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A prospective study of obesity and incidence and progression of lower urinary tract symptoms

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Abstract

Purpose—We prospectively evaluated the association between adiposity and risk of lower urinary tract symptoms (LUTS) incidence and progression in the Health Professionals Follow-up Study (HPFS).

Materials and Methods—Participants reported their current height and weight and their weight at age 21 at baseline, a year later their waist and hip circumferences, and then every two years their weight. Periodically, participants completed the International Prostate Symptom Score (IPSS) survey and reported surgery or medication use for LUTS. We used Cox proportional hazards regression to estimate the multivariable-adjusted association between adiposity and LUTS incidence and progression. The incidence analytic cohort (n=18,055) were men without LUTS at baseline. Men entered the progression analytic cohort (n=6,461) when they first experienced LUTS.

Results—Risk of LUTS (n=4,088) increased with increasing body mass index (BMI ≥35 vs 23-<25 kg/m^2: HR=1.61; 95% CI 1.31–1.99, *p-trend*<0.0001), waist circumference (>42 vs ≤33 in: HR=1.39, 95% CI 1.19–1.63, *p-trend*<0.0001), and weight gain from age 21 (≥50 lbs vs stable weight: HR=1.31, 95% CI 1.17–1.46, *p-trend*=<0.0001). Risk of LUTS progression (n=1,691) increased with BMI (≥35 vs 23-<25 kg/m^2: HR=1.44, 95% CI 1.04–2.00, *p-trend*=<0.0001), weight gain from 21 years of age (≥50 lbs vs stable weight: HR=1.35, 95% CI 1.14–1.60, *p-trend*=<0.0001), and waist circumference (>42 vs ≤33 in: HR=1.32, 95% CI 0.95–1.85, *p-trend*=0.005).

Conclusions—Men with higher total and abdominal adiposity or who gained weight were more likely to develop LUTS or experience progressive LUTS. Our findings support that obesity may be an important target for LUTS prevention and intervention.

Keywords

Lower urinary tract symptoms; obesity; men

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Introduction

Lower urinary tract symptoms (LUTS), often secondary to benign prostatic hyperplasia (BPH), are a health concern for older men. As many as 31% of men 50 and older may suffer from moderate to severe LUTS [1]. Effective treatments for LUTS, including medication use and surgery, are available. However, these treatments are expensive and contribute to the growing cost of healthcare in the United States [2]. Lifestyle factors play an important role in the etiology of LUTS [3]; therefore, one cost-effective strategy for addressing LUTS may be to intervene on modifiable lifestyle factors before treatment becomes necessary. The 2008 National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Prostate Strategic Plan stated, “The search for and study of primary prevention for benign prostate disease, such as male LUTS, is an important priority for the future.”, and indicated that a research priority was to, “Develop specific clinical trial concepts, including…behavioral and lifestyle interventions…” [4]. One highly modifiable lifestyle factor that is ripe for intervention is obesity.

Few studies have prospectively examined the obesity and LUTS incidence or progression. Three prospective studies found that higher body mass index (BMI) was associated with increased incidence of LUTS [5–7], and one also found that a higher waist to hip ratio was similarly associated with an increased risk of LUTS [5]. Another prospective study recently reported that higher BMI was associated with an increase of ≥3 points in LUTS symptom score [8]. Two other prospective studies found no association between BMI and risk of LUTS, but did not adjust for any possible confounding factors, including age [9, 10]. Only one study has prospectively examined obesity and progression of symptomatic LUTS to a worsened state, finding no association [11]. These previous studies were all relatively small (largest n=7,318) and had relatively short follow-up times (longest = 7 years). We undertook a prospective analysis examining LUTS incidence and progression in a large cohort of US men followed for over 16 years.

Methods

Study Design and Population

We conducted a prospective analysis in the Health Professionals Follow-up Study (HPFS), a cohort of 51,529 US men aged 40–75 years at baseline in 1986. At baseline, participants completed a mailed questionnaire that included information including birth date, race, medical, lifestyle, and diet information. Exposure and outcome information has been updated every two years, and dietary information has been updated every four years. Deaths are reported by family members or the postal system, or are discovered by searching the National Death Index. As of 2008, 94% of eligible men responded to the biennial survey. This study was approved by Institutional Review Boards at the Harvard School of Public Health and the Johns Hopkins Bloomberg School of Public Health; all participants provided written informed consent.

