

Review: Analysis of Smoking and Obesity Therapy Pathway Mapping Using DEG (Differentially Expressed Genes) Data

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Abstract: Therapeutic pathway impacts of smoking and obesity can be mapped through analysis of Differentially Expressed Gene (DEG) datasets. Data used in this study were obtained from the National Center for Biotechnology Information (NCBI) Gene Expression Omnibus (GEO), a reputable biomedical data repository. This study identified a total of 17 eligible GEO datasets for analysis to detect genes with differential expression (DEGs) in response to smoking and obesity exposure. Identified DEGs were further categorized according to their functional profiles. Our findings provide deeper insights into the molecular impacts of smoking and obesity and hold potential for therapeutic strategy development and biomarker discovery related to tobacco exposure and adiposity. Retrieved datasets were synthesized into eight distinct functional gene categories covering metabolism, immunity, cell cycle, and cardiovascular pathways.

Keywords: Smoking; Obesity; DEG; GEO; Transcriptomics

Introduction

Smokers expose themselves to nicotine, which is rapidly absorbed into systemic circulation. The health risks associated with tobacco use are substantial. Cigarette smoke contains more than 9,500 chemical compounds. As early as 2012, the United States Food and Drug Administration identified 79 tobacco constituents as established or probable human carcinogens. Over the past decade, the International Agency for Research on Cancer (IARC) has further expanded this list, classifying 83 tobacco components as carcinogenic—with no measurable decline in exposure prevalence since 2012. Strict regulatory oversight and public health monitoring are therefore essential to mitigate cancer burden and other smoking-related diseases (Li & Yupeng, 2022).

Evidence-based interventions—including tobacco taxation, public education campaigns, and brief clinical counseling—effectively motivate quit attempts. Combined behavioral support and pharmacotherapy

further improve cessation outcomes. National comprehensive tobacco control programs have demonstrated measurable reductions in smoking prevalence and associated morbidity and mortality. As the leading preventable cause of death worldwide, tobacco use remains a critical priority for clinical and public health researchers alike (Di Cicco et al., 2016; West, 2017).

Recent analyses attribute more than twice as many annual deaths to tobacco use as the combined mortality burden of alcohol and illicit drugs (Xu et al., 2022; Widysanto et al., 2022). Cigarette smoking and obesity frequently co-occur in clinical settings and exert compounded health effects. Low-grade systemic inflammation, reflected in circulating proinflammatory cytokines, has been associated with post-traumatic stress disorder (PTSD); however, current evidence suggests that comorbid smoking and obesity—rather than PTSD itself—primarily drive this inflammatory signature (Iyer et al., 2022). Obesity and tobacco use rank as the two leading preventable causes of death in the United States.

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Although epidemiological links between obesity and nicotine use disorder (NUD) are well documented, the central nervous system mechanisms underlying this comorbidity remain incompletely characterized. The present investigation employs arterial spin labeling functional magnetic resonance imaging (ASL-fMRI) to characterize brain responsivity to smoking-related and neutral cues across weight strata. Seventy-nine treatment-seeking adults with NUD—including 26 normal-weight, 28 overweight, and 25 obese participants—completed imaging protocols (Vely et al., 2020).

In Indonesia, adult smoking prevalence increased from 32.8% (2016) to 33.8% (2018). Age-stratified prevalence estimates from Tegal Municipality indicate 21.01% among individuals aged 15–24 years, 33.13% among those aged 25–34 years, and 30.07% among those aged 45–54 years (National Institute of Health Research and Development, 2018; Ministry of Health Republic of Indonesia, 2013). Nationwide, adult obesity prevalence reached 26.6% in 2015 (Ministry of Health Republic of Indonesia, 2015). Central obesity prevalence in Central Java Province, based on the 2018 Basic Health Research (Riskesmas) dataset, was recorded at 24.7% among individuals aged 15 years and older (National Institute of Health Research and Development, 2018). In China, approximately one-third of global tobacco production and consumption occurs domestically. Despite tobacco control policies, an estimated 350 million active smokers and 740 million passive smokers remain exposed. Rising prevalence among adolescents and women is particularly concerning. Tobacco-attributable mortality currently exceeds 1.2 million annually, with projections exceeding 2 million annual deaths by 2025 (Zang et al., 2011).

The health consequences of tobacco use extend far beyond direct toxicity, including adverse fetal developmental outcomes, malignancy, rheumatoid arthritis, and cardiovascular and pulmonary disease. In this context, the National Center for Biotechnology Information (NCBI; <https://www.ncbi.nlm.nih.gov/gds>) provides critical open-access biomedical data resources—most notably the Gene Expression Omnibus (GEO) repository, established in 2000 as a centralized public archive of high-throughput functional genomic data. The 17 curated datasets analyzed in this study include: GSE206037 (obesity; Rasool et al., 2022), GSE197285 (obesity; Schutte et al., 2022), GSE196900 (oncology; Roy et al., 2022), GSE155213 (immunology; Liu et al., 2021), GSE114043 (immune response; Hughes-Austin et al., 2018), GSE103657 (oncology; van Dijk et al., 2017), GSE74988 (oncology; Mujagic et al., 2017), GSE77962 (lipid metabolism; Tareen et al., 2017), GSE89181 (neurobiology; Kaz et al., 2016), GSE53232 (lipid

metabolism; Esser, 2015), GSE46699 (obesity; Eckel-Passow, 2014), GSE45927 (cholesterol biosynthesis; Mattison et al., 2014), GSE66818 (vascular biology), GSE43580 (oncology; Tarca et al., 2013), GSE234304 (oncology; Stone et al., 2024), GSE261205 (immunology; Shanthamallu et al., 2024), and GSE271452 (obesity; Sellers et al., 2024). Through continuous technological advancement and standardized curation, NCBI and GEO have become foundational infrastructure for transcriptomic research into tobacco-related disease (Clough & Barrett, 2016).

