Table 3, Model 2), whereas health behaviours accounted for 53.9% of the income gradient (Table 3, Model 3).

Health behaviours explained 53.5% of the inequalities between semi-skilled/unskilled workers and professional/managerial. Prevalent diseases explained by 12% the occupational differences in low-grade inflammation (Table 3; model 2).

When considered simultaneously, diseases and health behaviours explained 92.4, 56.9, and 55.6% of the inequalities for education, income, and occupation, respectively.

Regarding health behaviours, BMI and abdominal obesity offered the greatest contribution in explaining SES inequalities in inflammation (Table 4). A modest role was detected for physical activity, while adherence to the healthy MD was found to have a weak impact (Table 4).

Table 3 Association of low-grade inflammation with SES indicators and role of diseases and health behaviours (Moli-sani study, 2005–2010, Italy)

	Model 1	Model 2		Model 3		Model 4	
	Regression coefficient (95% CI)	Regression coefficient (95% CI)	Reduction* (%)	Regression coefficient (95% CI)	Reduction (%)	Regression coefficient (95% CI)	Reduction (%)
Education							
University or higher	Reference	Reference		Reference		Reference	
Secondary school	0.026 (−0.019 to 0.072)	0.007 (−0.038 to 0.052)	73.1	−0.021 (−0.065 to 0.023)	180.8	−0.030 (−0.074 to 0.014)	215.4
Up to middle school	0.132 (0.088 to 0.176)	0.100 (0.056 to 0.144)	24.2	0.020 (−0.023 to 0.064)	84.9	0.010 (−0.033 to 0.053)	92.4
Household income (EUR/year)							
>60,000	Reference	Reference		Reference		Reference	
40,000–60,000	0.033 (−0.052 to 0.119)	0.025 (−0.060 to 0.110)	24.2	0.011 (−0.072 to 0.094)	66.7	0.008 (−0.075 to 0.091)	75.8
25,000–40,000	0.089 (0.013 to 0.165)	0.081 (0.005 to 0.156)	9.0	0.045 (−0.029 to 0.120)	49.4	0.044 (−0.030 to 0.118)	50.6
10,000–25,000	0.141 (0.067 to 0.215)	0.126 (0.052 to 0.200)	10.6	0.069 (−0.004 to 0.140)	51.1	0.065 (−0.007 to 0.137)	53.9
<10,000	0.167 (0.074 to 0.260)	0.148 (0.056 to 0.240)	11.4	0.077 (−0.014 to 0.167)	53.9	0.072 (−0.019 to 0.162)	56.9
Non respondents	0.177 (0.102 to 0.252)	0.156 (0.082 to 0.230)	11.9	0.097 (0.024 to 0.170)	45.2	0.092 (0.019 to 0.164)	48.0
Occupational class							
Professional and managerial	Reference	Reference		Reference		Reference	
Skilled non-manual	0.045 (0.007 to 0.084)	0.040 (0.001 to 0.078)	11.1	0.016 (−0.021 to 0.054)	64.4	0.015 (−0.022 to 0.052)	66.7
Skilled manual	0.092 (0.048 to 0.137)	0.082 (0.037 to 0.126)	10.9	0.031 (−0.013 to 0.074)	66.3	0.028 (−0.016 to 0.072)	69.6
Semi-skilled/ Unskilled	0.142 (0.097 to 0.186)	0.125 (0.081 to 0.169)	12.0	0.066 (0.022 to 0.110)	53.5	0.063 (0.019 to 0.106)	55.6
Unclassified	0.106 (0.037 to 0.175)	0.084 (0.016 to 0.153)	20.8	0.040 (−0.027 to 0.107)	62.3	0.032 (−0.035 to 0.099)	69.8

95% CI 95% confidence intervals

Model 1 adjusted for age, sex and marital status

Model 2 = Model 1 + cardiovascular disease, cancer, diabetes, hypercholesterolemia, hypertension, depression

Model 3 = Model 1 + smoking habit, adherence to the Mediterranean diet, energy intake, leisure-time physical activity, sport activity, BMI, abdominal obesity.

Model 4 = Model 1 + Model 2 + Model 3

Percentage reduction in regression coefficients from Model 1 obtained by (regression coefficient$_{\text{Model 1}}$ − regression coefficient$_{\text{Model 2/3/4}}$)/(regression coefficient$_{\text{Model 1}}$)

Discussion

SES and INFLA score

Findings from this large community-based cohort confirmed that low-grade inflammation is socioeconomically patterned with low SES groups showing a less favourable inflammatory condition.

