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Association of anthropometric measures and hemostatic factors in postmenopausal women: A longitudinal study

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Abstract *Background and aims:* Obesity has been associated with increased levels of hemostatic factors. However, few studies have compared change in different anthropometric measures of adiposity in relation to change in levels of hemostatic factors. Our aim was to examine prospectively the association of change in body mass index (BMI), waist-hip ratio (WHR), waist circumference (WC), and waist circumference-height ratio (WHtR) with change in markers of hemostasis in a population of postmenopausal women.

Methods and results: A subsample of women in the Women's Health Initiative (WHI) cohort had fasting blood samples and anthropometric measurements obtained at multiple time points over 12.8 years of follow-up. Of these, we studied the 2593 women who were not in the intervention arm of any WHI clinical trial. Their blood samples were used to measure plasma fibrinogen, factor VII antigen activity, and factor VII concentration at baseline, and at years 1, 3, and 6. We conducted mixed-effects linear regression analyses to examine the longitudinal association between change in anthropometric factors and change in hemostatic factors, adjusting for a wide range of potential confounding factors.

In longitudinal analyses using repeated measures, change in BMI, WC, and WHtR were all positively associated with change in all 3 hemostatic factors. Change in anthropometric variables was most strongly associated with change in fibrinogen.

Conclusions: Our results suggest that an increase in adiposity over time is robustly associated with increased levels of hemostatic factors.

Registration number of clinical trial: NCT00000611.

Introduction

Obesity and central adiposity are established risk factors for cardiovascular disease, diabetes, and certain cancers [1–3]. Obesity, defined as an excess accumulation of body fat, is associated with dysregulation of both metabolic processes involved in energy storage and of the hemostatic and fibrinolytic systems [4–6]. Fibrinogen plays a key role in the coagulation cascade, providing the substrate for thrombin [7], and is a key regulator of inflammation in a wide range of diseases, including some cancers [8]. Given the increase in the prevalence of obesity over the past few decades, the link between obesity and thrombotic risk has important implications for public health [5].

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Most studies that have examined the association of obesity or abdominal obesity with hemostatic factors have been cross-sectional [9–17] and have varied widely in sampling methods, number of subjects, study design, and analysis. Several anthropometric measures have been used as indices of obesity, including body mass index (BMI), waist circumference (WC), waist-to-height ratio (WHtR), and waist-hip ratio (WHR). Few studies have examined the association of these different anthropometric measures with hemostatic factors, and, in particular, it is unclear whether body mass index or waist circumference is a superior predictor of hemostatic risk [11,15,16]. Additionally, no previous study has examined WHtR as a predictor of hemostatic measures. WHtR has been shown in some studies to be superior to BMI and WC in predicting total mortality, cardiovascular mortality, and the metabolic syndrome [18–20]. The present investigation was designed to examine prospectively the association of change in anthropometric measures of obesity and abdominal adiposity with change in markers of hemostasis in a large population of postmenopausal women in which extensive data on personal characteristics, lifestyle factors, and metabolic factors were available.

Methods

The current study was conducted using data from the Women's Health Initiative (WHI), a large, multi-center prospective study designed to identify determinants of major chronic diseases in older women [21]. The WHI is composed of a Clinical Trial (CT, $N = 68{,}132$) and an Observational Study (OS, $N = 93{,}676$). Women between the ages of 50 and 79 and representing major racial/ethnic groups were recruited from the general population at 40 clinical centers throughout the US between 1993 and 1998. Details of the design and reliability of the baseline measures have been published [21,22]. The study was approved by the institutional review board of each clinical center.

The study population for the present analysis consisted of a 6% random sample of women in the CT [$N = 4544$] who provided fasting blood samples at baseline and years 1, 3, and 6 during follow-up and a 1% sample of women in the OS [$N = 1062$] who provided a fasting blood sample at baseline and at year 3. Of the 5606 women with measured analytes ("core analytes subsample"), we restricted our analysis to the approximately 2700 women with baseline measurements of the analytes who were not in an intervention arm of any clinical trial (Fig. 1). Approximately 52%, 46%, and 44% of those with baseline measurements also had measurements in years 1, 3, and 6, respectively. Hemostatic markers studied here included fibrinogen, factor VII antigen activity, and factor VII concentration.

Data collection and variable definition

At study entry, self-administered questionnaires were used to collect information on demographics, reproductive and medical history, and dietary and lifestyle factors, including smoking history, alcohol consumption, and recreational physical activity. All participants had their weight, height, and waist and hip circumferences measured by trained staff at baseline. Weight was measured to the nearest 0.1 kg, and height to the nearest 0.1 cm. Waist circumference at the natural waist or narrowest part of the torso, and hip circumference at the maximal circumference, were recorded to the nearest 0.1 cm. Anthropometric measurements were also made during follow-up (in years 1, 3, and 6 for the majority of the cohort). Anthropometric measurements at the different time points were available for almost all women (>97%). Body mass index (BMI) was computed as weight in kilograms divided by the square of height in meters. In addition to waist circumference (WC) and waist-hip ratio (WHR), we computed the variable waist-to-height ratio (WHtR). Blood pressure was measured in the right arm with a mercury sphygmomanometer after the participant was seated and had rested for 5 min; 2 measures, taken 30 s apart, were recorded, and the average of the two measurements was used in the analysis. Questions about physical activity at baseline referred to a woman's usual pattern of activity, including walking and recreational physical activity. A variable "current total leisure-time physical activity" (MET-hours/week) was computed by multiplying the number of hours per week of specific leisure-time physical activities by the metabolic equivalent (MET) value of the activities and summing over all types of

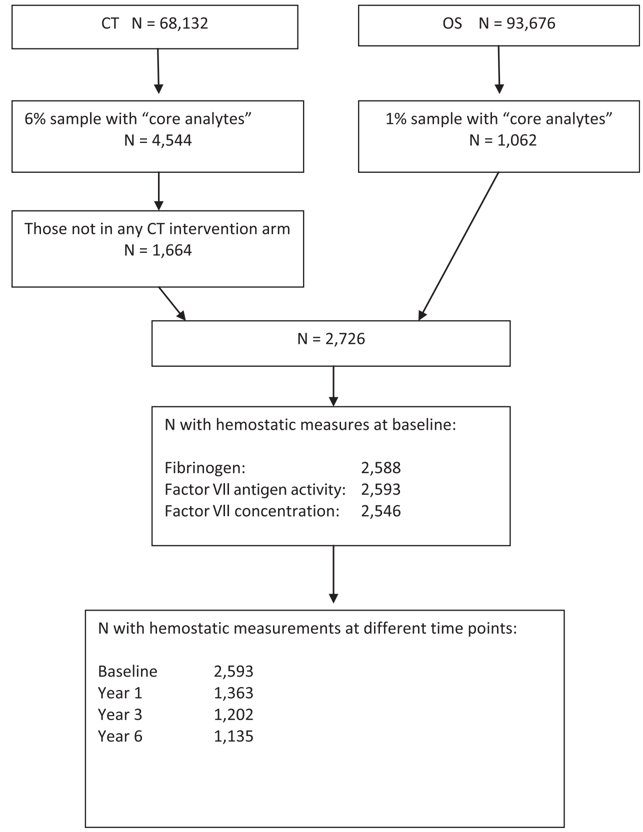

Figure 1 Flowchart showing selection of WHI participants included in the present analysis.