Analysis of cardiovascular risk factors associated with serum testosterone levels according to the US 2011–2012 National Health and Nutrition Examination Survey

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ABSTRACT

Objective: To investigate associations between cardiovascular disease risk factors, including fasting glucose, cholesterol, high density lipoprotein cholesterol (HDL-c), LDL-c, blood pressure, body mass index (BMI), C-peptide, creatinine kinase, smoking, alcohol use, physical activity, C-reactive protein as well as homocysteine levels and cardiovascular events.

Methods: Data from 1545 men aged ≥40 years, with testosterone deficiency (TD) (<300 ng/dL) and non-TD (≥300 ng/dL) which were extracted from the National Health and Nutrition Examination Survey database 2011–2012 and analyzed.

Results: Multivariate logistic regression analysis showed positive associations between TD and BMI (≥35 vs. <18.5: OR = 2.51, 95% CI: 1.19–5.32, p = .016), HDL-c ( <0.91 vs. ≥0.91: OR = 1.60, 95% CI: 1.14–2.24, p = .006) and diabetes (diabetes vs. non-diabetes: OR = 1.48, 95% CI: 1.14–1.92, p = .004) as well as negative associations between TD and metabolic equivalent scores (≥12 vs. <12: OR = 0.69, 95% CI: 0.52–0.91, p = .009) and smoking (Ever vs. never: OR = 0.69, 95% CI: 0.51–0.94, p = .018). Furthermore, total serum testosterone levels were lower in patients with heart failure (p = .04) and angina/angina pectoris (p = .001) compared with subjects without these cardiac problems.

Conclusion: Low serum testosterone was associated with multiple risk factors for CHD.

Introduction

Testosterone is an androgen steroid which plays an important role in the growth of male reproductive tissues and other secondary sexual characteristics. Normal testosterone levels generally range from 300 to 1000 ng/dL [1–3] and previous studies have shown that low serum levels of testosterone are associated with an increased risk of developing metabolic syndrome including obesity, diabetes, atherosclerosis and osteoporosis [4–12]. In particular, obesity has been proposed to correlate with male hypogonadism (HG) in a bidirectional relationship since obesity increased the incidence of HG and HG increased the risk of visceral obesity [13] and several studies underlined the effect of testosterone replacement on obesity and diabetes [14–17]. Sexual symptoms – particularly erectile dysfunction (ED) are specific symptoms in identifying patients with low testosterone and have been proposed as indicators of comorbidities [18–22] and ED has been associated with endothelial dysfunction and cardiovascular disease (CVD) [23]. A recent study of 83,010 men revealed that testosterone replacement therapy leading to normal levels of serum testosterone had positive effects on the safety of the cardiovascular system in aging males [24] after several observational studies over previous years suggested a possible increased cardiovascular (CV) risk in men with low serum testosterone levels [25,26].

However, the evidence generally came from retrospective data with endpoints as “events,” but some studies have also shown that testosterone replacement...
therapy might increase the risk of myocardial infarction and ischemic stroke [27,28]. In addition, established risk factors related to CVBs include non-modifiable factors such as age, gender, genotypes and ethnic origin, and modifiable factors such as smoking, diet, physical activity and complicated co-morbidities [29–32]. Therefore, we conducted a database analysis to investigate associations between various CVD risk factors and demographic variables with serum testosterone levels in middle aged and older men using data from the National Health and Nutrition Examination Survey (NHANES) 2011–2016.

Material and methods

Study subjects

This study was based on the NHANES data cycles 2011–2012. NHANES is a US-based national representative cross-sectional survey conducted by the National Center for Health Statistics, a branch of the US Centers for Disease Control and Prevention (CDC). The survey employed a multistage stratified probability sample based on selected countries, blocks, households and persons within households. The quality and integrity of the NHANES database have shown its value in various aspects of human health topics, including the men’s health field, via a number of publications. The present study was approved by the National Center for Health Statistics Institutional Ethics Review Board.

