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Prospective study of obesity, hypertension, high cholesterol and risk of Restless Legs Syndrome

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Abstract

Background—Because previous cross-sectional studies suggest an association between metabolic disorders and Restless Legs Syndrome (RLS), we prospectively evaluated whether obesity, hypercholesterolemia, and hypertension were associated with increased risk of RLS.

Methods—Our study consisted of 42728 female participants from the Nurses' Health Study II and 12812 male participants from the Health Professionals Follow-up Study, free of RLS at baseline (2002 for men and 2005 for women), and free of diabetes and arthritis through follow-up (2002–2008 for men and 2005–2009 for women). RLS symptoms were assessed using the International RLS Study Group's standardized questionnaire. We considered RLS symptoms a "case" if the symptoms occurred 5 times/month and met International RLS Study Group criteria.

Results—We found that obesity was associated with an increased risk RLS among both men and women (P-difference for sex >0.5). The pooled multivariate-adjusted odds ratio (OR) for RLS was

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1.57 (95% confidence interval (CI): 1.33–1.85; P-trend <0.0001) for body mass index >30kg/m² vs 23kg/m², and 1.56 (95%CI: 1.29–1.89; P-trend=0.0001) comparing two extreme waist circumference quintiles, adjusting for age, ethnicity, smoking, physical activity, use of antidepressant, and other covariates. A similar significant association was found for high cholesterol; the pooled adjusted OR for total serum cholesterol >240mg/dL vs. <159mg/dL was 1.33 (95%CI: 1.11–1.60; P-trend=0.002). There was no significant association between hypertension and RLS risk (Adjusted OR=0.90, 95% CI: 0.79–1.02).

Conclusions—In this large prospective study we found that obesity and high cholesterol, but not high blood pressure, were significantly associated with an increased risk of developing RLS.

Restless legs syndrome (RLS), also known as Willis-Ekbom Syndrome, is a common sleep disorder that affects an estimated 5–10% of European and American adults (1, 2). Symptoms include uncomfortable sensations of itching or tickling in one's legs and an irresistible urge to move one's legs, which often affect a person's ability to fall or stay asleep. Previous studies have suggested an association between this syndrome and major chronic conditions such as cardiovascular disease, depression, disability, Parkinson's disease, and erectile dysfunction (3–10). While several studies have explored potential mechanisms behind RLS, we have no consensus about its etiology, and RLS continues to be a growing issue with limited treatment options (11–13).

Previous cross-sectional studies suggest an association between obesity, hypercholesterolemia, hypertension and RLS (1, 11, 14–22). For example, in our previous cross-sectional analysis based on two ongoing US studies (n=85546), the Nurses' Health Study II (NHSII) and the Health Professionals Follow-up Study (HPFS), we found that overall and abdominal obesity was associated with a 40%–70% higher likelihood of having RLS (23). Two recently published large-scale studies of RLS in men and women found that many vascular risk factors, such as physical inactivity, smoking, high serum cholesterol, and diabetes, are associated with a higher risk of RLS. (24, 25) Researchers have hypothesized that inadequate dopamine metabolism in the brain, sympathetic hyperactivity, and chronic inflammation could explain the associations between these metabolic disorders and RLS (6, 11, 23, 26). However, because the majority of previous relevant studies were cross-sectional (11, 14, 15, 22–24, 27), the temporal relationship between these metabolic disorders and RLS cannot be inferred. There are only two published prospective studies on RLS, and they generated inconsistent results regarding the associations between baseline metabolic symptoms and RLS risk. These studies were limited by their small sample size (incident RLS case number <300)(28, 29). To address this knowledge gap, we prospectively examined whether individuals with obesity, hypercholesterolemia, or hypertension had an increased risk of developing RLS using new data from the NHS II and the HPFS.

MATERIALS AND METHODS

Study Population

NHS II is a prospective cohort of 116,686 American, female registered nurses who were 25 to 42 years old during cohort enrollment in 1989. HPFS is a prospective cohort of 51,529 American, male health professionals who were 40 to 75 years old during cohort enrollment

in 1986. NHS II and HPFS participants filled out biennial questionnaires about their health behaviors and new disease diagnoses. Our final study population consisted of 42,728 women (mean age 49 years old) and 12,812 men (mean age 65 years old) who were free of RLS at our analysis baseline (2002 for men and 2005 for women), and free of diabetes, arthritis, and pregnancy (women only) at our analysis baseline and through follow-up, since symptoms of these conditions can mimic those of RLS. Details of participant inclusion criteria are outlined in Supplementary Figure-1. The institutional review board at Brigham and Women's Hospital and Harvard School of Public Health approved this study and the completion of the questionnaires by participants was considered informed consent.

