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Weight change over 9 years and subsequent risk of venous thromboembolism in the ARIC cohort.

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Abstract

Background/Objectives: Weight gain increases risk of cardiovascular disease, but has not been examined extensively in relationship to venous thromboembolism (VTE). The association between weight change over 9 years and subsequent VTE among participants in the Atherosclerosis Risk in Communities (ARIC) study was examined, with a hypothesis that excess weight gain is a risk factor for VTE, relative to no weight change.

Subjects/Methods: Quintiles of 9-year weight change were calculated (visit 4 1996–1998 weight minus visit 1 1987–1989 weight in kg: Quintile 1: ≥ −1.81 kg; Quintile 2: <−1.81 to ≥ 1.36 kg; Quintile 3: >1.36 to ≤4.08 kg; Quintile 4: >4.08 to ≤7.71 kg; Quintile 5: > 7.71 kg). Incident VTEs from visit 4 (1996–1998) through 2015 were identified and adjudicated using medical records. Hazard ratios (HRs) were calculated using Cox models.

Results: 529 incident VTEs were identified during an average of 19 years of follow up. Compared to Quintile 2, participants in Quintile 5 of weight change had 1.46 times the rate of incident VTE (HR = 1.46 (95% CI 1.09, 1.95), adjusted for age, race, sex, income, physical activity, smoking and prevalent CVD). The HR for Quintile 5 was modestly attenuated to 1.38 (95% CI 1.03, 1.84) when visit 1 BMI was included in the model. When examined separately, results were significant for unprovoked VTE, but not for provoked VTE. Among those obese at visit 1, both weight gain (HR 1.86 95% CI 1.27,2.71) and weight loss (HR 2.11 95% CI 1.39, 3.19) were associated with incident VTE, compared with normal weight participants with no weight change.

Conclusions: Weight gain later life was associated with increased risk for unprovoked VTE. Among those with obesity, both weight gain and weight loss were associated with increased risk for VTE.

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Introduction

Deep venous thrombosis and pulmonary embolism, collectively, venous thromboembolism (VTE), is a life-threatening disease and a serious public health issue (1,2,3). It affects almost more than 1 million Americans annually (4) and results in approximately 100,000 deaths (1), making it the third leading cause of cardiovascular mortality behind heart attack and stroke (4,5).

Obesity is a well-established independent risk factor for VTE (4, 6–9). People with obesity (body mass index BMI>= 30 kg/m^2) have 2–3 times higher risk of VTE compared with people with normal weight (3,6,8). This association is observed consistently across various measures of obesity, including BMI, waist circumference, waist-hip-ratio and calf circumference (6,7,10), and persists after adjustment for other VTE risk factors (6,7,9,10).

Adult weight gain has adverse effects on both arterial vascular and VTE risk factors (12–17). A possible hypothesis is that adult weight gain increases risk for incident VTE, as it does for incident arterial vascular disease. Although many studies show an association between a single weight measure with VTE, we are aware of only one study that examined weight change and VTE risk (18). In the Tromsø Study, weight gain of 7.5 kg. or more over six years was associated with a 1.9-fold higher incidence of subsequent VTE compared to weight gain less than 7.5 kg (18). The highest risk of VTE was observed among those with BMI >=30 at baseline who gained any weight (6.6-fold greater VTE risk compared to normal weight people with no weight gain).

The present study is the first US study to examine the prospective association between weight change over 19 years and incident VTE, using data from participants in the Atherosclerosis Risk in Communities (ARIC) study (19). We hypothesized that greater weight gain would be associated with increased risk of VTE, and that the highest risk of incident VTE would be observed among participants who were obese at baseline and gained appreciable weight.

Methods

Study Design and Participants

The ARIC cohort includes N=15,792 study participants aged 45–64 years from four US communities (Forsyth County, North Carolina; Jackson, Mississippi; suburban Minneapolis, Minnesota; and Washington County, Maryland) (19). Following clinic visit 1 in 1987–1989, participants were contacted annually or semi-annually by telephone, and periodic in-person clinical follow up visits were conducted, including visit 2 (1990–1992), visit 3 (1993–1995), and visit 4 (1996–1998). The present analysis focused on cohort members who attended visit 4 (N=11,656). Follow-up time began at visit 4 and continued to either incident VTE, loss to follow-up, death, or administrative censoring at December 31, 2015. IRB approval for ARIC was received by the Human Subjects Protection Board at each of the participating universities.