Assessment of Obesity

In 1986, participants were asked to report their current height and weight and their weight at age 21, and their current weight on every questionnaire thereafter. A supplemental questionnaire was mailed in 1987 to obtain additional exposure information, including waist and hip circumference measurements. Participants were asked to use a tape measure included in the mailing to measure their waist at the umbilicus and their hips at the largest circumference between waist and thighs. Waist and hip circumference were collected again in the same manner on the 1996 questionnaire. We modeled adiposity in several different ways (categorizations are shown in Tables 2–3): 1) time-dependent current BMI, 2) time-dependent 2-year lagged BMI (i.e. the BMI measurement from 2 years prior was applied to each time period), 3) time-dependent cumulative average BMI, 4) BMI at age 21, 5) time-dependent waist circumference, 5) time-dependent hip circumference, and 6) time-dependent waist to hip ratio. We further examined the association between time-dependent current weight change since age 21 and risk of LUTS. Lagged BMI and BMI at age 21 were examined to address whether there might be a latency or induction period between BMI and risk of LUTS. We categorized current, 2-year lagged, and cumulative average BMI using the World Health Organization classification with additional cutpoints with slight modifications to accommodate the distribution of BMI in our cohort.

Assessment of LUTS Incidence and Progression

The assessment of LUTS in the HPFS is discussed in detail elsewhere[12].Every two years since 1988, HPFS participants were asked, “have you had any of the following professionally diagnosed conditions?”, one of which was “Prostatic enlargement, surgically treated (e.g. TURP)”. Participants who responded “yes” to this question were defined as having had surgery for LUTS. On each questionnaire, participants were asked to report medications that they took regularly (2+/week) during the previous 2-year period by responding “yes” or “no” to a provided a list of classes of medications. Beginning in 1996 this list included “Finasteride (Proscar, Propecia)” and “Alpha-blocker for BPH (i.e. Hytrin, Minipress)”. Men who responded “yes” to either of these questions were defined as having used medications to treat LUTS. The American Urological Association Symptom Index [13], now called the International Prostate Symptom Score (IPSS), was assessed in 1992, 1994, 1998, 2000, and 2008 as described previously [14]; the possible number of points ranged from 0 to 35.

We defined two separate analytic cohorts for incidence and progression. Men diagnosed with prostate cancer were excluded. The incidence analytic cohort consisted of 18,055 men who returned the 1992 survey, did not have a cancer diagnosis in 1992 or earlier, returned a valid food frequency questionnaire in 1986, had not had surgery to treat LUTS in 1992 or earlier, had an IPSS of 0–7 in 1992, and were not missing any of the anthropometric measures. We used two definitions of incident LUTS: 1) a less stringent definition of “modest or worse LUTS” defined as IPSS of ≥8 or surgery or medication use (n=7,792) and 2) a more stringent definition of “moderate or worse LUTS” defined as IPSS of ≥15 or surgery or medication use (n=4,088). Surgery or medication use was included as a “case” for both definitions of LUTS incidence regardless of reported IPSS score because these interventions likely improve the score making it an unreliable measure of underlying disease; it is assumed that LUTS requiring treatment were severe.

For analyses of progression, men entered the analytic cohort when they first experienced an IPSS of 8 to 14, but did not have a cancer diagnosis then or earlier, returned a valid food frequency questionnaire in 1986, had not had surgery or used medications to treat LUTS, and were not missing any of the anthropometric measures. The progression analytic cohort consisted of 6,461 men. We used two definitions of LUTS progression: 1) a less stringent definition of "moderate or worse LUTS" defined as IPSS of ≥15 or surgery or medication use (n=1,680), and 2) a more stringent definition of "severe LUTS" defined as IPSS of ≥20 or surgery or medication use (n=1,691). LUTS requiring either medication or surgery were assumed to be severe and, therefore, use of these treatments was a qualifying criterion for both definitions of LUTS progression. For both LUTS incidence and progression we focused on the results for the more stringent definition because the less stringent definition may reflect a different constellation of underlying biologic factors.

