

Yale University Open Data Access (YODA) Project

RESEARCH PROPOSAL TEMPLATE

Research Proposal

Project Title

Association Between Body Mass Index (BMI) and Prognosis in Cancer Patients:
Analysis of Baseline, Trajectories, and Mediating Effects

Narrative Summary

Obesity, measured by Body Mass Index (BMI), is a major global health issue linked to increased risk of many cancers. Surprisingly, some studies show that obese cancer patients may live longer—a phenomenon known as the “obesity paradox.” The reasons for this are unclear and may be due to research limitations such as reverse causation, confounding factors, or selection bias. This study will use detailed data from multiple clinical trials to examine how BMI—both at the start of treatment and over time—affects survival, treatment response, and side effects in patients with various solid tumors. We will group patients by similar BMI patterns and analyze whether these patterns influence how long patients live, how well treatments work, and whether they experience side effects. We will also explore whether side effects help explain the relationship between BMI and cancer outcomes. The results of this study may help doctors personalize treatment plans and improve care for cancer patients by better understanding the role of body weight in cancer prognosis and treatment safety.

Scientific Abstract

Background: The “obesity paradox” describes the counterintuitive association between higher BMI and improved survival in certain cancers. The mechanisms remain poorly understood, and methodological issues may contribute to conflicting findings.

Objective: To evaluate the association between BMI and prognosis (overall survival, progression-free survival) and safety (adverse events) in patients with solid tumors receiving targeted therapy, immunotherapy, or chemotherapy, and to explore mediating effects of adverse events.

Study Design: Individual participant data meta-analysis of multiple clinical trials.

Participants: Patients with non-small cell lung, breast, prostate, gastric, or colon cancer from selected trials.

Primary and Secondary Outcome Measures: Primary: overall survival (OS) and progression-free survival (PFS). Secondary: incidence of adverse events (AEs), and early mortality (within 60 days).

Statistical Analysis: Cox models for survival outcomes, mediation analysis for adverse events,

random-effects meta-analysis to pool estimates across trials. Subgroup analyses by PD-L1 expression and gender.

Brief Project Background and Statement of Project Significance

Obesity is a growing global health concern associated with increased cancer risk. However, the “obesity paradox” suggests that in some cancers, higher BMI may be associated with better survival. This may be due to methodological limitations such as reverse causality, confounding, or selection bias. This study uses repeated BMI measurements and advanced causal inference methods to clarify the relationship between BMI and cancer outcomes across multiple solid tumors and treatment types. Findings will contribute to generalizable knowledge about the role of BMI in cancer prognosis and treatment safety, potentially informing future trial design and personalized treatment strategies.

Specific Aims of the Project

To evaluate the association between BMI and survival outcomes (OS, PFS) in patients with solid tumors.

To assess the relationship between BMI and incidence of treatment-related adverse events.

To explore whether adverse events mediate the relationship between BMI and survival.

To determine whether BMI should be considered a stratification factor in future cancer trials.

What is your Study Design?

Individual trial analysis

Meta-analysis (analysis of multiple trials together)

Other

Please explain: Individual participant data (IPD) meta-analysis of multiple trials.

What is the purpose of the analysis being proposed?

New research question to examine treatment effectiveness on secondary endpoints and/or within subgroup populations

New research question to examine treatment safety

Participant-level data meta-analysis

Meta-analysis using only data from the YODA Project

Develop or refine statistical methods

Research Methods

We will use individual participant data from multiple trials available through YODA. Analyses will be conducted within the secure data platform using R. Our primary analysis will utilize Latent Class Growth Mixed Models (LCGMM) to identify distinct trajectories of BMI change over time during treatment. We will combine data from patients with the same cancer type or treatment for increased power. The identified trajectory classes will serve as the main exposure variable in Cox proportional hazards models to assess their effect on survival. Mediation analysis will test whether adverse events mediate the trajectory – outcome relationship. Random-effects meta-analysis will pool estimates across trials. Confounders such as age, gender, smoking status, performance status, and tumor characteristics will be adjusted for.

Software to be used:

R

Data Source and Inclusion/Exclusion Criteria

Data will be sourced from YODA-provided trials listed in the proposal. Inclusion: patients with solid tumors (non-small cell lung, breast, prostate, gastric, colon) who received targeted, immunotherapy, or chemotherapy. Exclusion: missing baseline height or weight data.

Primary and Secondary Outcome Measure(s) and how they will be categorized/defined for your study

Primary:

OS: time from randomization to death from any cause.

PFS: time from randomization to disease progression or death.

Secondary:

AEs: incidence of any grade adverse events (NCI CTCAE v4.0/4.03).

Early mortality: death within 60 days post-randomization.

Main Predictor/Independent Variable and how it will be categorized/defined for your study

The main predictor will be BMI trajectories identified through Latent Class Growth Mixed Models (LCGMM) analysis. These trajectories represent distinct patterns of BMI change over time during treatment. Additionally, baseline BMI (kg/m²) will be categorized per WHO: underweight (<18.5), normal (18.5–24.9), overweight (25–29.9), obese (≥30). The main predictor will be BMI trajectories identified through Latent Class Growth Mixed Models (LCGMM) analysis. These trajectories represent distinct patterns of BMI change over time during treatment. Additionally, baseline BMI (kg/m²) will be categorized per WHO: underweight (<18.5), normal (18.5–24.9), overweight (25–29.9), obese (≥30).

Other Variables of Interest that will be used in your analysis and how they will be

categorized/defined for your study

Demographics (age, gender, region, race), clinical confounders (smoking, ECOG status, tumor type, PD-L1 expression, etc.), concomitant medications (e.g., metformin, corticosteroids), and adverse events related to weight/metabolism.

Statistical Analysis Plan

Patients with missing baseline height or weight will be excluded. BMI will be categorized (normal, overweight, obese; ≥ 25 vs <25 kg/m²). Baseline characteristics will be summarized descriptively and compared using chi-square or t/Wilcoxon tests. Overall and progression-free survival will be estimated by Kaplan - Meier methods and compared by log-rank tests. Associations between BMI and outcomes will be assessed using multivariable Cox proportional hazards models adjusting for prespecified demographic and clinical confounders. Longitudinal BMI trajectories will be identified using latent class growth mixture models, and trajectory groups will be evaluated as exposures in Cox models. Treatment-related adverse events will be analyzed with regression models. Study-specific estimates will be synthesized using fixed- or random-effects meta-analysis based on heterogeneity. All analyses will be conducted in R within the Vivli environment.

Project Timeline

Start date: January 1, 2026

Analysis completion: December 31, 2028

Manuscript drafted and submitted: Within 6 months of analysis completion

Results reported to YODA: Concurrent with submission

Dissemination Plan

Results will be submitted to high-impact oncology journals such as ESMO or HHS Public Access. Findings will be presented at international conferences and shared with the clinical research community to inform future trial design and treatment guidelines.

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