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Meredithe McNamara, Emory University
Ana Antun, Emory University
Christine Kempton, Emory University

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The Role of Disease Severity in Influencing Body Mass Index in People with Haemophilia: A Single Institutional Cross-Sectional Study

Dr. Meredith McNamara, MD, MSc, Dr. Ana Antun, MD, and Dr. Christine L. Kempton, MD, MSc
Emory University School of Medicine (Dr. McNamara), Emory University School of Medicine, Department of Hematology and Medical Oncology, Emory University School of Medicine, Atlanta, (Drs. Kempton, and Antun); Aflac Cancer and Blood Disorders Center, Atlanta (Dr. Kempton)

Summary

Aim—The aim of this study is to evaluate the effect of haemophilia disease severity and potential intermediaries on body mass index (BMI) in patients with hemophilia.

Methods—A secondary analysis of a cross-sectional study eighty-eight adults with haemophilia was undertaken.

Results—On bivariate analysis, persons with severe haemophilia had 9.8% lower BMI (95% CI −17.1, −3.0) than persons with non-severe hemophilia. The effect of haemophilia severity on BMI varied significantly by HIV status. Among HIV positive subjects, haemophilia severity was not associated with BMI (+5.0%, 95% CI −22.4, 41.9). Among HIV negative subjects, severe haemophilia was associated with 15.1% lower BMI (95% CI, −23.6, −5.7). Older (>41 years) HIV negative subjects with severe haemophilia had a BMI that was 24.8% lower (95% CI −39.1, −7.0) than those with non-severe haemophilia. No statistically significant association was detected between BMI and severe versus non-severe haemophilia for younger HIV negative subjects. Although joint disease, as measured by the WFH joint score, did not influence the association between haemophilia disease severity and BMI, adjustment for the atrophy component of the WFH score reduced the association between haemophilia severity and BMI by 39.1–69.9%. This suggested that muscle atrophy mediated at least part of the relationship between haemophilia severity and BMI.

Conclusion—Haemophilia disease severity is associated with BMI and appears to be mediated by muscle atrophy of surrounding joints. This association appears to be possibly modified by HIV status and age.

Keywords

body mass index; disease severity; haemophilia; HIV; chronic liver disease; activity

Introduction

Persons with haemophilia (PWH) of all disease severities now enjoy a lifespan that approaches that of the general population, paralleling a trend in improved care and greater
access to safe replacement products [1, 2]. Estimates project that PWH live 63–75 years depending on haemophilia severity, whereas males in the general population live 75 years [3, 4].

As PWH live longer, they have more opportunity to acquire common chronic diseases including obesity which is known to increase in frequency with age [5]. Obesity is estimated to affect between 18–33% of PWH, compared to 25–35% of the general population [6–8]. Well-known complications of obesity include osteoarthritis from increased weight bearing, diabetes, cardiovascular diseases, and malignancy. The public health burden includes higher costs of care, rising disability and unemployment. These complications also affect PWH, but joint disease is particularly burdensome. In PWH, obesity is associated with more frequent bleeding and activity limitation, particularly with those activities that involve the lower limb [9]. In young PWH, adiposity has been demonstrated to cause loss of joint range of motion over time [10, 11]. Also, costs of haemophilia care are exacerbated by obesity due to increased factor demand and weight-based dosing [9, 12]. Severe haemophilia is associated with known or potential risk factors for weight gain, though it is not known how the severity of disease impacts BMI. Patients with severe haemophilia are more likely to be sedentary both for fear of traumatic bleeding and because of worsening arthropathy [13–15]. Also, patients with severe disease diagnosed before human immunodeficiency virus (HIV) and hepatitis C virus (HCV) screening are more likely to be afflicted by infectious complications such as HIV and HCV. When treated, HIV is known to be associated with obesity, through the metabolic derangements caused by anti-retroviral (ARV) medication [16, 17]. Chronic liver disease, the vast majority of which is caused by hepatitis C (HCV) in PWH, is loosely associated with pro-inflammatory metabolic effects and may predispose to weight gain [18].

To date, only prevalence studies have examined the relationship between haemophilia disease severity and obesity with discrepant findings [6, 8, 19]. These studies have either had few participants or have been exclusively of pediatric populations. With no adjustment of potential intermediaries and confounders, a mechanism for any association has yet to be investigated.