Statistical Analysis

We used Cox proportional hazards regression to estimate the hazard ratio (HR) and 95% confidence interval (CI) of LUTS incidence or progression. All models were adjusted for age (years). Multivariable models were further adjusted for factors known or hypothesized to be associated with both adiposity and LUTS including vigorous physical activity (quintiles of MET-hours/week); dietary intake of total energy, polyunsaturated fatty acids, fruit, vegetables, red meat, and alcohol (all in quintiles); use of supplemental vitamin E (none, <100, 100–250, >250–500, >500 IU/day) and selenium (none, <80, 80–130, >130–250, >250 IU/day); and aspirin use. The linear trend across categories was assessed by entering into the multivariable model an ordinal variable and assessing its significance using the Wald test.

Results

Table 1 shows the age-adjusted baseline characteristics of the incidence analytic cohort by BMI. Men with higher BMI tended to have a larger waist circumference, were more likely to have smoked cigarettes in the 10 years prior to baseline, were less active, and were more likely to use aspirin, have high blood pressure, or a history of type 2 diabetes (Table 1).

LUTS Incidence

After adjustment for age, there was a statistically significantly increased risk of incident modest or worse LUTS (IPSS ≥8) with increasing adiposity as measured by BMI, waist circumference, hip circumference, waist to hip ratio, and with increasing weight gain from age 21 (Table 2). These associations were only very slightly changed with multivariable adjustment and were stronger for incident moderate or worse LUTS (IPSS ≥15) than for incident modest or worse LUTS (data not shown). A similar positive association was observed when BMI was lagged by 2 years (lagged BMI >35 vs. 23-<25 kg/m^2: moderate or worse LUTS HR=1.63, 95% CI=1.33–2.01, *p-trend<0.0001*), and when cumulative average BMI was examined (cumulative average BMI >35 vs. 23–25 kg/m^2: moderate or worse

LUTS HR=1.61, 95% CI=1.25–2.09, *p-trend<0.0001)*. There was a weaker, but still positive association between BMI at age 21 and risk of incident LUTS after multivariable adjustment (BMI at age 21 ≥25 vs. <21 kg/m^2: moderate or worse LUTS HR=1.13, 95% CI=1.03–1.23, *p-trend=0.02*). All findings were unchanged when men using diuretic medications or type 2 diabetics were excluded. The association with measures of adiposity was similar for incidence of both obstructive symptoms (incomplete emptying, hesitancy, weak stream and intermittency) and irritative symptoms (frequency, urgency, and nocturia) (data not shown).

LUTS Progression

After adjustment for age, there was a statistically significantly increased risk of progression to severe LUTS (IPSS ≥20) with higher BMI and greater weight gain from age 21. We also observed a suggestion of an increased risk of progression to severe LUTS with higher waist circumference, and higher hip circumference although there was no association with waist to hip ratio (Table 3). Examination of joint categories of waist and hip circumference supported that either higher waist or higher hip circumference was associated with progression, but the risk was not higher for those with large measurements for both (data not shown). The positive findings were slightly stronger after multivariable adjustment. Although the HRs comparing the top category to the referent category were not statistically significant for the association between waist circumference or hip circumference and risk of progression to severe LUTS, the trend across categories was significant for both waist and hip circumference (*p-trend=0.005 and 0.02*, respectively, Table 3). These findings were similar, but not as strong for progression to modest or worse LUTS (IPSS ≥15) (data not shown). There was a similar positive association when BMI was lagged by 2 years (lagged BMI >35 vs. 23-<25 kg/m^2: severe LUTS HR=1.27, 95% CI=0.91–1.79, *p-trend<0.0001*), and when cumulative average BMI was examined (cumulative average BMI >35 vs. 23-<25 kg/m^2: severe LUTS HR=1.55, 95% CI=1.05–2.28, *p-trend<0.0001)*. However, we observed no association between BMI at age 21 and progression to severe LUTS after multivariable adjustment (data not shown). All findings were unchanged when men who used diuretic medications or men with type 2 diabetes were excluded.

Discussion

In this large, prospective study of US men, we found that higher total or abdominal adiposity, as well as adult weight gain, are associated with increased LUTS incidence and progression. The patterns of association were similar using both less stringent and more stringent definitions of the outcome. These results are consistent with the few previous multivariable-adjusted, prospective studies on this topic, which found an increased risk of LUTS incidence with higher BMI or waist circumference. However, to our knowledge, this is the first study to report an increased risk of progression of symptomatic LUTS to a worsened state with higher total or abdominal adiposity, with the one previous prospective study finding no association. These findings suggest that obesity may be an important target for preventing the development or worsening of LUTS.