Measures

Body Weight Change.—Weight and height were measured according to standardized protocols at every clinic visit (19). BMI was calculated as weight in a scrub suit in kg/height in m^2. BMI categories were defined as normal weight, overweight, and obese by BMI < 25kg/m^2, 25 kg/m^2 to <30kg/m^2 and >=30 kg/m^2. Quintiles of 19-year weight change were calculated (visit 4 1996–1998 weight minus visit 1 1987–1989 weight in kg): Quintile 1: ≥ −1.81 kg; Quintile 2 (referent): <−1.81 to ≤ 1.36 kg; Quintile 3: >1.36 to ≤4.08 kg; Quintile 4: >4.08 to ≤ 7.71 kg; Quintile 5: > 7.71 kg. Quintile 2 was selected as the referent because it includes the "no weight change" group, and small loss and small gain. Since small weight gain is typical in population-based cohorts, this quintile was viewed as the most appropriate to serve as a reference group[14–17;21,22]. We also categorized weight change using broader categories for some analyses (described below) where sparse data were a concern: weight loss (> −2.7 kg); no change (- 2.7 kg to + 2.7 kg); weight gain (> +2.7 kg).

Covariates.—Age, sex, race, prevalent cardiovascular disease, and smoking status (never, former or current smoker) were self-reported. Race- center (Forsyth County whites, Forsyth County blacks, Jackson blacks, Minneapolis whites, and Washington County blacks) was included as a covariate due to differences in sample racial composition at ARIC sites. Physical activity was measured at visit 1 and visit 3 using the self-report Baecke questionnaire (20) Participants self-reported the types and frequency of sports currently engaged in, and a sports score was computed using MET codes for specific types of activities.

Venous Thromboembolism Ascertainment.—Hospitalizations were identified by participant report during follow-up calls and through systematic searches of local hospital discharges for cohort members. International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) or ICD-10-CM discharge codes of hospitalizations were recorded and used to identify possible cases of VTE from visit 4 through 2015.

To classify VTE occurrence, information from hospital records for each potential VTE was reviewed independently by two physicians (MC, ARF), as previously described (3). Differences in classification were resolved by discussion. Clinical diagnoses without objective tests were not validated as cases. Definite deep vein thrombosis was defined as a positive duplex ultrasound or venogram or, in rare cases, by computed tomography or impedance plethysmography. Pulmonary embolism was classified using results of computed tomography, ventilation/perfusion scans, or, rarely, angiography or autopsy.

VTEs also were classified as unprovoked or provoked (occurring within 90 days of major trauma, surgery, or marked immobility, or associated with active cancer or chemotherapy). Venous thromboses not in the leg or vena cava were not considered as VTE for this analysis.

Statistical Analysis

Cox proportional hazards regression models were used to estimate hazard ratios (HRs) with 95% confidence intervals for incident VTE for quintiles of weight change, using quintile 2 as the referent category. Model 1 adjusted for age, race-center and sex; model 2 adjusted for

these variables plus income at visit 4, smoking status at visit 1 and 4, physical activity at visit 1 and 3, and prevalent cardiovascular disease at visit 1; and model 3 adjusted for model 2 variables plus visit 1 BMI.

Additional analyses examined the associations between weight change category (loss, no change, gain) and incident VTE stratified by visit 1 body mass index (normal weight; overweight; obese). Categories of weight change (defined above) were used in this analysis for ease of presentation and interpretation. Interactions between baseline weight and weight change category over time were tested using cross-product terms.

Sensitivity analyses were conducted to examine results (i) for provoked and unprovoked VTE separately and (ii) additionally adjusting for post visit 4 (time-varying) use of anticoagulants (results were not affected and are not shown).

Results

Description of the Cohort at Visit 4

Among ARIC participants who attended visit 4 in 1996–1998 (N=11,656; 73.8% of initial ARIC cohort), the following exclusions were made: prevalent VTE at visit 4 (N=339); anticoagulant use at visit 4 (N=236); prevalent cancer self-reported at visit 1 or visit 4 (N=1404); missing visit 1 or visit 4 weight (N=42); or not White or Black at certain ARIC Centers (N=69; see above “Covariates”). The final analytic cohort (N=9710) had a higher proportion of Blacks (24% versus 16%) and was slightly younger (62 yrs versus 64 yrs), compared to those excluded from analysis.

At visit 4, included participants averaged 62 yrs and had BMI 29.6 kg/m^2; 56% were female, 24% were Black, 17% had diabetes, and 15% were current smokers. Table 1 shows participant characteristics by quintiles of weight change from visit 1 to visit 4. Participants who had gained greater weight were more likely to be female, younger, and former smokers at visit 4, compared to those in the lower quintiles of weight gain.

