INTRODUCTION

Review question / Objective: Epicardial fat represents visceral adiposity. Many observational studies have reported that increased epicardial is associated with adverse metabolic profile, cardiovascular risk factors, and coronary atherosclerosis in patients with cardiovascular diseases and in general population. We and others have previously reported the association of increased epicardial fat with left ventricular (LV) hypertrophy and diastolic dysfunction as well as the development of heart failure (HF) in these populations. In some studies, however, the association did not reach statistical significance. The inconsistent results may be due to limited power, different imaging modalities for quantifying epicardial fat volume, and different outcome definitions. Accordingly, we aim to perform the systematic review and meta-analysis of studies on the association of epicardial fat with cardiac structure and function and cardiovascular outcomes.

Condition being studied: Patients with cardiovascular diseases and in general population.

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 31 August 2022 and was last updated on 31 August 2022 (registration number INPLASY202280109).
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**Condition being studied:** Patients with cardiovascular diseases and in general population.

**METHODS**

**Participant or population:** Adult (>18 years) patients.

**Intervention:** Not applicable.

**Comparator:** Not applicable.

**Study designs to be included:** Observational cohort studies.

**Eligibility criteria:** Inclusion criteria for this meta-analysis included: (1) included adult (>18 years) patients; (2) quantified epicardial fat volume using CT or MRI; (3) measured cardiac structure and function on echocardiography or assessed cardiovascular outcomes; and (4) described the relation of epicardial fat volume with cardiac structure and function or cardiovascular outcomes.

**Information sources:** The electronic databases for literature search will include PubMed, Web of Science, and Scopus.

**Main outcome(s):** The primary outcome will be cardiac structure and function. In the measures of cardiac structure, LV mass and left atrial volume will be extracted. In the measures of LV systolic function, LV ejection fraction and early systolic mitral annular velocity (s') will be extracted. In the measures of LV diastolic function, early diastolic mitral annular velocity (e') and the ratio of early diastolic mitral inflow to annular velocities (E/e') will be extracted given the linear relationship with LV diastolic dysfunction grade.

**Additional outcome(s):** The secondary outcome will be cardiovascular events including cardiovascular death, hospitalization for HF, and a composite of cardiovascular death and hospitalization for HF.

**Quality assessment / Risk of bias analysis:** The quality of observational studies will be evaluated by Newcastle-Ottawa Scale tool (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp).

**Strategy of data synthesis:** To assess the association of pericardial fat with cardiac structure and function, correlation coefficients between pericardial fat volume and indices of cardiac structure and function will be synthesized. To assess the association of epicardial fat with cardiovascular outcomes, hazard ratios adjusted by variables of age and sex at least will be synthesized. For each outcome, heterogeneity will be assessed using the Cochran's Q and I² statistic; for the Cochran's Q and I² statistic, a p value of 50%, will be considered significant, respectively. When there is significant heterogeneity, the data will be pooled using a random-effects model, otherwise a fixed-effects model will be used.

**Subgroup analysis:** Subgroup analysis stratified by study design (prospective or retrospective), modalities for quantifying epicardial fat volume (CT or MRI), and baseline patient characteristics (patients with cardiovascular diseases or general population) will be performed.

**Sensitivity analysis:** Meta-regression will be used to determine whether the association of increased epicardial fat with outcomes will be confounded by baseline clinical characteristics.

**Country(ies) involved:** Japan.

**Keywords:** epicardial fat; adipose, cardiac structure and function; heart failure; meta-analysis.
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