Data from the National Health and Nutrition Examination Survey indicate that in 2010, 35.5% of adult men (i.e. >20 years old) were obese (i.e. had a BMI ≥30 kg/m^2) and 73.9% were overweight or obese (i.e. had a BMI ≥25 kg/m^2), and that these prevalences were even higher among older men [15]. Thus, assuming the association we observed between BMI and risk of LUTS is causal, nearly 20% of severe LUTS cases in the United States could be prevented if men maintained a normal body weight. Because adiposity is modifiable, this makes it an extremely attractive target for prevention and, perhaps, treatment of LUTS.

Although the biologic mechanisms underlying the role of obesity in LUTS are not clear, several pathways are hypothesized to play a role. Men who are obese have been shown in several studies to have larger prostates, which may increase LUTS symptoms, particularly obstructive symptoms. Due to the aromatization of testosterone to estrogen in adipose tissue, obese men have an increased estrogen to testosterone ratio, which may play a role in prostate tissue hyperplasia [16]. One recent study showed that obese men have increased prostate volumes over time compared with normal weight men [17]. Finally, there is some suggestion that obesity may be linked to increased sympathetic nervous system activity, which increases smooth muscle contraction in the prostate leading to increased irritative LUTS symptoms [16].

Strengths of our study include the prospective design, very large sample size, our ability to examine multiple different measures of adiposity at different points throughout adulthood, and our ability to control for multiple potential confounding factors. One possible limitation is that our anthropometric measures are self-reported. However, a validation study in the HPFS showed that the correlation between self-reported and technician-measured waist, hip, and weight measurements was quite high (0.94, 0.87, and 0.97, respectively) [18]. In addition, it is unlikely that the extent of any misclassification would be different between the men who subsequently became cases and those who did not in our cohort. Thus, any measurement error would bias our findings toward the null; the true association between measures of adiposity and LUTS may be stronger than that which we report. Our findings do not directly address whether weight loss in adult life may prevent the onset of LUTS or improve LUTS symptoms. However, the associations we observed between BMI and LUTS were weaker when BMI at age 21 was examined vs. current adult BMI, suggesting that one's current adiposity may have the most influence on LUTS symptoms. This would imply that weight loss may be effective strategy for prevention of or treatment for LUTS, but clinical trials examining this directly and replication in other populations, particularly in individuals of other race/ethnicities, are warranted.

Conclusions

In this large, prospective study of US men, obesity and weight gain during adult life were associated with an increased risk of development or worsening of LUTS. These findings suggest that, in addition to a myriad of well-established health benefits, maintaining a healthy body weight may also prevent LUTS in older men. Clinical trials are warranted to establish whether weight loss may be an effective strategy for treatment of LUTS.

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Table 1

Age-Standardized* Baseline Characteristics by Body Mass Index (BMI), HPFS 1992–2008