By systematically mining publicly available transcriptomic datasets, this review aims to identify conserved gene expression signatures associated with tobacco exposure. Such evidence may inform rational therapeutic development strategies targeting the molecular pathways perturbed by tobacco use (Clough & Barrett, 2016).

Method

This study systematically analyzed transcriptomic profiles associated with tobacco exposure and obesity using NCBI GEO Series (GSE) datasets. Data were retrieved from the National Center for Biotechnology Information repository (<https://www.ncbi.nlm.nih.gov/gds>). The Gene Expression Omnibus (GEO) database was selected as the primary data source due to its standardized curation, comprehensive metadata, and global accessibility. Keyword search terms included tobacco AND obesity, smoking AND obesity, and nicotine AND obesity. Retrieved records were filtered to include only studies involving human subjects (*Homo sapiens*). Final inclusion required relevance to tobacco exposure and obesity, human study populations, and availability of series-level expression data.

Predefined inclusion and exclusion criteria were applied during study selection. Eligible studies reported original empirical transcriptomic data investigating molecular links between tobacco exposure and obesity, involved human participants, and included full or sufficiently detailed public metadata. Records lacking direct relevance to tobacco or obesity, non-human studies, and non-omic investigations were excluded.

After systematic screening, eligible datasets were reviewed to verify relevance and interpret biological context. Data synthesis employed descriptive analytical methods. Retrieved GSE records were aggregated and grouped according to biological function through standardized functional annotation (Zeller, 2022).

Result and Discussion

This study analyzes seventeen publicly available GEO datasets to identify differentially expressed genes associated with smoking and obesity. Seventeen curated GEO datasets reveal distinct gene expression signatures

across eight major biological functional categories. Identified genes represent key regulatory molecules in metabolism, immunity, cell cycle control, and vascular function. These findings provide molecular insights into how smoking and obesity alter biological pathways at the transcriptome level.

Table 1. Articles involved in gene expression due to smoking and obesity

Article Code	References	Title	Research Methodology
GSE206037	Aisha Rasool, Taysir Mahmoud, [...], and Perrie, 2022.	Obesity downregulates lipid metabolism genes in first trimester placenta	Expression profiling by array
GSE197285	Sophie Schutte, Diederik Esser, [...], and The Wageningen Belly Fat Study team, 2022	Diverging metabolic effects of two energy restricted diets differing in nutrient quality: a 12-week randomized controlled trial in subjects with abdominal obesity	Expression profiling by array
GSE196900	Souvick Roy, Yinghui Zhao, Yate-Ching Yuan, Ajay Goel, 2022	Metformin and ICG-001 Act Synergistically to Abrogate Cancer Stem Cells-Mediated Chemoresistance in Colorectal Cancer by Promoting Apoptosis and Autophagy	Expression profiling by high throughput sequencing
GSE155213	Cuining Liu, Jeanette Gaydos, Rebecca Johnson-Paben, Katerina Kechris, Ellen L. Burnham, Sunita Sharma Am J Respir Cell Mol Biol, 2022	Chronic Marijuana Use Is Associated with Gene Expression Changes in BAL	Expression profiling by high throughput sequencing
GSE66818	Scholz CJ, Schulz CA, Niehaus D, Dietz UA, 2020.	Global gene expression profiling of tissue engineered neofascia of hernia patients with good and bad healing characteristics.	Expression profiling by array
GSE114043	Jan M. Hughes-Austin, Kevin D. Deane, Jon T. Giles, Lezlie A. Derber, Gary O. Zerbe, Dana M. Dabelea, Jeremy Sokolove, William H. Robinson, V. Michael Holers, Jill M. Norris, 2018.	Plasma adiponectin levels are associated with circulating inflammatory cytokines in autoantibody positive first-degree relatives of rheumatoid arthritis patients	Protein profiling by protein array
GSE103657	van Dijk SJ, Peters TJ, Buckley M, Zhou J, Jones PA, Gibson RA, Makrides M, Muhlhausler BS, Molloy PL, 2022.	DNA methylation in blood from neonatal screening cards and the association with BMI and insulin sensitivity in early childhood	Methylation profiling by genome tiling array
GSE74988	Mujagic Z, de Vos P, Boekschoten MV, Govers C, Pieters HH, de Wit NJ, Bron PA, Masclee AA, Troost FJ, 2019	The effects of Lactobacillus plantarum on small intestinal barrier function and mucosal gene transcription; a randomized double-blind placebo controlled trial	Expression profiling by array
GSE77962	Vink RG, Roumans NJ, Fazelzadeh P, Tareen SH, Boekschoten MV, Mariman EC, van Baak MA, 2020	Adipose tissue gene expression is differentially regulated with different rates of weight loss in overweight and obese humans	Expression profiling by array
GSE89181	Kaz AM, Wong C, Varadan V, Willis JE, Chak A, Grady WM, 2020	Global DNA methylation patterns in Barrett's esophagus, dysplastic Barrett's, and esophageal adenocarcinoma are associated with BMI, gender, and tobacco use	Methylation profiling by genome tiling array
GSE53232	Esser D, Afman L, 2016	High fat challenges with different fatty acids affect distinct atherogenic gene expression pathways in immune cells from lean	Expression profiling by array