Subjects were excluded if they were <40 years old and had any of the following conditions which may have affected endogenous testosterone levels: a history of receiving testosterone; history of drug abuse; AIDS; pituitary hypothalamus disease; hyperthyroidism; end stage renal disease; or a history of using anti-epilepsy or 5a-reductase medicines. As a result, a total of 1545 male participants, who were ≥40 years old and had levels of serum testosterone monitored in NHANES 2011–2016, were included. All participants provided written informed consent.

Study procedure and variables

Publicly available NHANES data of CVD risk factors, serum total testosterone levels and demographic characteristics were exported using SAS® Version 9.3 (Cary, NC).

An isotope dilution liquid chromatography tandem mass spectrometry method was used to quantify the total serum testosterone levels based on the National Institute for Standards and Technology’s (NIST) reference method. Serum should be separated from red cells within 6 h of collection. Serum specimens were processed, stored, and shipped to the Division of Environmental Health Laboratory Sciences, National Center for Environmental Health, Centers for Disease Control and Prevention for analysis. Vials were stored under appropriate frozen (−20°C) conditions until they were shipped to National Center for Environmental Health for testing. There were no information available at which day time the samples have been obtained. The detection limit of the assay was 0.36 ng/dL with a reportable range of 2.5–1000 ng/dL. Within day coefficients of variations (CV) were 2.6%, 2.2% and 2.8% and among days the CV were 5.5%, 3.4% and 5.3% for low, medium and high QC samples.

Risk factors related to CV events were defined as: fasting glucose, cholesterol, high density lipoprotein cholesterol (HDL-c), low density lipoprotein cholesterol (LDL-c), blood pressure, body mass index (BMI), C-peptide, creatinine kinase, smoking, alcohol use, C-reactive protein and homocysteine as well as physical activity, which was evaluated as metabolic equivalent (MET) scores. MET scores were defined according to the amount of physical activity (e.g. moderate related work activity = 4 and vigorous related work activity = 8). Testosterone deficiency (TD) was defined as a serum testosterone level <300 ng/dL (10.4 nmol/L) [33,34] after excluding any external factors such as a history of receiving testosterone, history of drug abuse, AIDS, pituitary hypotalamus disease, hyperthyroidism, end stage renal disease or a history of using anti-epilepsy medicine or a 5a-reductase inhibitor. These variables, regardless of being continuous or dichotomous, were included in the logit model of logistic regression, in which the log odds of the outcomes were modeled as a combination of the predictor variables. Covariates consisted of CVD risk factors and demographic characteristics, which included age, race/ethnicity, educational level and income.

Statistical analysis

Statistical analyses were performed using SAS® Version 9.3 (Cary, NC). The full analysis set population was based on the data of NHANES 2011–2012 extracted for all ≥40-year old male subjects, including risk factors related to CV events and demographic characteristics.

All continuous data are presented as means (interquartile range) for abnormal distributed variables and as means (standard deviation, SD) for variables that were normally distributed. Categorical variables were reshaped as low and normal total serum testosterone (<300 ng/dL and ≥300 ng/dL), age (≤50, 51–60, 61–70
and >71 years), race (Mexican-American, other Hispanic, non-Hispanic-white, non-Hispanic-black, non-Hispanic-Asian and other races), educational level (<9th grade, 9–11th grade (including 12th grade without diploma), high school graduate/GED or equivalent, college AA degree and college graduate or above), marital status (married, widowed, divorced, separated, never married and living with partner), BMI (<18.5, 18.5–24.9, 25–29.9, 30–34.9 and ≥35), HDL (≥0.91 and <0.91 mmol/L), triglyceride (≥1.7 and <1.7 mmol/L), LDL (≥3.1 and <3.1 mmol/L), MET score (≥12 and <12), smoking (never, yes but not now and yes), and yes or no for hypercholesterolemia, diabetes, hypertension, congestive heart failure, coronary heart disease, angina/angina pectoris, stroke and had ≥12 alcoholic drinks per year, respectively. Categorial data are presented as frequency counts and percentages.

