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Pericardial fat is associated with all-cause mortality but not incident CVD: The Rancho Bernardo Study

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ABSTRACT

Objective: Pericardial and intra-thoracic fat are associated with prevalent cardiovascular disease (CVD) and CVD risk factors. However, it is unclear if these fat depots predict incident CVD events and/or all-cause mortality. We examined prospective associations between areas of pericardial and intra-thoracic fat and incident CVD and mortality over a 12-year follow-up in a subset of participants without baseline clinical CVD from the Rancho Bernardo Study (RBS).

Methods: Participants were 343 community-dwelling older adults (mean baseline age = 67) who completed a clinic visit in 2001-02, including a computed tomography scan of the chest. Incident CVD and mortality were recorded through January 2013.

Results: Over a 12.6-year median follow-up, there were 60 incident CVD events and 49 deaths. Pericardial fat was associated with all-cause mortality, such that each standard deviation increment predicted a 34% higher chance of death after adjusting for demographics, lifestyle factors, comorbidities, and visceral fat (95% CI = 1.01–1.78). When categorized by tertile, those in the middle tertile of pericardial fat showed no increased risk of mortality, while those in the highest tertile had 2.6 times the risk (95% CI = 1.10–5.97) compared to the lowest tertile. There was a marginal association between intra-thoracic fat and mortality ($p = 0.06$). Neither pericardial nor intra-thoracic fat was significantly associated with incident CVD. There were no significant interactions by sex.

Conclusions: Higher pericardial, but not intra-thoracic, fat was associated with earlier all-cause mortality in older adults over a 12-year follow-up. This association was primarily driven by a higher mortality rate in those in the highest tertile of pericardial fat.

1. Introduction

There is robust evidence that central body fat distribution is predictive of chronic disease and is often a better predictor than body mass index (BMI) [1,2] or total body fat [3,4]. Specific fat depots, such as fat in the pericardial, visceral, and intra-thoracic cavities, are associated with a range of cardiovascular and metabolic risk factors and conditions, including diabetes and hypertension [5]. These associations remain significant after adjusting for BMI and/or total body fat, suggesting that the location of fat in the body, rather than the overall quantity, is a key factor in determining disease risk.

Not surprisingly, pericardial fat in particular has been associated with cardiovascular outcomes. Pericardial fat is associated with prevalent cardiovascular disease (CVD) [6,7] and incident coronary heart disease (CHD) [8], suggesting it is not simply a marker of existing disease, but contributes to the development of CHD. Intra-thoracic fat, or fat external to the pericardial sac and within the thoracic cavity, is anatomically close to pericardial fat, and is also associated with cardiovascular [5] and metabolic risk factors [9,10]. However, there is little research reporting the associations between intra-thoracic fat and incident morbidity. Similarly, little is known about the associations between fat depositions in the chest and all-

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cause mortality. One study using data from the Framingham Heart Study found no association between pericardial fat and mortality, but this sample was quite young, and associations with intra-thoracic fat were not reported [11].

Given the robust relationship between pericardial and intra-thoracic fat deposition and CVD risk factors, further examination of the associations between these measures and future morbidity and mortality is warranted. Therefore, the purpose of this paper was to examine the associations between pericardial fat and intra-thoracic fat with incident CVD and all-cause mortality in a sub-sample of older non-Hispanic white men and women from the Rancho Bernardo Study, and to determine if these associations varied by sex.

2. Methods

2.1. Study design

The Rancho Bernardo Study (RBS) is a prospective cohort study established between 1972 and 1974 in a suburb of San Diego, California, when 82% of community-dwelling adults in this predominantly older, non-Hispanic White, middle to upper-middle class area agreed to participate in a survey of heart disease risk factors. A full account of inclusion/exclusion criteria and recruitment details has been published [12]. Participants have subsequently completed periodic clinic examinations in the Rancho Bernardo research clinic as well as follow-up via phone and mailers. A subsample of the majority of surviving participants who attended a 1997–1999 clinic visit, were free of clinical CVD, and were at least 55 years of age, completed a follow-up clinical examination in 2001–2002 at which time computed tomography (CT) scans of the chest and abdomen were obtained to determine the presence and extent of coronary artery calcium. These scans were also evaluated for region-specific fat deposition. In the current study, we report on 187 women and 156 men who had pericardial and intra-thoracic fat data and complete follow-up for cardiovascular events and mortality through January 2013.

The RBS was approved by the Institutional Review Board of the University of California, San Diego, and all participants gave written informed consent.