GSE45927	Mattison JA, Wang M, Bernier M, Zhang J, Park S, Maudsley S, An SS, Santhanam L, Martin B, Faulkner S, Morrell C, Baur JA, Pearson KJ, Lakatta EG, de Cabo R, 2020	Resveratrol prevents diet- induced arterial degeneration and stiffening in nonhuman primates and obese subjects	Expression profiling by array
GSE46699	Serie DJ, Eckel- Passow JE, 2019	Smoking and Obesity Related Molecular Alterations in Clear Cell Renal Cell Carcinoma	Expression profiling by array
GSE43580	Talikka M, Schlage W, Boue S, Xiang Y, Martin F, Ansari S, Hoeng J, Peitsch MC, 2019	SBV - Gene Expression Profiles of Lung Cancer Tumors - Adenocarcinomas and Squamous Cell Carcinomas	Expression profiling by array
GSE234304	Greathouse KL, Stone JK, Vargas AJ, Choudhury A et al.	Co-enrichment of cancer-associated bacterial taxa is correlated with immune cell infiltrates in esophageal tumor tissue	Expression profiling by high throughput sequencing
GSE261205	Shanthamallu US, Kilpatrick C, Jones A, Rubin J et al.	A network-based framework to discover treatment-response-predicting biomarkers for complex diseases	Expression profiling by high throughput sequencing
GSE271452	Sellers AJ et al	Shivering improves metabolic health in adults with overweight or obesity	Expression profiling by high throughput sequencing

Table 2. Functional Annotation of Genes Derived from Seventeen GEO Datasets

Dataset ID	Biological Context	Sample Size	Key Genes and Functional Roles
GSE206037	Lipid metabolism in first-trimester placental tissue	32	PPAR α (Peroxisome Proliferator-Activated Receptor Alpha): A nuclear receptor transcription factor governing fatty acid oxidation and energy homeostasis. Additional roles include inflammatory modulation and regulation of cholesterol and triglyceride homeostasis. Pharmacological agonists are used clinically for dyslipidemia management. PPAR α research informs therapeutic strategies for metabolic and hepatic disease.
GSE197285	Lipid and cholesterol metabolism in abdominal obesity	288	LDLR: Mediates hepatic lipoprotein cholesterol clearance. INSIG1: Regulates de novo cholesterol and fatty acid synthesis. LPIN1: Phosphatidic acid phosphatase regulating lipid synthesis and adipocyte differentiation. HMGCS1: Rate-limiting enzyme in cholesterol and ketone body biosynthesis. SREBF1: Master transcriptional regulator of lipogenic gene expression. ANGPTL8: Endocrine factor governing lipid and glucose flux. ACLY: Cytosolic enzyme generating lipogenic acetyl-CoA. THRSP: Transcriptional cofactor regulating lipogenesis.
GSE196900	Colorectal cancer biology and chemoresistance	8	CD44: Transmembrane glycoprotein mediating cell adhesion, migration, and stem cell maintenance; isoform expression varies in malignancy and inflammation. RAS / BRAF: Proto-oncogenes frequently mutated in colorectal carcinoma and melanoma; BRAF V600E is a major actionable therapeutic target.
GSE155213	Pulmonary immune modulation	41	TLR6 (Toll-Like Receptor 6): Pattern recognition receptor detecting microbial ligands; triggers proinflammatory cytokine cascades upon activation. Essential for antimicrobial host defense and vaccine development.

Dataset ID	Biological Context	Sample Size	Key Genes and Functional Roles
GSE114043	Adipokine-immune signaling in autoimmunity	257	Immunoglobulin isotypes: IgM: Early response antibody mediating pathogen agglutination and complement activation. IgG: Predominant circulating isotype mediating sustained immunity and placental transfer. IgA: Mucosal barrier antibody providing secretory immunity.
GSE66818	Extracellular matrix remodeling in tissue repair	17	Collagen biosynthesis genes: COL1A1/COL1A2: Structural component of bone, dermis, and connective tissue. COL3A1: Fibrillar collagen enriched in distensible organs and vasculature.
GSE103657	Developmental epigenetic programming of adiposity	586	nc886 / VTRNA2-1: Non-coding vault RNA implicated in tumor suppression, cellular stress response, and antiviral immunity. Altered expression modulates proliferation and metabolic phenotypes.
GSE74988	Intestinal immune homeostasis and microbial signaling	38	CD161 / KLRB1: NK and T-cell surface receptor regulating innate cytotoxicity and adaptive immunity. CD79a / CD79b: B-cell receptor subunits essential for antigen-triggered signaling and development. CD27: Co-stimulatory receptor promoting T-cell memory and plasma cell differentiation.
GSE77962	Adipose transcriptional responses to weight loss	152	PPAR γ : Nuclear receptor governing adipogenesis, insulin sensitivity, and anti-inflammatory pathways; target of thiazolidinedione antidiabetic agents. FASN: Multifunctional enzyme catalyzing de novo fatty acid synthesis. SCD: Rate-limiting enzyme generating monounsaturated fatty acids.
GSE89181	Esophageal carcinogenesis and tobacco exposure	127	NTRK2 / NTRK3 (TrkB): Neurotrophin receptors regulating neuronal survival and plasticity; dysregulation in neurodevelopmental and psychiatric disease. HIF3A: Hypoxia-responsive transcription factor governing oxygen-dependent gene expression.
GSE53232	Lipid exposure and immune cell activation	128	PPAR α : Nuclear receptor activated by fatty acid ligands; drives fatty acid oxidation, glucose sparing, and anti-inflammatory programs. Fibrate drugs function as synthetic agonists.
GSE46699	Renal carcinoma: tobacco and obesity signatures	130	ENRAGE: Soluble RAGE ligand propagating proinflammatory signaling. EFCAB6: Calcium-binding EF-hand domain protein implicated in signal transduction. NCRNA00263: Long non-coding RNA with emerging regulatory roles.
GSE45927	Vascular aging and dietary intervention	24	DHCR24 / Seladin-1: Final enzyme in cholesterol biosynthesis; confers cellular protection against oxidative stress and amyloid toxicity. FBN2: Extracellular matrix microfibril component maintaining tissue elasticity. MED1: Transcriptional co-activator integrating nuclear receptor signaling. SNIP1: Transcriptional repressor modulating growth factor and oncogenic signaling. NOS3 / eNOS: Endothelial enzyme generating nitric oxide; critical for vascular tone and cardiovascular health.