The purpose of this study is to explore the association between severity of haemophilia and BMI. With a view towards investigating the role of variables that may mediate the relationship between haemophilia severity and BMI, we also seek to evaluate HIV, HCV chronic liver disease, joint disease and physical activity.

Materials and Methods

Subjects

After approval by the Emory University Institutional Review Board, patients with haemophilia A or B aged ≥ 25 years were recruited from the Emory/Children’s Health Care of Atlanta (CHOA) Comprehensive Haemophilia Treatment Center (HTC) to participate in a study of bone density [20]. Originally, 163 patients were eligible for inclusion based on age and receipt of treatment at the Emory/CHOA HTC. Mailings for recruitment into the original study were sent to the homes of 163 potential subjects. If patients did not respond to the mailings, they were approached during a regularly scheduled clinic appointment for their interest in participation. Of the total approached (n = 145), 57 declined to participate and 88 subjects were enrolled between 4/22/2010 and 9/1/2011. All 88 subjects enrolled in the original study were included in this secondary analysis.

Measurements

All measurements and questionnaires used for this analysis were completed during a single visit. Race was derived from patient self-report. BMI was calculated according to World
Health Organization methods [21]: subject’s weight in kilograms/(subject’s height in meters)$^2$. BMI was categorized into normal, overweight and obese categories using WHO criteria: normal ≤ 25 kg/m$^2$, overweight 25–30 kg/m$^2$ and obese > 30 kg/m$^2$. Physical activity was assessed using the Framingham Physical Activity Index, commonly used to assess physical activity [22]. A composite score was derived from summing the product of average hours spent at different activity levels and a weighting factor that takes oxygen consumption of said activity into account. A score of ≤27 is considered sedentary [22]. The World Federation of Hemophilia (WFH) Joint Score was used to quantify joint disease. It was measured by one of three physical therapists and is the sum of the scores for six joints [ankles (0–12), knees (0–12), and elbows (0–10); sum 0–68] [23]. The atrophy component of the WFH score was evaluated separately. The presence (score=1) or absence (score=0) of muscle atrophy for each of the six joints was measured and summed for all 6 joints (maximum score =6). Haemophilia disease severity was assigned based on the baseline factor level as recorded in the medical record and categorized into severe (<1%) or non-severe haemophilia [moderate (1–5%) or mild (>5–40)]. The presence of an inhibitor to factor VIII or IX was obtained from review of the medical record. Current use of prophylaxis was determined from patient interview. HIV status was also abstracted from review of the medical record. HCV chronic liver disease status was assigned if the patient was HCV antibody positive and (1) had a liver biopsy showing fibrosis, (2) had HCV detectable in serum, or (3) was currently receiving HCV antiviral medication.

Statistical Methods

Cohort characteristics were summarized with means and standard deviations for normally distributed variables and by medians and the interquartile range (IQR) in the case of skewed data. Skewedness was determined with kurtosis and discrepancies between the median and mean. Differences in baseline characteristics between categories of haemophilia disease severity were determined with chi-square tests for discrete variables, T-tests for normally distributed variables and non-parametric testing (Wilcoxon-rank sum test) for continuous skewed variables.

Analyses proceeded with simple linear regression. To achieve normality of the outcome, BMI was logarithmically transformed. Linearity of all covariates was verified with individual scattering of residual plots. Independence of all covariates was verified with variance inflation factors and conditional indices. Outliers were identified and sensitivity analyses were performed to determine their influence. No outliers were found to affect the analyses. In order to interpret results, % change in BMI = $e^{(Parameter\ estimate*level\ of\ covariate)} \times 100$. A variable was a candidate for model inclusion if it was known to be associated with BMI or demonstrated a p-value of less than 0.20 on bivariate analysis. Variables were included in the multivariable model if they were found to be associated with BMI, previously known to be associated with BMI, or determined to confound the association between haemophilia severity and BMI. A series of stratified analyses were conducted to evaluate possibilities for statistical interaction. This was further studied with the p-value for an interaction term modeled with linear regression. All analyses were conducted using SAS v 9.3. (Cary, NC)

