Included human studies (2019-2025) on FTO, MC4R, APOA2, and POMC (plus related loci PCSK1, SIM1, BDNF, NTRK2) and obesity-related outcomes, with emphasis on gene–diet interactions.

	Tier	Author (Year)	Country/Ancestry	Design (Cross-sec/CC/Cohort/RCT/Non-RCT)	N (total / per-genotype if given)	Locus / Variant (rsID)	Exposure (e.g., SFA g/day; %E; overall diet; PA; sleep)	Exposure measurement tool	Outcome (BMI/Obesity/Waist/Weight change/…)	Model & Covariates (age/sex/PCs/energy/PA/…)	Effect (unit)	Gene–diet test	Prespecified interaction	Multiplicity control (Y/N; method)	Quality (tool/score)	Notes
1	Primary	Lai et al. (2025, DIETFITS)	USA (multi-ethnic)	RCT (12 months)	609 randomized (genotype strata reported)	APOA2 rs5082	Diet type (HLC versus HLF); SFA threshold SAT22 (≤22 g/d compared with >22 g/d)	FFQ (trial protocol)	ΔWeight (kg) at 3/6/12 months; waist	ITT; baseline weight; age/sex; site	TT: 12 months HLC −8.39 kg (95% CI NR) compared with HLF −5.96 kg (95% CI NR); 6 months −9.81 kg compared with −7.19 kg (95% CI NR); 3 months −7.58 kg compared with −5.43 kg (95% CI NR)	Yes; Pinteraction = 0.035 (12 months)	Y	NR	RoB2: Low risk	Primary gene–diet RCT signal for APOA2; ITT
2	Primary	Namjou et al. (2021)	USA (eMERGE; multi-ancestry)	Cohort (sequencing + GWAS/PheWAS)	20,537 sequenced; 77,454 genotyped	MC4R (coding + common; incl. V103I)	—	—	BMI; obesity classes	Linear/logistic; age/sex; site; ancestry PCs; relatedness	Any MC4R coding carrier versus non-carrier: OR_overweight = 2.20 (95% CI NR); OR_obesity = 2.76 (95% CI NR); OR_extreme obesity = 5.59 (95% CI 4.71 to 6.65); others NR	No (diet interaction not tested)	N/A	N/A	NOS: High (8/9)	V103I protective; anchor human genetics

3	**Secondary**	Pokushalov et al. (2024)	Russia/USA (adults)	RCT, double-blind, placebo-controlled ≈180 d)	112 (≥1 minor allele in FTO/LEP/LEPR/MC4R)	FTO rs9939609; MC4R rs17782313 (±LEP/LEPR)	Fiber blend compared with placebo	Intervention assignment (capsules); diet tool NR	ΔBMI; ΔWeight (%); fat mass; visceral fat	ANCOVA; baseline; age/sex	ΔBMI = −1.4 kg/m² (95% CI −1.7 to −1.2); Δweight = −4.9% (95% CI −6.9 to −2.9); fat mass −13.0% (95% CI −14.4 to −11.7)	No (no prespecified gene–diet term)	N	NR	RoB2: Low risk	Overall treatment effect; no prespecified G×D
4	**Secondary**	Doaei et al. (2019)	Iran (adolescents)	Non-RCT (18 wk lifestyle)	62 (Interv 30; Ctrl 32)	FTO rs9930506 (±IRX3 expression)	Diet + PA program versus usual	Program-based; dietary assessment NR	BMI; FTO/IRX3 expression	Regression by genotype; baseline	Expression: IRX3 ↑ (P = 0.007); FTO ↑ in AA, ↓ in AG/GG (P = 0.017). β (BMI): NR	No	N	NR	JBI: Moderate	Molecular endpoints primary
5	**Secondary**	Czogała et al. (2021a)	Poland (children)	Cross-sec	232	FTO; PLAG1 (expression/methylation)	—	—	BMI; lipid/glucose traits	Multivariable linear	FTO expression correlated with BMI (r = 0.445; P = 0.023) and with BMI z-score (r = 0.430; P = 0.028).	No	N	NR	JBI: Moderate	Mechanistic; small N
6	**Secondary**	Czogała et al. (2021b)	Poland (children)	Prospective (peptide follow-up)	236	FTO; PLAG1 (expression; FTO methylation)	—	—	Adipokines & GI peptides; anthropometry	Linear mixed	Examples: GLP-1 AUC versus PLAG1: r = −0.638 (pBH = 0.003); B(GLP-1) = −0.25 (95% CI NR); B(adiponectin) = 1.94 (95% CI NR)	No	N	Y; BH/FDR (reported for peptides)	NOS: Moderate	Companion pediatric cohort

