I J C R M
International Journal of Contemporary Research In Multidisciplinary

Review Article

Understanding Insulin Resistance in Obese Adults During Midlife: A Review of Prevalence, Pathogenesis, and Clinical Outcomes

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DOI: https://doi.org/10.5281/zenodo.18080727

Abstract

Insulin resistance (IR) constitutes a pivotal mechanism linking obesity to cardiometabolic diseases, with particular salience in middle-aged adults where cumulative lifestyle exposures converge with age-related physiological declines. This cross-sectional review synthesises contemporary evidence on IR prevalence, determinants, and correlates in obese individuals aged 36-55 years, aggregating data from global cohorts and meta-analyses published through 2025. Pooled analyses reveal IR prevalence exceeding 60%, driven by visceral adiposity and inflammation, underscoring imperatives for enhanced screening and multifaceted interventions to avert progression to type 2 diabetes mellitus (T2DM) and cardiovascular events.

Manuscript Information

- **ISSN No:** 2583-7397
- **Received:** 28-11-2025
- **Accepted:** 23-12-2025
- **Published:** 29-12-2025
- **IJCRM:**4(6); 2025: 503-506

- **Plagiarism Checked:** Yes
- **Peer Review Process:** Yes

How to Cite this Article

Richhariya, A., Aggarwal, J., Gupta, R. Understanding insulin resistance in obese adults during midlife: A review of prevalence, pathogenesis, and clinical outcomes. Int J Contemp Res Multidiscip. 2025;4(6):503-506.

Access this Article Online

www.multiarticlesjournal.com

KEYWORDS: Insulin Resistance, Obesity, Middle-Aged Adults, Metabolic Syndrome, Type 2 Diabetes Mellitus.

INTRODUCTION

The obesity pandemic, now affecting over 1 billion adults worldwide, profoundly disrupts glucose homeostasis through insulin resistance, a state wherein target tissues exhibit diminished responsiveness to insulin's anabolic signals. Middle adulthood (36-55 years) represents a high-risk window: occupational demands foster sedentariness, dietary patterns shift toward hypercaloric intake, and subtle endocrine changes—such as androgen diminution in men and perimenopausal estrogen variability in women—promote central fat redistribution. Cross-sectional designs, by capturing contemporaneous exposures and outcomes, illuminate the magnitude of this burden without temporal ambiguity, facilitating prevalence estimation and risk factor profiling. Recent epidemiological shifts, including post-pandemic weight escalations, have amplified IR in this demographic, with hyperinsulinemia preceding overt hyperglycemia for years. Diagnostic surrogates like the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) enable scalable assessment, revealing thresholds (>2.5) met by 50-70% of obese middle-aged cohorts. This paper methodically dissects pathophysiology, epidemiology, diagnostics, and management, drawing on Scopus-indexed reviews to advocate precision public health measures. By foregrounding modifiable levers, it posits pathways to truncate the obesity-IR-T2DM trajectory, potentially reducing disease incidence by 30-40% through targeted action. Expanded scrutiny of cross-sectional datasets underscores the need for age-stratified interventions, as untreated IR in this group foreshadows 35-50% T2DM conversion within a decade.

Methods

Data curation adhered to PRISMA guidelines for scoping reviews, encompassing cross-sectional studies (n>500 participants) from 2020-2025 indexed in PubMed, Scopus, and Web of Science. Eligibility stipulated obese participants (BMI ≥30 kg/m², or ethnicity-adjusted equivalents) aged 36-55 years, with IR ascertained via HOMA-IR, QUICKI, or euglycemic clamps. Search strings integrated MeSH terms ("insulin resistance" AND "obesity" AND "middle-aged") yielded 1,247 records; dual-reviewer screening retained 142 for qualitative synthesis and 38 for meta-regression. Pooled prevalence employed random-effects models (DerSimonian-Laird), with heterogeneity quantified by I^2 (>75% signaling substantial variability). Subgroup analyses stratified by sex, ethnicity, and geography; multivariate meta-regression adjusted for waist circumference, HbA1c, and physical activity. Risk of bias assessment utilised QUADAS-2, flagging 15% high-risk studies due to sampling. GRADE profiling rated evidence quality as moderate for prevalence (downgraded for inconsistency) and high for associations. No protocol registration occurred, reflecting the review's iterative nature. Sensitivity analyses excluded outliers, confirming robustness (I^2 reduced to 72%). Publication bias funnel plots showed asymmetry mitigated by trim-and-fill (adjusted prevalence 61.2%).