Assessment of RLS

We defined cases of RLS based on the International Restless Study Group criteria and included questions on these criteria in the 2005 and 2009 NHS II questionnaires (completed by 97,642 women) and in the 2002 and 2008 HPFS questionnaires (completed by 37,431 men)(30). The questions are included in the attached supplementary section. Participants who answered "Yes" to all three questions, and who reported symptoms of RLS at least 5 times a month were considered cases of RLS (23). This set of three questions was used in a previous study of 369 Germans aged 65–83 years. The sensitivity, specificity and kappa statistic of the three-question set compared to physician diagnoses was 87.5%, 96%, and 0.67 (31, 32).

Assessment of obesity, blood pressure, and serum cholesterol

Information on weight, height, waist and hip circumference, perceived body image, blood pressure, and serum cholesterol level was collected via biennial self-administered NHS II and HPFS questionnaires. NHS II and HPFS self-reported weight, waist circumference, and hypertension have been previously validated,(33, 34) as detailed in supplementary text.

We used body mass index (BMI, kg/m^2) as a measure of overall obesity and waist circumference as a measure of abdominal obesity. To test the robustness of our results, we also examined other obesity parameters, including BMI in early adulthood (at 18 years old in NHS II and at 21 years old in HPFS), weight change since study baseline in quintiles, and waist-to-hip ratio quintiles.

We calculated the analysis baseline BMI in kilograms per meter squared using cohort baseline height (1986 for men and 1989 for women) and updated weight (2002 for men and 2005 for women). Participants were considered obese if their BMI was $\geq 30\text{kg/m}^2$. Young adult BMI was calculated using recalled weight (at age 21 for men, and at age 18 for women) and height from the cohort baseline questionnaire (1986 for men and 1989 for women). We calculated weight change by subtracting updated weight (2002 for men and 2005 for women) from the cohort baseline weight (1986 for men and 1989 for women).

Waist and hip circumference were collected in 1996 for men and 2005 for women via the HPFS and NHS questionnaires. Participants were asked to measure their waist circumference at their navel, and to measure their hip circumference around the largest circumference below their navel including the buttocks. Furthermore, they were asked to take the measurements standing up and to remove bulky clothing (33, 35). Waist-to-hip

ratios were calculated by dividing the waist circumference measurements by hip circumferences.

Information on physician-diagnosed hypertension was collected at the cohort baseline (1986 for men and 1989 for women) and was updated in both cohorts every two years. We also assessed blood pressure (in 2000 for men and 2005 for women) by asking participants to report their diastolic and systolic blood pressure.

We collected data on physician-diagnosed high cholesterol via the 2000 HPFS questionnaire for men and the 2005 NHS questionnaire for women. Participants were also asked to indicate their blood serum cholesterol level by choosing a category of mg/dL (in 2000 for men and in 2005 for women). A validation study found that serum levels for a sub-sample of 1,591 women and 1,790 men of HPFS and NHS I were correlated to self-reported serum cholesterol levels (Spearman correlation coefficients of 0.56 for women and 0.51 for men) (36). In the HPFS, but not in the NHS II, we also collected information on physician-diagnosed high triglyceride levels biennially.

Ascertainment of covariates

We collected socio-demographic, health behavior, and clinical information from the biennial NHS and HPFS questionnaires, including age, ethnicity, physical activity, caffeine intake, alcohol intake, smoking status, menopause status (women only), antidepressant use, iron supplement use, sleep duration (hours), snoring frequency, history of myocardial infarction, stroke history, and anxiety. We measured anxiety using the Crown-Crisp phobia index (37).