Dataset ID	Biological Context	Sample Size	Key Genes and Functional Roles
GSE43580	Lung carcinoma cell cycle regulation	150	CDKN1C / p57Kip2: Cyclin-dependent kinase inhibitor enforcing cell cycle arrest during development and differentiation. CDKN2A / p16-ARF: Two-gene tumor suppressor locus activating RB and p53 pathways; commonly inactivated in malignancy.
GSE261205	Predictive therapeutic biomarkers	600	MAPK3 / MAPK1 (ERK1/2): Serine-threonine kinases central to growth factor and stress signaling; small-molecule inhibitors are established and investigational anticancer agents.
GSE234304	Esophageal carcinoma tumor microenvironment	500	TP53 / p53: "Guardian of the genome" tumor suppressor; integrates DNA damage sensing with cell cycle arrest, DNA repair, and apoptosis. Loss-of-function mutations drive aneuploidy, chemoresistance, and progression across cancer types.
GSE271452	Cold-induced metabolic remodeling	30	GLUT4 / SLC2A4: Insulin-responsive glucose transporter. INSR / AKT2: Insulin signal transduction cascade. UCP1 / PPARGC1A / PRDM16: Thermogenic and mitochondrial biogenesis regulators. AMPK / PRKAA2: Cellular energy sensor. PPAR α / LEP / ADRB3: Lipid and energy homeostasis modulators.

Obesity Reduces Lipid Metabolism Gene Expression in First-Trimester Placentas (GSE206037)

This study demonstrates that the placentas of women with obesity exhibit reduced mitochondrial fatty acid (FA) β -oxidation and lipid accumulation at late gestation. This condition creates a lipotoxic environment and impairs placental efficiency. Researchers propose that FA metabolism in the placenta is disrupted in women with obesity as early as the beginning of pregnancy. They evaluated the expression of key regulators of placental FA metabolism in first-trimester placentas from women with normal weight and women with obesity. Fasting maternal triglyceride and insulin levels were measured in plasma collected during procedures. Genes involved in FA oxidation (FAO; ACOX1, CPT2, AMPK α), FA uptake (LPL, LIPG, MFSD2A), FA synthesis (ACACA), and lipid storage (PLIN2) showed significantly reduced expression in the placentas of women with obesity compared to those with normal weight. This effect was more pronounced in placentas carrying male fetuses. Placental ACOX1 protein levels were higher in women with obesity and correlated with circulating maternal triglyceride concentrations. The PPAR α signaling pathway was enriched in genes altered by obesity in the placenta, and PPAR α inhibition significantly reduced ^{3} H-palmitate oxidation in first-trimester placental explants. These findings indicate that obesity and hyperlipidemia alter placental FA metabolism as early as 7 weeks of gestation.

Distinct Metabolic Effects of Two Energy-Restricted Diets Differing in Nutrient Quality: A 12-Week Randomized Controlled Trial in Subjects with Abdominal Obesity (GSE197285)

Although energy restriction (ER) is associated with beneficial metabolic health outcomes, the optimal nutritional composition of weight-loss diets remains a subject of debate. This study concludes that a nutrient-rich weight-loss diet with a 25 % energy restriction confers greater cardiovascular and metabolic benefits than a nutritionally inadequate diet with equivalent energy reduction. Individuals who are overweight and insulin-sensitive may derive particular benefit from nutrient-dense diets rather than nutrient-poor diets matched for weight loss, potentially due to reduced glucose-driven lipogenesis in adipose tissue.

RNA-Seq Profiles of Human Stem Cells and 5-Fluorouracil-Resistant Colorectal Cancer Cell Lines HCT116 and SW480 (GSE196900)

Colorectal cancer (CRC) remains the third most commonly diagnosed malignancy in the United States. Standard treatment involves surgical resection followed by 5-fluorouracil (5-FU)-based chemotherapy. Cancer stem cells (CSCs) have been identified as a key driver of 5-FU chemoresistance and are associated with poor prognosis. In this study, the combination of metformin with ICG-001, a Wnt signaling inhibitor, was tested as a strategy to overcome CSC-mediated chemoresistance in CRC. The results show that 5-FU-resistant (5FUR) CRC cells display increased expression of CSC markers and enhanced sphere-forming capacity.

Whole-transcriptome profiling revealed enrichment of Wnt signaling, cancer metastasis pathways, and other gene sets in 5FUR CRC cells. Notably, selective inhibition of Wnt signaling by ICG-001 combined with metformin reversed CSC-associated chemoresistance by reducing CSC marker expression while concurrently inducing autophagy and apoptosis. Studies using patient-derived tumor organoids further confirmed the antitumor activity of the metformin and ICG-001 combination.

