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Socio-demographic and lifestyle factors associated with the neutrophil-to-lymphocyte ratio.

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Abstract

Background: The neutrophil-to-lymphocyte ratio (NLR) is a marker of systemic inflammation with established prognostic value in cancer patients. While high NLR is associated with poorer clinical outcomes, factors that influence the magnitude of NLR independently of disease are poorly understood.

Methods: We identified 48,023 adults who participated in the National Health and Nutrition Examination Survey (1999–2016). Demographic, socio-economic and lifestyle factors associated with the magnitude of NLR after adjusting for comorbidities including heart disease, cancer, diabetes and hypertension, and medications including aspirin, were identified. Effect modification by comorbidity status and demographics was explored.

Results: Female gender, age less than 60 years, and non-Hispanic black race/ethnicity were associated with lower NLR. Marital statuses of widowed, separated, or never married demonstrated increased NLR as compared to those who were currently married. Never-smoking and moderate alcohol consumption were associated with lower NLR. Participation in physical activity was associated with decreased NLR after adjustment for potential confounders, primarily among non-Hispanic whites.

Conclusions: Multiple demographic and lifestyle factors are independently associated with NLR. Sex, age, race, marital status, BMI, physical activity, smoking history and alcohol consumption should all be routinely collected and adjusted for to improve the accuracy of assessment of the prognostic power of NLR.

Keywords

Inflammation; Biomarkers; Survival; Neutrophil-to-Lymphocyte

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Introduction

Acute and chronic inflammation play an appreciable role in a wide range of medical conditions, including cancer [1–6]. This has led to increased interest in identifying markers of systemic inflammation that can serve as a clinically useful proxy for the overall immune status of the individual. Such markers may have the potential to facilitate risk stratification at diagnosis, and guide therapeutic selection.

Alterations in circulating white blood cells accompany systemic inflammation. These alterations include the development of neutrophilia and concurrent relative lymphocytopenia [7], both of which are detectable in the routine complete blood count (CBC). The neutrophil-to-lymphocyte ratio (NLR) captures the balance between the detrimental effects of neutrophilia and the benefits of an active adaptive immune response, and is prognostic of patient outcomes across multiple diseases [8–11].

The majority of published association studies focus on a baseline NLR measurement obtained when the individual is diagnosed with, or exhibiting symptoms of, disease. While several additional studies have sought to characterize the range of “normal” NLR in a healthy population [12], little is known about factors that influence the magnitude of NLR independently of disease status. For example, while average NLR differs between subgroups stratified by race [13], and exercise can lower NLR in certain individuals [14], few studies have examined demographic, socioeconomic and lifestyle correlates of NLR in the general population. Such studies are useful for identifying potential confounders of the strength of association between baseline NLR and disease outcomes. In addition, consideration of lifestyle factors may lead to the identification of targets for behavioral intervention leading to reduced systemic inflammation and potentially impacting the burden of disease in the individual.

The objective of this study was to systematically evaluate socio-demographic and lifestyle influences on the magnitude of NLR after adjustment for potential confounding by comorbidities and medications. The study was based on 48,023 adult participants in the US National Health and Nutrition Examination Survey (NHANES) from 1999–2016 for whom survey data and a complete blood count for NLR determination were available.

Methods

Study population

The National Health and Nutrition Examination Survey (NHANES) aims to assess the health status of adults and children across the US by obtaining representative samples of the population using multistage sampling [15]. We exported NHANES laboratory and questionnaire data from the 9 surveys between 1999 and 2016 (1999–00, 2001–02, 2003–04, 2005–06, 2007–08, 2009–10, 2011–12, 2013–14, 2015–16) for all participants aged 18 years or older, resulting in 48,023 unique participants to include in the study (a CONSORT flow chart can be found in Supplementary Figure 1).

Laboratory data

Complete blood count (CBC) was available for all adults who participated in NHANES between 1999 and 2016. CBCs for all years were conducted using the Coulter Unicel DxH 800 analyzer, a quantitative, automated hematology analyzer for in-vitro diagnostic use. The analyzer provided the leukocyte 5-part differential on whole blood, which includes absolute numbers of neutrophils and lymphocytes and their relative percentage of total white blood cells. Samples were run in duplicate, and the average of two measurements was reported. Absolute numbers of lymphocytes and neutrophils were reported in units of 1000 cells per microliter. Full details on the laboratory methods relating to the complete blood count and components can be found in [16]. Ratios of neutrophils to lymphocytes were calculated for both percentage measures (percent of total white blood cell count, WBC) and absolute numbers. Correlation between the two measures was $R^2 = 0.99$ (Supplementary Figure 2), the former was arbitrarily selected for presentation of results. Variation in neutrophil and lymphocyte counts and percentages between survey years was minimal (Supplementary Figure 3). The distribution of NLR and its respective components across all included participants can be found in Supplementary Figure 4.

Questionnaire data

Age, race, and sex were available for all participants. Factors relating to socioeconomic status including education level, marital status, household size, income, poverty income ratio (ratio of family income to poverty threshold), and health insurance were extracted for analysis. Indices relating to intensity and duration of physical activity, as well as ever-smoking status, alcohol use, body mass index (BMI) and diet and nutrition (vegetable consumption, fast food) were also included. We also obtained information on pre-existing health conditions including mental health diagnoses (depression, panic, generalized anxiety disorder), arthritis, heart disease, emphysema, cancer, diabetes, hypertension and the use of aspirin. The 19 demographic, socioeconomic and lifestyle factors and additional 13 factors relating to comorbidities and medications are listed in Table 1. Shown are the NHANES variable name, description, and years the variable was included in the survey. For many factors collected as continuous data, responses were clustered rather than distributed uniformly across the available range. As an example, in questions relating to time in minutes, the majority of participants entered multiples of 15 or 30 minutes with sparse data for other responses. In these cases, we created discrete response categories (Table 1) to permit more intuitive interpretation of regression results. Where the variable identifier changed between the years of 1999 and 2016, both identifiers are listed. All socio-economic, lifestyle and health-related questions included an additional response category for ‘refused to answer’ or ‘don’t know’. Only body mass index (BMI) was obtained from a physical exam. The remaining variables were collected via questionnaire or interview (self-report).

Statistical methods

We initially conducted descriptive univariate analyses comparing median NLR across levels of each respective factor, (e.g. males vs females, under 60 vs 60 years and over). For factors with two levels, Mann Whitney U tests were performed to identify differences in NLR. For variables with more than two levels, the Kruskal-Wallis omnibus test was performed.

