**Peer Review File**

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**Reviewer Comments：**

Congratulations on your study. This study is significant for its comprehensive analysis of the causal relationships between 1400 plasma metabolites and 24 types of cancer. By using Mendelian randomization analysis, it identifies specific plasma metabolites causally associated with various cancers, spanning diverse metabolic pathways like glucose, fatty acid, amino acid, and caffeine metabolism. These findings not only provide potential biomarkers for cancer detection and therapeutic targets but also advance our understanding of cancer metabolism and tumorigenesis mechanisms. I find your article well-executed, highly interesting, and progressive in advancing our understanding of cancer metabolism.

**A minor comment:**

*The authors didn't specify whether the metabolites were detected in the early stages of cancer. Without such information, it's important to clarify that while the study identifies plasma metabolites causally associated with various cancers, it doesn't explicitly state that these associations are indicative of early-stage cancer detection.*

**Response：** We feel great thanks for your professional review work and sincerely appreciate the valuable comments. Metabolic processes have always been a hot point in tumor research, and it has been more than a decade since Hanahan reviewed the reprogramming of energy metabolism in tumors and proposed metabolism as an emerging marker for tumors in his “Hallmarks of Cancer: New Dimensions”(1). In recent years, with the rapid development of histology and liquid chromatography, more and more researchers have turned their attention to this field and hoped to find plasma metabolites with tumor-predicting ability. For example, Shi et al. analyzed plasma from children with medulloblastoma and with other intracranial tumors by ultra-performance liquid chromatography tandem mass spectrometry (UPLC-MS/MS) in an attempt to find the “ Yes/No” markers for medulloblastoma(2). Our study was similar in that it

only differentiated between cancerous and healthy populations, and did not differentiate between tumor stages or follow the population over time. VVidman et al. started collecting data from patients before they developed cancer, followed them up, and obtained detailed changes in plasma metabolites as colorectal cancer changed from absence to presence in the population(3). Wei et al. collected plasma metabolites data from people with breast cancer at different STAGES to obtain a specific marker for early breast cancer(4). Due to the limitation of data sources, our data do not realistically reflect the relationship between early-stage cancer and plasma metabolites. We will make further changes in the revised manuscript. (Please see the revised manuscript for details).

**Reference**

1. Hanahan D, Weinberg RA. Hallmarks of Cancer: The Next Generation. Cell. 2011 Mar;144(5):646–74.
2. Shi Z, Yang C, Xu X, Wu W, Jiang D, Yan D. Plasma metabolite profiles identify pediatric medulloblastoma and other brain cancer. Anal Bioanal Chem. 2023 Jan;415(3):471–80.
3. Vidman L, Zheng R, Bodén S, Ribbenstedt A, Gunter MJ, Palmqvist R, et al. Untargeted plasma metabolomics and risk of colorectal cancer-an analysis nested within a large-scale prospective cohort. Cancer Metab. 2023 Oct 17;11(1):17.
4. Wei Y, Jasbi P, Shi X, Turner C, Hrovat J, Liu L, et al. Early Breast Cancer Detection Using Untargeted and Targeted Metabolomics. J Proteome Res. 2021 Jun 4;20(6):3124–33.