Collectively, these findings highlight that metformin and ICG-001 act synergistically and may form part of a therapeutic strategy to overcome 5-FU-induced chemoresistance in CRC. Combining metformin with CSC-targeted therapies may also reduce adverse effects and toxicity associated with conventional chemotherapy. Furthermore, given its relatively low cost compared to other anticancer agents, metformin represents a cost-effective adjuvant therapy that could be administered alongside standard chemotherapy for patients with CRC.

Chronic Cannabis Use Is Associated with Altered Gene Expression in Bronchoalveolar Lavage Cells (GSE155213)

This article characterizes gene expression patterns associated with chronic cannabis use. Previous research on alveolar macrophage (AM) gene expression in tobacco smokers has identified molecular pathways linked to clinical outcomes. However, comparable data regarding cannabis smokers remain limited, despite growing public health interest in cannabis use. This study performed genome-wide gene expression profiling on lung immune cells from cannabis smokers to test the hypothesis that cannabis exposure alters AM transcriptional programs, potentially contributing to immune dysfunction. AMs were isolated from bronchoalveolar lavage fluid obtained from 15 cannabis smokers, 15 tobacco smokers, and 10 non-smokers, and subjected to RNA sequencing. Differential gene expression analysis was conducted to identify transcripts with statistically significant expression differences across groups, with particular emphasis on genes regulating M1/M2 macrophage polarization and immune response pathways.

Global Gene Expression Profiling of Engineered Neofascia from Hernia Patients with Favorable versus Impaired Healing Outcomes (GSE66818)

This study presents a comprehensive gene expression analysis of surgically engineered neofascia tissue obtained from hernia patients displaying variable wound healing characteristics. Abdominal wall hernia recurrence following laparotomy is reported to range between 2 % and 15 %. Independent risk factors include male sex, tobacco use, overweight status (BMI > 25

kg/m²), and advanced age (older than 45 years). To improve wound healing outcomes, synthetic surgical mesh has become standard practice in abdominal wall reconstruction. To stratify hernia recurrence risk, the ratio of type I to type III collagen may serve as a prognostic biomarker when quantified using picrosirius red staining.

Plasma Adiponectin Concentrations Correlate with Circulating Inflammatory Cytokines in Autoantibody-Positive First-Degree Relatives of Rheumatoid Arthritis Patients (GSE114043)

Rheumatoid arthritis (RA) manifests with systemic extra-articular complications, including cardiovascular disease and sarcopenic obesity, driven by chronic multi-organ inflammation. Adiponectin, an adipokine derived from adipose tissue, has been implicated in RA-associated inflammatory processes, yet its role in the preclinical phase of disease remains poorly understood. Accordingly, this study aimed to examine whether adiponectin concentrations correlate with established inflammatory biomarkers in individuals at elevated familial risk for RA, and whether RA-associated autoimmunity modulates these relationships.

In summary, among individuals free of clinical arthritis but at high future risk of RA, adiponectin exhibits divergent associations with inflammatory markers depending on autoimmunity status. Specifically, adiponectin correlated positively with proinflammatory cytokines only among autoantibody-positive first-degree relatives of RA patients. These observations, together with prior reports, suggest that the autoimmune milieu modulates the immunomodulatory function of adiponectin. Further investigation is warranted to characterize the systemic effects of RA-related autoantibodies and adiponectin on inflammation during the asymptomatic preclinical phase of RA.

Neonatal Bloodspot DNA Methylation Correlates with Childhood Body Mass Index and Insulin Sensitivity (GSE103657)

Accumulating evidence indicates that metabolic disease originates in early life, with epigenetic dysregulation proposed as a critical mechanism of developmental metabolic programming. These observations support the hypothesis that epigenetic biomarkers detectable at birth may predict future risk of obesity and type 2 diabetes. In this study, investigators examined whether DNA methylation signatures in neonatal blood spots correlate with body mass index (BMI) and insulin sensitivity in childhood.

Lactobacillus plantarum Strains Enhance Human Mucosal and Systemic Immunity and Prevent Nonsteroidal Anti-Inflammatory Drug-Induced Regulatory T Cell Reduction (GSE74988)

Oral probiotic bacteria interact directly with the intestinal mucosa and modulate host immunity, although the molecular mechanisms underlying these effects remain incompletely defined. In this randomized, double-blind, placebo-controlled crossover trial, healthy human volunteers received supplementation with one of three *Lactobacillus plantarum* strains (TIFN101, CIP104448, or WCFS1) or placebo daily for seven days. The primary objective was to evaluate immunomodulatory efficacy by comparing strain-specific effects on systemic and intestinal mucosal immunity, including memory responses to tetanus toxoid (TT) vaccination and mucosal transcriptomic profiles.

Lactobacillus plantarum strain TIFN101 prevented the nonsteroidal anti-inflammatory drug (NSAID)-induced reduction in circulating CD4⁺/Foxp3⁺ regulatory T cells. T cell polarization studies demonstrated that TIFN101 augmented antigen-specific responses to TT, indicative of enhanced immunological memory. Strain-specific immunostimulatory activity was further confirmed using cellular extracts, where WCFS1 and TIFN101 induced distinct immune activation profiles. Duodenal biopsies revealed that TIFN101 upregulated genes involved in T and B cell function and antigen presentation in the small intestinal mucosa. Conversely, both TIFN101 and WCFS1 downregulated canonical immune signaling pathways while concurrently modulating small nucleolar RNA expression, suggesting involvement in cellular homeostasis and tissue repair processes.

