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Research letter

Visceral adipose tissue dysfunction and mortality among a population-based sample of males and females

1. Introduction

Visceral adipose tissue (VAT) is one of the most deleterious fat deposits in the body, increasing the risk of developing cardiovascular disease [1], and certain types of cancer [2]. VAT is a complex endocrine organ that is associated with inflammation, insulin resistance, and immune function [2,3]. The accumulation of VAT often co-occurs with the dysregulation of lipid and liver metabolism, manifesting as elevated triglyceride and γ-glutamyl-transferase (GGT) concentrations, and depleted high-density lipoprotein (HDL) cholesterol concentrations [2,3]. The Visceral Adiposity Index (VAI) and Fatty Liver Index (FLI) are composite measures derived from mathematical models that combine anthropometric [body mass index (BMI) and waist circumference (WC)] and biochemical variables (triglycerides, HDL cholesterol, GGT) to quantify adipose tissue distribution and function [4,5]. As aggregate measures of adipose tissue dysfunction, the VAI and FLI may have clinical utility in predicting cardiovascular events, cerebrovascular events, and hepatic steatosis [4,5]. However, the capacity for the VAI and FLI to predict all-cause and cause-specific mortality in a general population of adults has not been studied. We tested the hypothesis that the VAI and FLI would predict all-cause, cardiovascular-specific, and cancer-specific mortality among a large population-based sample of males and females living in the United States.

2. Methods

2.1. Study design and participants

The Third National Health and Nutrition Examination Survey, 1988–1994 (NHANES III), was a stratified multistage study designed to provide health information on a nationally-representative sample of civilians living within the United States. Study participants included males and females age ≥ 18 years [6]. All participants provided written informed consent before completing any study-related activities.

2.2. Visceral Adiposity Index

The VAI was calculated as described by Amato et al. [4], using the following sex-specific equations:

$$\text{Males}: \text{VAI} = \left(\frac{\text{WC}}{39.68 + (1.88 \times \text{BMI})}\right) \times \left(\frac{\text{TG}}{1.03}\right) \times \left(\frac{1.31}{\text{HDL}}\right);$$

$$\text{Females}: \text{VAI} = \left(\frac{\text{WC}}{36.58 + (1.89 \times \text{BMI})}\right) \times \left(\frac{\text{TG}}{0.81}\right) \times \left(\frac{1.52}{\text{HDL}}\right),$$

where WC is expressed in centimeters, BMI in kg/m^2, and triglycerides (TG) and high-density lipoprotein (HDL) cholesterol in mmol/L. A VAI of 1.0 depicts a non-obese person with a normal ratio between subcutaneous adipose tissue (SAT) and VAT and normal levels of triglyceride and HDL cholesterol. The VAI is correlated with VAT volume as quantified by magnetic resonance imaging ($r = 0.744$; $P < 0.001$), and insulin resistance ($r = -0.721$; $P < 0.001$) in patients with cardiovascular and cerebrovascular risk factors [4].

2.3. Fatty Liver Index

The FLI was calculated as described by Bedogni et al. [5], using the following equation:

$$FLI = \frac{e^L}{(1 + e^L)} \times 100$$

where $L = 0.953 \times \log_e(\text{triglycerides}) + 0.139 \times \text{BMI} + 0.718 \times \log_e(\text{GGT}) + 0.053 \times \text{WC} - 15.745$, with TG measured in mmol/L, GGT in U/L, BMI in kg/m^2, and WC in cm. The FLI ranges from 0–100, with higher values indicating a greater likelihood of having hepatic steatosis [5]. The FLI is associated with abdominal fat mass ($r = 0.662$; $P < 0.001$) and insulin sensitivity ($r = -0.335$; $P < 0.001$) in obese adults in the general population [7].

2.4. Mortality outcome

Vital status and cause of death were identified using the National Death Index (NDI) database with follow-up through December 31, 2011. Cause of death was categorized using the International Classification of Diseases, 10th Edition (ICD-10). Cardiovascular-specific mortality was categorized using ICD-10 codes I00-I079. Cancer-specific mortality was categorized using ICD-10 codes C00-C97.

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2.5. Covariates

Demographic information including date of birth and sex were self-reported using a standardized questionnaire. Height, body mass, and waist circumference were measured by study technicians. BMI was calculated as body mass divided by the square of height (kg/m^2). Clinical characteristics including smoking history, the presence of comorbid health conditions including cancer, myocardial infarction, heart failure, and diabetes, and the use of medications for cholesterol, hypertension, and diabetes were assessed using standardized questionnaires. Blood samples were collected and quantified using standardized laboratory procedures that have been previously described in detail [8]. The Healthy Eating Index was calculated from a 24-hour food recall to form a score than ranges from 0 to 100 to quantify aspects of a healthy diet [9]. Bouts of walking in the past week were self-reported and included any bout of walking that was estimated to be ≥ 1 mile in duration, and of moderate or vigorous intensity. Sleeping difficulty was operationalized as a self-report of recent insomnia or trouble staying asleep.