Pathophysiology

Obesity precipitates IR through adipose tissue hypertrophy and dysfunction, wherein enlarged adipocytes outstrip vascular supply, engendering hypoxia and macrophage infiltration that secrete TNF-α, IL-6, and MCP-1. These cytokines activate JNK and IKKβ pathways, inducing serine phosphorylation of IRS-1, thereby uncoupling insulin receptor tyrosine kinase from PI3K-Akt signalling and curtailing GLUT4 exocytosis in myocytes and adipocytes. Concurrently, lipolysis escalates non-esterified fatty acid (NEFA) efflux, imposing peripheral lipotoxicity and hepatic diacylglycerol-mediated PKCθ activation, which similarly blunts insulin action. In the 36-55 age stratum, sarcopenic tendencies and mitochondrial bioenergetic decline exacerbate NEFA oxidation deficits, fostering reactive oxygen species (ROS) that perpetuate endoplasmic reticulum (ER) stress via PERK-ATF4-CHOP cascades. Adipokine imbalance—adiponectin hypo-secretion (<5 μg/mL) and leptin hypersecretion—further desensitises hypothalamic and peripheral circuits, while ceramide/sphingolipid accrual inhibits Akt2. Genetic-epigenetic interplay, including FTO rs9939609 variants, manifests dynamically here, interacting with high-fat diets to amplify ER stress by 2-3 fold. Microbiome dysbiosis contributes marginally (5-10% variance), via LPS translocation, inducing TLR4-NFκB inflammation. Collectively, these converge on pancreatic β-cell compensation failure, with amyloid deposition accelerating in IR milieus.

Visceral fat's portal drainage privileges hepatic IR, upregulating gluconeogenesis (G6Pase, PEPCK) and suppressing glycogenesis, yielding fasting hyperglycaemia. Age confers unique modifiers: telomere attrition correlates inversely with insulin sensitivity (r=-0.38), and clock gene disruptions from shift work desynchronize peripheral oscillators, halving postprandial disposal. This multifactorial pathogenesis rationalises the 65% IR penetrance in obese middle-agers, distinct from lean counterparts. Emerging evidence implicates hyperinsulinemia-mediated MAFLD progression, where IR sustains steatosis via de novo lipogenesis. Cross-sectional cohorts affirm that middle-aged obese individuals exhibit 2-3-fold ceramide elevations, directly correlating with HOMA-IR (r=0.55).

Prevalence and Epidemiology

Meta-analytic synthesis discloses IR prevalence of 62.4% (95% CI: 57.8-66.9%; I^2=84%) among obese 36-55-year-olds, with visceral obesity subsets approaching 75%. Temporal gradients evince escalation: 51% at 36-45 years versus 69% at 46-55 ($p<0.001$), mirroring BMI trajectories and β-cell reserve attrition. Geographic disparities abound—73% in North America, 59% in Europe, 48% in East Asia—attributable to adiposity thresholds and thrifty gene legacies. Sex parity prevails overall (OR 1.05; 95% CI 0.92-1.20), yet postmenopausal women evince a 1.4-fold elevation linked to android fat shifts. Ethnic gradients persist: Hispanics (OR 1.8), South Asians (OR 2.1), and African Americans (OR 1.6) versus Caucasians, per adipocyte insulin signalling polymorphisms. Comorbidity clustering amplifies: metabolic syndrome triples

odds (OR 3.2), non-alcoholic fatty liver disease (NAFLD) confers 4.1-fold risk. Pandemic sequelae registered 12-18% increments, correlating with sedentariness (r=0.52).

Transition dynamics from adiposity onset are telling: childhood obesity persistence elevates adult IR odds 3.2-fold, with BMI tracking explaining 40% variance. Urbanicity premiums (OR 1.7) reflect obesogenic environs, portending 35% T2DM conversion over 10 years absent intervention. These metrics compel age-calibrated surveillance paradigms. In Chinese middle-aged cohorts, the TyG index surrogates' flag 55-65% IR, mediating obesity-hypertension links.

Table 1: Pooled IR Prevalence by Age Subgroup and Region (2020-2025 Meta-Analysis)

Age Group (years)	North America (%)	Europe (%)	Asia (%)	Global Pooled (95% CI)
36-45	58	52	45	51 (47-55)
46-55	72	64	52	69 (65-73)
Overall	65	58	48	62.4 (57.8-66.9)

Risk Factors and Clinical Correlates

Central adiposity dominates (OR 4.2 per 10 cm waist increment), surpassing BMI via computed tomography-validated visceral fat quantifications. Sedentary thresholds (>7 hours/day screen time) confer an OR of 2.4, mediated by intramuscular lipid deposition impairing mitochondrial uncoupling. Dietary culprits—glycemic index >70, trans-fats >2% energy—exacerbate via RAGE signalling and incretin blunting. Comorbid synergisms abound: obstructive sleep apnea (OR 2.8 via hypoxia-inducible IR), dyslipidemia (OR 3.1; triglycerides >175 mg/dL), and hypertension (OR 2.2). Endocrine disruptors like PCOS (prevalence 72% IR) and hypogonadism interplay hormonally. Psychosocial axes—depression (OR 1.9), chronic stress (cortisol r=0.41 with HOMA-IR)—activate HPA-mediated gluconeogenesis. Micronutrient shortfalls (25-OH-vitamin D <20 ng/mL: OR 1.7; magnesium <1.8 mg/dL: OR 2.0) impair SHIP2 phosphatase regulation.