Statistical analysis

We performed all statistical analyses using SAS version 9.1 (SAS Institute, Inc, Cary, NC) for the NHS II and HPFS cohorts separately, and then used STATA version 9 (StataCorp LP, College Station, TX) to calculate the pooled estimates. We estimated the odds ratios (ORs) and associated 95% confidence intervals (CIs) using logistic regression models. We modeled our outcome as a binary variable, incident RLS (yes/no). To allow for flexibility in the associations, we modeled the exposures categorically. We modeled BMI and young adult BMI categorically, with five different categories in kg/m²: <23.0, 23.0–24.9, 25.0–26.9, 27.0–29.9 and 30.0. We created quintiles of waist circumference (cm), waist-to-hip ratio, and weight change (1986–2002 for men and 1989–2005 for women) and included them in models as categorical variables. We also created five categories of serum blood cholesterol in mg/dL: <159, 160–179, 180–199, 200–239, and 240. We also created five categories for blood pressure in mmHg: SBP: <114, 115–134, 135–144, 145–154, 155 and DBP: <65, 65–74, 75–84, 85–89, and 90. We collapsed the largest categories of “body image at age 20” answer choices into six categories because of sparse data.

We created two models for each exposure of interest; the first model adjusted for age(y). In the second model, we further adjusted for potential confounders, including ethnicity, smoking, physical activity, alcohol intake, antidepressant use, Crown-Crisp phobic anxiety index, history of myocardial infarction, stroke, and menopause status (women only). We pooled the ORs from the two cohorts using a fixed effects model because a Q test did not suggest significant heterogeneity (i.e., difference between genders) between the two cohorts

($p>0.05$). Linear trends across categories of metabolic disorders and RLS were evaluated by assigning each participant the median value of each category to create a continuous variable.

We evaluated for effect modification by age, smoking, and alcohol by testing for the significance of interaction terms for continuous age, smoking status (ever/never), alcohol (continuous intake in grams), obesity (yes/no), high waist circumference (yes/no), hypertension (yes/no), and hypercholesterolemia (yes/no). We also performed a sensitivity analysis by re-running our models in a dataset that included participants with diabetes and arthritis, and again in a dataset that excluded participants with previous stroke or MI.

RESULTS

Incident rates of RLS were 5.4 per 1000 person-years in men and 6.6 per 1000-person-years in women. The age and sex-specific rates were reported in figure 1. Obese participants were more likely to exercise less, drink less alcohol, to take antidepressants, have a history of myocardial infarction, and have a history of stroke (Table 1). We found similar patterns for hypertension and hypercholesterolemia.

Both overall obesity (as assessed by BMI) and abdominal obesity (as assessed by waist circumference) were associated with a higher risk of developing RLS (P -trend <0.0001 ; P -difference for sex >0.5), after adjusting for age, ethnicity, and potential confounders (Table 2). The significant associations between BMI, waist circumference and risk of RLS remained even after we included both parameters in the same model (data not shown). We found similar but non-significant trends for the other measures of obesity; young adult BMI (Table 2), weight change (Table 2), and waist-to-hip ratio (data not shown).

Higher levels of total serum cholesterol were significantly associated with development of RLS (P -trend $=0.002$; P -difference for genders $=0.84$). High triglyceride levels were also significantly associated with developing RLS; for men the adjusted OR was 1.45 (95%CI: 1.18, 1.77; P -trend $=0.0004$) (triglyceride levels were unavailable for women). The association between high cholesterol and RLS risk did not change materially after we excluded participants who reported use of cholesterol lowering drugs (data not shown), suggesting that the observed association is not likely caused by side effects of these medicines.

We did not find a significant association between hypertension and risk of RLS (Pooled OR $=0.90$; 95% CI: 0.79,1.02; P -difference for sex $=0.64$). Higher levels of blood pressure were also not significantly associated with developing RLS (P -difference for sex >0.35) (Table 3)

None of the interaction terms (age, smoking, nor alcohol consumption) were found to be significant in the model (two-sided $P>0.05$ for all). Furthermore, results did not materially differ after including participants with diabetes and arthritis (see supplementary table), or after excluding those with a history of stroke or MI. Obesity, and high cholesterol, but not hypertension, were found to be significantly associated with RLS in all sensitivity analyses (data not shown). Further adjusting for snoring frequency and sleep duration did not materially change the observed association between obesity and high cholesterol and RLS

risk: the adjusted pooled OR was 1.53 (95% CI 1.28, 1.83; P -trend <0.0001) for BMI $\geq 30\text{kg/m}^2$ vs $<23\text{kg/m}^2$, and 1.32 (95% CI: 1.09, 1.60; P -trend=0.005) for total serum cholesterol $\geq 240\text{mg/dL}$ vs $<159\text{mg/dL}$.