Where a monotonic increase or decrease in a statistic (median, regression coefficient) was observed across ordinal levels of a factor, p values for trend are provided based on the Jonckheere-Terpstra (JT) statistic for ordered differences across levels of the variate [17].

Regression analyses were conducted to further evaluate relationships between NLR and socio-demographic and lifestyle factors as well as comorbid conditions factors. All available factors were assessed in univariate regression models. Where several factors addressed the same research question - for example multiple separate factors relating to aspects of physical activity - the factor with the lowest p-value(s) in univariate analysis was included in multivariable modeling. Due to inherent challenges in imputing missing values on such a large scale [18] and with no overlap in participants between years, only participants with complete data were included in multivariable models.

With the exception of vegetable intake, fast food, depression, GAD, panic disorder, and aspirin use (collected in only a subset of survey years) all studied factors were included in a primary multivariable model encompassing a total of 20,237 participants with complete data. Where univariate analysis of these six factors omitted from the primary model produced significant results, independent multivariable analyses were conducted including all the factors included in the primary model.

We tested for interactions between demographic risk factors (age, sex and race) by incorporating interaction terms in the primary multivariable model. We then conducted further subgroup analysis by repeating multivariable analyses in independent subsets of participants stratified by comorbidity status (diagnoses of arthritis, heart disease, cancer, diabetes, hypertension or emphysema), race, sex and age.

All statistical tests were two-sided. All statistical analyses were performed using R version 3.3.2 (R core development team, Vienna, Austria).

Results

Median NLR across levels of all socio-demographic, lifestyle and comorbidity factors are presented in Table 2, Table 3 and Supplementary Table 1, respectively. Table 4 presents univariate regression results for all factors included in 5 or more survey years. All factors listed in Table 4 are included in the primary multivariable model. 20,237 participants had complete data for these factors, and thus were included in this primary multivariable model. Supplementary Table 2 presents univariate regression results for all factors included in only a small subset of survey years. These factors were omitted from the primary multivariable model as their inclusion reduced the number of available participants with complete data to below 5,000. Where these factors were found to have a significant association with NLR in the univariate model, additional multivariable analyses were conducted including the same core set of covariates as the primary model (Table 4). Multivariable model results for these factors are also presented in Supplementary Table 2. Note that in Table 4 and Supplementary Table 2 beta coefficients for levels of each categorical factor represent the change in mean NLR when transitioning from the referent to the exposure level of interest. Where factors are

also treated as continuous, this coefficient represents the change in NLR per unit change in the factor.

Table 5 presents results from multivariable models for participants stratified by comorbidity status (has comorbid condition vs. does not have comorbid condition), race, age and sex. Supplementary Table 3 presents results from multivariable models for participants stratified by specific comorbidity (arthritis, heart conditions, cancer, diabetes, and hypertension).

Co-morbidity

Participants with any comorbidity (diagnoses of arthritis, heart disease, cancer, diabetes, hypertension or emphysema) had higher NLRs than healthy participants (median NLR 2.03 and 1.91, respectively; p<2E-16). This pattern was consistent regardless of gender, age, race, education and marital status (not shown).

Demographic Factors

Sex—Women exhibited slightly lower NLR on average than men (1.96 versus 1.99, p=0.03), although both groups remained close to the overall cohort median of 1.98 (Table 2). An association between female sex and lower NLR was observed in univariate regression analysis (β=−0.03, p=0.008), and became stronger after multivariate adjustment (β=−0.13, p=4.13E-12) (Table 4).

NLR associations for sex across demographic strata and lifestyle factors are shown in Table 5. Among persons with any co-morbidity (Panel A), a lower NLR was observed in women than men, mainly among persons aged 60 or older. This pattern was consistent regardless of race. Among persons without co-morbidity (Panel B), a similar pattern was observed for non-Hispanic whites with lower NLR observed in females aged 60 or older and no association by sex in persons under age 60. Weaker associations were observed in African Americans. By contrast, among Hispanics, women under age 60 had higher NLRs than men. The association between sex and NLR was maintained in subgroups of participants with arthritis, heart disease, cancer, diabetes and hypertension (Supplementary Table 3).

Age—Participants aged 60 years or older demonstrated a higher NLR than participants younger than 60 (2.11 versus 1.92, p<2.2E-16, Table 2). Older age remained a risk factor for higher NLR after multivariate adjustment (β=0.12, p=7.05E-07) (Table 4). An association between age and NLR was observed among Non-Hispanic white males (β=0.39, p=6.43E-07 with comorbidity, β=0.34, p=1.56E-05 without comorbidity) and Hispanic males (β=0.26, p=0.02 with comorbidity, β=0.18, p=0.02 without comorbidity), but not non-Hispanic black males or females (Table 5). The association between age and NLR was also maintained in subgroups of participants with arthritis, heart disease, diabetes and hypertension, but not in participants with cancer (Supplementary Table 3).

Race—Black participants demonstrated lower median NLR than white participants, with intermediate values observed among other races (non-Hispanic white: 2.14; Mexican American: 2.00; other Hispanic: 1.93; other race: 1.86; non-Hispanic black: 1.60; p<2E-16) (Table 2). In multivariable analysis, non-Hispanic black race remained strongly and

independently associated with lower NLR (β=−0.53, p<2E-16; non-Hispanic white referent) (Table 4). In all age and sex subgroups (under 60, 60 and over, male, female), non-Hispanic black and Hispanic participants demonstrated lower NLR than non-Hispanic white participants, regardless of presence or absence of comorbidities (not shown). The association between race and NLR was also maintained in subgroups of participants with arthritis, heart disease, cancer, diabetes and hypertension (Supplementary Table 3).

Socio-economic status—Higher educational attainment was associated with an increase in NLR in multivariate analysis (high school / GED or equivalent: β=0.05, p=0.02, college graduate or above: β=0.08, p=0.01, less than 12th grade referent). Marital statuses of widowed (β=0.19, p=9.99E-07), separated (β=0.11, p=0.02) or never married (β=0.05, p=0.04) were all associated with increased NLR after multivariable adjustment, as compared to a status of currently married. Widowed participants had a higher mean NLR than persons in all other marital groups (p<2E-16) with a median of 2.17, one of the highest values observed in any subgroup. Household size, income, and health insurance status were not independently associated with NLR after multivariate adjustment.