	<21 (n=673)	**21 – <23 (n=2,639)**	**23 – <25 (n=4,881)**	**25 – <27.5 (n=5,748)**	**27.5 – <30 (n=2,568)**	**30 – <35 (n=1,305)**	**≥35 (n=242)**
Age in 1992 (years)	59.0 (10.2)	57.6 (9.5)	57.3 (9.0)	57.4 (9.0)	56.9 (8.5)	56.8 (8.1)	55.6 (8.0)
Waist circumference (inches)	33.0 (2.4)	34.3 (2.1)	35.7 (2.2)	37.5 (2.4)	39.8 (2.6)	42.3 (3.2)	46.7 (4.4)
Cigarette smoking in the 10 years before 1992 (%)	18	14	17	20	22	24	27
Vigorous physical activity in 1992 (MET-hours/wk)	20.7 (33.1)	19.6 (32.3)	17.7 (25.9)	14.6 (26.7)	11.8 (27.3)	8.9 (18.0)	7.5 (17.0)
Intakes in 1990							
Energy (kcal/d)	1,995 (517)	1,982 (528)	1,974 (539)	1,961 (552)	1,975 (565)	1,957 (558)	2,009 (548)
Dietary lycopene (μg/d)	6,815 (4,433)	7,054 (4,184)	7,270 (4,239)	7,342 (4,389)	7,390 (4,436)	7,772 (4,879)	8,175 (4,476)
Dietary beta-carotene (μg/d)	5,080 (3,280)	4,892 (3,148)	4,697 (2,651)	4,720 (2,899)	4,660 (2,831)	4,580 (2,733)	4,769 (2,893)
Dietary lutein (μg/d)	3,462 (2,361)	3,309 (2,005)	3,221 (1,878)	3,259 (1,981)	3,246 (2,008)	3,152 (2,041)	3,230 (2,630)
Dietary vitamin C (mg/d)	165 (72)	166 (70)	165 (67)	161 (67)	157 (69)	154 (65)	151 (55)
Polyunsaturated fatty acids (g/d)	12.9 (3.8)	12.9 (3.4)	13.1 (3.4)	13.1 (3.4)	13.1 (3.2)	13.1 (3.3)	13.8 (4.3)
Supplemental vitamin E (IU/d)	39.1 (83.2)	38.7 (81.5)	34.8 (75.7)	32.9 (74.8)	31.2 (74.4)	34.9 (79.9)	27.4 (74.1)
Supplemental selenium (μg/d)	10.9 (37.1)	12.3 (38.6)	10.9 (36.2)	9.9 (34.5)	9.8 (33.9)	10.9 (37.1)	8.2 (29.4)
Fruit (servings†/d)	2.5 (1.6)	2.5 (1.6)	2.4 (1.4)	2.3 (1.4)	2.2 (1.4)	2.2 (1.4)	2.1 (1.1)
Vegetables (servings†/d)	3.6 (1.9)	3.6 (2.0)	3.5 (1.8)	3.5 (1.8)	3.5 (1.9)	3.6 (1.9)	3.7 (1.8)
Cruciferous vegetables (servings†/d)	0.5 (0.4)	0.5 (0.4)	0.5 (0.4)	0.5 (0.4)	0.5 (0.4)	0.5 (0.4)	0.5 (0.4)
Alcohol (g/d)	10.9 (14.9)	10.9 (13.9)	11.2 (13.7)	11.4 (14.1)	11.7 (15.0)	10.7 (15.1)	8.4 (13.2)
Red meat (servings†/d)	0.5 (0.4)	0.5 (0.4)	0.6 (0.4)	0.6 (0.4)	0.6 (0.4)	0.7 (0.4)	0.7 (0.4)
Regular use of aspirin in 1992 (%)	29	32	34	35	36	38	38
History of high blood pressure by 1992 (%)	14	17	21	26	32	42	56
History of type 2 diabetes mellitus by 1992 (%)	4	3	2	3	4	6	13

*Values are means (SD) or percentages and are standardized to the age distribution of the study population.

†One-half cup of fruit or vegetables equals one serving; 4–6 oz of red meat equals one serving.

Table 2

Association between measures of adiposity and incidence of moderate or worse (IPSS ≥15) LUTS