It is well established that disadvantaged individuals usually present higher concentrations of inflammatory biomarkers and lower prevalence of health-promoting behaviours that are inversely associated with subclinical inflammation (O'Connor et al. 2010; Pampel et al. 2010).

Yet, low-grade inflammation has been generally assessed to date by the use of a single inflammatory biomarker (Deverts et al. 2012; Kershaw et al. 2010) or by

Table 4 Association of low-grade inflammation with SES indicators and role of dietary and lifestyle factors (Moli-sani study, 2005–2010, Italy)

	Model 2	Model 2 + leisure PA + sport activity		Model 2 + abdominal obesity + BMI		Model 2 + smoking habit		Model 2 + Mediterranean diet**	
	Regression coefficient (95% CI)	Regression coefficient (95% CI)	Reduction* (%)	Regression coefficient (95% CI)	Reduction (%)	Regression coefficient (95% CI)	Reduction (%)	Regression coefficient (95% CI)	Reduction (%)
Education									
University or higher	Reference	Reference		Reference		Reference		Reference	
Secondary school	0.007 (−0.038 to 0.052)	−0.001 (−0.046 to 0.044)	114.3	−0.016 (−0.060 to 0.029)	328.6	−0.0003 (−0.045 to 0.044)	104.3	0.004 (−0.041 to 0.049)	42.9
Up to middle school	0.100 (0.056 to 0.144)	0.080 (0.036 to 0.125)	20.0	0.034 (−0.010 to 0.077)	66.0	0.096 (0.052 to 0.140)	4.0	0.093 (0.049 to 0.137)	7.0
Household income (EUR/year)									
>60,000	Reference	Reference		Reference		Reference		Reference	
40,000–60,000	0.025 (−0.060 to 0.110)	0.015 (−0.070 to 0.100)	40.0	0.013 (−0.071 to 0.097)	48.0	0.028 (−0.057 to 0.112)	−12.0	0.023 (0−0.061 to 0.108)	8.0
25,000–40,000	0.081 (0.005 to 0.156)	0.066 (−0.010 to 0.141)	18.5	0.055 (−0.020 to 0.130)	32.1	0.082 (0.007 to 0.157)	−1.2	0.077 (0.001 to 0.152)	4.9
10,000–25,000	0.126 (0.052 to 0.200)	0.103 (0.029 to 0.177)	18.3	0.081 (0.008 to 0.154)	35.7	0.131 (0.058 to 0.204)	−4.0	0.118 (0.045 to 0.192)	6.4
<10,000	0.148 (0.056 to 0.240)	0.122 (0.030 to 0.215)	17.6	0.093 (0.002 to 0.184)	37.2	0.151 (0.059 to 0.242)	−2.0	0.137 (0.045 to 0.229)	7.4
Non respondents	0.156 (0.082 to 0.230)	0.123 (0.049 to 0.197)	21.2	0.116 (0.042 to 0.189)	25.6	0.161 (0.088 to 0.235)	−3.2	0.146 (0.072 to 0.220)	6.4
Occupational class									
Professional and managerial	Reference	Reference		Reference		Reference		Reference	
Skilled non-manual	0.040 (0.001 to 0.078)	0.031 (−0.007 to 0.069)	22.5	0.028 (−0.009 to 0.066)	30.0	0.034 (−0.004 to 0.072)	15.0	0.037 (−0.001 to 0.075)	7.5
Skilled manual	0.082 (0.037 to 0.126)	0.067 (0.022 to 0.111)	18.3	0.047 (0.002 to 0.090)	42.7	0.080 (0.036 to 0.124)	2.4	0.074 (0.030 to 0.119)	9.8
Semi-skilled/ unskilled	0.125 (0.081 to 0.169)	0.100 (0.055 to 0.144)	20.0	0.074 (0.030 to 0.118)	40.8	0.135 (0.091 to 0.179)	−8.0	0.117 (0.073 to 0.162)	6.4
Unclassified	0.084 (0.016 to 0.153)	0.074 (0.004 to 0.140)	11.9	0.040 (−0.028 to 0.107)	52.4	0.090 (0.022 to 0.158)	−7.1	0.078 (0.010 to 0.147)	7.1

95% CI 95% confidence intervals

Model 2 adjusted for age, sex, marital status, cardiovascular disease, cancer, diabetes, hypercholesterolemia, hypertension, and depression

*Percentage reduction in regression coefficients from Model 1 obtained by (regression coefficient$_{\text{Model 1}}$ − regression coefficient$_{\text{Health behaviours}}$)/(regression coefficient$_{\text{Model 1}}$)

**Further adjusted for energy intake (Kcal/day)

considering a number of markers simultaneously (Schnabel et al. 2013; Jousilahti et al. 2003; Danesh et al. 2000).