Lifestyle Factors

Ever smoker status—Never smokers (participants who had smoked less than 100 cigarettes in their lifetime) demonstrated lower NLR (1.93) than those who had ever smoked (2.04; p<2.2E-16) (Table 3). In univariate regression analysis, never smoker status was associated with lower NLR (β=−0.14, p<2E-16); results were attenuated after multivariate adjustment (β=−0.06, p=0.0007) (Table 4). In subgroup analysis, the association between never-smoker status and decreased NLR was strongest among older non-Hispanic white participants with any comorbidity (β=−0.15, p=0.02) (Table 5).

Alcohol use—Participants who did not drink at all (zero drinking days per year), and those who drank frequently (>100 drinking days per year) both exhibited a higher NLR (2.06 and 2.01, respectively) when compared to less frequent drinkers (NLR = 1.95–1.96) (Table 3). In univariate regression analysis, any alcohol consumption was associated with lower NLR, though without evidence of dose response (β coefficients of −0.16, −0.18, −0.19, and −0.11 for increasing drink-day categories per year) (Table 4). Associations were attenuated after multivariate adjustment (between 1 and 10 drinking days per year: β=−0.09, p=0.001, between 50 and 100 drinking days per year: β=−0.08, p=0.009, p trend = 0.31, no drinking days per year as referent) (Table 4).

Among participants with comorbidities, an association was demonstrated between drinking <10 drinks per year and decreased NLR (β=−0.16, p=0.02) in non-Hispanic white females. In the absence of comorbidities, a similar relationship for light drinking was observed among Hispanic participants (under 60s: β=−0.19, p=0.002; males: β=−0.18, p=0.03; females: β=−0.17, p=0.04)(Table 5).

BMI—A higher BMI was positively associated with NLR in crude analyses (p-trend=5.39E-05) (Table 3). However, after multivariable adjustment, a higher body weight was associated with reduced NLR. A similar inverse pattern was observed for overweight

(BMI greater than 25 and less than or equal to 30) and obese (BMI above 30) BMI categories (β=−0.17, p=0.02 and β=−0.16, p=0.02, respectively) (Table 4). In non-Hispanic whites, an association of increased body weight (BMI greater than 25) with decreased NLR was restricted to persons aged 60 or over, with (β=−0.27, p=0.0001) or without (β=−0.29, p=0.007) comorbidity. A similar association was observed among non-Hispanic blacks with comorbidities (β=−0.36, p=0.0001) (Table 5).

Physical activity—Two questions each were included relating to moderate and vigorous physical activity: “Do you do any moderate/vigorous activity for at least ten minutes at a time”, and “How much time do you spend doing moderate/vigorous activity per day. Participants that reported no physical activity for at least ten minutes at a time demonstrated higher NLR (1.99) than those who engaged in at least 10 minutes of moderate activity (1.95), vigorous activity (1.79) or both (1.84) (Table 3). NLR did not change significantly with increasing time spent engaging in moderate or physical activity (p=0.19, p=0.13, respectively) (Table 3). In univariate regression analysis, physical activity for at least ten minutes was associated with reduced NLR for moderate activity NLR (β=−0.08, p=1.67E-05) with further reduction in NLR for vigorous activity alone (β=−0.26, p<2E-16), or vigorous combined with moderate activity (β=−0.23, p=<2E-16). Associations were attenuated after multivariate adjustment (Table 4). Increasing hours of moderate or vigorous activity was not associated with further reduction in NLR (Supplementary Table 2).

Associations between physical activity and NLR varied by demographic subgroup and comorbidity status (Table 5). In non-Hispanic whites with any co-morbidity (panel A), moderate activity was associated with lower NLR in older persons (β=−0.31 p=3.64E-06), and in both genders (male: β=−0.25 p=0.0007, female: β=−0.18 p=0.003) whereas only vigorous activity (β=−0.31 p=0.006) or a combination of moderate and vigorous (β=−0.24 p=0.002) activity was associated with lower NLR in younger participants. Similar, though attenuated, results were observed among non-Hispanic whites without co-morbidities (Panel B). Among Hispanics, reductions in NLR with physical activity were observed only in participants with comorbidities: a combination of moderate and vigorous physical activity was associated with decreased NLR for those under age 60 (β=−0.20 p=0.05), aged 60 or over (β=−0.53 p=0.03), and in females (β=−0.29 p=0.03), only. Vigorous activity alone was also associated with decreased NLR in persons under age 60 (β=−0.26 p=0.04). Physical activity demonstrated no association with NLR in non-Hispanic black participants regardless of age, sex, and comorbidity status. Interestingly, when stratifying by specific comorbidity (Supplementary Table 3), physical activity is the only lifestyle factor for which the association with NLR remains significant.

Greater sedentary behavior – more time spent sitting or reclining in an average day - was associated with higher NLR (p-trend=2.99E-09) (Table 3). As compared to a referent of ≤1 hour per day, spending two to four hours per day sitting or reclining was associated with higher NLR (β=0.11 p=3.76E-05) after multivariate adjustment. Few subjects reported greater levels of sedentary behavior (>4 hours per day).

Diet and aspirin use—Increasing servings per day of vegetables was not found to be associated with increasing NLR; however, data were sparse (only 12 participants reported

more than four servings per day) and results were thus imprecise (Supplementary Table 2). An increasing number of meals eaten at fast food restaurants was associated with a lower NLR (p-trend=0.02). This result was not maintained after multivariate adjustment.

Participants who were taking regular aspirin upon the advice of a medical professional had a significantly higher NLR than those who were not taking regular aspirin (p=1.25E-13) (Supplementary Table 2). For those who were taking a regular aspirin but had not been advised to do so by a medical professional, NLR was not significantly increased as compared to those not taking an aspirin (p=0.65). Of participants who reported taking aspirin, those who did so at less frequent intervals than once per day tended to have a lower NLR (p=0.02–0.04). None of these results maintained significance after multivariable adjustment (Supplementary Table 2).

Discussion

Based on data from over 48,023 participants in the National Health and Nutrition Survey from 1999 to 2016, we evaluated associations between 19 socio-demographic and lifestyle factors and the NLR. Overall, participants with existing comorbidities (arthritis, heart disease, cancer, diabetes, emphysema and hypertension) had higher NLR than those without. After adjustment for pre-existing conditions, we found that sex, age, race, and marital status were independently associated with NLR. Furthermore, we observed relationships between NLR and smoking, alcohol use, BMI and physical activity that differed by age and race, suggesting opportunities for targeted reductions in NLR through changes in lifestyle.