Weight Change and Incident VTE

Over an average of 19.4 years (sd=4.7) of follow-up, 526 incident VTEs were identified. Table 2 shows weight change quintiles and hazard ratios for VTE. In an adjusted model (model 2), relative to Quintile 2, the Quintile 5 (weight gain of > +7.7 kg) HR was 1.46 (95% CI 1.09, 1.95) for incident VTE. In analysis of provoked VTE, compared with Quintile 2 of weight change, neither greater weight gain nor loss tended to be associated with VTE (Table 2). However, a large weight gain (> +7.71 kg, Quintile 5) was associated with a greater incidence of unprovoked VTE compared to Quintile 2 of weight change (adjusted model 2: HR 2.03, (95% CI 1.29, 3.19)). Although slightly weaker, weight loss (Quintile 1) was also associated with greater incidence of unprovoked VTE compared with Quintile 2 (adjusted model 2: HR 1.61 (95% CI 1.01, 2.56)).

Among the normal weight at visit 1, those who gained weight were at risk of VTE comparable to those who did not gain weight (Table 3). Among those obese at visit 1, weight gain > +2.7 kg was associated with an adjusted (model 2) HR of 1.86 (95% CI 1.27, 2,71)

compared with those of normal weight at visit 1 who did not gain weight. The crude incidence rate among those obese at visit 1 who gained weight was 5.14/1000 PY, compared with 2.47/1000 PY among those of normal weight at visit 1 who did not gain weight. Among those obese at visit 1, weight loss also was significantly associated with an adjusted (model 2) HR for VTE of 2.11 (95% CI 1.39, 3.19) compared with those normal weight at visit 1 with no weight change.

Discussion

This research demonstrated a modest association between a large weight gain over 9 years and greater future unprovoked VTE in a large cohort of black and white adults with average age 62 yrs over an average follow up of 19 yrs. Specifically, those who gained more than 7.7 kg, compared to those who lost up to −1.8 kg or gained up to 1.4 kg, had 1.46 times the rate of VTE after adjusting for risk factors, while the rate was 2.03 times higher for unprovoked VTE. It was hypothesized that the risk of VTE would be more pronounced among participants with obesity at visit 1 who gained significant weight during the follow up. Relative to normal weight participants who did not gain weight, obese participants who gained +2.7 kg or more had 1.86 times the rate of VTE risk during follow up, after adjustment for income, smoking and physical activity. Obese participants who lost weight were also at 2.11 times higher risk for VTE compared with normal weight participants who did not gain weight.

A lack of association of weight gain with provoked VTE suggests that causes of provoked VTE, such as underlying disease or immobility, are more relevant pathophysiologically than weight gain. Alternatively, it may be that these conditions over the 19 year weight change period caused weight change and thus confounded the analysis of provoked VTE.

In the present study, excess weight gain seemed to be a significant risk factor for VTE, regardless of initial body weight, although associations for weight gain were attenuated by adjustment for starting BMI. These findings are inconsistent with the Tromsø results, where risk for VTE with weight gain was magnified among those who were already obese at the start of the observation period (18). Differences in VTE incidence rates, follow up length, and weight change category definitions may explain some of the differences in the results between the two studies. For example, the Tromso study (average baseline age 59 yrs) had a 6 yr follow up period and the present ARIC analyses (average visit 4 age 62 yrs) had a 19 yr follow up period; crude VTE incidence rate was 1.8/1000 PY in Tromsø (18) and 3.5/1000 PY in the present ARIC analyses, and Tromsø defined no weight change as a gain of 0 through +7.4, compared to the present study's definition of a loss of −2.7 through a gain of +2.7 kg. Among those obese at visit 1, Tromsø observed a HR of 6.6 (95% CI 3.61, 12.22) of VTE in adjusted models with the referent of normal weight with no weight change. In the present study, the HR for those obese at visit 1 was 1.86 (95% CI 1.27, 2.71) in adjusted models with the same referent group of normal weight with no weight change. Additional studies are needed to clarify whether, independent of initial BMI, excess weight gain is an independent risk factor for both provoked and unprovoked VTE.

The present study had several strengths, such as the inclusion of black and white participants across four diverse US geographic locations, a lengthy follow-up duration of 19 years, and a large number of incident and adjudicated VTEs. A limitation is a lack of data on intentionality of weight change. Previous research on the association between weight change and health outcomes has largely shown that unintentional weight loss, but intentional weight loss less so, is associated with greater subsequent disease onset and mortality (15,21,22). Another limitation is that other factors that impact weight gain, such as physical activity, are measured with error which could result in residual confounding.

These data provide evidence that a large weight gain later in life contributes to increase risk for unprovoked VTE. Among those with existing obesity, large gain or loss is associated with increased risk of unprovoked VTE.