7	**Secondary**	Cheshmeh et al. (2020)	Iran (infants)	Cross-sec	180	FTO; CPT1A; PPAR-α (expression)	Feeding type (breast versus formula/mixed)	Parental report (NR)	Gene expression; growth indices	ANCOVA/linear	Differential expression by feeding group (β/OR 95% CI NR); growth indices secondary	No	N	NR	JBI: Moderate	Molecular; anthropometry secondary
8	**Secondary**	Cheshmeh et al. (2023)	Iran (infants)	CC (birth-weight groups)	120	Panel incl. MC4R; NTRK2; PCSK1; PPAR-α; FTO	Birth-weight groups (LBW/normal/HBW)	Medical records (birth weight); lab assays	Gene expression	Logistic/linear	Selected genes ↑ in LBW (e.g., NTRK2; PCSK1); PPAR-α correlated with birth-weight: r = 0.19 (P = 0.005)	No	N	NR	JBI: Moderate	Developmental; molecular
9	**Secondary**	King et al. (2024)	UK (young adults)	RCT (genotype-based advice via email; 8 wk)	160	FTO rs9939609	Genotype-based versus generic advice	Intervention (email advice); diet tool NR	Healthy-eating motivation (primary); BMI/BF% (secondary)	ANCOVA	No significant anthropometric change; motivation NS (F = 0.881; P = 0.417)	No	N	NR	RoB2: Some concerns	Behavioral; no weight effect

Data synthesis map (2019-2025) across core loci (APOA2, FTO, MC4R, POMC) and related loci.

Evidence class	Locus	Variant (rsID)	Exposure / Comparator	Outcome	Effect (unit, 95% CI)	Gene–diet interaction (Pinteraction)	Study (Year), Population
Core	**APOA2**	rs5082	Diet type (HLC versus HLF); SAT22 (≤22 g/day compared with >22 g/day)	Body-weight change (kg) at 12 months (also 3/6 months)	TT genotype weight change: HLC, −8.39 kg (95% CI not reported [NR]); HLF, −5.96 kg (95% CI NR). At 6 months: HLC, −9.81 kg; HLF, −7.19 kg. At 3 months: HLC, −7.58 kg; HLF, −5.43 kg.	Yes; Pinteraction = 0.035 (12 months)	Lai et al. (2025, DIETFITS), USA multi-ethnic RCT
Core	**FTO**	rs9939609	Fiber blend (glucomannan+inulin +psyllium) compared with placebo (≈180 d)	ΔBMI; Δweight; fat mass	ΔBMI = −1.4 kg/m² (−1.7 to −1.2); Δweight = −4.9% (−6.9 to −2.9); fat mass −13.0% (−14.4 to −11.7)	No (no prespecified G×D)	Pokushalov et al. (2024), adults (Russia/USA), RCT
Core	**MC4R**	coding variants (incl. V103I)	— (genetic main effects)	Overweight/obesity classes	Any coding-variant carrier versus non-carrier: OR (overweight) = 2.20 (95% CI NR); OR (obesity) = 2.76 (95% CI NR); OR (extreme obesity) = 5.59 (95% CI 4.71 to 6.65)	No	Namjou et al. (2021), USA multi-ancestry eMERGE, cohort/GWAS
Supporting	**FTO**	rs9930506	Lifestyle program (diet + PA) versus usual (18 wk)	BMI; FTO/IRX3 expression	BMI β (unit NR) = NR; direction: BMI ↓ with intervention. Expression: IRX3 ↑ (P = 0.007); FTO ↑ in AA & ↓ in AG/GG (P = 0.017)	No (no formal G×D)	Doaei et al. (2019), Iran adolescents, Non-RCT
Supporting	**FTO**	expression/ methylation	—	BMI; BMI z-score	r (FTO expression, BMI) = 0.445 (P = 0.023); r (FTO expression, BMI-z) = 0.430 (P = 0.028)	No	Czogała et al. (2021a), Poland children, Cross-sec