Post-menopausal women have demonstrated lower NLR than men, and this trend has been found to reverse for women aged 50 and under [19]. In line with these earlier observations, females included in the present study also demonstrated lower NLR than males within the older age group, with a trend towards higher NLR in younger females. This reversal of the association between sex and NLR between age groups was only identified among participants without any comorbidity. If not due to chance, the female advantage with respect to NLR among older subjects may reflect differential effects of aging on the immune system. Females tend to remain immune-privileged later in life, in contrast to males who experience more rapid decreases in lymphocytes with advancing age [20,21].

We observed a lower NLR in non-Hispanic black subjects across all demographic subgroups. When compared to other racial groups, lifestyle appeared to play only a minor role in NLR among black participants: as shown in Table 3, beta coefficients were similar before (−0.59) and after (−0.53) multivariate adjustment for socioeconomic and lifestyle factors. A lower NLR in non-Hispanic blacks has been reported previously and may be attributed to a higher prevalence of benign ethnic neutropenia in persons of African descent [22]. Mechanisms underlying this phenomenon are unclear [22]. Due to the limited sample size and non-specific survey questions, it was not possible to rule-out differences in lifestyle or specific medical conditions as explanations for disparate NLR values by race. Further investigation of this association is warranted.

Participants who were widowed, separated or never married exhibited higher NLR than married persons. Previous studies suggest that married individuals experience less psychological stress, leading to lower levels of cortisol and improved inflammatory regulation when compared to unmarried individuals [23]; such a potential biologic mechanism is in line with observations in the present study which found reduced NLR in married persons even after controlling for lifestyle and other demographic factors.

The association between smoking and increased levels of inflammatory markers has been previously established [24,25]; here, never smoker status was linked to a lower NLR, only among older non-Hispanic whites with comorbidities. Moderate drinking (<100 drinking days per year) was associated with decreased NLR as compared to complete abstinence from alcohol in non-Hispanic white females with comorbidities, and Hispanic individuals without comorbidities. While potential benefits of moderate alcohol consumption remain under debate [26], the present study offers some limited support for the hypothesis that modest alcohol consumption may favorably impact health through reductions in systemic inflammation.

Physical activity can contribute to reducing markers of systemic inflammation [27]; participating in at least ten minutes of physical activity at a time was also identified as the modifiable lifestyle factor most strongly associated with NLR in the NHANES cohort. While no dose-response effect was observed (in that no association was found between increasing duration of moderate or vigorous activity and NLR), participating in at least ten minutes of physical activity on a regular basis (moderate activity being optimal for those aged 60 or over, and vigorous being optimal for under 60s) led to lower NLR. A combination of both moderate and vigorous physical activity demonstrated the most universally beneficial effect on NLR. However, the strong association between physical activity and NLR was only observed among non-Hispanic white and Hispanic participants, but not non-Hispanic blacks. This racial difference in systemic response to physical activity also warrants further study. Interestingly, associations between alcohol use and NLR and smoking history and NLR were no longer apparent in subgroups of participants with specific comorbidities (arthritis, heart conditions, cancer, diabetes and hypertension). Physical activity, however, maintains significant associations with NLR in participants with arthritis, cancer, diabetes and hypertension, suggesting there may be potential for further study of the impact of physical activity on NLR in the setting of these specific diseases.

While increased time sitting or reclining per day (2 to 4 hours as compared to less than or equal to one hour) demonstrated an association with increased NLR, the reliability of self-report of this variable is brought into question by the small number of persons reporting 4 or more hours sitting or reclining per day (<5% of participants).

BMI demonstrated a negative association with NLR, notably in participants aged 60 or over. While a link between adiposity and inflammation has been established [28, 29], lower NLR has also been observed in obese individuals (BMI>30) as compared to those of normal weight, supporting the findings of the present work [30]. Higher BMI is associated with increased lymphocyte count [31]; if obesity induces a more substantial increase in lymphocytes than neutrophils, this could potentially be driving the observed inverse

relationship between BMI and NLR. Greater consumption of vegetables has demonstrated both positive and negative associations with inflammatory biomarkers in earlier studies [32–34]. No conclusions could be drawn from the findings of the present work, particularly with only a limited number of participants reporting 3 or more servings per day. The relationship between fast food and NLR was also not upheld after multivariable adjustment. Further study of the association between NLR and diet and nutrition is thus warranted. Finally, while the association between aspirin use and NLR was not found to be significant in our multivariable models, it is worth noting that participants who were taking aspirin based on the recommendations of a medical professional, and those taking aspirin at an increased frequency (once per day as compared to every other day or another schedule) tended to have higher NLR. We may speculate that these participants were taking aspirin in response to an existing inflammatory condition, contributing to the elevated NLR observed in these groups.

Several limitations in the present analysis should be acknowledged. The cross-sectional nature of NHANES warrants cautious interpretation, as it is not possible to determine temporal relationships between studied factors and NLR. Inherent measurement error in a single blood biomarker may also have biased all results toward the null. Retrospective self-report data presents additional challenges, particularly with regard to drinking and smoking habits and other potentially sensitive topic areas. Finally, in spite of the large overall sample size, data were sparse and results imprecise in a number of the demographically homogeneous subgroups examined (Table 5). Further studies are needed to confirm the present results and to examine the utility of NLR for evaluating the efficacy of lifestyle interventions. It should also be noted that in the present study, the NLR was only weakly correlated (r=0.25) with C-reactive protein (CRP), another established marker of systemic inflammation. This also suggests a need for a clearer understanding of the underlying mechanisms driving alterations in each of these respective biomarkers.

NLR is an established marker of systemic inflammation, and is strongly associated with survival outcomes across multiple diseases. Present findings suggest that age, race, sex, and marital status, as well as a range of comorbidities, are all associated with NLR.