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Table 1

Participant Characteristics (N=9710) at ARIC Visits 1 (1987–89) and 4 (1996–98) by 9-Year Weight Change Quintile (Visit 4-Visit 1) 9-Year Weight Change Quintile [*]

Variable Mean (sd) or % (N)		Q1 (<= −1.81kg)	Q2 (>−1.81 to <=1.36 kg)	Q3 (>1.36 to ≤ 4.08 kg)	Q4 (>4.08 to ≤ 7.71 kg)	Q5 (>7.71kg)
N		1921	1976	1858	1963	1992
Weight Change [*]		−6.2 (4.2)	−-0.3 (0.9)	2.6 (0.7)	5.5 (1.0)	12.2 (4.8)
Age (yrs; visit 4)		63.8 (5.8)	63.3 (5.7)	62.6 (5.5)	61.8 (5.5)	60.9 (5.2)
Sex (% female)		52.4	51.9	54.5	57.9	62.3
Race (% black)		29.7	22.0	19.6	23.8	24.0
Diabetes (%; visit 4)		29.0	15.4	12.1	12.3	15.0
Weight (kg; visit 1)		83.1 (17.4)	76.3 (15.3)	75.2 (15.5)	76.2 (15.4)	79.6 (16.7)
Weight (kg; visit 4)		76.9 (16.8)	76.0 (15.3)	77.7 (15.5)	81.7 (15.4)	91.8 (18.0)
Height (cm; visit 1)		168.8 (9.3)	168.7 (9.3)	168.3 (9.4)	168.0 (9.3)	168.3 (9.1)
Height (cm; visit 4)		167.7 (9.5)	167.9 (9.4)	167.7 (9.5)	167.4 (9.3)	167.7 (9.2)
Body Mass Index (kg/m^2; visit 1)		29.3 (5.9)	26.8 (4.8)	26.5 (4.5)	27.0 (4.7)	28.1 (5.2)
Sports Index Score (visit 1)		2.4 (0.8)	2.5 (0.8)	2.5 (0.8)	2.5 (0.8)	2.4 (0.8)
Sports Index Score (visit 3)		2.5 (0.8)	2.6 (0.8)	2.6 (0.8)	2.5 (0.8)	2.4 (0.8)
Smoking (% current; visit 1)		25.6	20.5	17.0	20.0	26.0
Smoking (% current; visit 4)		23.9	16.8	11.9	11.4	11.5

[*] Weight (kg) at visit 4 – weight at visit 1

sd=standard deviation

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Table 2

Incidence Rates and Hazard Ratios (HR) with 95% Confidence Intervals for Venous Thromboembolism (VTE) from 1996 through 2015 by 19-Year Weight Change Quintile (Visit 4-Visit 1), ARIC

Weight Change Quintile	Person Years Follow Up	VTE Events N=526	Incidence Rate per 1,000 PY (95% CI)	Model 1: HR (95% CI)[A]	Model 2: HR (95% CI)[B]	Model 3: HR (95% CI)[C]
(N=9710)		**All VTE Events**		N=9710	N=8840	N=8840
***Q1* (<= −1.81kg)**	27089	113	4.17(3.47,5.02)	1.33 (1.01, 1.75)	1.35 (1.01, 1.80)	1.22 (0.91, 1.63)
***Q2* (>−1.81 to ≤ 1.36 kg)**	30891	94	3.04(2.49,3.72)	Ref=1	Ref=1	Ref=1
***Q3* (>1.36 to ≤4.08 kg)**	29897	94	3.14(2.57,3.85)	1.09 (0.82,1.45)	1.05 (0.78,1.43)	1.06 (0.78,1.44)
***Q4* (>4.08 to ≤ 7.71 kg)**	31766	101	3.18(2.62,3.86)	1.12 (0.85,1.49)	1.10 (0.82,1.48)	1.09 (0.81,1.47)
***Q5* (> 7.71 kg)**	31588	124	3.93(3.29,4.68)	1.49 (1.13,1.95)	1.46 (1.09,1.95)	1.38 (1.03,1.84)
(N=9500)		**Provoked VTE**		N=9500	N=8646	N=8646
***Q1* (<= −1.81kg)**	26601	67	2.52(1.98,3.20)	1.19 (0.84,1.68)	1.21 (0.82,1.77)	1.09 (0.75,1.59)
***Q2* (>−1.81 to ≤ 1.36 kg)**	30495	62	2.03(1.59,2.61)	Ref=1	Ref=1	Ref=1
***Q3* (>1.36 to ≤4.08 kg)**	29515	58	1.97(1.52,2.54)	1.02 (0.71,1.46)	0.99 (0.67,1.46)	0.99 (0.67,1.47)
***Q4* (>4.08 to ≤ 7.71 kg)**	31379	63	2.01(1.57,2.57)	1.04 (0.73,1.49)	1.06 (0.73,1.55)	1.06 (0.72,1.54)
***Q5* (> 7.71 kg)**	30934	66	2.13(1.68,2.72)	1.18 (0.83,1.67)	1.16 (0.79, 1.69)	1.09 (0.74, 1.60)
(N=9394)		**Unprovoked VTE**		N=9394	N=8566	N=8566
***Q1* (<= −1.81kg)**	26401	46	1.74(1.31,2.33)	1.60 (1.02,2.51)	1.61 (1.01,2.56)	1.44 (0.90,2.30)
***Q2* (>−1.81 to ≤ 1.36 kg)**	30171	32	1.06(0.75,1.50)	Ref=1	Ref=1	Ref=1
***Q3* (>1.36 to ≤4.08 kg)**	29297	36	1.23(0.86,1.70)	1.24 (0.77,1.99)	1.15 (0.70,1.89)	1.15 (0.70,1.89)
***Q4* (>4.08 to ≤ 7.71 kg)**	31049	38	1.22(0.89,1.68)	1.27 (0.79, 2.04)	1.16 (0.71,1.89)	1.15 (0.70, 1.87)
***Q5* (> 7.71 kg)**	30888	58	1.88(1.45,2.43)	2.13 (1.37, 3.30)	2.03 (1.29,3.19)	1.90 (1.21, 2.99)

