frontiers in Endocrinology

TYPE Review
PUBLISHED 04 November 2026
DOI 10.3389/fendo.2026.1966524

Check for updates

OPEN ACCESS

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RECEIVED 13 August 2026
REVISED 18 September 2026
ACCEPTED 12 October 2026
PUBLISHED 04 November 2026

CITATION
García AH, De Sanctis JB and Celli Kubler GA (2026) Before the storm: insulin resistance as a sentinel biomarker across the cardiometabolic continuum. A comprehensive narrative review.
Front. Endocrinol. 17:1966524.
doi: 10.3389/fendo.2026.1966524

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Before the storm: insulin resistance as a sentinel biomarker across the cardiometabolic continuum. A comprehensive narrative review

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Insulin resistance (IR) is often seen as a curiosity associated with prediabetes and polyendocrine metabolic ovarian syndrome (PMOS, formerly PCOS). However, it is a significant early indicator of progression towards type 2 diabetes, cardiovascular disease, heart failure, chronic kidney disease, and liver disease. This review covers the pathophysiology of IR in the vascular, hepatic, renal, and cardiac systems, its epidemiological impact, and diagnostic tools, including the hyperinsulinemic-euglycemic clamp and accessible indices like HOMA-IR and the triglyceride-glucose (TyG) index. We reviewed the 2023 and 2026 American Heart Association clinical guideline framework for cardiovascular-kidney-metabolic (CKM) syndrome, which highlights insulin resistance and dysfunctional adiposity as early factors in a multi-organ continuum that precedes abnormal conventional risk factors. When assessing routine IR testing in preventive practice, it is crucial to consider diagnostic accuracy, costs, implementation feasibility, and outcomes from prevention trials. These components are essential for evaluating the effectiveness and value of testing in healthcare. While no universally validated IR index exists for population-wide screening, targeted assessment is recommended for individuals with excess adiposity, a family history of type 2 diabetes, or early metabolic risk markers. This research-oriented, risk-stratified approach is preferable to a general recommendation. It may help identify individuals who would benefit from closer monitoring and lifestyle interventions at CKM stage 0-1, pending data from outcome-driven trials. In conclusion, key research priorities include standardizing cutoffs across populations and designing outcome trials to determine whether IR-guided interventions improve the cardiometabolic continuum compared with those based solely on glycemic thresholds.

KEYWORDS
biomarkers, cardiometabolic continuum, cardiovascular-kidney-metabolic syndrome, HOMA-IR, insulin resistance

1 Introduction

For decades, cardiovascular prevention has focused on specific risk factors like hypertension and obesity, leading to separate management strategies. While this has saved lives, it often overlooks underlying metabolic issues such as insulin resistance (IR), which may go unnoticed until blood glucose levels become abnormal. IR is characterized by a diminished response to insulin, particularly affecting glucose disposal in muscle and lipid metabolism (1). Compensatory hyperinsulinemia can cause endothelial dysfunction, hepatic lipogenesis, and low-grade inflammation before diagnostic markers such as fasting glucose or HbA1c levels rise (2–8). The cardiometabolic continuum suggests that obesity, prediabetes, type 2 diabetes, and hypertension are overlapping manifestations of a shared pathophysiological process, rather than separate diseases (9).

The American Heart Association's cardiovascular-kidney-metabolic (CKM) syndrome framework, detailed in Section 4, stages this continuum from no risk factors (Stage 0) to established cardiovascular disease (Stage 4), with IR as a key upstream driver (1, 10, 11).

A key question arises: should IR be routinely tested before any signs of cardiometabolic issues appear? This review explores the physiological rationale, available diagnostic tools and their performance, evidence for early intervention, and cautions against indiscriminate testing, aiming to provide a balanced, evidence-based perspective for clinicians and researchers.

This synthesis is positioned alongside several reviews published in 2025–2026 that address related aspects of the cardiometabolic continuum, but with a distinct scope and organization. Caturano et al. reframe type 2 diabetes and cardiovascular disease as co-evolving manifestations of a shared continuum, emphasizing integrated care models and emerging pharmacotherapy (115); Gusev et al. synthesize the links among insulin resistance, meta-inflammation, and convergent cellular stress programs at the molecular level (22). The present review differs in adopting an explicitly organ-by-organ architecture, systematically working through vascular, hepatic, renal, cardiac, reproductive, neurocognitive, and oncological mechanisms under a single convergent-signaling framework, and in devoting dedicated sections to weighing the arguments for and against routine IR screening, a clinical-translation question that these companion reviews do not address in comparable depth.