A major weakness of this approach is the lack of accounting for possible synergistic effects of inflammation biomarkers that are usually strongly auto-correlated and may produce multi-collinearity when simultaneously studied in a regression model (Pounis et al. 2016). On the other side, the individual biomarker approach appears to be

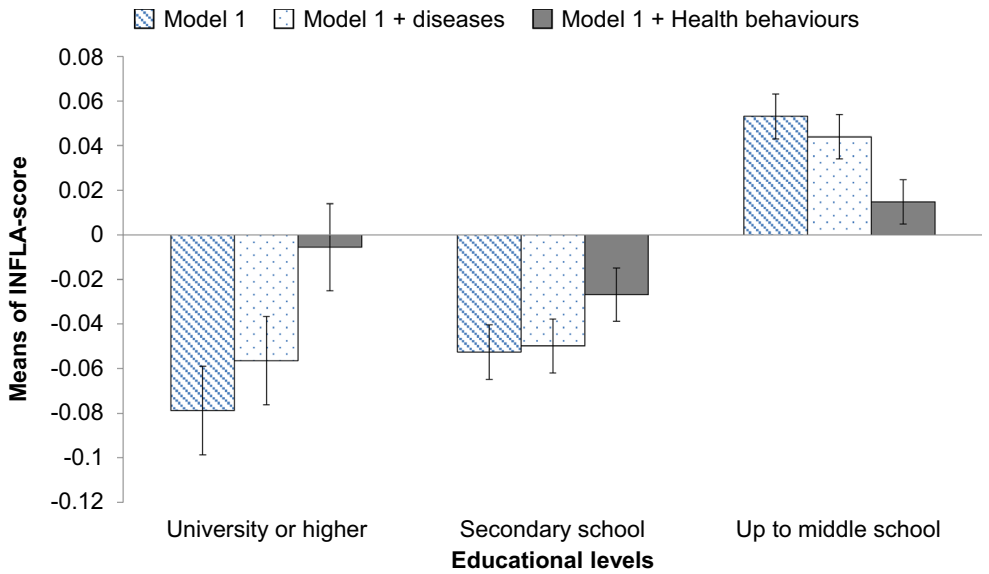

Fig. 1 (Moli-sani study, 2005–2010, Italy). Means of low-grade inflammation (±SE) as measured by the INFLA score across educational groups and after further adjustment for prevalence of diseases and health behaviours. Model 1 is adjusted for age, sex, and marital status. Prevalent diseases include cardiovascular disease, cancer, diabetes, hypercholesterolemia, hypertension, and depression. Health behaviours include leisure-time physical activity, sport activity, BMI, abdominal obesity, smoking, adherence to the Mediterranean diet, and energy intake

too restrictive to define a complex phenomenon as low-grade inflammation. To overcome such limitations, we tested the association of a number of SES indicators with a condition of low-grade inflammation as measured by a composite score of plasmatic and cellular biomarkers. Advantages of using such an approach have been already discussed elsewhere (Pounis et al. 2016) and include the possibility of summarising the variability of inflammation as a plasmatic and cellular phenomenon at an epidemiological scale. The use of an index also limits the source of biased estimations likely deriving from multi-collinearity of variables (Pounis et al. 2016).

As another novelty of the study, we provided evidence on the relative contribution of behavioural factors, which are usually considered without discriminating one from another (Koster et al. 2006).

Explanatory models

A substantial portion of the inverse association between high SES and inflammation observed in the present study was explained by health-related behaviours rather than by prevalent diseases.

Our data are in line with the previous findings, which highlighted a prominent role of behavioural factors over diseases in accounting for SES inequalities in inflammation (Fraga et al. 2015; Koster et al. 2006). In our population, both behavioural factors and diseases were found socioeconomically patterned with high SES groups reporting higher prevalence of healthy behaviours and lower presence of prevalent diseases, in agreement with other studies (Kaplan and Keil 1993).

In general, the unequal distribution of diseases across SES strata poorly accounted for the observed differences in inflammation, and their contribution was found to be more important for educational (24.2%) rather than for income (11.4%) or occupational (12%)-related inequalities.

Within health-related behaviours, BMI, adiposity, and physical activity were found to make a greater contribution to explain social inequalities in low-grade inflammation, likely due to their clear socioeconomic patterning. Our results are in agreement with the previous evidence showing that both household income and education were associated with inflammation as a likely result of the socioeconomic patterning of adiposity and other factors (Ranjit et al. 2007), while being physically active was suggested as an effective tool to control low-grade inflammation (Marthur and Pedersen 2008).