All risk factors related to CV events and demographic characteristic variables were analyzed using a univariate logistic regression model. Only significant factors that were analyzed by the univariate logistic regression analysis were included for multivariate logistic regression analysis. The odds ratios (OR) and 95% confidence intervals (CI) in both the univariate and multivariate logistic regression models were used to quantify relationships between each variable and the outcome event (TD). The final predictive model was built by step-wise regression analysis with collinearity taken into consideration.

Fisher’s exact or chi-squared tests were used to analyze the relationship between categorical variables and serum testosterone levels. The significance of differences of continuous data between participants with different serum testosterone levels was evaluated using unpaired two-sided Student’s t-tests for normal distribution variables and a Mann–Whitney U test for abnormally distributed variables. The significance level was set at p < .05 for all statistical analyses.

### Results

**Base line information of all enrolled subjects**

The frequency and percentage (categorical variables) and mean and standard deviation (baseline level of risk) of 1545 male subjects from the NHANES 2011–2012 database are shown in Tables 1 and 2. All the participants were ≥40 years old. Among them, the first two races with the highest percentages were non-Hispanic-white and non-Hispanic-black. Notably, of the 1545 included subjects, 23.0%, 77.4% and 77.2% were current smokers, drinkers of ≥12 alcoholic drinks per year and physically inactive people with MET scores <12, respectively. In addition, 53.4% of the participants were hypertensive and 42.9% were using antihypertensive drugs (Table 1).

**Association between serum testosterone levels with CVD risk factors and demographic variables**

There were statistically significant differences in the variables associated with serum testosterone levels among the different ethnic groups (see supplementary Table 1).

According to the average total serum testosterone level of all participants (Table 2), subjects were divided

| Table 1. Demographic characteristics of all enrolled subjects. |
|---------------------------------------------------------------|
| **Subjects** | **n = 1545 (%)** |
| **Age (years)** |  |
| ≤50 | 430 (27.8) |
| 51–60 | 400 (25.9) |
| 61–70 | 382 (24.8) |
| >70 | 332 (21.5) |
| **Race** |  |
| Mexican-American | 148 (9.6) |
| Other Hispanic | 157 (10.2) |
| Non-Hispanic-white | 614 (39.7) |
| Non-Hispanic-black | 387 (25.0) |
| Non-Hispanic-Asian | 198 (12.8) |
| Other Race | 41 (2.7) |
| **Education level** |  |
| Less than 9th grade | 209 (13.5) |
| 9–11th grade (includes 12th grade with no diploma) | 225 (14.6) |
| High school graduate/GED or equivalent | 347 (22.5) |
| Some college or AA degree | 383 (24.8) |
| College graduate or above | 380 (24.6) |
| **Cigarette smoker** |  |
| Never | 621 (40.2) |
| Yes but not now | 567 (36.7) |
| Current | 355 (23.0) |
| **Had ≥12 alcohol drinks per year** |  |
| Yes | 1,196 (77.4) |
| No | 212 (13.7) |
| **MET scores** |  |
| <12 | 1,192 (77.2) |
| ≥12 | 353 (22.8) |
| **Hypertension** |  |
| No | 720 (46.6) |
| Yes | 825 (53.4) |
| **Antihypertensive drugs** | 664 (42.9) |

Note: MET: integrated movement.