Supporting	**FTO / PLAG1**	expression/ methylation	—	GLP-1 AUC; adiponectin; peptides	Examples: GLP-1 AUC versus PLAG1 r = −0.638 (p_BH = 0.003); B(GLP-1) = −0.25 (95% CI NR); B(adiponectin) = 1.94 (95% CI NR)	No	Czogała et al. (2021b), Poland children, Prospective
Supporting	**FTO; CPT1A; PPAR-α**	expression	Feeding type (breast versus formula/mixed)	Gene expression; growth indices	Differential expression by feeding group (β/CI NR); growth indices secondary	No	Cheshmeh et al. (2020), Iran infants, Cross-sec
Supporting	Panel incl. **MC4R; NTRK2; PCSK1; PPAR-α; FTO**	expression	Birth-weight group (LBW/normal/HBW)	Gene expression	Selected genes ↑ in LBW; PPAR-α correlated with birth-weight r = 0.19 (P = 0.005)	No	Cheshmeh et al. (2023), Iran infants, CC
Supporting	**FTO**	rs9939609	Genotype-based advice versus generic (8 wk)	BMI / BF% (secondary)	No significant anthropometric change; motivation NS (F = 0.881; P = 0.417)	No	King et al. (2024), UK young adults, RCT (behavioral)

Relative expression of circ_0001756 across different clinicopathological variables in breast cancer patients.

		low		high		P-Value
		N	%	N	%	
Group	**ER/PR +, Her2+ (TP)** **ER/PR +, Her2-** **Her2+** **TNBC**	13 14 10 3	%32.5 %35 %25 %7.5	4 2 2 1	%44.4 %22.2 %22.2 %11.1	0.8
Estrogen receptor	**Negative** **Positive**	14 26	%35 %65	3 6	%33.3 %66.7	0.7
Progesterone receptor	**Negative** **Positive**	15 5	%37.5 %62.5	3 6	%33.3 %66.7	0.6
HER2	**Negative** **Positive**	21 9	52.5% 47.5%	5 4	55.6% 44.4%	0.5
Age at diagnose	**<40** **>40**	5 30	12.5% 87.5%	2 7	22.2% 77.8%	0.7
Tumor size	**<2cm** **≥2cm**	9 31	22.5% 77.5%	2 7	22.2% 77.8%	0.5
Lymph node	**Negative** **Positive**	13 27	32.5% 67.5%	3 6	33.3% 66.3%	0.4
Grade	**1.2** **3**	30 6	83.3% 16.9%	6 3	66.7% 33.3%	0.8
Stage	**Low** **High**	23 17	57.5% 42.5%	8 1	88.9% 11.1%	0.2
Metastasis	**Metastatic** **Non-Metastatic**	28 12	70% 30%	7 2	77.8% 22.2%	0.3

Statistical analysis results for the *time* factor in the Morris Water Maze test (3-week group).

TIME 3 week	
Test	
[F(3,28)= 6.277=p<0.002]	
Train	
[F(7,196)= 28,266,p<0.0001]	TRAINS
[F(21,196)= 2,585,p<0. 0001]	TRAINS & GROUPS
[F(3,28)= 400,783=p<0.0001]	AVERAGE (Between-Subjects Effects)

Statistical analysis results for the *distance traveled* factor in the Morris Water Maze test (3-week group).