	# Cases	# Person-Years	HR (95% CI)*	HR (95% CI)†
Updated BMI (kg/m^2)				
<21	150	8,209	0.89 (0.75 – 1.06)	0.88 (0.74 – 1.05)
21 – <23	532	28,294	1.06 (0.96 – 1.18)	1.06 (0.95 – 1.18)
23 – <25	934	54,641	1.0 (ref)	1.0 (ref)
25 – <27.5	1,253	67,002	1.11 (1.02 – 1.21)	1.11 (1.02 – 1.21)
27.5 – <30	688	33,509	1.25 (1.13 – 1.38)	1.25 (1.13 – 1.38)
30 – <35	428	19,394	1.33 (1.18 – 1.49)	1.31 (1.17 – 1.48)
≥ 35	103	3,752	1.70 (1.38 – 2.08)	1.61 (1.31 – 1.99)
p-trend			<0.0001	<0.0001
Updated Waist Circumference (in)				
≤ 33	231	17,599	1.0 (ref)	1.0 (ref)
>33 – 34	225	16,734	0.92 (0.77– 1.11)	0.93 (0.78 – 1.12)
>34 – 36	819	45,281	1.18 (1.02 – 1.36)	1.20 (1.03 – 1.39)
>36 – 38	891	48,997	1.11 (0.96 – 1.28)	1.13 (0.98 – 1.32)
>38 – 40	757	37,003	1.19 (1.03 – 1.38)	1.23 (1.05 – 1.43)
>40 – 42	531	23,400	1.32 (1.13 – 1.54)	1.35 (1.15 – 1.59)
> 42	634	25,787	1.37 (1.18 – 1.60)	1.39 (1.19 – 1.63)
p-trend			<0.0001	<0.0001
Updated Hip Circumference (in)				
≤ 36	282	14,820	1.0 (ref)	1.0 (ref)
>36 – 38	678	42,800	0.81 (0.71 – 0.93)	0.82 (0.71 – 0.95)
>38 – 40	1,194	64,589	0.92 (0.81 – 1.05)	0.94 (0.82 – 1.07)
>40 – 42	947	49,281	0.94 (0.82 – 1.08)	0.97 (0.84 – 1.11)
>42 – 44	575	25,299	1.10 (0.95 – 1.27)	1.12 (0.97 – 1.30)
>44 – 46	231	10,636	1.04 (0.87 – 1.24)	1.06 (0.88 – 1.26)
> 46	181	7,378	1.12 (0.92 – 1.35)	1.11 (0.91 – 1.35)

	# Cases	# Person-Years	HR (95% CI)*	HR (95% CI)†
p-trend			<0.0001	<0.0001
Updated Waist to Hip Ratio				
≤ 0.87	287	21,381	1.0 (ref)	1.0 (ref)
>0.87 – 0.89	315	21,535	1.05 (0.89 – 1.23)	1.05 (0.89 – 1.23)
>0.89 – 0.91	449	26,501	1.16 (1.00 – 1.35)	1.16 (1.00 – 1.35)
>0.91 – 0.93	576	31,968	1.17 (1.01 – 1.35)	1.18 (1.02 – 1.36)
>0.93 – 0.95	637	33,333	1.16 (1.01 – 1.33)	1.16 (1.01 – 1.34)
>0.95 – 0.97	500	23,904	1.25 (1.08 – 1.44)	1.24 (1.07 – 1.43)
>0.97 – 0.99	453	19,579	1.31 (1.13 – 1.52)	1.29 (1.11 – 1.50)
≥ 0.99	871	36,600	1.34 (1.17 – 1.54)	1.33 (1.16 – 1.52)
p-trend			<0.0001	<0.0001
Weight Change from Age 21 (lbs)				
Lost >10	429	21,985	1.08 (0.96 – 1.21)	1.07 (0.95 – 1.20)
No change (+/− 10)	842	48,379	1.0 (ref)	1.0 (ref)
Gained 10 – <20	737	41,666	1.07 (0.97 – 1.18)	1.07 (0.97 – 1.18)
Gained 20 – <30	665	36,656	1.08 (0.97 – 1.20)	1.08 (0.97 – 1.19)
Gained 30 – <40	487	25,631	1.10 (0.98 – 1.23)	1.09 (0.97 – 1.22)
Gained 40 – <50	320	15,741	1.15 (1.01 – 1.30)	1.14 (1.00 – 1.30)
Gained 50+	608	24,744	1.33 (1.20 – 1.48)	1.31 (1.17 – 1.46)
p-trend			<0.0001	<0.0001

*Adjusted for age.

†Adjusted for age, smoking in the past 10 years, physical activity, intake of total energy, polyunsaturated fatty acids, fruit, vegetables, red meat, alcohol, supplemental vitamin E, supplemental selenium, and use of aspirin. Models of waist circumference and hip circumference are further adjusted for height.

Table 3

Association between measures of adiposity and progression to severe (IPSS ≥ 20) LUTS