| Table 2. Baseline levels of risk factors for CV and total serum testosterone for all enrolled subjects. |
|---------------------------------------------------------------|
| **Mean (SD) (n = 1545)** |
| Systolic blood pressure (mmHg) | 128.3 (17.6) |
| Diastolic blood pressure (mmHg) | 72.9 (13.0) |
| BMI (kg/m²) | 28.7 (5.8) |
| Waist circumference | 102.8 (14.7) |
| HDL (mmol/L) | 1.2 (0.4) |
| Triglyceride (mmol/L) | 1.7 (1.3) |
| LDL (mmol/L) | 2.9 (0.9) |
| Fasting glucose | 6.5 (2.3) |
| HbA1c | 6.0 (1.3) |
| Total testosterone (ng/dL) | 388.8 (192.8) |
into normal (≥300 ng/dL) and low (<300 ng/dL) serum testosterone level groups (Table 3). As shown in Table 3, significant differences were found between serum testosterone groups according to age (p = 0.002), marital status (p = 0.034), BMI (p < 0.001), HDL (p < 0.001), triglyceride (p = 0.001), diabetes (p < 0.001), MET scores (p = 0.000) and smoking (p = 0.001). Among the age groups, the percentage of participants with normal testosterone (≥300 ng/dL) serum concentrations were almost constant from <50 years to 61–70 years, but dropped in the >70-year-old group (19.3%). The percentage of participants with low testosterone levels (<300 ng/dL) fluctuated within the age groups from 30% in the ≤50-year-olds, to 25.6% in the >70-year-old participants.

Among the marital status subgroups, the proportion of subjects with testosterone levels ≥300 ng/dL and testosterone <300 ng/dL was highest in the married group. Higher testosterone serum concentrations were related to BMIs between 18.5 and 29.9 but lower testosterone levels occurred more frequently in the BMI 30 to ≥35 subgroups. Interestingly, smoking had a positive effect on testosterone serum concentrations.

Multivariate logistic regression analysis was performed to explore further the association of TD with CVD risk factors and demographic variables that were found to be significant in the univariate logistic regression analysis model. As shown in Table 4, low serum TD correlating risk factors for CVD were a BMI ≥35 (OR 2.51 [1.19–5.32], p = 0.16), HDL <0.91 mmol/L (OR 1.60 [1.14–2.24], p = 0.006) and diabetes (OR 1.48 [1.14–1.92], p = 0.004). In contrast, 61–70 years of age (OR 0.59 [0.43–0.81], p = 0.001), MET ≥12 (OR 0.69 [0.52–0.91], p = 0.009) and smoking (OR 0.69 [0.51–0.94], p = 0.018) yielded a decreased OR for TD-related CVD events.

**Association of total serum testosterone level in CVDs**

As shown in Table 5, the total serum testosterone level among all the patients in various CVD groups were calculated and the possible correlation with CVDs were analyzed. The total testosterone serum levels in patients with heart failure (p = 0.04) and angina/angina pectoris (p = 0.001) were lower than in those men who never had these cardiac conditions. However, no significant difference in total serum testosterone levels was found in patients with coronary heart disease and stroke.

**Discussion**

This was a cross-sectional study designed to determine whether high levels of risk factors related to CV events were associated with low serum testosterone levels based on NHANES data. After analyzing the relationship between various CVD risk factors and serum testosterone levels, we found that a high BMI, low HDL and the presence of diabetes were associated with TD. However, whether TD is the cause or the result of metabolic health problems and concomitant CVD incidence remains unclear.

Normal serum testosterone levels (both total and free) are commonly defined as between 300 and 1000 ng/dL. However, there was no clear cut-off limit for low testosterone levels and some studies suggested cut-off ranges from high 200 ng/dL to low-to-mid 300 ng/dL [35,36]. In our study, we used the commonly applied cut-off value of 300 ng/dL to divide the participants into low (<300 ng/dL) and normal total serum testosterone (≥300 ng/dL) groups. The mean (SD) serum testosterone concentration of the enrolled 1545 participants aged ≥40 years was 388.8 (192.8) ng/dL, which was just a little higher than the cut-off value.