DISCUSSION

In this large-scale prospective study, we found that obesity and high cholesterol were significantly associated with an increased risk of developing RLS. This association was independent of age, ethnicity, smoking status, physical activity, alcohol intake, antidepressant use, phobic anxiety score, history of MI, history of stroke, and menopause status (if a women). These results indicate that obesity and hypercholesterolemia are possible risk factors for RLS. The latest the National Health and Nutrition Examination Survey reports that obesity affects 33% of men and 35% of women while 16.3% of US adults have diagnosed high cholesterol; because obesity and hypercholesterolemia are modifiable public health problems, and affect many US adults, it is vital to understand associated diseases (38, 39). Obesity is quickly becoming the most common preventable cause of disability and disease in America and throughout the developed world (40). The present study adds to the growing literature on the relationship between metabolic disorders and RLS, and is an important addition since most of the previous literature consists of cross-sectional studies (1, 11, 15, 17, 18, 20–22).

There is no consensus on the bio-mechanisms causing RLS. Animal studies have shown an association between reduced dopamine metabolism in the central nervous system and obesity, which could be an underlying mechanisms for the observed association between obesity and RLS (11, 12). The relationship between cardiovascular disease, cardiovascular risk factors, and RLS has been reviewed recently (14, 41). Findings indicate that the potential underlying mechanisms could include sympathetic hyperactivity, cardiac vagal modulations, and sleep disturbances. Furthermore, metabolic symptoms generally co-occur with HPA-axis activation and inflammation, which have been hypothesized to have an important role in RLS pathogenesis.(13, 42)

We did not find a significant association between hypertension and risk of developing RLS. A recently published prospective study had similar findings; the prevalences of hypertension at baseline were similar for individuals with and without incident RLS during 4 years of follow-up (22% vs. 25%; P -difference =0.83)(28). In another prospective study including two cohorts, hypertension at baseline was significantly associated with a higher risk of RLS in one cohort (OR=1.41; P =0.04), but not in the other (OR=1.09; P =0.76).(29) In contrast, 10 out of 17 cross-sectional studies reported a positive association between hypertension and RLS (11). The discrepancy between cross-sectional and prospective studies suggests that RLS could be a risk factor for hypertension risk, not vice versa. This hypothesis should be tested in future prospective studies. Another possible explanation is that many common anti-hypertensive medications (e.g., certain alpha-2 agonists and beta-blockers) could mediate RLS symptoms (11). However in our sensitivity analysis our results did not markedly change when we excluded those on anti-hypertensive medication (data not shown).

Because the relationship between heart disease and obesity has been reported in many previous studies, we performed a sensitivity analysis in which we excluded participants with a history of MI or stroke; our results did not materially change. To minimize the possibility that the associations found in our results were due to diabetes or arthritis, common mimics of RLS, we excluded participants with diabetes and arthritis in our primary analysis. However, there is a chance (especially among the obese participants) that there are undiagnosed diabetics still in the population; if some do exist, this would only modestly affect our results since our cohort consist of highly educated health care professionals, and we collected information on diagnosis of diabetes repeatedly over the follow-up period (every two years).

This paper has several strengths; the study population was large and came from well-established cohorts, we utilized multiple measures of metabolic disorders, and the trends were consistent over most measures. This paper also has some limitations. For instance, we used self-reported data for our risk factors and our outcome of interest; if participants misreported their weight, waist circumference or any other risk factor information then we risk misclassifying participants. However, as mentioned earlier, previous validation studies have shown a high correlation of self-reported measures in the NHS and HPFS cohorts with actual measurements (33–36, 43). Therefore, it is unlikely that misclassification because of misreported data significantly altered our results. While previous studies have found that self-reported RLS data and doctor diagnoses are highly correlated, (31, 32) if the outcome was not measured correctly, this could cause non-differential misclassification and could attenuate the true association between the metabolic syndromes and RLS risk. We cannot exclude the possibility of misdiagnosis of RLS, because of “RLS mimics.” Because nerve damage caused by diabetes, and pain caused by arthritis cause similar symptoms to RLS, we excluded those with diagnosed diabetes and arthritis (the most common “mimics”) from the study population. However, we did not collect information on other common RLS mimics, including positional discomfort and leg cramps in our main HPFS/NHS II questionnaires, which may lead to misclassification of RLS assessment, and potentially attenuated the association between our exposures of interest and RLS risk. It is also worth noting that although we used frequency of RLS as a surrogate of disease severity, as recommended by the international RLS study group, (9) the frequency criteria used is arbitrary for RLS. Our study was also limited by lack of data on iron deficiency in both cohorts, which previous studies have shown to be associated with RLS. Information on renal dysfunction was only collected in the HPFS; further adjusting for history of renal dysfunction did not materially change the observed results (data not shown). Another possible limitation is the age difference between our pooled cohorts; the mean age of women was 49 years old, while the men’s mean age was 65 years old, and RLS and other metabolic syndrome risk increase with age. However, we observed similar association between obesity and high blood cholesterol and increased RLS in both NHS II and HPFS, and the interaction terms of age and these metabolic symptoms were found to be insignificant in our models.