Modifiable exposures including alcohol use, physical activity and smoking status were also found to impact NLR. Inclusion and appropriate control of these factors in multivariate analyses may improve the accuracy of, and consistency among, studies of the association between NLR and clinical outcomes. Furthermore, differences observed in the magnitude of association according to health status and demographics also offer the potential for targeting recommendations for lifestyle modifications to at-risk populations. Finally, given the already established link between NLR and multiple medical conditions, studies aiming to influence the magnitude of NLR are likely to become more commonplace; the present findings may also provide guidance for future interventional study design by suggesting optimal characteristics for participant matching.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Summary of 32 included socio-demographic, lifestyle and health factors extracted from NHANES, including NHANES identifier, factor description, discrete response categories and years included in the study.

	Factor	NHANES Identifier	Description	Discrete response categories	Survey years
Demographic	**Sex**	RIAGENDR	Gender	Male, female	1999 – 2016
	Age	RIDAGEYR	Age at screening	> 60, ≥ 60 [1]	1999 – 2016
	Race	RIDRETH1	Race/Ethnicity	Non-Hispanic white, non-Hispanic black, Mexican American, other Hispanic, other race	1999 – 2016
Socio-economic	**Education Level**	DMDEDUC2	What is the highest grade or level of school you have completed or the highest degree you have received?	Less than 12th grade, high school/GED or equivalent, college graduate or above	1999 – 2016
	Marital status	DMDMARTL	Marital status	Married, widowed, divorced, separated, never married, living with partner	1999 – 2016
	Household size	DMDHHSIZ	Total number of people in the household	1, 2, 3, 4, 5, 6, 7+	1999 – 2016
	Income	INDHHINC / INDHHIN2 [2]	Annual household income	< $20,000, > $20,000 and ≤ $44,999, > $45,000 and ≤ $74,999, ≥ $75,000	1999 – 2016
	Poverty income ratio	INDFMPIR	Poverty income ratio (PIR)	< 1, ≥ 1	1999 – 2016
	Health insurance	HID010 / HIQ011 [2]	Are you covered by health insurance or some other kind of health care plan?	Yes, no	1999 – 2016
Lifestyle	**Ever smoker**	SMQ020	Have you smoked at least 100 cigarettes in your entire life?	Yes, no	1999 – 2016
	Alcohol use I	ALQ120Q / ALQ120U [2]	In the past 12 months, how often did you drink any type of alcoholic beverage? [days]	0, > 0 and ≤ 10, > 10 and ≤ 50, > 50 and ≤ 100, > 100 [1]	1999 – 2016
	Alcohol use II	ALQ130	In the past 12 months, on those days that you drank alcoholic beverages, on average, how many drinks did you have?	1, 2 or 3, 4 or 5, > 5 [1]	1999 – 2016
	BMI	BMXBMI	Body mass index (kg/m^2)	≤ 18.5, > 18.5 and ≤ 25, > 25 and ≤ 30, > 30 [1]	1999 – 2016
	Vigorous activity I	PAQ650	Do you do any vigorous-intensity sports, fitness, or recreational activities that cause large increases in breathing or heart rate like running or basketball for at least 10 minutes continuously?	Yes, no	2007 – 2016
	Vigorous activity II	PAD660	How much time do you spend doing vigorous-intensity sports, fitness or recreational activities on a typical day? [hours]	≤ 1, > 1 and ≤ 2, > 2 and ≤ 4, > 4 [1]	2007 – 2016
	Moderate activity I	PAD665	Do you do any moderate-intensity sports, fitness, or recreational activities that cause a small increase in breathing or heart rate	Yes, no	2007 – 2016

	Factor	NHANES Identifier	Description	Discrete response categories	Survey years
			such as brisk walking, bicycling, swimming, or golf for at least 10 minutes continuously?		
	Moderate activity II	PAD675	How much time do you spend doing moderate-intensity sports, fitness or recreational activities on a typical day? [hours]	≤ 1, > 1 and ≤ 2, > 2 and ≤ 4, > 4 [1]	2007 – 2016
	Time sitting/reclining	PAD680	How much time do you usually spend sitting or reclining on a typical day? [hours]	≤ 1, > 1 and ≤ 2, > 2 and ≤ 4, > 4 [1]	2007 – 2016
	Vegetable intake	DBD270D	On an average day, how many helpings of the following kinds of foods do you eat? Vegetables, including vegetable salads.	0, 1 or 2, 3 or 4, > 5 [1]	1999 – 2000
	Fast food	DBD900	How many [meals you did not eat at home] did you get from a fast-food or pizza place? [meals per week]	0, > 0 and ≤ 5, > 5 and ≤ 10 [1]	2007 – 2014
Comorbidities & Medications	**Depression**	CIDDSCOR	Depression score (diagnosis)	Yes, no	1999 – 2004
	GAD	CIDGSCOR	Generalized anxiety disorder score (diagnosis)	Yes, no	1999 – 2004
	Panic	CIDPSCOR	Panic disorder score (diagnosis)	Yes, no	1999 – 2004
	Arthritis	MCQ160A	Has a doctor or other health professional ever told you that you had arthritis?	Yes, no	1999 – 2016
	Heart disease	MCQ160B-F [3]	Has a doctor or other health professional ever told you that you had congestive heart failure OR coronary heart disease OR angina OR myocardial infarction OR a stroke?	Yes, no	1999 – 2016
	Emphysema	MCQ160G	Has a doctor or other health professional ever told you that you had emphysema?	Yes, no	1999 – 2016
	Cancer	MCQ220	Have you ever been told by a doctor or other health professional that you had cancer or a malignancy of any kind?	Yes, no	1999 – 2016
	Diabetes	DIQ010	Other than during pregnancy, have you ever been told by a doctor or health professional that you have diabetes or sugar diabetes?	Yes, no, borderline	1999 – 2016
	Hypertension	BPQ020	Have you ever been told by a doctor or other health professional that you had hypertension, also called high blood pressure?	Yes, no	1999 – 2016
	Aspirin use (recommended)	RXQ510 / RXQ515 [2]	Doctors and other health care providers sometimes recommend that you take a low-dose aspirin each day to prevent heart attacks, strokes, or cancer. Have you ever been told to do this? Are you now following this advice?	Yes, no	2011 – 2014
	Aspirin use (independent)	RXQ520	On your own, are you now taking a low-dose aspirin each day to prevent heart attacks, strokes, or cancer?	Yes, no	2011 – 2014
	Aspirin frequency	RXQ525G	How often do you take an aspirin?	Every day, alternate days, another schedule	2011 – 2014

[1] also available as continuous

[2] identifier changed during 1999 – 2016 period

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[3] heart condition variables combined for purposes of present study

Table 2.