WFH joint scores were missing for 18 subjects. This was primarily due to joint replacement or other major surgical intervention on the joint, precluding accurate scoring. Missing values were multiply imputed using the Monte Carlo Markov Chain (MCMC) method, allowing the whole sample to be analyzed using methods described by McKnight et al [24]. As surgical joint interventions are associated with severe arthropathy, we also performed a separate analysis by assigning the worst possible score to each joint that had undergone a procedure. Simple linear regression was repeated and a sensitivity analysis was performed to determine the utility of this method. This method was not found to be superior to multiple imputations.
conducted with the MCMC method. Muscle atrophy was assessed regardless of prior surgical intervention and thus was available on all patients.

Results

Patient Characteristics

From the Emory/CHOA Comprehensive Haemophilia Treatment Center, 88 adult males had a median age (IQR) of 41 years (20) and 61.4% of whom were of white non-Hispanic race (Table 1). The oldest participant was 85 years and the youngest was 25 years. Haemophilia A accounted for 81% of subjects. Severe disease was found most frequently, 43%, with mild and moderate disease affecting 30% and 27%, respectively. Those who declined enrollment (n=57) were similar to those who participated in the study with regards to age, race, type and severity of hemophilia (data not shown). Subjects with severe haemophilia did not differ in age from those with non-severe haemophilia, (p= 0.339). An inhibitor was present in only 5 subjects (6%) and inhibitor status was not included further in the analysis. The median BMI (IQR) of this cohort was 26.2 kg/m² (6), falling within the overweight range. A normal BMI was found in 32.9% (n=29), whereas 48.9% (n=43) were overweight and 18.2% (n=16) were obese. The highest BMI was 51.1 kg/m² and the lowest BMI was 15.8 kg/m². Using non-parametric testing, a significant difference in the BMI of severe versus non-severe subjects was detected (p = 0.029). The median (IQR) BMI in subjects of white race (n=58) was 26.3 kg/m² (4.8) and was 25.4 kg/m² (9.1) in those of black race (n=27) (p=0.755). The population was relatively inactive, with a mean physical activity index of 32.5 ± 7, and 15.9% had a sedentary threshold score of ≤27. The mean WFH score was 15.3 ± 9.4, where those with severe haemophilia had a significantly higher score than those of non-severe haemophilia (p < 0.001). The median atrophy score was 3.0 (IQR 2.0) in those with severe haemophilia and 1.0 (IQR 2.0) in those with non-severe haemophilia (p<0.0001). Prophylaxis was used by 23% (n=20) at the time of study. HIV status was positive in 30% (n = 26), with 11 patients on antiretroviral medications at the time of study (3 with non-severe haemophilia and 8 with severe haemophilia). The mean CD4 count of those who were HIV positive was 575 ± 384 (610 ± 487 in severe and 496 ± 265 in those with non-severe haemophilia). Only two subjects had CD4 counts below 200, indicating well-controlled disease in most subjects. HCV chronic liver disease was present in 53% of patients (n=47).

Bivariate Analyses

On bivariate analysis, patients with severe haemophilia were found to weigh 9.8% less than those with non-severe haemophilia (95% CI −17.1, −3.0) (Table 2). The remaining covariates were tested because they were suspected to either mediate or confound the relationship between BMI and haemophilia severity. The least active quartile of the physical activity score weighed 11.6% less than the most active quartile (95% CI −91.0, −0.01). Subjects with severe haemophilia were more likely to be in the least active quartile (57%) compared with subjects with non-severe haemophilia (44%). There were no significant associations for comparisons involving the second and third quartiles of physical activity. For each joint where atrophy was present, the BMI was 5.5% lower (95% CI −7.8, −3.1). No other bivariate association with BMI was suggestive of or achieved statistical significance, including joint disease assessed by the WFH score (with either imputed method), HIV, HCV chronic liver disease, age, white non-Hispanic versus any other race and current use of prophylaxis.