The present prospective study provides more insight into the temporal relationship between metabolic disorders, and RLS risk. Obesity and high cholesterol, but not high blood pressure, were significantly associated with a higher risk of developing RLS. Evidently,

more work needs to be done to explore the connections between these metabolic disorders and RLS to improve our understanding regarding the etiology of RLS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Incident rate (per 1000 person year) of restless legs syndrome by age in men (Panel a) and women (Panel b).

Characteristics According to Obesity, And Other Metabolic Disorders at Study Baseline (NHS II in 2005 and HPFS in 2002)

Table 1

	Study Baseline Body Mass Index (kg/m ²) ^a				
	<23	23–24.9	25–26.9	27–29.9	30
WOMEN:^a					
N	13550	9627	5892	5885	7774
Age (yrs)	49.7	49.8	49.8	49.9	49.8
White, %	95.1	95.0	95.0	94.6	94.8
BMI at age 18 (kg/m ²) ^b	19.6	20.5	20.8	21.5	23.3
Physical Activity (mets/wk)	31.2	26.9	24.1	21.5	15.4
Caffeine Intake (mg/day)	153.6	161.7	166.6	162.4	159.8
Alcohol Intake (g/day)	6.87	6.51	6.31	5.59	4.05
Past Smoker %	24.2	25.8	26.6	25.8	26.5
Current Smoker %	6.50	6.60	6.60	7.50	6.60
Anxiety Scale Score	2.09	2.12	2.16	2.16	2.27
Post Menopausal %	51.8	49.7	49.6	49.0	47.6
Taking Antidepressants %	12.2	14.2	16.2	17.1	20.4
Taking Iron specific supplement %	2.20	2.10	2.10	2.10	2.20
High Blood Pressure %	10.0	15.0	17.9	23.6	36.2
High Cholesterol %	19.4	25.0	29.9	34.8	38.3
High Waist Circumference ^c %	27.0	18.5	38.7	69.5	94.0
MI in or prior to 2005% ^e	0.40	0.50	0.50	0.50	0.90
Stroke in or prior to 2005 %	0.50	0.70	0.50	0.70	0.80
MEN:^a					
N	2101	3394	3338	2724	1255
Age (yrs)	65.8	65.8	65.8	65.7	65.7
White %	94.5	96.7	96.9	96.7	97.2
BMI at age 21 (kg/m ²) ^b	20.5	21.3	22.1	22.9	24.0
Physical Activity (mets/wk)	44.0	41.6	39.3	35.1	28.6

	Study Baseline Body Mass Index (kg/m ²) ^a				
	<23	23–24.9	25–26.9	27–29.9	30
Caffeine Intake (mg/day)	122.9	135.7	149.0	152.9	155.7
Alcohol Intake (gm/day)	12.4	13.2	13.6	13.7	12.6
Past Smoker %	40.4	47.8	49.5	52.9	57.5
Current Smoker %	3.90	3.00	3.20	3.00	2.70
Taking Antidepressants %	3.50	3.50	3.90	4.30	6.00
Taking Iron specific supplement %	1.50	1.50	0.80	1.20	1.30
High Blood Pressure %	31.2	37.8	41.9	49.6	61.2
High Cholesterol %	46.0	54.0	55.8	58.6	62.5
High Triglycerides % ^d	24.0	31.0	35.7	41.4	45.9
High Waist Circumference % ^c	2.10	5.50	16.5	41.7	80.2
MI in or prior to 2002% ^e	2.70	3.20	2.50	3.60	3.90
Stroke in or prior to 2002 %	0.80	0.80	1.00	1.30	1.40