This human crossover trial demonstrates that orally administered *L. plantarum* exerts strain-dependent immunomodulatory effects. Selected strains mitigate immune dysregulation triggered by mucosal injury such as that induced by NSAID exposure. Whereas TIFN101 conferred beneficial immunomodulatory properties, strains CIP104448 and WCFS1 exhibited less favorable transcriptional profiles. These findings underscore the critical importance of precise strain selection even among closely related probiotic organisms. The capacity of certain strains to expand memory lymphocyte populations further supports rational screening of probiotic candidates for vaccine adjuvant and immunoprophylactic applications. Comparative genomic analyses provide a valuable framework for identifying genetic determinants responsible for strain-specific immunomodulation in humans.

Temporal Gene Expression Profiling Characterizes Adipose Tissue Remodeling During Weight Loss (GSE77962)

Obesity represents a major global public health challenge and established risk factor for multiple chronic diseases. Calorie restriction remains a cornerstone intervention for weight reduction. Although adipose tissue is profoundly remodeled during diet-induced weight loss, the underlying molecular mechanisms remain incompletely elucidated. This study describes an integrated analytical framework for characterizing biological pathways modulated by weight loss in subcutaneous adipose tissue. Transcriptomic profiles were analyzed across sequential time points in subjects receiving diverse dietary interventions to identify differentially expressed genes. Co-expression network analysis was subsequently applied to identify transcriptional modules whose expression patterns change dynamically over time. Using the network analysis platform Cytoscape, distinct gene clusters were identified that correspond to core metabolic pathways, adipogenesis, and extracellular matrix remodeling.

In conclusion, this study establishes a scalable analytical workflow for identifying candidate regulatory genes and biological processes associated with weight loss through differential expression and temporal transcriptome analysis. The approach reliably recovered biological pathways previously implicated in obesity, type 2 diabetes, cardiovascular disease, and metabolic syndrome. These findings validate this methodology as a foundation for predictive and mechanistic modeling of adipose tissue biology. The workflow is designed for broad applicability using open-source analytical tools, facilitating adaptation across diverse study designs and clinical cohorts. The method accommodates biological and technical variability in constructing correlation networks, enabling integrative analysis of RNA sequencing data and non-coding RNA expression profiles that were previously underrepresented in human dietary intervention studies.

Global DNA Methylation Patterns in Barrett's Esophagus, Dysplastic Barrett's Esophagus, and Esophageal Adenocarcinoma Are Associated with Body Mass Index, Gender, and Smoking (GSE89181)

Risk of Barrett's esophagus (BE) and esophageal adenocarcinoma (EAC) correlates with demographic and lifestyle exposures, including male sex, obesity (measured by body mass index; BMI), and tobacco smoking. Aberrant DNA methylation, a heritable yet reversible epigenetic modification that alters gene expression in response to environmental exposures, occurs frequently in BE and EAC. Epigenetic dysregulation is hypothesized to contribute to BE pathogenesis and progression to EAC. However, it remains unclear whether obesity and smoking directly alter DNA methylation to influence BE/EAC risk.

To investigate this relationship, genome-wide DNA methylation profiling was performed on 81 esophageal tissue specimens representing non-dysplastic BE, dysplastic BE, and EAC using the Illumina HumanMethylation450 BeadChip platform. Obesity and smoking exposure were shown to significantly alter DNA methylation in the esophageal epithelium. These findings support a model whereby established risk factors modify the epigenetic landscape at biologically relevant loci, thereby promoting BE development, dysplastic progression, and malignant transformation to EAC.

High-Fat Challenges Containing Distinct Fatty Acids Induce Divergent Atherogenic Gene Expression Programs in Immune Cells from Lean and Obese Individuals (GSE53232)

Subclinical vascular dysfunction can be detected by measuring transcriptional responses to standardized high-fat dietary challenges. This approach was employed to characterize how nutrient stress alters global gene expression according to metabolic health. The primary objective was to identify pathway-level differences in peripheral blood mononuclear cell (PBMC) gene expression following high-fat meals enriched in either monounsaturated fatty acids (MUFA) or saturated fatty acids (SFA) in individuals stratified by cardiovascular disease risk profile, and to define fatty acid-specific transcriptional signatures.

In this controlled crossover study, 17 lean and 15 obese men aged 50–70 years consumed two isocaloric high-fat test meals containing 95 g total fat, one rich in SFA and the other rich in MUFA. PBMC transcriptome profiles were determined at baseline (fasting) and four hours postprandially. Differential expression analyses were performed comparing lean versus obese groups and comparing fatty acid interventions. At fasting baseline, 294 genes were differentially expressed between lean and obese individuals. Postprandial challenge amplified transcriptional divergence to 607 genes following the SFA meal and to 2,516 genes following the MUFA meal.

In both subject groups, SFA consumption downregulated genes governing cholesterol biosynthesis and uptake while upregulating pathways mediating cholesterol efflux. In contrast, MUFA consumption upregulated inflammatory pathways and induced PPAR α target genes involved in fatty acid β -oxidation. Collectively, these results demonstrate that high-fat dietary exposure unmask latent transcriptional differences according to adiposity, particularly following MUFA consumption. Furthermore, SFA and MUFA elicit fundamentally distinct transcriptional programs governing lipid metabolism in circulating immune cells.