The association between haemophilia disease severity and BMI was further explored through a series of stratified analyses. In HIV positive subjects, BMI did not vary significantly by haemophilia severity. Specifically, those with severe haemophilia had a BMI that was only 3.2% higher than those with non-severe haemophilia (95% CI −9.8,
In contrast, in HIV negative subjects, severe haemophilia was associated with 13.7% lower BMI than those with non-severe haemophilia (95% CI −22.6, −3.8). In subjects who were younger than the median age of 41 years, haemophilia severity was not significantly associated with BMI (−5.3% 95% CI −15.9, 6.7). In subjects who were older than the median age of 41 years, severe haemophilia was associated with 15.4% lower BMI when compared with non-severe haemophilia (95% CI −24.4, −5.4). Associations between haemophilia severity and BMI were not meaningfully different when stratified by HCV chronic liver disease, physical activity index above and below the mean, WFH joint score above and below the mean, white non-Hispanic versus other race and current use of prophylaxis.

**Multivariable Analyses**

To further evaluate the potential for effect modification seen in stratified simple linear regression, the interaction between HIV and haemophilia severity after adjusting for age and race was assessed (p-value for interaction = 0.035). Among HIV positive subjects, severe haemophilia was associated with 4.9% higher BMI (95% CI −22.4, 41.9); whereas in HIV negative subjects severe haemophilia was associated with a 15.1% lower BMI (95% CI −23.6, −5.7). To account for the impact of both HIV and age on the association between haemophilia severity and BMI, multivariable models for HIV negative and positive subjects were separately constructed. Among HIV positive subjects with adjustment for race, haemophilia severity remained unassociated with BMI (−5.0, 95% CI −22.4, 41.9) with no evidence of interaction between age (above or below the median, 41 years) and haemophilia severity. HCV liver disease, WFH joint score, physical activity, prophylaxis use, and atrophy were also not associated with BMI in the HIV positive group. Among HIV negative subjects after adjustment for race, effect modification was suggested by categories of age above and below the median. For those younger than 41 years, BMI, though not statistically significant, was 10.3% lower in those with severe haemophilia compared with non-severe haemophilia (95% CI −42.5, 42.4). For those subjects older than or equal to 41 years, BMI was 24.8% lower in those with severe haemophilia compared with non-severe haemophilia (95% CI −39.1, −7.0) (Table 3). After the total atrophy score was included in the model, the effect of haemophilia severity on BMI was reduced (< 41 years 10.3% to 3.1% and ≥41 years from 24.8% to 15.1%). Liver disease, WFH joint score, physical activity and prophylaxis use were not associated with BMI nor did they influence the association between haemophilia severity and BMI in the HIV negative group. Although the effect of haemophilia severity in older subjects appeared to be greater than younger subjects, the interaction between age and severe versus non-severe haemophilia was not found to be statistically significant (p = 0.167).

**Discussion**

In this study, severe haemophilia was associated with a lower BMI when compared with non-severe haemophilia in subjects who were HIV negative. This affect was more significant in those over 41 years of age and was mediated, at least in part, by muscle atrophy. Physical activity, HCV liver disease, and total WFH joint score did not influence the relationship between haemophilia severity and BMI. In a crude comparison with the general population of the state of Georgia, the prevalence of BMI > 25 kg/m² is similar [64.8% in the general population vs 67.1% in this haemophilia population], though the prevalence of obesity appears lower [29.6% in the general population vs. 18.2% in this haemophilia population] [25]. Importantly, these comparisons are of different age groups (≥ 18 years in the general population group and ≥25 years in this hemophilia population) and there was no adjustment for race or ethnicity which could affect comparisons between populations [25]. The available data from the Universal Data Collection Project reports

*Haemophilia. Author manuscript; available in PMC 2015 March 01.*
33.1% of PWH 19 years and older are overweight or obese. This number is lower than our population though firm comparisons are difficult with different age cohorts and without adjustment for age, race and ethnicity [26]. In comparison to the adult PWH (≥20 years) in Mississippi reported by Majumdar et al, the current study population from Georgia had a greater proportion of overweight individuals (32% vs. 48.9%) but a lower proportion of obese individuals (36% vs. 18.2%) [27].