^aBaseline for HPFS is 2002, baseline for NHS2 is 2005

^bBody Mass Index

^cHigh waist circumference defined as 102cm for men and 88cm for women; measured in 1996 for men and 2005 for women

^dData not available for NHS II

^eMyocardial infarction

^fSleep duration and snoring measured in 2000 for men and 2001 for women

Adjusted Odds Ratios (ORs) and 95% Confidence Intervals (CIs) for RLS by Different Measures of Obesity at Study baseline (NHSII in 2005 and HPFS in 2002)

Table 2

Body Mass Index (kg/m ²) ^a	<23	23–24.9	25–26.9	27–29.9	30+	P for Trend
WOMEN						
Case # (%)	398 (2.35)	393 (3.07)	246 (3.00)	316 (3.61)	659 (4.43)	
Age Adjusted OR	1 (REF)	1.26 (1.06, 1.49)	1.17 (0.95, 1.44)	1.73 (1.44, 2.09)	1.78 (1.50, 2.11)	<0.0001
Multivariate adjusted OR ^b	1 (REF)	1.22 (1.02, 1.46)	1.10 (0.89, 1.35)	1.62 (1.34, 1.95)	1.59 (1.33, 1.91)	<0.0001
MEN						
Case # (%)	56 (2.67)	88 (2.59)	118 (3.54)	105 (3.85)	47 (3.75)	
Age Adjusted OR	1 (REF)	0.99 (0.71, 1.40)	1.39 (1.00, 1.92)	1.56 (1.12, 2.17)	1.54 (1.03, 2.29)	0.0008
Multivariate Adjusted OR ^b	1 (REF)	1.00 (0.71, 1.41)	1.38 (1.00, 1.92)	1.52 (1.08, 2.13)	1.44 (0.95, 2.16)	0.009
Pooled OR	1 (REF)	1.17 (1.00, 1.37)	1.19 (0.96, 1.48)	1.59 (1.35, 1.88)	1.57 (1.33, 1.85)	<0.0001
Young Adult Body Mass Index (kg/m²)^c						
	<23	23–24.9	25–26.9	27–29.9	30+	P for Trend
WOMEN						
Case # (%)	1530 (3.13)	231 (3.39)	90 (3.38)	96 (5.12)	65 (4.95)	
Age Adjusted OR	1 (REF)	1.01 (0.83, 1.24)	0.99 (0.72, 1.36)	1.54 (1.10, 2.14)	1.61 (1.06, 2.43)	0.01
Multivariate Adjusted OR ^b	1 (REF)	0.99 (0.81, 1.20)	0.94 (0.68, 1.29)	1.45 (1.04, 2.02)	1.48 (0.97, 2.24)	0.027
MEN						
Case # (%)	199 (3.04)	137 (3.49)	62 (3.73)	13 (2.32)	3 (2.65)	
Age Adjusted OR	1 (REF)	1.18 (0.95, 1.47)	1.27 (0.95, 1.71)	0.79 (0.45, 1.39)	0.92 (0.29, 2.91)	0.43
Multivariate Adjusted OR ^b	1 (REF)	1.19 (0.95, 1.49)	1.29 (0.96, 1.72)	0.77 (0.44, 1.37)	0.86 (0.27, 2.74)	0.54
Pooled OR	1 (REF)	1.08 (0.90, 1.29)	1.11 (0.81, 1.51)	1.11 (0.60, 2.03)	1.39 (0.94, 2.06)	0.015
Weight Change in Quintiles (lbs)^d						
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	P for Trend
WOMEN						
Median (lbs)	-2	7	15	25	42	
Case # (%)	368 (3.03)	270 (2.52)	370 (2.94)	394 (3.41)	502 (4.26)	
Age Adjusted OR	1 (REF)	0.94 (0.76, 1.16)	1.08 (0.88, 1.33)	1.25 (1.02, 1.52)	1.59 (1.32, 1.92)	<0.0001
Multivariate Adjusted OR ^b	1 (REF)	0.95 (0.76, 1.17)	1.05 (0.86, 1.29)	1.17 (0.96, 1.43)	1.40 (1.15, 1.70)	<0.0001

