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The association between serum cathepsin L and mortality in older adults

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ABSTRACT

Background and aims: Research suggests that the protease cathepsin L is causally involved in atherosclerosis. However, data on cathepsin L as a risk marker are lacking. Therefore, we investigated associations between circulating cathepsin L and cardiovascular mortality.
Methods: Two independent community-based cohorts were used: Uppsala Longitudinal Study of Adult Men (ULSAM); n = 776; mean age 77 years; baseline 1997–2001; 185 cardiovascular deaths during 9.7 years follow-up, and Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS); n = 993; 50% women; mean age 70 years; baseline 2001–2004; 42 cardiovascular deaths during 10.0 years follow-up.
Results: Higher serum cathepsin L was associated with an increased risk for cardiovascular mortality in age- and sex-adjusted models in both cohorts (ULSAM: hazard ratio (HR) for 1-standard deviation (SD) increase, 1.17 [95% CI, 1.01–1.34], $p = 0.032$ PIVUS: HR 1.35 [95% CI, 1.07–1.72], $p = 0.013$). When merging the cohorts, these associations were independent of inflammatory markers and cardiovascular risk factors, but non-significant adjusting for kidney function. Individuals with a combination of elevated cathepsin L and increased inflammation, kidney dysfunction, or prevalent cardiovascular disease had a markedly increased risk, while no increased risk was associated with elevated cathepsin L, in the absence of these disease states.
Conclusions: An association between higher serum cathepsin L and increased risk of cardiovascular mortality was found in two independent cohorts. Impaired kidney function appears to be an important moderator or mediator of these associations. Further studies are needed to delineate the underlying mechanisms and to evaluate whether the measurement of cathepsin L might have clinical utility.
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1. Introduction

The cysteine cathepsins are a group of proteases located both intra- and extracellularly [1–3]. The cathepsins have been shown to be involved not only in protein modifications in the regulation of the cell cycle, but also as important players in several physiological processes, such as within the immune system, regulating antigen presentation by major histocompatibility complex (MHC) class II and MHC class I-like molecules, bone and cartilage turnover degrading matrix, and endocrine systems involved in proteolytic processing of hormones [4–7].

Being one of the most ubiquitously expressed cathepsin proteases, cathepsin L has been shown to be involved in numerous organ diseases, such as in the process of tumour progression and invasiveness and the enlargement of adipose tissue and development of obesity and increased cardiovascular risk [8,9]. Upregulation of the cathepsin L gene in type II diabetes indicates a possible role in glucose tolerance and transport [10]. The facilitation of MHC class II maturation to countervail immune defects, and the detrimental effects of cathepsin L proteolytic cleavage is involved in the subsequent development of kidney disease [11–13]. Finally,

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cathepsin L has also been suggested to be causally involved in atherosclerosis, among other processes, through apoptosis and plaque destabilization [14–16]. Yet to date, previous studies on cathepsin L are mainly experimental and clinical data is scarce.

Based on available data, we hypothesized that cathepsin L plays a causal role in the development of cardiovascular disease (CVD). Accordingly, we discovered and replicated the longitudinal associations between circulating levels of cathepsin L and the risk for cardiovascular and total mortality in two independent community-based samples of elderly.

2. Material and methods

2.1. Study samples

2.1.1. The Uppsala Longitudinal Study of Adult Men (ULSAM)

This study cohort, in progress since 1970, focusing on cardiovascular risk factors [17], is described in detail on http://www.pubcare.uu.se/ULSAM. Inclusion criteria were male sex, age 50 years (birth year 1920–24) and resident in Uppsala County, Sweden. For this examination cycle (the fourth examination cycle of ULSAM when participants were approximately 77 years old), 1398 were invited and 838 agreed to participate. Due to missing data on cathepsin L, we excluded 62 participants, leaving 776 participants as study sample (Fig. 1).

2.1.2. The Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS)

Both male and female study participants were recruited between 2001 and 2004 in the PIVUS cohort which is described in detail on http://www.medsci.uu.se/pivus/pivus.htm. Inclusion criteria were age 70 years and resident in Uppsala County, Sweden [18]. 2025 were invited to participate and a total of 1016 agreed. Twenty three had missing data on cathepsin L, leaving 993 participants as study sample (Fig. 1).

2.2. End point definitions

Incident cardiovascular disease and mortality data were collected from The Swedish Cause-of-Death register, and total mortality and cardiovascular mortality were defined accordingly (Death from cardiovascular causes; International Classification of Diseases, 10th Revision [ICD-10] I00-I99). Prevalent cardiovascular disease was defined as having been hospitalized for ischemic heart disease or cerebrovascular disease prior to baseline (ICD-10 I20-I25, or I60-I69/G4 respectively).