Three prevalence studies have arrived at discrepant findings on the relationship between haemophilia severity and BMI [6, 8, 19]. Revel-Vilk et al in a large cohort found that younger boys with severe haemophilia were more likely to be obese [19]. Majumdar et al reported the highest prevalence of obesity and overweight among PWH in a study conducted with a cohort from Mississippi and found that BMI did not significantly vary according to haemophilia severity, without adjustment for age or other potential confounders [8]. However, the extremely high prevalence of obesity among the small study population and Mississippians in general may have masked an association between haemophilia severity and BMI, if at all present. Hofstede et al performed a prevalence analysis of a cohort of adults and found that overweight was more prevalent in persons with non-severe haemophilia compared to those with severe haemophilia, while obesity was equally prevalent [6]. The detection of an association between older age and higher BMI among those with non-severe haemophilia in this study may corroborate the findings of Hofstede et al.

In current study it was found that haemophilia severity was most associated with BMI in those that were HIV negative and over the age of 41 years. We did not find that age alone was associated with BMI. However, in larger studies of the general population the proportion of people that are obese increases with age [5]. The lack of direct association between age and BMI in the current study, likely reflects our small sample size. Muscle atrophy mediated 69.9% and 39.1% of the effect of haemophilia severity in those less than or more than 41 years of age respectively. These findings suggest that the lower BMIs observed in patients with severe hemophilia may not necessarily reflect healthy habits, but rather may imply a wasting state involving joints most commonly affected by hemophilic bleeding. This effect of atrophy on BMI, although intuitive, has not previously been previously documented in this population.

The main limitation of this study is a lack of statistical power resulting from the relatively small sample size. Associations for HIV positive subjects and younger HIV negative subjects yielded wide confidence intervals. Furthermore, interaction between categories of age and haemophilia severity in the multivariable model was not statistically significant; however, effect modification was suggested by different results among different strata. Some cross sectional data was used, including BMI, HIV status, HCV chronic liver disease, prophylaxis use and age. It is important to note, however, that haemophilia severity is a longitudinal variable and preceded changes in BMI. Though our population is racially diverse, all subjects were recruited from a single center. Lastly the Framingham Physical Activity index is subject to recall bias.

This study had several strengths. The use of a multivariable linear model allowed for a quantification of a change in BMI in comparing severe to non-severe haemophilia. This approach deepened our understanding beyond traditional classification of BMI into normal, overweight and obese categories. Cut points for continuous variables such as BMI can be helpful for clinically conceptualization, but variability exists within categories that can exaggerate or underestimate the effect of the exposure on the outcome. Also, with information available on potential intermediaries, including muscle atrophy, we were able to begin to evaluate the extent to which physical activity and infectious complications were
responsible for the change in BMI associated with haemophilia severity. A survey of confounding and statistical interaction offered a new understanding of how HIV status, race and age affect the relationship between haemophilia severity and BMI.

As PWH live longer, they are at greater risk of acquiring chronic diseases that afflict the general population. Obesity is of particular concern, adding risk of mortality and morbidity among PWH. Although obesity is determined by BMI, a normal BMI may not entirely reflect a healthy body habitus. In future studies of obesity and aging in this population, both BMI and muscle atrophy should be evaluated. Additionally, efforts to address obesity and healthy living in PWH will need to focus not only on BMI, but other measures of health and fitness as well.

Acknowledgments
C.K., A.A. and M.M designed the study. C.K. and A.A. completed the data collection. M.M. and C.K. performed the analysis and wrote the manuscript. C.K., M.M. and A.A. critically reviewed and edited the manuscript. This work was supported by grants from the National Institutes of Health, (UL1TR000454 and TL1TR000456 to MM) and (1K23HL105785 to CK).