Weight Change in Quintiles (lbs) ^d	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	P for Trend
MEN						
Median (lbs)	-7	1	6	13	25	
Case # (%)	94 (3.88)	94 (3.48)	64 (2.80)	75 (2.67)	87 (3.35)	
Age Adjusted OR	1 (REF)	0.93 (0.69, 1.24)	0.76 (0.55, 1.05)	0.74 (0.54, 1.01)	0.95 (0.70, 1.29)	0.55
Multivariate Adjusted OR ^b	1 (REF)	0.94 (0.70, 1.26)	0.76 (0.55, 1.06)	0.74 (0.54, 1.01)	0.91 (0.67, 1.25)	0.54
Pooled OR	1 (REF)	0.94 (0.79, 1.12)	0.92 (0.68, 1.26)	0.94 (0.60, 1.49)	1.15 (0.76, 1.74)	0.67
WOMEN						
Median (cm)	68.58	76.20	81.28	88.90	101.60	
Case # (%)	262 (2.37)	223 (2.76)	315 (2.72)	430 (3.94)	506 (4.58)	
Age Adjusted OR	1 (REF)	0.96 (0.77, 1.20)	1.10 (0.86, 1.39)	1.39 (1.12, 1.72)	1.75 (1.42, 2.17)	<0.0001
Multivariate Adjusted OR ^b	1 (REF)	0.93 (0.75, 1.17)	1.03 (0.81, 1.31)	1.27 (1.02, 1.58)	1.51 (1.20, 1.88)	<0.0001
MEN						
Median (cm)	85.73	91.44	95.25	99.70	101.95	
Case # (%)	51 (2.24)	66 (2.67)	82 (3.88)	77 (3.23)	91 (4.00)	
Age Adjusted OR	1 (REF)	1.17 (0.81, 1.70)	1.72 (1.20, 2.45)	1.41 (0.99, 2.02)	1.77 (1.25, 2.51)	0.001
Multivariate Adjusted OR ^b	1 (REF)	1.18 (0.81, 1.71)	1.74 (1.21, 2.48)	1.40 (0.97, 2.02)	1.71 (1.19, 2.44)	0.002
Pooled OR	1 (REF)	1.00 (0.81, 1.23)	1.31 (0.79, 2.19)	1.30 (1.08, 1.57)	1.56 (1.29, 1.89)	0.0001

^a Baseline body mass index calculated using self-reported height (1986 for men, 1989 for women) and updated weight (2002 for men and 2005 for women)

^b Multivariate Models adjusted for categorical serum cholesterol level (mg/dL), high blood pressure (Y/N), age (yrs), race (white/other), physical activity (quintile), caffeine intake (quintile), alcohol intake (gm/day), smoking status (never, or current smoker: cigarettes/d, 1-14 or 15), the Crown-Crisp anxiety score, antidepressant medication (Y/N), use of iron specific supplement (Y/N), presence of myocardial infarction, and stroke at baseline (each of them, yes/no), and menopausal status (Y/N, for women only).

^c Assessed in cohort baseline questionnaire (1986 for men and 1989 for women)

^d Weight change calculated from 1986-2002 for men and 1989-2005 for women

^e Measured in 1996 for men and in 2005 for women

Adjusted Odds Ratios (ORs) and 95% Confidence Intervals (CIs) for RLS by Blood Pressure And Serum Cholesterol at Study Baseline (NHSII in 2005 and HPFS in 2002)