DISTANCE 3 week	
Test	
[F(3,28)= 2.444=p<0.008]	Z1
[F(3,28)= 12.659=p<0.0001]	TOTAL
[F(7,56)= 69.43=p<0.0001]	TOTAL , Z1
Train	
[F(7,196)= 14.690,p<0.0001]	TRAINS
[F(21,196)= 32.082,p<0. 0226]	TRAINS & GROUPS
[F(3,28)= 1071.952=p<0.0001]	AVERAGE (Between-Subjects Effects)

Overview of Artificial Intelligence and Its Subfields

Topic	Description
Artificial Intelligence (AI)	The science of creating machines or software that mimic human functions for learning and problem-solving. AI aims to perform human tasks. ML enables machines to learn from data without explicit programming. It allows computers to recognize patterns based on large datasets and make decisions based on training data.
Machine Learning (ML)	A subset of AI that uses input data and mathematical algorithms to train machines. ML doesn't require explicit programming for every step. It often involves supervised learning with labeled data.
Deep Learning (DL)	A specialized subset of ML. DL is a subset of AI. It involves neural networks with multiple layers, enabling complex pattern recognition. illustrates the relationship between AI, ML, and DL. DL involves complex artificial neural networks that mirror the human brain. These networks process complex data by simulating interconnected nodes similar to neurons. DL models consist of input layers, hidden layers, and an output layer, learning patterns through experience and correlation.
ML Process	1. Define a question or problem. 2. Collect relevant data and teach the computer program. 3. Test program performance. 4. Refine as needed. ML enhances diagnostics and therapeutics by improving detection and prediction.
Natural Language Processing (NLP)	NLP enables computers to understand language not generated using strict rules. Tasks include translation, question answering, text analysis, and sentiment analysis using ML.
Computer Vision (CV)	CV aims to enable computers to understand visual information like humans. It involves machine learning models for tasks like face recognition and image analysis.

Relative BDNF mRNA expression in the 3-week group

	Placebo	Stress	Treatment	Stress & Treatment
Fold Change	1	1.89117E-10	237900	4.12243E-07
SD	0.2305	0.4253	0.1194	0.6486
Significant diff. among means (P < 0.05)?	**Yes**			
P value Summary	****			
P value	0.0001			

[F(3,28)= 57.21,p<0.0001]

AI Applications in Clinical Nutrition: Challenges and Opportunities

Aspect	Description
AI Systems in Clinical Nutrition	AI algorithms support dietary activities, assess disease risks related to food and nutrient patterns, and aid in supplementation research.
Reliability and Credibility Assessment	Ensuring reliable and credible results from AI techniques is crucial in clinical nutrition research.
Changing Dietician-Patient Relationship	AI systems may partially replace medical professionals, impacting the traditional dietician-patient relationship.
Trust in AI-Based Systems	Trust remains an open issue, especially among elderly patients. However, trust in AI is increasing with technological implementation.
Personalized Nutrition	AI enables personalized dietary assessments, prioritizing nutrition management in specific diseases.
Role of Clinical Dietitians	Certified clinical dietitians play a central role in clinical nutrition services, addressing nutritional problems and risk factors.
AI's Potential in Clinical Nutrition	AI can revolutionize clinical nutrition by analyzing complex data, interpreting medical images, and providing personalized interventions.
Evidence-Based Recommendations	AI algorithms identify associations between diet and disease outcomes, aiding evidence-based nutritional recommendations.
Ethical and Regulatory Concerns	Adoption of AI in clinical nutrition requires addressing privacy and bias issues.
Evidence-Based Practice	Clinical nutritionists rely on scientific research for recommendations, ensuring up-to-date and effective advice.
Integration into Healthcare System	Better integration of nutritional care is needed within the overall healthcare system.
Challenges and Opportunities	Clinical nutrition faces challenges but also opportunities, especially in addressing chronic diseases.
Clinical Nutrition's Importance	Clinical nutrition plays a vital role in maintaining and improving patient health.
Future Growth and Impact	As research continues, clinical nutrition will likely become even more integral to healthcare.

Food Recognition and Portion Size Estimation

- AI uses machine learning algorithms and image recognition to analyze food images, predict portion sizes, and estimate nutrient content with high accuracy.

Dietary Assessment Methods

- Innovative AI-based tools utilize different sensors, software, or image/voice-based approaches to improve health outcomes. For instance, sound-based recognition systems accurately measure the weights of food bites, while voice-based mobile systems like Speech2Health compute calorie intake with over 90% accuracy.