Median NLR across levels of each socio-demographic factor examined. A detailed description of each variable can be found in Table 1.

Factor [1]	Level	N (level)	N (factor)	NLR median [IQR]	p-val [2]
Sex	Male	23,206	48,023	1.99 [1.18]	0.03
	Female	24,817		1.96 [1.17]	
Age	<60	33,039	48,023	1.92 [1.10]	<2.2E-16
	≥60	14,984		2.11 [1.33]	
Race	Non-Hispanic White	21,254	48,023	2.14 [1.23]	<2.2E-16
	Non-Hispanic Black	9,928		1.60 [1.10]	
	Mexican American	9,138		2.00 [1.07]	
	Other Hispanic	3,847		1.93 [1.06]	
	Other Race	3,856		1.86 [1.09]	
Education Level	Less than 12th grade	12,430	44,597	1.98 [1.18]	0.5 p-trend: 0.23
	High school/GED or equivalent	22,657		1.99 [1.19]	
	College graduate or above	9,452		1.99 [1.15]	
	Refused/Don't know	58		1.76 [1.46]	
Marital Status	Married	23,641	46,207	2.00 [1.15]	<2.2E-16
	Widowed	3,856		2.17 [1.40]	
	Divorced	4,465		1.99 [1.18]	
	Separated	1,468		1.94 [1.16]	
	Never married	9,432		1.92 [1.18]	
	Living with partner	3,323		1.88 [1.12]	
	Refused/Don't know	22		2.01 [1.73]	
People in Household	1	6,391	48,023	2.07 [1.34]	<2.2E-16 p-trend: <2.2E-16
	2	14,156		2.02 [1.22]	
	3	8,683		1.96 [1.16]	
	4	7,857		1.94 [1.12]	
	5	5,240		1.93 [1.07]	

Factor [1]	Level	N (level)	N (factor)	NLR median [IQR]	p-val [2]
	6	2,647		1.91 [1.09]	
	7+	3,049		1.85 [1.10]	
Income	< $20,000	10,662		2.01 [1.26]	
	$20,000 to $44,999	13,860		1.99 [1.20]	
	$45,000 to $74,999	8,762	46,175	1.96 [1.18]	6.95E-07 p-trend: 6.58E-09
	≥ $75,000	10,327		1.95 [1.07]	
	Refused/Don't know	2,564		1.93 [1.18]	
Poverty Income Ratio	< 1	9,686	44,016	1.96 [1.20]	0.002
	≥ 1	34,330		1.99 [1.17]	
Health Insurance	Yes	37,185		2.00 [1.21]	
	No	10,601	47,874	1.91 [1.07]	<2.2E-16
	Refused/Don't know	88		1.88 [1.06]	

[1] Detailed descriptions of all factors can be found in Table 1

[2] p values for difference in median NLR between factor levels: calculated using Mann Whitney test for 2 levels and Kruskal Wallis omnibus test for >2 levels. P-trend obtained from Jonckheere-Terpstra test for ordered differences among levels.

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Table 3.

Median NLR across levels of each lifestyle factor examined. A detailed description of each variable can be found in Table 1.

Factor [1]	Level	N (level)	N (factor)	NLR median [IQR]	p-val [2]
Ever Smoker	Yes	20,596	45,131	2.04 [1.24]	<2.2E-16
	No	24,494		1.93 [1.12]	
	Refused/Don't know	41		1.79 [1.12]	
Alcohol use I (drinking days per year)	None	7,988	35,335	2.06 [1.30]	<2.2E-16
	≤ 10	7,995		1.96 [1.16]	
	> 10 and ≤ 50	7,209		1.95 [1.13]	
	> 50 and ≤ 100	3,838		1.95 [1.11]	
	> 100	8,263		2.01 [1.18]	
	Refused/Don't know	42		2.43 [1.26]	
Alcohol use II (drinks per drinking day)	1	9,586	27,346	2.00 [1.19]	2.91E-06
	2 or 3	11,295		1.94 [1.12]	
	4 or 5	3,205		1.96 [1.13]	
	> 5	3,220		1.99 [1.14]	
	Refused/Don't know	40		2.04 [1.30]	
BMI	≤ 18.5	914	47,175	1.91 [1.30]	0.008 p-trend: 5.39E-05
	> 18.5 and ≤ 25	14,285		1.95 [1.21]	
	> 25 and ≤ 30	15,676		1.96 [1.14]	
	> 30	16,300		2.00 [1.16]	
Physical Activity	None	14,627	28,029	1.99 [1.20]	<2.2E-16
	Moderate only	7,136		1.95 [1.11]	
	Vigorous only	2,257		1.79 [0.99]	
	Moderate and vigorous	4,001		1.84 [0.99]	
	Refused/Don't know	8		1.69 [0.43]	
Vigorous Activity Duration	≤ 1 hour	4,025	6,248	1.84 [0.97]	0.19
	> 1 hour and ≤ 2 hours	1,575		1.78 [1.01]	

Factor [1]	Level	N (level)	N (factor)	NLR median [IQR]	p-val [2]
	> 2 hours and ≤ 4 hours	575		1.80 [1.02]	
	> 4 hours	72		1.94 [1.01]	
	Refused/Don't know	1		3.62 [0.00]	
Moderate Activity Duration	≤ 1 hour	8,564		1.91 [1.05]	
	> 1 hour and ≤ 2 hours	1,624		1.89 [1.04]	
	> 2 hours and ≤ 4 hours	764	11,115	1.99 [1.19]	0.13
	> 4 hours	159		1.98 [1.01]	
	Refused/Don't know	4		1.63 [0.42]	
Time sitting/reclining	≤ 1 hour	4,371		1.88 [1.04]	
	> 1 hour and ≤ 2 hours	12,820		1.93 [1.14]	
	> 2 hours and ≤ 4 hours	9,789	27,992	1.96 [1.16]	1.67E-07 p-trend: 2.99E-09
	> 4 hours	903		2.00 [1.11]	
	Refused/Don't know	109		2.00 [1.17]	
Vegetable intake (servings per day)	0	152		2.11 [1.12]	
	1 or 2	1,163		2.10 [1.31]	
	3 or 4	177	1,509	2.22 [1.17]	0.43
	> 4	12		2.74 [1.39]	
	Refused/Don't know	5		1.93 [1.44]	
Fast food (meals per week)	0	5,559		1.96 [1.16]	
	> 0 and ≤ 5	10,283		1.95 [1.13]	
	> 5 and ≤ 10	1,107	17,309	1.94 [1.11]	0.007 p-trend: 0.02
	> 10	357		1.84 [1.12]	
	Refused/Don't know	3		0.99 [0.50]	

[1] Detailed descriptions of all factors can be found in Table 1

[2] p values for difference in median NLR between factor levels: calculated using Mann Whitney test for 2 levels and Kruskal Wallis omnibus test for >2 levels. P-trend obtained from Jonckheere-Terpstra test for ordered differences among levels.