Although the precise role of testosterone in maintaining CV health remains an open question, we have found in accordance with previous research that normal testosterone levels (defined as serum total testosterone >300 ng/dL) in elderly men is associated with less CVD risk factors [37], compared to those with lower levels. Univariate analysis in our study revealed that independent risk factors of CVD, including BMI, HDL, triglyceride, diabetes, MET scores and tobacco use, were associated with serum testosterone levels. Furthermore, multivariate logistic regression analysis suggested that a BMI ≥35, HDL <0.91, diabetes and MET score <12 were correlated with TD, which was in agreement with previous studies, indicating that testosterone negatively correlated with BMI and diabetes but positively correlated with HDL and physical activity [38–40]. In the participants of the study, there was no association between age and low testosterone serum concentrations beside in men >70 years (Table 3), which is in line with a previous study in which male total testosterone concentrations showed increasing variance but no decline after age of 40 years [41].

Interestingly, our study showed that serum testosterone levels in smokers were significantly higher than in nonsmokers and that tobacco use was negatively correlated with TD, which is in line with previous research [42,43]. This finding could be partially explained by the notion that a metabolite of nicotine
Table 3. Univariate analysis of risk factors and covariates related to cardiovascular events on different serum testosterone group.

| Risk Factor                        | Serum testosterone | p-value |
|------------------------------------|--------------------|---------|
|                                    | ≥300 ng/dL (n = 1,001) | <300 ng/dL (n = 544) | |
| Age (years)                        |                    |         |
| <50                                | 267 (26.7%)        | 163 (30.0%)       | .002 |
| 51–60                              | 269 (26.9)         | 131 (24.1)        | |
| 61–70                              | 272 (27.2)         | 111 (20.4)        | |
| >70                                | 193 (19.3)         | 139 (25.6)        | |
| Race                               |                    |         |
| Mexican-American                   | 102 (10.2)         | 46 (8.5)          | .532 |
| Other Hispanic                     | 105 (10.5)         | 52 (9.6)          | |
| Non-Hispanic-white                 | 382 (38.2)         | 232 (42.6)        | |
| Non-Hispanic-black                 | 258 (25.8)         | 129 (23.7)        | |
| Non-Hispanic-Asian                 | 126 (12.6)         | 72 (13.2)         | |
| Other Race                         | 28 (2.8)           | 13 (2.4)          | |
| Education level                    |                    |         |
| Less than 9th grade                | 129 (12.9)         | 80 (14.7)         | .345 |
| 9–11th grade (includes 12th grade with no diploma) | 140 (14.0) | 85 (15.6) |
| High school graduate/GED or equivalent | 231 (23.1)       | 116 (21.3)        | |
| Some college or AA degree          | 261 (26.1)         | 122 (22.4)        | |
| College graduate or above          | 239 (23.9)         | 141 (25.9)        | |
| Marital status                     |                    |         |
| Married                            | 608 (60.7)         | 355 (65.4)        | .034 |
| Widowed                            | 60 (6.0)           | 41 (7.5)          | |
| Divorced                           | 143 (14.3)         | 47 (8.7)          | |
| Separated                          | 38 (3.8)           | 17 (3.1)          | |
| Never married                      | 97 (9.7)           | 53 (9.8)          | |
| Living with partner                | 55 (5.5)           | 30 (5.5)          | |
| BMI (kg/m²)                        |                    |         |
| <18.5                              | 25 (2.5)           | 14 (2.6)          | <.000 |
| 18.5–24.9                          | 299 (29.9)         | 83 (15.3)         | |
| 25–29.9                            | 406 (40.6)         | 198 (36.4)        | |
| 30–34.9                            | 202 (20.2)         | 150 (27.6)        | |
| ≥35                                | 69 (6.9)           | 99 (18.2)         | |
| HDL (mmol/L)                       |                    |         |
| ≥0.91                              | 911 (91.0)         | 454 (83.5)        | <.000 |
| <0.91                              | 90 (9.0)           | 90 (16.5)         | |
| Triglyceride (mmol/L)              |                    |         |
| <1.7                               | 394 (71.6)         | 129 (58.4)        | .000 |