	# Cases	# Person-Years	HR (95% CI)*	HR (95% CI)†
Updated BMI (kg/m^2)				
<21	55	1,502	0.73 (0.55 – 0.97)	0.73 (0.55 – 0.98)
21 – <23	221	4,833	0.95 (0.80 – 1.12)	0.95 (0.80 – 1.12)
23 – <25	406	8,932	1.0 (ref)	1.0 (ref)
25 – <27.5	494	10,947	1.01 (0.88 – 1.15)	1.02 (0.89 – 1.17)
27.5 – <30	291	5,471	1.22 (1.04 – 1.42)	1.24 (1.06 – 1.45)
30 – <35	181	3,392	1.26 (1.05 – 1.51)	1.30 (1.08 – 1.56)
≥ 35	43	766	1.44 (1.05 – 1.98)	1.44 (1.04 – 2.00)
p-trend			<0.0001	<0.0001
Updated Waist Circumference (in)				
≤ 33	44	1,099	1.0 (ref)	1.0 (ref)
>33 – 34	150	3,747	1.02 (0.72 – 1.43)	1.03 (0.73 – 1.45)
>34 – 36	315	7,040	1.08 (0.78 – 1.49)	1.10 (0.80 – 1.52)
>36 – 38	373	8,107	1.11 (0.81 – 1.52)	1.14 (0.83 – 1.58)
>38 – 40	309	6,475	1.11 (0.81 – 1.54)	1.15 (0.83 – 1.60)
>40 – 42	220	4,271	1.22 (0.88 – 1.69)	1.26 (0.90 – 1.76)
> 42	280	5,105	1.27 (0.92 – 1.76)	1.32 (0.95 – 1.85)
p-trend			0.007	0.005
Updated Hip Circumference (in)				
≤ 36	106	2,266	1.0 (ref)	1.0 (ref)
>36 – 38	314	6,993	0.93 (0.74 – 1.16)	0.93 (0.74 – 1.17)
>38 – 40	462	10,612	0.91 (0.74 – 1.13)	0.92 (0.74 – 1.15)
>40 – 42	393	8,247	0.98 (0.79 – 1.22)	0.99 (0.79 – 1.25)
>42 – 44	241	4,229	1.23 (0.98 – 1.56)	1.24 (0.97 – 1.59)
>44 – 46	91	1,987	0.94 (0.71 – 1.25)	0.95 (0.70 – 1.27)
> 46	84	1,510	1.14 (0.85 – 1.52)	1.14 (0.84 – 1.55)

	# Cases	# Person-Years	HR (95% CI)*	HR (95% CI)†
p-trend			0.02	0.02
Updated Waist to Hip Ratio				
≤ 0.87	133	2,986	1.0 (ref)	1.0 (ref)
>0.87 – 0.89	112	3,024	0.80 (0.62 – 1.03)	0.81 (0.63 – 1.05)
>0.89 – 0.91	182	3,944	0.94 (0.75 – 1.18)	0.95 (0.76 – 1.20)
>0.91 – 0.93	229	4,985	0.93 (0.75 – 1.16)	0.95 (0.76 – 1.18)
>0.93 – 0.95	258	5,553	0.94 (0.76 – 1.17)	0.97 (0.78 – 1.20)
>0.95 – 0.97	201	4,147	0.95 (0.76 – 1.19)	0.98 (0.78 – 1.23)
>0.97 – 0.99	189	3,903	0.98 (0.78 – 1.23)	1.00 (0.79 – 1.26)
≥ 0.99	387	7,300	1.01 (0.83 – 1.24)	1.04 (0.85 – 1.28)
p-trend			0.16	0.11
Weight Change from Age 21 (lbs)				
Lost >10	177	3,746	1.08 (0.90 – 1.30)	1.09 (0.91 – 1.32)
No change (+/− 10)	343	8,068	1.0 (ref)	1.0 (ref)
Gained 10 – <20	289	6,689	1.03 (0.88 – 1.21)	1.05 (0.90 – 1.24)
Gained 20 – <30	264	5,704	1.11 (0.94 – 1.30)	1.14 (0.96 – 1.34)
Gained 30 – <40	216	4,163	1.23 (1.04 – 1.47)	1.27 (1.07 – 1.52)
Gained 40 – <50	142	2,693	1.30 (1.06 – 1.58)	1.36 (1.11 – 1.67)
Gained 50+	260	4,779	1.31 (1.11 – 1.55)	1.35 (1.14 – 1.60)
p-trend			0.0002	<0.0001

*Adjusted for age.

†Adjusted for age, smoking in the past 10 years, physical activity, intake of total energy, polyunsaturated fatty acids, fruit, vegetables, red meat, alcohol, supplemental vitamin E, supplemental selenium, and use of aspirin. Models of waist circumference and hip circumference are further adjusted for height.

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