Note:

A: Model 1: adjusted for age, race-center and sex

B: Model 2: model 1 plus income at visit 4, smoking status at visit 1 and visit 4; physical activity at visit 1 and visit 3; prevalent CVD at visit 1

C: Model 3: model 2 plus visit 1 body mass index

Table. 3

Incidence Rates and Hazard Ratios (HR) with 95% Confidence Intervals for Venous Thromboembolism (VTE) by ARIC Visit 1 Body Weight Category and 19-Year Weight Change Category (Visit 4 1996 - Visit 1 1987) Followed Up Through 2015

Visit 1 Weight Category	Person-Years (FU)	VTE events N	Incidence rate/ 1000PY (95% CI)	HR (95% CI) model 1*	HR (95% CI) model 2**	HR (95% CI) model 3***
Normal BMI (<25kg/m^2)						
Loss (< − 2.7 kg)	5763	15	2.60 (1.57,4.32)	1.04 (0.58,1.85)	0.96 (0.51,1.78)	0.93 (0.50,1.74)
No Change (− 2.7 to +2.7 kg)	18589	46	2.47 (1.85,3.30)	Ref=1	Ref=1	Ref=1
Gain (> +2.7 kg)	27853	67	2.41 (1.89,3.06)	1.08 (0.74,1.57)	1.01 (0.68,1.50)	1.01 (0.68,1.50)
Overweight (25− < 30 kg/m2)						
Loss (< − 2.7 kg)	9107	37	4.06 (2.94,5.61)	1.45 (0.94,2.24)	1.35 (0.85,2.14)	1.06 (0.66,1.70)
No Change (- 2.7 to + 2.7 kg)	19773	54	2.73 (2.09,3.57)	1.01 (0.68,1.51)	1.01 (0.68,1.50)	0.81 (0.53,1.25)
Gain (> +2.7 kg)	32355	114	3.52 (2.93,4.23)	1.44 (1.02,2.04)	1.37 (0.95,1.97)	1.10 (0.75,1.61)
Obese (>=30 kg/m2)						
Loss (< − 2.7 kg)	9557	53	5.54 (4.24,7.26)	2.02 (1.36,3.02)	2.11 (1.39,3.19)	1.17 (0.69,1.97)
No Change (− 2.7 to +2.7 kg)	9167	42	4.59 (3.39,6.20)	1.67 (1.09,2.55)	1.44 (0.91,2.28)	0.84 (0.49,1.45)
Gain (> +2.7 kg)	19066	98	5.14 (4.22,6.27)	2.00 (1.40,2.85)	1.86 (1.27,2.71)	1.07 (0.66,1.74)

*Model 1 (N=9710): Adjusted for age, race-center and sex; p-value for BMI cat x Weight Change cat interaction =0.83

**Model 2 (N=8840): model 1 + income, smoking status, PA, Prevalent CVD; p-value for BMI cat x Weight Change cat interaction)=0.73

***Model 3(N=8840): model 2 + Visit 1 Weight; p-value for BMI cat x Weight Change cat interaction=0.76