2.6. Statistical analysis

The primary outcome was all-cause mortality. The secondary outcomes were cardiovascular-specific and cancer-specific mortality. We fit Cox proportional hazards regression models to estimate the hazard ratio (HR) and 95% confidence interval (CI) of tertiles of VAI and FLI with mortality. We confirmed the assumption of proportional hazards by visual inspection of log-log plots. Sample weights were incorporated into all statistical analyses to account for nonresponse bias and multistage sampling probabilities.

3. Results

Among 11,463 men and women, we observed 3347 deaths during a median of 18.7 years of follow-up; 1056 and 749 deaths occurred as a result of cardiovascular disease and cancer, respectively. The mean age of study participants was 44.0 ± 0.21 years and 51.8% were male (Table S1; see supplementary data associated with this article online). The mean BMI was 26.5 ± 0.08 kg/m^2, WC was 91.8 ± 0.21 cm, VAI was 2.3 ± 0.03, and FLI was 41.9 ± 0.45. The VAI and FLI were correlated ($r = 0.48$; $P < 0.0001$). Average tertiles of the VAI were: 0.81 ± 0.006, 1.68 ± 0.008; and 4.65 ± 0.077. Average tertiles of the FLI were 10.8 ± 0.18, 42.9 ± 0.33, and 84.2 ± 0.26.

3.1. Visceral Adiposity Index and mortality

Higher VAI was associated with an increased risk of all-cause (Fig. 1A), cardiovascular-specific, and cancer-specific mortality. In multivariable-adjusted analyses that accounted for demographic, clinical, and behavioral characteristics, higher VAI was associated with an increased risk of all-cause ($P_{trend} < 0.0001$), cardiovascular-specific ($P_{trend} < 0.0001$), and cancer-specific mortality ($P_{trend} = 0.024$) (Table 1). Excluding participants with a history of cancer, myocardial infarction, heart failure, or diabetes did not substantively alter effect estimates.

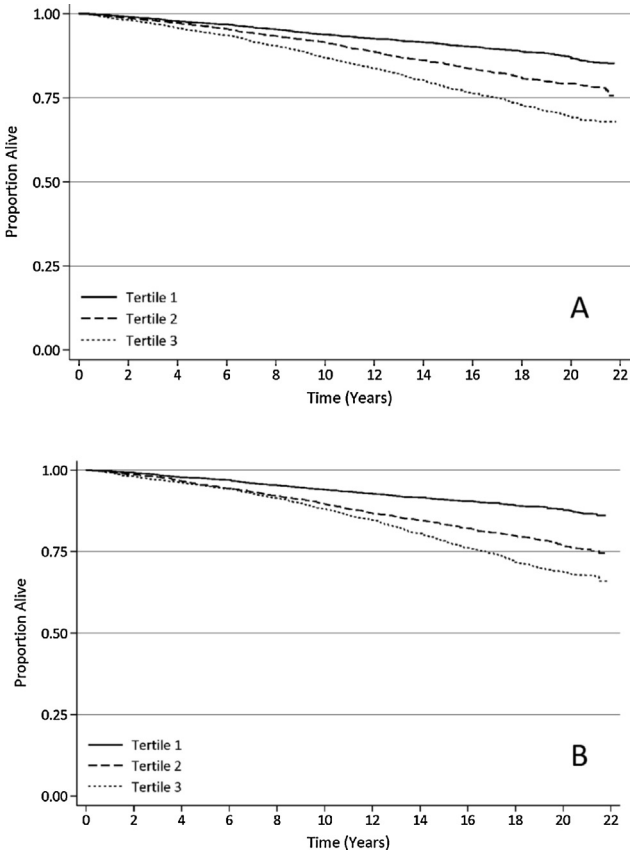

Fig. 1. Relationship between tertiles of (A) the Visceral Adiposity Index and (B) the Fatty Liver Index with all-cause mortality.

3.2. Fatty Liver Index and mortality

Higher FLI was associated with an increased risk of all-cause (Fig. 1B), cardiovascular-specific, and cancer-specific mortality. In multivariable-adjusted analyses that accounted for demographic, clinical, and behavioral characteristics, higher FLI was associated with an increased risk of all-cause ($P_{trend} < 0.0001$), cardiovascular-specific ($P_{trend} < 0.0001$), and cancer-specific mortality ($P_{trend} = 0.003$) (Table 1). Excluding participants with a history of cancer, myocardial infarction, heart failure, or diabetes did not substantively alter effect estimates.

4. Discussion

The principal finding of this study is that males and females with a higher VAI or FLI are more likely to die compared to those with a lower VAI or FLI in a large population-based cohort. Increasing tertiles of VAI or FLI were associated with a consistent increase in the risk of all-cause, cardiovascular-specific, and cancer-specific mortality. These data add to a growing literature that indicates that VAT dysfunction may have important implications for multiple health outcomes, including longevity.

An attractive characteristic of the VAI or FLI as potentially valuable metrics to quantify VAT dysfunction is the