| ≥1.7                               | 156 (28.4)         | 92 (41.6)         | |
| LDL (mmol/L)                       |                    |         |
| <3.1                               | 319 (59.6)         | 139 (65.6)        | .133 |
| ≥3.1                               | 216 (40.4)         | 73 (34.4)         | |
| Hypercholesterolemia               |                    |         |
| No                                 | 337 (33.7)         | 169 (31.1)        | .298 |
| Yes                                | 664 (66.3)         | 375 (68.9)        | |
| Diabetes                           |                    |         |
| No                                 | 806 (80.5)         | 378 (69.5)        | <.000 |
| Yes                                | 195 (19.5)         | 166 (30.5)        | |
| Hypertension                       |                    |         |
| No                                 | 470 (47.0)         | 250 (46.0)        | .708 |
| Yes                                | 531 (53.0)         | 294 (54.0)        | |
| Congestive heart failure           |                    |         |
| No                                 | 954 (95.6)         | 511 (94.1)        | .199 |
| Yes                                | 44 (4.4)           | 32 (5.9)          | |
| Coronary heart disease             |                    |         |
| No                                 | 927 (93.4)         | 499 (92.1)        | .348 |
| Yes                                | 66 (6.6)           | 43 (7.9)          | |
| Angina/angina pectoris             |                    |         |
| No                                 | 966 (97.1)         | 516 (95.2)        | .058 |
| Yes                                | 29 (2.9)           | 26 (4.8)          | |
| Stroke                             |                    |         |
| No                                 | 935 (93.5)         | 519 (95.4)        | .127 |
| Yes                                | 65 (6.5)           | 25 (4.6)          | |
| MET score                          |                    |         |
| <12                                | 744 (74.3)         | 448 (82.4)        | .000 |
| ≥12                                | 257 (25.7)         | 96 (17.6)         | |
| Smoking                            |                    |         |
| Never                              | 386 (38.6)         | 235 (43.2)        | .001 |
| Ever but not now                   | 353 (35.3)         | 214 (39.3)        | |
| Yes                                | 260 (26.0)         | 95 (17.5)         | |
| Had ≥12 alcoholic drinks per year  |                    |         |
| Yes                                | 785 (86.2)         | 411 (82.7)        | .082 |
| No                                 | 126 (13.8)         | 86 (17.3)         | |
in cigarettes, named “cotinine,” shares a metabolic disposal pathway with androgens and may competitively inhibit androgen breakdown, resulting in increased testosterone levels in smokers [44]. However, it must be borne in mind that smoking is a well-established cause of CVD [45] and therefore the result of higher testosterone concentrations and lower TD incidence in smokers in our study was not likely to lead to the conclusion that smoking is able to reduce the incidence of CVD. In addition, Wu et al. reported that smoking caused higher total testosterone and sex hormone-binding globulin (SHBG) levels but no difference in free testosterone [46]. Hence, the elevated testosterone level has no apparent biological effects, and is likely due to liver toxicity of some components present in inhaled smoke, thus elevating SHBG. The role of testosterone in the development of coronary artery disease in men is controversial and previous studies suggested that though low testosterone is related to ischemic stroke in men [47] as well as an independent risk factor for 90-day hospital readmission and mortality in heart failure patients [48], testosterone replacement therapies have been reported to increase the risks of cardiovascular events, strokes and non-calcified carotid plaque [27,28,49]. Thus, there may be different physiological effects between endogenous vs. exogenously substituted testosterone.

In the current study, we found no significant effect of serum testosterone levels on the incidence of coronary heart disease or strokes. The different findings might be explained by a different sample size, times of testosterone measurement and CVD classification. However, in the present study, individuals with heart failure or angina/angina pectoris had significantly lower testosterone levels, which is in line with previous studies that bedside others TD may be a marker of heart failure prognosis [50].