Table 4.

Univariate and multivariable regression results for association between NLR and all factors included in 5 or more survey years.

		Univariate			Multivariable		
Factor	**Level**	**N (level)** [1]	**Coefficient**	**p-val**	**N (level)** [1]	**Coefficient**	**p-val**
Sex	Male	23,206	Ref		10,704	Ref	
	Female	24,817	−0.03	0.008	9,533	−0.13	**4.13E-12**
Age	<60	33,039	Ref		13,685	Ref	
	≥60	14,984	0.28	<2E-16	6,552	0.12	**7.05E-07**
	Continuous	48,023	0.0066	<2E-16	20,237		
Race	Non-Hispanic White	21,254	Ref		9,251	Ref	
	Non-Hispanic Black	9,928	−0.59	<2E-16	4,066	−0.53	**<2E-16**
	Mexican American	9,138	−0.20	<2E-16	3,019	−0.10	**3.42E-04**
	Other Hispanic	3,847	−0.28	<2E-16	2,089	−0.16	**2.34E-07**
	Other Race	3,856	−0.31	<2E-16	1,812	−0.21	**2.68E-11**
Education Level	Less than 12th grade	12,430	Ref		4,674	Ref	
	High school/GED or equivalent	22,657	0.009	0.51	10,707	0.05	**0.02**
	College graduate or above	9,452	−0.003	0.84	4,843	0.08	**0.01**
Marital Status	Married	23,641	Ref		10,419	Ref	
	Widowed	3,856	0.27	<2E-16	1,391	0.19	**9.99E-07**
	Divorced	4,465	−0.005	0.8	2,355	0.03	0.28
	Separated	1,468	−0.04	0.23	683	0.12	**0.02**
	Never married	9,432	−0.10	3.64E-11	3,691	0.05	**0.04**
	Living with partner	3,323	−0.12	1.06E-07	1,692	−0.05	0.17
People in Household	1	6,391	Ref		2,900	Ref	
	2	14,156	−0.06	2.00E-03	6,261	0.01	0.67
	3	8,683	−0.17	<2E-16	3,621	0.01	0.68
	4	7,857	−0.21	<2E-16	3,284	0.04	0.33
	5	5,240	−0.23	<2E-16	2,065	0.02	0.60

		Univariate			Multivariable		
Factor	**Level**	**N (level)** [1]	**Coefficient**	**p-val**	**N (level)** [1]	**Coefficient**	**p-val**
	6	2,647	−0.21	5.59E-13	1,051	0.06	0.24
	7+	3,049	−0.27	<2E-16	1,055	−0.07	0.17
	Continuous	48,023	−0.05	<2E-16	20,237		
Income	< $20,000	10,662	Ref		4,015	Ref	
	$20,000 to $44,999	13,860	−0.05	0.001	5,701	0.004	0.89
	$45,000 to $74,999	8,762	−0.08	5.67E-06	3,855	−0.04	0.17
	≥ $75,000	10,327	−0.13	9.27E-15	5,295	−0.06	**0.05**
Health Insurance	Yes	37,185	Ref		15,746	Ref	
	No	10,601	−0.15	<2E-16	4,474	−0.03	0.18
Ever Smoker	Yes	20,596	Ref		10,218	Ref	
	No	24,494	−0.14	<2E-16	10,002	−0.06	**0.0007**
Alcohol use I (drinking days per year)	None	7,988	Ref		4,306	Ref	
	≤ 10	7,995	−0.16	1.57E-15	4,522	−0.09	**0.001**
	> 10 and ≤ 50	7,209	−0.18	<2E-16	4,226	−0.05	0.09
	> 50 and ≤ 100	3,838	−0.19	3.41E-15	2,243	−0.08	**0.009**
	> 100	8,263	−0.11	2.65E-08	4,915	−0.02	0.44
	Continuous	35,293	−0.02	1.72E-06	20,212		
BMI	≤ 18.5	914	Ref		307	Ref	
	> 18.5 and ≤ 25	14,285	−0.01	0.77	5,558	−0.10	0.14
	> 25 and ≤ 30	15,676	−0.02	0.66	6,740	−0.17	**0.02**
	> 30	16,300	−0.02	0.57	7,632	−0.16	**0.02**
	Continuous	47,175	−0.09	0.4	20,237		
Physical Activity	None	14,627	Ref		10,280	Ref	
	Moderate only	7,136	−0.08	1.67E-05	5,360	−0.08	**0.0002**
	Vigorous only	2,257	−0.26	<2E-16	1,560	−0.13	**0.0002**
	Moderate and vigorous	4,001	−0.23	<2E-16	3,030	−0.13	**8.11E-07**

		Univariate			Multivariable		
Factor	**Level**	**N (level)** [1]	**Coefficient**	**p-val**	**N (level)** [1]	**Coefficient**	**p-val**
Time sitting/reclining	≤ 1 hour	4,371	Ref		2,977	Ref	
	> 1 hour and ≤ 2 hours	12,820	0.08	9.47E-05	9,412	0.04	0.12
	> 2 hours and ≤ 4 hours	9,789	0.15	5.51E-12	7,138	0.11	**3.76E-05**
	> 4 hours	903	0.16	0.0003	648	0.05	0.4
	Continuous	27,883	0.07	5.88E-13	20,175		
Arthritis	Yes	11,739	Ref		5,470	Ref	
	No	32,775	−0.19	<2E-16	14,728	−0.02	0.43
Heart condition	Yes	4,925	Ref		2,165	Ref	
	No	39,611	−0.43	<2E-16	18,053	−0.22	**5.82E-13**
Emphysema	Yes	910	Ref		473	Ref	
	No	43,630	−0.72	<2E-16	19,744	−0.33	**1.59E-08**
Cancer	Yes	3,997	Ref		1,970	Ref	
	No	40,553	−0.37	<2E-16	18,250	−0.15	**8.95E-07**
Diabetes	Yes	5,252	Ref		2,491	Ref	
	No	41,876	−0.20	<2E-16	17,268	−0.16	**2.33E-08**
	Borderline	862	−0.13	0.003	465	−0.17	**0.00473**
Hypertension	Yes	15,457	Ref		7,268	Ref	
	No	32,330	−0.17	<2E-16	12,946	−0.07	**0.00129**

[1] Univariate models include all available participants. Lower N values in multivariable model reflect restriction to only participants with complete data for all included variables. Note that participants reporting “refused/don#x2019;t know#x201D; are excluded from this table for brevity, and thus slight variations from these participant totals may be observed.