2.2. Measurement of covariates

Information on demographics, lifestyle factors, and cardiovascular risk factors ascertained at the 1997–1999 clinic visits included standard self-administered or interviewer-administered questionnaires were used to record age, sex, physical activity, and smoking status. Medication use was assessed via a medication inventory. Height and weight were measured with participants in light clothing and no shoes, and used to compute body mass index (BMI; kg/m^2). Blood pressure was recorded as the average of two measurements taken with participants resting in a seated position after rest for 5 min. Hypertension was defined as $\geq$140 mmHg systolic and/or $\geq$90 mmHg diastolic, and/or use of anti-hypertension medication.

Fasting plasma glucose, cholesterol, and triglycerides were measured in morning fasting blood samples obtained after an 8–12-h fast. Diabetes was defined as use of diabetes medication, or fasting plasma glucose of $\geq$126 mg/dL. Low-density cholesterol (LDL) was calculated using the Friedewald equation [13], and high-density cholesterol (HDL) was determined using precipitation analysis.

Adipocytokines were measured using EDTA fasting plasma samples stored at −70 °C. Adiponectin was measured via radio-immunoassay (Millipore Linco Research, St Charles, MO) with intra- and inter-assay coefficients of variation (CVs) ranging from 1.97% to 7.32%. Interleukin (IL)-6 was measured via ELISA (R&D Systems, Minneapolis, MN) with intra- and inter-assay CVs for IL-6 of 4.9%–10.5%

2.3. Measurement of regional adiposity

During the 2001-02 exam, areas of pericardial and intra-thoracic fat were measured from the computed tomography (CT) scans of the chest. Full details of regional fat measurement and quantification, including intra-thoracic and pericardial fat with accompanying example CT images, have been published elsewhere [9]. In brief, 15 CT slices of 3 mm thickness were selected originating from the right coronary artery (slice 1), 4 slices above the right coronary artery and 10 slices below. The anterior border of the total thoracic fat volume was defined by the interior margin of the chest wall and the posterior border by the aorta and bronchus. The pulmonary vessels were excluded. The anterior border of the pericardial area was defined by the line of the fibrous pericardium and the posterior border was shared with the thoracic area. Intra-thoracic fat area was defined as the total thoracic fat area minus the pericardial fat area. Using a 6 mm cross sectional CT slice taken at the umbilicus, visceral fat was measured at the same visit. The chest and abdominal CT scans were read by three experienced CT analysts using body composition segmentation software (MIPAV 4.1.2, National Institutes of Health) on networked computers. CT reader intra- and inter-rater reliability in the lab ranged from 0.85 to 0.99. Tissues with a voxel count between −190 and −30 Hounsfield units were counted as adipose tissue, and reported in cm^2. With the non-contrast CT scans and the current MIPAV software, epicardial fat cannot be adequately or precisely quantified; thus, it was not measured in this study.

2.4. Incident cardiovascular disease and total mortality outcomes

Follow-up for mortality and cardiovascular events was obtained through January 2013 for all 343 RBS participants who completed regular clinic visits, annual mailings, and/or telephone surveys. Incident CVD included fatal and non-fatal myocardial infarction (MI), stroke, and transient ischemic attack (TIA), coronary artery bypass, angioplasty, and/or carotid endarterectomy. Information on non-fatal CVD events was obtained via self-report of physician diagnosis at clinic exams, or on annual mailed questionnaires or telephone surveys. Additionally, evidence of a previous MI on a 12-lead electrocardiogram was taken into account, including Minnesota codes 1.1 to 1.2 (major Q-wave) and 7.1.1 (left branch bundle block). As indicated elsewhere [14], validation of self-reported physician diagnosis has been previously performed in a sample of 30% of cases in the RBS, and was validated in 85% of those cases.

All-cause mortality was confirmed by death certificates in approximately 95% of all decedents, with underlying cause of death coded by a certified nosologist using the ninth revision of the International Classification of Diseases (ICD-9), Adapted. CVD death codes included 401-414, 426-438, and 440-448, all causes codes were 0–999.

2.5. Statistical analysis

Univariate associations were assessed using ANOVA, chi-square or t-tests as appropriate. Unadjusted event rates were calculated per 1000 person-years. To examine the multivariate associations of intra-thoracic and pericardial fat with all-cause mortality and incident CVD events, staged Cox proportional hazards regression models were used. The first model stage included age and sex. Then, for model 2 we added physical activity, ever smoking, height,