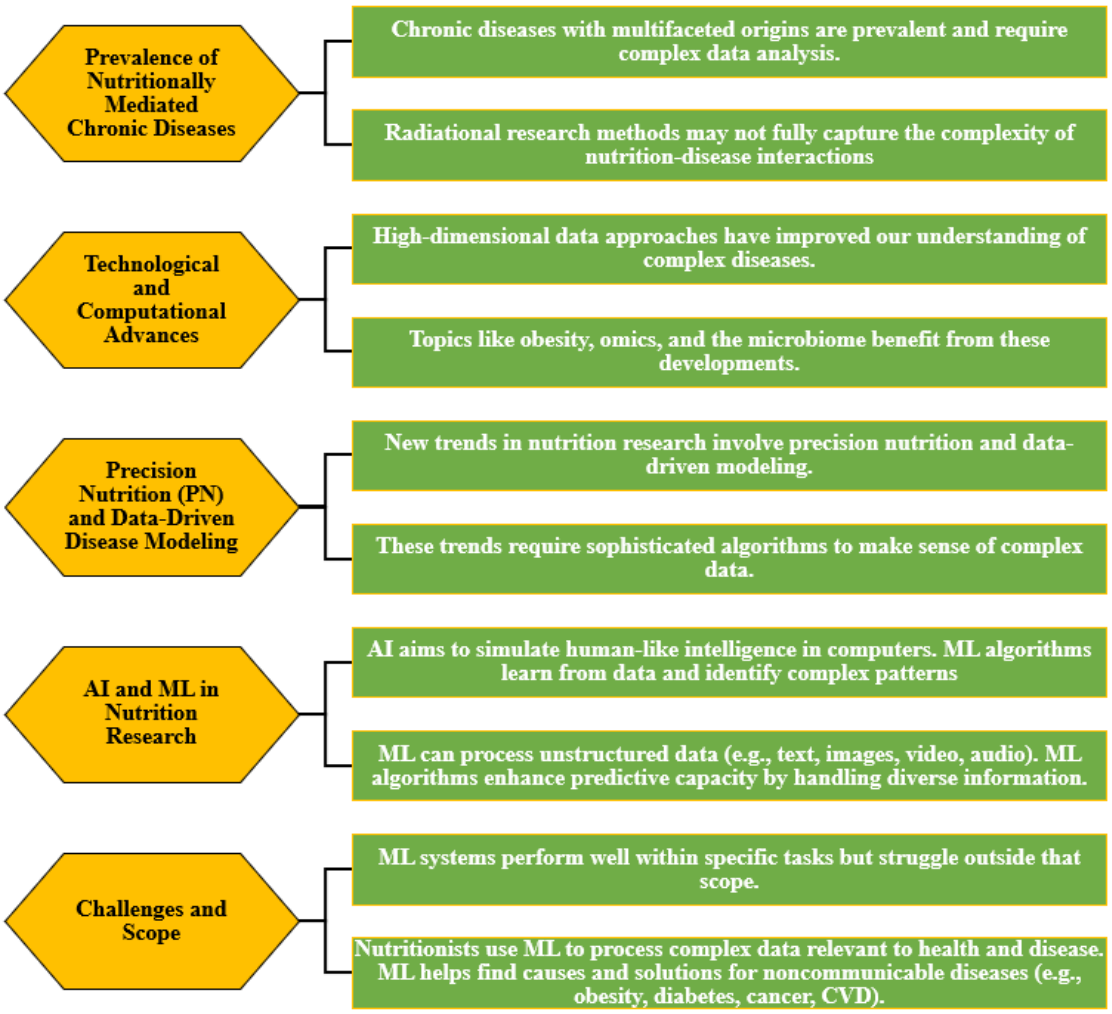
Nutritional Profiling and Personalized Recommendations

- AI-driven meal planning platforms assess an individual's nutritional needs based on factors like age, gender, activity level, dietary restrictions, and health goals, generating personalized meal plans .

Challenges and Future Directions

- Despite progress, challenges remain, including standardizing data collection protocols, ensuring accuracy across diverse populations, and integrating AI into practical dietary assessment tools .

Overview of Current Trends in Nutrition and Machine Learning Research



Different circRNAs regulate breast cancer–related phenotypes by modulating miRNAs.