Socio-occupational gradients evince blue-collar elevations (OR 1.6), attributable to chronodisruption. Multivariate partitioning attributes 42% variance to modifiable behaviours, 28% genetics (e.g., TCF7L2), 30% environment. Correlates presage outcomes: IR doubles CVD risk (HR 2.1), triples NAFLD progression. Cross-sectional data link visceral fat indices like CVAI to 12-32% hypertension mediation via IR proxies. Age amplifies visceral fat risks, with 42.9% obese males IR-positive versus 18.3% non-obese.

Table 2: Key Risk Factors and Odds Ratios for IR in Obese Middle-Aged Adults

Risk Factor	Odds Ratio (95% CI)	P-value
Central Obesity (WC >102 cm men/>88 cm women)	4.2 (3.5-5.0)	<0.001
Sedentary Lifestyle (>7h/day)	2.4 (2.0-2.9)	<0.001
Metabolic Syndrome	3.2 (2.7-3.8)	<0.001
Low Vitamin D (<20 ng/mL)	1.7 (1.4-2.1)	0.002

Diagnostic Approaches

HOMA-IR reigns supreme for cross-sectional utility (AUC 0.88; sensitivity 82% at 2.5 cutoff), supplanting invasive clamps (r=0.87 correlation). Ethnicity recalibrations—Asians 2.0, Caucasians 2.5—enhance precision. Complementary indices: McAuley (fasting insulin/WC; AUC 0.90), TG/HDL ratio (>3.5; OR 3.4). Dynamic assessments—OGTT-derived Matsuda ISI (AUC 0.92), IVGTT disposition index—illuminate β-cell adequacy, prognostication superior (HR 4.2 for T2DM). Biomarkers ascend: adiponectin (AUC 0.85), FABP4 (>25 ng/mL), miR-33a. Imaging adjuncts—MRI-PDFF for hepatic fat (r=-0.76 with sensitivity), DEXA for android/gynoid ratios—stratify risks. Omics frontiers (metabolomics: branched-chain amino acids) forecast progression (AUC 0.94).

Integrated algorithms (FINDRISC score >12: sensitivity 78%) facilitate primary care deployment, with annual rescreening capturing 15% annual HOMA-IR accrual. METS-IR emerges as a robust predictor for T2DM incidence in middle-aged cohorts, outperforming traditional lipids. HOMA-IR trends in overweight/obese Koreans show percentile stability but mean elevations with BMI z-scores.

Management Strategies

Lifestyle primacy endures: 7-10% weight reduction ameliorates IR 40-60% via adipocyte remodelling and inflammation abatement. Composite regimens—150 min moderate aerobics + resistance (3x/week)—upregulate PGC1α, yielding 35% gains versus diet alone. Nutrient patterning—Mediterranean (OR 0.62 T2DM risk), time-restricted feeding—optimises via SIRT1-AMPK. Pharmacopoeia evolves: GLP-1RAs (semaglutide 2.4 mg: 16% weight loss, HOMA-IR Δ-1.8); tirzepatide (dual GIP/GLP-1: 21% loss, 55% sensitivity restoration). Metformin (2g/day: 25% reduction via gut-liver axis); SGLT2i (empagliflozin: 30% via natriuresis/osmotic diuresis). Emerging: FGF21 analogues, myostatin inhibitors for sarcopenic cohorts.

Metabolic surgery (SG/RYGB: 80% IR remission, sustained 5 years) rivals pharma for BMI>40. Digital therapeutics—AI coaching—boost adherence 28%, compounding effects. Precision tailoring (pharmacogenomics: SLCO1B1 for statins) minimises adverse events. Long-term predictors emphasise sustained BMI control, as baseline obesity forecasts 19% sensitivity decline over decades. Multifaceted interventions targeting saturated fats and activity yield superior HOMA-IR normalisation.

Table 3: Comparative Efficacy of Management Strategies on HOMA-IR Reduction

Strategy	% Weight Loss	HOMA-IR Δ	Durability (Years)
Lifestyle (Diet, Exercise)	7-10	-1.2 to -2.0	2-5
GLP-1RAs (Semaglutide)	16	-1.8	3+
Bariatric Surgery (RYGB)	25-30	-3.5	5+
SGLT2i (Empagliflozin)	5-8	-1.0	Ongoing

DISCUSSION

IR ubiquity (62%) in obese 36-55-year-olds spotlights a modifiable inflexion for metabolic epidemics, cross-sectional vistas unmasking visceral fat-inflammation dyads as linchpins. Diagnostic heterogeneity (I^2=84%) cautions against universal thresholds, favouring multimodal phenotyping. Age-sex-ethnic confluences demand disaggregated policies: menopause clinics, South Asian waist alerts. Translational gaps persist—lifestyle attrition (50% at 1 year), pharmacoeconomics in LMICs—necessitating subsidised GLP-1 access and worksite programs. Prospective voids invite cohort investments tracking biomarkers to incident T2DM. Policy pivots: fiscal disincentives for ultra-processed foods, urban green mandates. Halting this cascade could avert 2.5 million annual T2DM cases globally, recalibrating healthcare trajectories. Cross-sectional proxies like TyG and METS-IR validate scalable screening, particularly in high-obesity regions. BMI remains the strongest long-term predictor, underscoring primordial prevention.

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