The strength of the present study was the population-based sample coupled with the long follow-up period which increased the validity of our results. Since multiple risk factors were evaluated at baseline, we were also able to assess multiple relationships.

On the other hand, a limitation of the study has been that due to the cross-sectional design of the NHANES project we cannot confirm any causality and further longitudinal studies are needed to confirm the correlation between CVD risk factors and serum testosterone levels.

In conclusion, the findings of our study suggest that low serum testosterone concentrations are associated with a BMI ≥35, HDL <0.91, diabetes and a MET score <12 in male participants aged ≥40 years. A low total serum testosterone level is likely to be a marker of risk factors associated with heart failure and angina/angina pectoris.

### Table 4. Multivariable analysis of CVD risk factors and age variables on TD outcome events.

| Age (years) | Wald^2 | OR (95% CI) | p-value |
|-------------|--------|-------------|---------|
| 51–60 vs. ≤50 | 3.684  | 0.75 (0.55–1.01) | .055 |
| 61–70 vs. ≤50 | 10.7282 | 0.59 (0.43–0.81) | .001 |
| >70 vs. ≤50 | 0.0681 | 1.05 (0.75–1.45) | .794 |
| BMI 18.5–24.9 vs. <18.5 | 2.2104 | 0.58 (0.28–1.19) | .137 |
| 25–29.9 vs. <18.5 | 0.0305 | 0.94 (0.47–1.88) | .861 |
| 30–34.9 vs. <18.5 | 0.7554 | 1.37 (0.67–2.79) | .385 |
| ≥35 vs. <18.5 | 5.7969 | 2.51 (1.19–5.32) | .016 |
| HDL <0.91 vs. ≥0.91 | 7.5405 | 1.60 (1.14–2.24) | .006 |
| Diabetes Yes vs. No | 8.4401 | 1.48 (1.14–1.92) | .004 |
| MET scores ≥12 vs. <12 | 6.8717 | 0.69 (0.52–0.91) | .009 |
| Smoking Ever but not now vs. never | 0.0038 | 1.01 (0.78–1.3) | .951 |
| Ever vs. Never | 5.6398 | 0.69 (0.51–0.94) | .018 |

### Table 5. Comparison of total serum testosterone concentration in several CVDs.

| Disease | Total testosterone (ng/dL) | p-value |
|---------|--------------------------|---------|
| Heart failure No | 390.7 (193.7) | .040 |
| Yes | 350.8 (174.0) |
| Coronary heart disease No | 390.6 (194.8) | .173 |
| Yes | 362.1 (168.1) |
| Angina/angina pectoris No | 392.2 (194.0) | .001 |
| Yes | 302.2 (141.3) |
| Stroke No | 389.2 (193.7) | .969 |
| Yes | 381.0 (180.3) |

### Acknowledgements

The authors were solely responsible for the conception and performance of this study and the writing of this manuscript.

### Disclosure statement

CX and BP are employees of MSD during the conduct of the study. CD, ZZ, HL and ASD have no competing financial or other interests to declare.

### Funding

This study was supported by funding from Merck Sharp & Dohme (MSD; Whitehouse Station, NJ, USA). Editorial assistance was provided by Dr. Endler of Shanghai BIOMED Science Technology (Shanghai, China) through funding provided by MSD China.
Authors’ contributions
CD, ZZ, HL, CX, BP and ASD were responsible for the conception and design of the study. CD and ZZ were responsible for acquisition of data. HL, CX, BP and ASD performed the data analysis. HL and ASD drafted the manuscript. All authors participated in interpretation of the findings and approved the final version of the manuscript. All authors confirm that the content has not been published elsewhere and does not overlap with or duplicate their published work.

Data availability statement
All data generated or analyzed during this study are included in this published article.

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