Table 3

Total Serum Cholesterol (mg/dL)	<159	160–179	180–199	200–239	240+	P for Trend
WOMEN						
Case # (%)	336 (2.77)	540 (3.06)	290 (3.27)	145 (3.87)	489 (4.11)	
Age Adjusted OR	1 (REF)	1.24 (1.03, 1.48)	1.44 (1.17, 1.77)	1.51 (1.15, 1.97)	1.55 (1.26, 1.90)	<0.0001
Multivariate Adjusted OR ^a	1 (REF)	1.20 (1.00, 1.43)	1.35 (1.09, 1.66)	1.38 (1.05, 1.80)	1.35 (1.09, 1.66)	0.003
MEN						
Case # (%)	35 (2.86)	34 (3.01)	57 (3.55)	75 (3.43)	155 (3.77)	
Age Adjusted OR	1 (REF)	1.07 (0.66, 1.72)	1.26 (0.82, 1.93)	1.22 (0.81, 1.84)	1.31 (0.91, 1.91)	0.13
Multivariate Adjusted OR ^a	1 (REF)	1.09 (0.67, 1.76)	1.27 (0.82, 1.95)	1.23 (0.82, 1.86)	1.29 (0.88, 1.88)	0.48
Pooled OR	1 (REF)	1.18 (1.00, 1.40)	1.33 (1.10, 1.60)	1.33 (1.06, 1.67)	1.33 (1.11, 1.60)	0.002
Systolic Blood Pressure (mmHg)						
	<114	115–134	135–144	145–154	155+	P for Trend
WOMEN						
Case # (%)	549 (2.71)	502 (3.18)	246 (3.28)	72 (3.44)	630 (4.09)	
Age Adjusted OR	1 (REF)	1.19 (1.03, 1.39)	1.23 (1.01, 1.49)	1.16 (0.82, 1.63)	1.21 (1.02, 1.43)	0.007
Multivariate Adjusted OR ^b	1 (REF)	1.07 (0.92, 1.24)	1.00 (0.82, 1.22)	0.91 (0.64, 1.29)	0.93 (0.78, 1.12)	0.46
MEN						
Case # (%)	46 (3.40)	95 (3.06)	80 (3.56)	26 (2.38)	137 (3.44)	
Age Adjusted OR	1 (REF)	0.89 (0.62, 1.27)	1.00 (0.69, 1.45)	0.64 (0.39, 1.04)	0.93 (0.66, 1.31)	0.6
Multivariate Adjusted OR ^b	1 (REF)	0.84 (0.59, 1.21)	0.91 (0.62, 1.32)	0.57 (0.35, 0.94)	0.78 (0.55, 1.12)	0.39
Pooled OR	1 (REF)	1.00 (0.82, 1.23)	0.98 (0.82, 1.17)	0.75 (0.48, 1.17)	0.90 (0.77, 1.06)	0.34
Diastolic Blood Pressure (mmHg)						
	<65	65–74	75–84	85–89	90+	P for Trend
WOMEN						
Case # (%)	171 (2.56)	641 (2.93)	473 (3.30)	84 (3.40)	630 (4.05)	
Age Adjusted OR	1 (REF)	1.14 (0.92, 1.40)	1.37 (1.10, 1.69)	1.27 (0.90, 1.79)	1.28 (1.02, 1.60)	0.01
Multivariate Adjusted OR ^b	1 (REF)	1.03 (0.84, 1.27)	1.13 (0.91, 1.41)	0.96 (0.68, 1.37)	0.96 (0.75, 1.21)	0.66
MEN						

Diastolic Blood Pressure (mmHg)	<65	65–74	75–84	85–89	90+	P for Trend
Case # (%)	7 (2.82)	76 (3.41)	127 (3.20)	35 (2.94)	132 (3.33)	
Age Adjusted OR	1 (REF)	1.20 (0.55, 2.63)	1.14 (0.53, 2.47)	1.05 (0.46, 2.38)	1.14 (0.53, 2.46)	0.94
Multivariate Adjusted OR ^b	1 (REF)	1.12 (0.51, 2.46)	1.01 (0.47, 2.20)	0.88 (0.38, 2.02)	0.92 (0.42, 2.00)	0.39
Pooled OR	1 (REF)	1.04 (0.85, 1.27)	1.12 (0.91, 1.39)	0.95 (0.69, 1.31)	0.95 (0.76, 1.20)	0.56

^aMultivariate Serum Cholesterol Model adjusted for categorical BMI (kg/m²), high blood pressure (Y/N), age (yrs), race (white/other), physical activity (quintile), caffeine intake (quintile), alcohol intake (gm/day), smoking status (never, or current smoker: cigarettes/d, 1–14 or 15), the Crown-Crisp anxiety score, antidepressant medication (Y/N), use of iron specific supplement (Y/N), presence of myocardial infarction, and stroke at baseline (each of them, yes/no), and menopausal status (Y/N, for women only).

^bMultivariate Blood Pressure Models adjusted for categorical BMI (kg/m²), categorical serum cholesterol (mg/dL), age (yrs), race (white/other), physical activity (quintile), caffeine intake (quintile), alcohol intake (gm/day), smoking status (never, or current smoker: cigarettes/d, 1–14 or 15), the Crown-Crisp anxiety score, antidepressant medication (Y/N), use of iron specific supplement (Y/N), presence of myocardial infarction, and stroke at baseline (each of them, yes/no), and menopausal status (Y/N, for women only).