In the CARDIA study (Deverts et al. 2012), physical activity, smoking, and fruit and vegetable intake each accounted for a significant proportion of the respective effects of education and income on CRP change over time.

Healthy eating patterns were associated with lower circulating concentrations of inflammatory markers (Barbaresko et al. 2013; Centritto et al. 2009) and part of the health benefits was ascribed to the modulation of key players in the pathogenesis of atherosclerosis, including a decrease in oxidative stress and inflammation (Vilahur and

Badimon 2013). Recent evidence from the PREDIMED trial showed that inflammatory biomarkers related to plaque instability, such as C-reactive protein and interleukin-6, were decreased in the groups assigned to an MD compared to the low-fat diet group (Casas et al. 2014). Indeed, the inverse relationship between MD and low-grade inflammation is well documented in observational rather than intervention studies (Ambring et al. 2006).

Of notice, smoking habit did not account for SES differences in inflammation and this appear to be in disagreement with the previous epidemiological studies showing a crucial role of smoking (Deverts et al. 2012); however, such inconsistencies may be due to the poor socioeconomic patterning of this risk behaviour in our population already documented in other Mediterranean epidemiological settings in which people with a high SES are more likely to smoke (Fraga et al. 2015).

Our findings confirm the well-established relationship between the MD and lower subclinical inflammation and provide further evidence on the socioeconomic patterning of such quality diets (Drewnowski 2009).

SES inequalities in health outcomes have been proven to be less pronounced in Mediterranean countries as compared to Northern European areas (Federico et al. 2013; Mackenbach et al. 2008), although evidence has lately suggested the presence of a SES gradient in mortality also in Italy (Bonaccio et al. 2016). To date, poor evidence is available on a likely socioeconomic gradient in inflammation in Mediterranean areas (Panagiotakos et al. 2004; Fraga et al. 2015); as a consequence, this study contributes to fill the gap in the understanding of the mechanisms through which SES inequalities in health establish in a Mediterranean epidemiological setting.

Strengths and limitations

Major strengths of this study include a large community-based cohort, a consistent number of SES indicators, and a wide set of explanatory variables, including a well-recognized index of diet quality as the Mediterranean diet.

A major limitation is represented by the cross-sectional design which does not allow to establish causality associations, and the unavailability of data on other markers of low-grade inflammation commonly used, such as fibrinogen or interleukin-6 (Jousilahti et al. 2003; Casas et al. 2014).The score of low-grade inflammation has not been validated (although it was used in Pounis et al. 2016). We have not assigned a specific weight to each component of the score, since we do not have any a priori hypothesis about a likely different weight for each component.

Information on a number of mediators is self-reported and this can lead to under- or over-estimates of some health behaviours, such as dietary habits or physical activity. Finally, there may be other factors, which could also be important in explaining SES differences in inflammatory marker levels. These factors may include psychological stress other than depression also related to both low SES and increased levels of inflammatory markers (Koster et al. 2006).

Data used in this study have been collected in a region located between Central and Southern Italy, Mediterranean by tradition and culture, thus caution is needed in extending the results to larger contexts. Yet, the main characteristics of our population sample are comparable to those of the Italian Cardiovascular Epidemiological Observatory; therefore, our sample could be considered representative at least of the Italian population (Di Castelnuovo et al. 2012).

Conclusions

To the best of our knowledge, this is the first study to assess the relationship between SES and low-grade inflammation as measured by a composite score, including both plasmatic and cellular biomarkers, thus overcoming limitations inherent to the traditional approaches. As compared to more advantaged individuals, low SES groups exhibit higher prevalence of unhealthy behaviours that largely account for the SES gradient in low-grade inflammation which might explain to some extent the higher risk of morbidity and mortality with decreasing SES (Deverts et al. 2012).

In light of this, and in agreement with the previous evidence, this study supports the need for targeting modifiable risk factors to decrease the level of a major health threat as low-grade inflammation. Moreover, our results suggest that health-promoting interventions may be useful in reducing the excess risk associated with inflammation in low SES strata, thus possibly leading to prevention of major adverse health outcomes.

However, the fact that the association of SES with inflammation still retained statistical significance after several adjustments should direct future studies to focus on additional unmeasured variables that may improve the understanding of SES inequalities in inflammation.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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Ethical approval All procedures performed in the present study, involving human participants, were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Written informed consent was obtained from all individual participants included in the study.

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