References
### Table 1

Cohort Characteristics.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall</th>
<th>Severe (n=38)</th>
<th>Nonsevere (n=50)</th>
<th>P-value+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (IQR)</td>
<td>41 (20)</td>
<td>40 (18.0)</td>
<td>42 (23)</td>
<td>0.339*</td>
</tr>
<tr>
<td>White non-Hispanic (%)</td>
<td>54 (61)</td>
<td>23 (61)</td>
<td>31 (62)</td>
<td>0.888</td>
</tr>
<tr>
<td>Median BMI (IQR)</td>
<td>26.2 (6)</td>
<td>25.4 (6)</td>
<td>26.8 (5)</td>
<td>0.029*</td>
</tr>
<tr>
<td>Haemophilia A (%)</td>
<td>71 (81)</td>
<td>33 (87)</td>
<td>38 (76)</td>
<td>0.201</td>
</tr>
<tr>
<td>Inhibitor present (%)</td>
<td>5 (6)</td>
<td>3 (8)</td>
<td>2 (6)</td>
<td>0.648*</td>
</tr>
<tr>
<td>Prophylaxis use (%)</td>
<td>20 (23)</td>
<td>14 (37)</td>
<td>6 (12)</td>
<td>0.005</td>
</tr>
<tr>
<td>Mean WFH score ± SD§</td>
<td>15.3 ± 9.4</td>
<td>22.7 ± 7.8</td>
<td>9.8 ± 6.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median atrophy score (IQR)</td>
<td>2.0 (2.0)</td>
<td>3.0 (2.0)</td>
<td>1.0 (2.0)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Mean physical activity ± SD</td>
<td>32.5 ± 7</td>
<td>31.5 ± 7.5</td>
<td>33.1 ± 7.5</td>
<td>0.250</td>
</tr>
<tr>
<td>HIV positive (%)</td>
<td>26 (30)</td>
<td>18 (47.4)</td>
<td>8 (16.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>HCV chronic liver disease (%)</td>
<td>47 (53)</td>
<td>28 (73.7)</td>
<td>21 (42.0)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

IQR, interquartile range; SD, standard deviation; BMI, body mass index; HIV, human immunodeficiency virus; ARV, anti-retroviral; WFH, World Federation of Haemophilia; HCV, hepatitis C virus.

* For statistical tests of differences in baseline characteristics between severe and non-severe groups.

§ Wilcoxon-rank sum test used, non-parametric variable

n=70
Table 2

Bivariate associations with percent change in body mass index (BMI).

<table>
<thead>
<tr>
<th>Variable</th>
<th>% change in BMI per unit</th>
<th>95% CI</th>
<th>P - value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe vs non-severe</td>
<td>−9.8</td>
<td>−17.1, −3.0</td>
<td>0.014</td>
</tr>
<tr>
<td>Physical activity*</td>
<td>−11.6</td>
<td>−91.0, −0.01</td>
<td>0.040</td>
</tr>
<tr>
<td>WFH joint score§</td>
<td>−1.8</td>
<td>−3.9, 0.01</td>
<td>0.149</td>
</tr>
<tr>
<td>Atrophy score (per joint)</td>
<td>−5.5</td>
<td>−7.8, −3.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HCV chronic liver disease</td>
<td>−5.1</td>
<td>−13.0, 3.4</td>
<td>0.223</td>
</tr>
<tr>
<td>HIV positive</td>
<td>−5.9</td>
<td>−14.3, 3.3</td>
<td>0.193</td>
</tr>
<tr>
<td>Current prophylaxis use</td>
<td>−6.9</td>
<td>−15.9, 3.0</td>
<td>0.162</td>
</tr>
<tr>
<td>Age (per 10 year increase)</td>
<td>−0.01</td>
<td>−0.3, 0.3</td>
<td>0.627</td>
</tr>
<tr>
<td>White vs any other race</td>
<td>0.9</td>
<td>−7.6, 10.2</td>
<td>0.844</td>
</tr>
</tbody>
</table>

CI, confidence interval; WFH, World Federation of Haemophilia; HCV, hepatitis C virus; HIV, human immunodeficiency virus

* Lease active quartile versus the most active quartile;
§ 5 point increment, multiple imputations used for missing data
Table 3
Influence of disease severity on body mass index (BMI).

<table>
<thead>
<tr>
<th>Variable</th>
<th>% change in BMI, severe versus non-severe</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV positive (n=26)</td>
<td>5.0</td>
<td>−22.4, 41.9</td>
</tr>
<tr>
<td>HIV negative (n=62)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &lt; 41 years</td>
<td>−10.3</td>
<td>−42.5, 42.4</td>
</tr>
<tr>
<td>Age ≥ 41 years</td>
<td>−24.8</td>
<td>−39.1, −7.0</td>
</tr>
</tbody>
</table>

CI, confidence interval

$^\S$ – Controlling for race

$^*$ – Controlling for age and race