3. Covariates

The collection of clinical and biochemical characteristics has been described in detail elsewhere [17,18]. In brief, the calculation of body mass index (BMI; kg/m^2) and assessment of blood pressure were performed using standardized methods. Participants were asked to fill in questionnaires regarding medical history, medication, physical activity, socioeconomic status, and smoking habits [17,19]. Fasting plasma glucose (≥7.0 mmol/l or ≥126 mg/dl) or use of antidiabetic medication was used to diagnose diabetes mellitus. Venous blood samples for biochemical analyses were drawn in the morning after an overnight fast and kept at −70 °C until the analysis. Measurements on glucose, cholesterols and creatinine were assessed by standard analytical methods. Serum cathepsin L was analyzed by a sandwich Enzyme-Linked Immunosorbent Assay (ELISA) (DY952; R&D Systems, Minneapolis, MN, USA). The total coefficient of variation (CV) for the assay was approximately 7%. High sensitivity C-reactive protein (CRP) measurements were performed with latex enhanced reagent (Dade Behring, Deerfield, IL) using a Behring BN ProSpec analyzer (Dade Behring), and the intra-assay CV of the CRP method was 1.4% at both 1.23 mg/l and 5.49 mg/l. In the ULSAM cohort, IL-6 was analyzed using a high-sensitivity ELISA kit (IL-6 HS; R&D Systems, Minneapolis, MN, USA). The total CV of the method was 7% and the inter-assay CV was 5%. In PIVUS, IL-6 was analyzed using the Evidence® array biochip

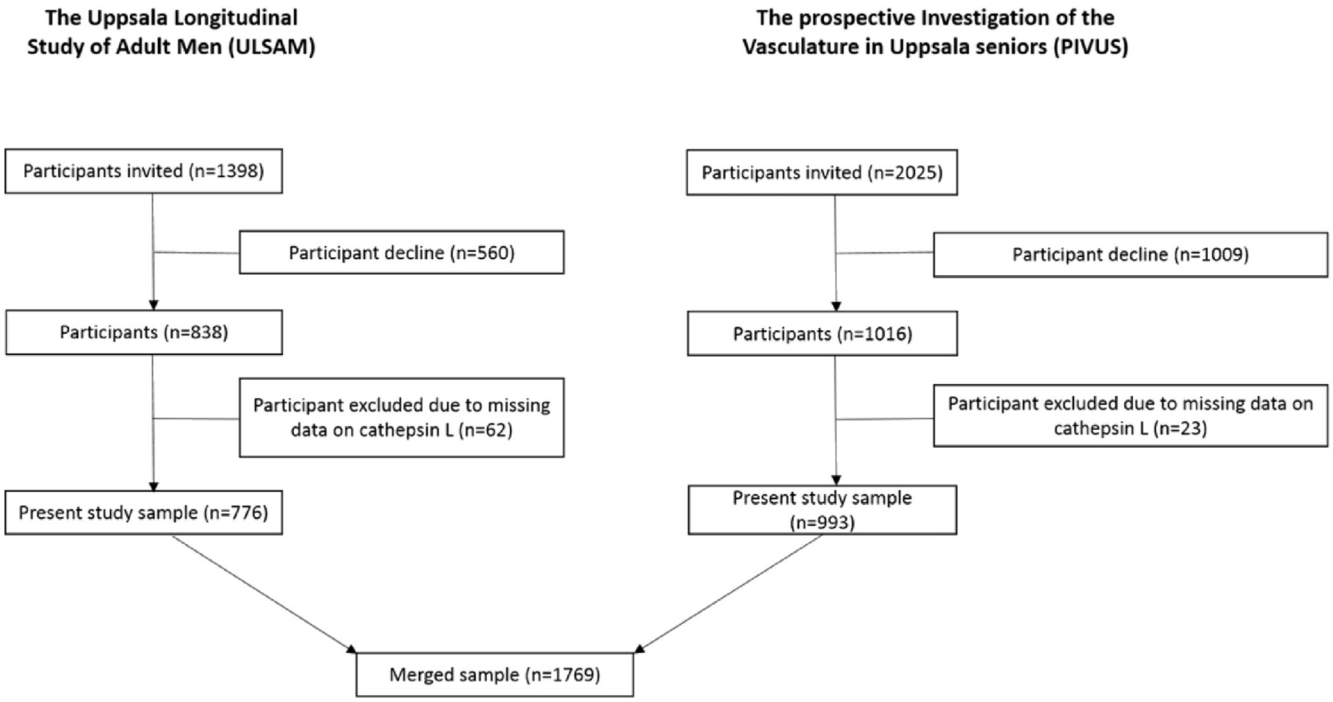

Fig. 1. Flow chart describing the number of participants in each cohort.

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