Resveratrol Attenuates High-Fat/High-Sucrose Diet-Induced Arterial Stiffness and Vascular Inflammation in Nonhuman Primates (GSE45927)

Central arterial stiffness driven by chronic perivascular inflammation is a primary determinant of cardiovascular morbidity and mortality in Western populations. Aortic pulse wave velocity (PWV), an in vivo measure of arterial stiffness, represents an established biomarker of cardiovascular risk. Currently, no pharmacotherapy specifically reduces elevated PWV. In a controlled study of rhesus macaques, consumption of a high-fat, high-sucrose (HFS) diet for two years caused increased body weight, dyslipidemia, progressive arterial stiffness, elevated aortic PWV, and vascular inflammation. Histological and molecular analyses revealed endothelial injury, lipid and macrophage infiltration, and medial calcification attributable to oxidative stress and proinflammatory signaling. Concurrent administration of resveratrol prevented diet-induced vascular inflammation and attenuated the associated increase in aortic PWV. These findings identify dietary resveratrol supplementation as a promising therapeutic strategy for preventing or reversing arterial stiffening in at-risk populations.

Somatic ENRAGE Expression Correlates with Obesity Status in Patients with Clear Cell Renal Cell Carcinoma (GSE46699)

Epidemiological studies consistently link elevated body weight with increased risk of clear cell renal cell carcinoma (ccRCC). However, the molecular mechanisms underlying this association remain poorly characterized. A multi-stage study design was therefore implemented to identify and validate obesity-associated transcriptional alterations in ccRCC. Transcriptomic microarray profiling compared gene expression in ccRCC tumors and matched normal renal tissue from overweight versus normal-weight patients, with adjustment for smoking status and subsequent validation in a combined cohort. The primary objective was to identify genes where the magnitude of differential expression between tumors from overweight and non-overweight individuals differed significantly from corresponding differences in matched normal renal parenchyma. Mixed-effects statistical models tested for tissue-type $\times$ obesity interaction terms. Quantitative reverse-transcription polymerase chain reaction (RT-PCR) validation was performed on an independent patient cohort. ENRAGE was identified through microarray analysis and subsequently validated by RT-PCR as exhibiting a statistically significant tissue-type $\times$ obesity interaction. Notably, ENRAGE expression was comparable in normal renal tissue regardless of adiposity, whereas tumor ENRAGE was selectively upregulated in tumors derived from overweight patients. Tumor ENRAGE overexpression

correlated with von Hippel-Lindau tumor suppressor gene status and independently predicted reduced overall survival. In aggregate, these data establish elevated ENRAGE expression in ccRCC as a somatic transcriptional alteration specifically associated with host adiposity. ENRAGE signaling may act through autocrine RAGE receptor activation to promote tumor progression and represents a novel obesity-dependent oncogenic pathway.

Predictive Phenotyping Using Microarray Data: Lessons from the IMPROVER Diagnostic Signature Challenge (GSE43580)

Despite over a decade of applying transcriptomic profiling to disease classification and outcome prediction, translation into routine clinical diagnostics—including disease screening and patient stratification for personalized therapy—remains incomplete. The IMPROVER Diagnostic Signature Challenge was established through international collaboration to objectively compare competing methodological approaches for developing robust predictive biomarkers. This report summarizes findings from this blinded validation study.

Fifty-four participating research teams developed predictive models for four disease phenotypes: multiple sclerosis, non-small cell lung carcinoma, psoriasis, and chronic obstructive pulmonary disease. Models were trained on public datasets and validated using independent, blinded testing samples. Predictive performance was evaluated using three complementary statistical metrics. This report presents aggregate results, details methodological frameworks employed by the three highest-performing teams, and documents open-source R software packages implementing validated algorithms.

Performance analysis and extensive computational simulation demonstrated that: (i) predictive accuracy depended primarily upon the clinical endpoint being modeled rather than the classification algorithm selected; (ii) optimal analytical pipelines including preprocessing, feature selection, and classifier architecture must be customized to each study design and dataset; and (iii) rigorous methodological adaptation to the specific dataset and disease phenotype is essential for achieving high predictive performance. Biomedical covariates including disease severity and diagnostic confidence further explained variability in classification error rates across participating teams.

Network-Based Biomarker Discovery Framework for Predicting Therapeutic Response in Complex Autoimmune Diseases (GSE261205)

Precision medicine for complex autoimmune diseases is frequently constrained by limited sample

availability relative to the high dimensionality of multi-omics datasets. To address this challenge, a novel computational framework termed P_{Ro}BeNet (Predictive Response Outcome Benchmarked on Network Medicine) was developed. P_{Ro}BeNet operationalizes the hypothesis that drug efficacy is mediated through perturbation of protein-protein interaction networks rather than isolated molecular targets. The framework prioritizes candidate predictive biomarkers by integrating three layers of biological evidence: (1) proximity to established therapeutic targets, (2) disease-specific molecular signatures, and (3) topology within the human protein interactome. Using P_{Ro}BeNet, biomarkers were identified that predict clinical response to the anti-tumor necrosis factor agent infliximab and to an investigational MAPK3/1 inhibitor. Predictive performance was validated using retrospective transcriptomic data from ulcerative colitis and rheumatoid arthritis cohorts, and prospectively in independent ulcerative colitis and Crohn's disease patient cohorts. Machine-learning models incorporating P_{Ro}BeNet-derived biomarkers significantly outperformed alternative models utilizing all transcripts or randomly selected gene sets, particularly when training data were limited to fewer than 20 samples. These results demonstrate P_{Ro}BeNet's capacity to reduce dimensionality and generate robust predictive models in data-scarce clinical settings. P_{Ro}BeNet facilitates the development of companion diagnostic tests to support therapeutic decision-making, patient stratification in clinical trials, accelerated drug approval, and improved clinical outcomes in immune-mediated inflammatory disease.