Table 5.

Associations between demographic and lifestyle factors (sex, age, ever-smoker status, alcohol use, BMI and physical activity) and NLR within independent subgroups of the participant population classified by race/ethnicity, age and sex. **A.** Participants with comorbidities. **B.** Participants without comorbidities.

Table 5a. Subjects with comorbidity

		Non-Hispanic white				Non-Hispanic black				Hispanic			
		Age		Sex		Age		Sex		Age		Sex	
Factor	**Level**	**<60**	**>60**	**M**	**F**	**<60**	**>60**	**M**	**F**	**<60**	**>60**	**M**	**F**
Sex	M	Ref				Ref				Ref			
	F	−0.08	**−0.50** ***			**−0.18** **	**−0.30** **			−0.13	**−0.38** **		
Age	<60			Ref				Ref				Ref	
	≥60			**0.39** ***	0.01			0.005	0.05			**0.26** *	−0.11
Ever Smoker	Yes	Ref		Ref		Ref		Ref		Ref		Ref	
	No	−0.05	**−0.15** *	−0.12	−0.09	0.04	0.01	0.007	0.08	−0.04	0.01	−0.09	0.05
Alcohol use 1 (drinking days per year)	None	Ref		Ref		Ref		Ref		Ref		Ref	
	≤ 10	−0.06	0.007	0.14	**−0.16** *	−0.02	−0.10	0.02	−0.16	−0.07	−0.17	−0.17	−0.09
	> 10 and ≤ 50	−0.03	0.04	0.14	−0.12	−0.003	−0.07	−0.04	−0.09	0.05	−0.21	−0.22	0.01
	> 50 and ≤ 100	−0.08	−0.008	0.05	−0.10	−0.04	−0.24	−0.13	−0.19	−0.02	0.04	0.04	−0.05
	> 100	−0.09	−0.10	−0.01	−0.15	0.09	−0.05	0.06	−0.07	0.06	−0.02	−0.04	0.20
BMI	≤ 25	Ref		Ref		Ref		Ref		Ref		Ref	
	>25	0.03	**−0.27** ***	**−0.13** **	0.01	−0.01	**−0.36** ***	−0.11	−0.13	−0.02	−0.003	−0.01	−0.03
Physical Activity	None	Ref		Ref		Ref		Ref		Ref		Ref	

	Moderate only	−0.10	**−0.31** ***	**−0.25** ***	**−0.18** **	0.03	−0.14	−0.10	−0.02	−0.02	0.04	−0.04	0.05
	Vigorous only	**−0.31** **	−0.15	−0.25	−0.28	−0.14	−0.07	−0.10	−0.10	**−0.26** *	−0.13	−0.23	−0.29
	Moderate and vigorous	**−0.24** **	−0.24	**−0.21** *	**−0.28** **	−0.10	−0.12	−0.15	0.02	**−0.20** *	**−0.53** *	−0.30	**−0.29** *

Table 5b. Subjects without comorbidity

		Non-Hispanic White				Non-Hispanic Black				Hispanic			
		Age		Sex		Age		Sex		Age		Sex	
Factor	**Level**	**<60**	**>60**	**M**	**F**	**<60**	**>60**	**M**	**F**	**<60**	**>60**	**M**	**F**
Sex	M	Ref				Ref				Ref			
	F	0.04	**−0.46** ***			0.08	−0.23			**0.11** **	−0.19		
Age	<60			Ref				Ref				Ref	
	≥60			**0.34** ***	−0.15			0.14	−0.18			**0.18** *	−0.22
Ever Smoker	Yes	Ref		Ref		Ref		Ref		Ref		Ref	
	No	−0.03	−0.10	−0.007	−0.07	−0.08	−0.09	−0.14	0.007	0.006	−0.27	−0.04	−0.71
Alcohol use 1 (drinking days per year)	None	Ref		Ref		Ref		Ref		Ref		Ref	
	≤ 10	−0.01	0.004	−0.06	0.06	−0.05	−0.10	−0.07	−0.14	**−0.19** **	−0.09	**−0.18** *	**−0.17** *
	> 10 and ≤ 50	−0.03	−0.08	−0.08	0.05	0.15	−0.08	0.19	−0.02	−0.11	−0.02	−0.08	−0.11
	> 50 and ≤ 100	−0.06	−0.05	−0.12	0.03	−0.02	−0.24	−0.01	−0.07	−0.08	−0.10	−0.13	0.06
	> 100	0.05	−0.006	−0.01	0.10	0.13	−0.10	0.12	−0.006	−0.0009	0.23	0.08	−0.08
BMI	≤ 25	Ref		Ref		Ref		Ref		Ref		Ref	
	>25	0.04	**−0.29** *	−0.03	0.04	−0.02	0.11	−0.03	0.02	0.02	−0.20	−0.02	0.02
Physical Activity	None	Ref		Ref		Ref		Ref		Ref		Ref	

Moderate only	−0.03	−0.03	−0.03	−0.02	−0.03	−0.08	−0.06	−0.05	−0.01	0.14	−0.05	0.02
Vigorous only	**−0.16** **	−0.13	**−0.17** *	−0.14	0.16	−0.65	0.15	0.19	−0.009	−0.11	−0.005	−0.02
Moderate and vigorous	**−0.12** *	−0.06	0.009	**−0.24** ***	0.04	−0.14	0.03	0.02	−0.07	0.10	−0.08	−0.02

Results represent b coefficient and p value from a multivariable regression model that included all factors included in the multivariable model of Table 4 and also presence of comorbidities (arthritis, heart disease, diabetes, cancer, emphysema and hypertension).

*** represents p<0.001

** represents p<0.01, and

* represents p<0.05.