Co-Enrichment of Cancer-Associated Bacterial Taxa Correlates with Immune Cell Infiltration in Esophageal Tumor Tissue (GSE234304)

The global incidence of esophageal adenocarcinoma continues to rise, driven by genetic and environmental risk factors including obesity, tobacco exposure, TP53 mutation, and Barrett's esophagus—a chronic inflammatory precursor lesion. These same exposures alter the gastrointestinal microbiome. To investigate potential interrelationships between microbial communities, inflammation, and esophageal adenocarcinoma, we integrated 16S ribosomal RNA gene sequencing and whole-transcriptome RNA sequencing data. Multiple bacterial taxa were identified that are significantly enriched within tumor specimens; differential abundance correlated with immune cell infiltration patterns inferred from transcriptomic data, including depletion of megakaryocyte-erythroid progenitor populations accompanied by thrombocytosis. These findings suggest that tumor-associated microbial dysbiosis may directly

promote malignant progression and stimulate thrombopoiesis. Collectively, these results characterize a remodeled immune microenvironment in esophageal adenocarcinoma and highlight novel microbial and therapeutic targets.

Cold Acclimation with Mild Shivering Improves Metabolic Health in Overweight and Obese Adults (GSE271452)

Cold exposure enhances peripheral insulin sensitivity, a physiological adaptation that appears to require low-intensity muscle contraction. This study enrolled 15 postmenopausal adults with overweight or obesity, most exhibiting prediabetic glucose intolerance. Participants underwent daily intermittent cold exposure for one hour over ten consecutive days, standardized to elicit consistent mild shivering. The primary outcome measure was change in oral glucose tolerance following an overnight fast. Secondary outcomes included skeletal muscle glucose transporter type 4 translocation. Cold acclimation with shivering significantly improved oral glucose tolerance and significantly reduced fasting glucose, circulating triglycerides, non-esterified fatty acids, and resting blood pressure. These findings identify controlled cold exposure with shivering as a promising lifestyle intervention for preventing and treating obesity-related metabolic disease.

A recapitulation of the functional gene classification across the investigated GSE studies is presented as follows: GSE206037 addresses obesity (A. Rasool et al., 2022), GSE197285 concerns obesity (S. Schutte et al., 2022), GSE196900 focuses on cancer (S. Roy et al., 2022), GSE155213 examines immune response (C. Liu et al., 2021), GSE114043 relates to the immune system (JM. Hughes-Austin et al., 2018), GSE103657 investigates cancer (SJ. van Dijk et al., 2017), GSE74988 pertains to cancer (Z. Mujagic et al., 2017), GSE77962 describes lipid metabolism (SHK. Tareen et al., 2017), GSE89181 addresses nervous system health (AM. Kaz et al., 2016), GSE53232 concerns lipid metabolism (D. Esser, 2015), GSE46699 examines obesity (JE. Eckel-Passow, 2014), GSE45927 relates to cholesterol biosynthesis (JA. Mattison et al., 2014), GSE66818 focuses on vascular health, GSE43580 investigates cancer and tumor biology (AL. Tarca et al., 2013), GSE261205 (Shanthamallu US, Kilpatrick C, Jones A, Rubin J et al., 2024), GSE234304 (Greathouse KL, Stone JK, Vargas AJ, Choudhury A et al., 2024), and GSE271452 addresses obesity (Sellers AJ, 2024).

Seventeen curated datasets were synthesized into eight major functional gene groups:

1. Peroxisome Proliferator-Activated Receptors (PPARs): PPAR α and PPAR γ (Huang, 2008)
2. Immune-Related Genes: CD44, TLR6, CD161, CD79a/CD79b, CD27 (Nolte et al., 2005), and TP53 (Greathouse et al., 2024)
3. Lipid and Metabolic Regulatory Genes: LDLR, INSIG1, LPIN1, HMGCS1, SREBF1, ANGPTL8, ACLY, THRSP, and RAS/BRAF (Brastianos, 2023)
4. Immunoglobulin Genes: IGHA, IGHD, IGHM, IGHG, IGHE constant regions encoding IgA, IgD, IgM, IgG, and IgE isotypes (Mazzini, 2021)
5. Regulatory and Non-Coding Elements: VTRNA2-1, HIF3A, ENRAGE, EFCAB6, NCRNA00263, and DHCR24 (Drzewińska, 2009)
6. Cell Cycle and Growth Regulatory Genes: NTRK2/NTRK3, CDKN1C, CDKN2A (Foulkes, 1997), and MAPK3/MAPK1 (Shanthamallu et al., 2024)
7. Transcriptional and Structural Genes: FBN2, MED1, and SNIP1 (Ammous, 2021)
8. Cardiovascular Homeostasis Genes: NOS3 and eNOS (Tran, 2022).

Conclusion

Systematic mining of publicly available NCBI GEO datasets has identified conserved transcriptional signatures perturbed by tobacco exposure and obesity. Across 17 curated studies, Differentially Expressed Genes (DEGs) define eight biological pathways: nuclear receptor signaling (PPARs), immune function, lipid and energy metabolism, immunoglobulin production, molecular and cellular homeostasis, cell cycle control, transcriptional regulation, and vascular biology. These findings establish a molecular framework linking tobacco and obesity to disease outcomes and provide candidate biomarkers and therapeutic targets for translational investigation.

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Author Contributions

Conceptualization: Azminah and Agung Budi Wicaksono; methodology: Azminah; software: —; validation: Azminah and Agung Budi Wicaksono; formal analysis: Azminah; investigation: Azminah; resources: —; data curation: Agung Budi Wicaksono; writing—original draft preparation: Azminah; writing—review and editing: Agung Budi Wicaksono; visualization: —; supervision: —; project

administration: –; funding acquisition: –. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

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