This narrative review is based on literature identified through PubMed/MEDLINE, Scopus, and Google Scholar (January 2000–July 2026, weighted toward the past five years), supplemented by hand-searching reference lists of key reviews and society statements; no protocol was registered, and formal PRISMA reporting was not followed. Priority was given to systematic reviews, meta-analyses, and guidelines from major cardiovascular, endocrine, and nephrology societies, as well as large cohort studies and mechanistic work directly relevant to the cardiometabolic continuum. The authors performed selection and synthesis without independent duplicate screening or formal risk-of-bias assessment, consistent with a narrative rather than systematic design; readers should keep these limitations in mind when interpreting the synthesis. Figures 1–3 are original schematic illustrations generated with the assistance of Gemini AI to visually summarize concepts discussed in the text; they are conceptual aids, not reproductions of primary data.

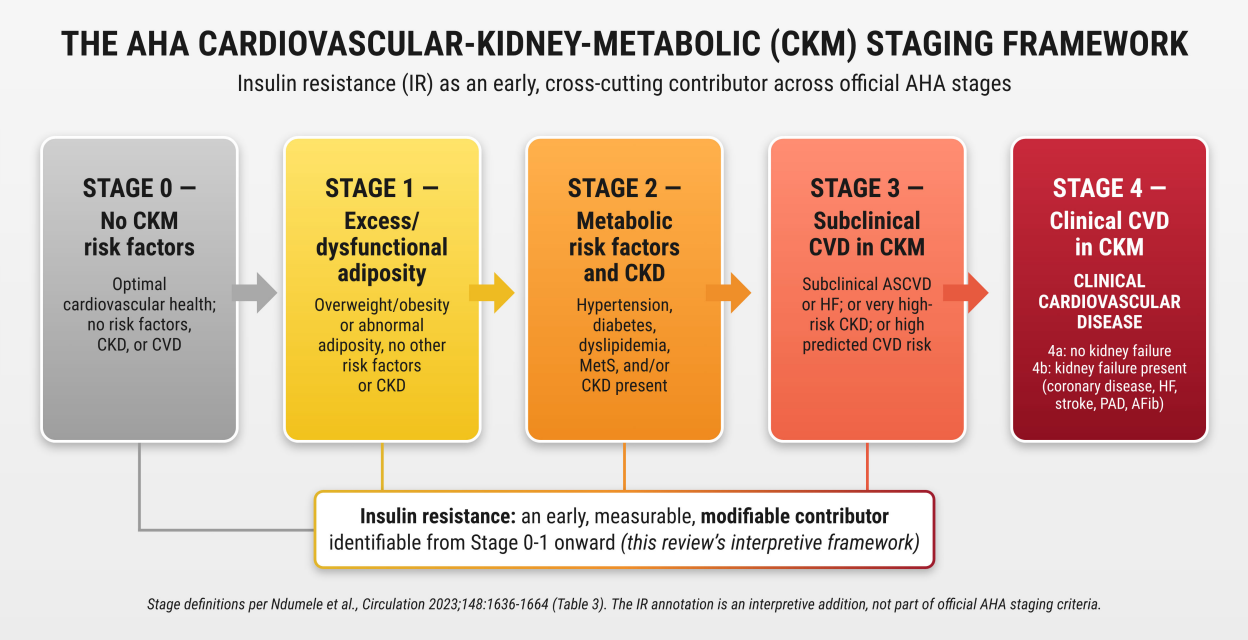


FIGURE 1
The American Heart Association's official cardiovascular-kidney-metabolic (CKM) staging framework (stages 0-4, with stage 4a/4b), based on the staging definitions in Ndumele et al. (10). Insulin resistance is annotated as an early, measurable, and modifiable contributor identifiable from Stage 0–1 onward; this IR-focused annotation reflects this review's interpretive framework and is not part of the official AHA staging criteria. Stage 4 is defined by clinical cardiovascular disease, with kidney failure as an optional sub-designation (4b), not by kidney damage alone. Created using Gemini AI.

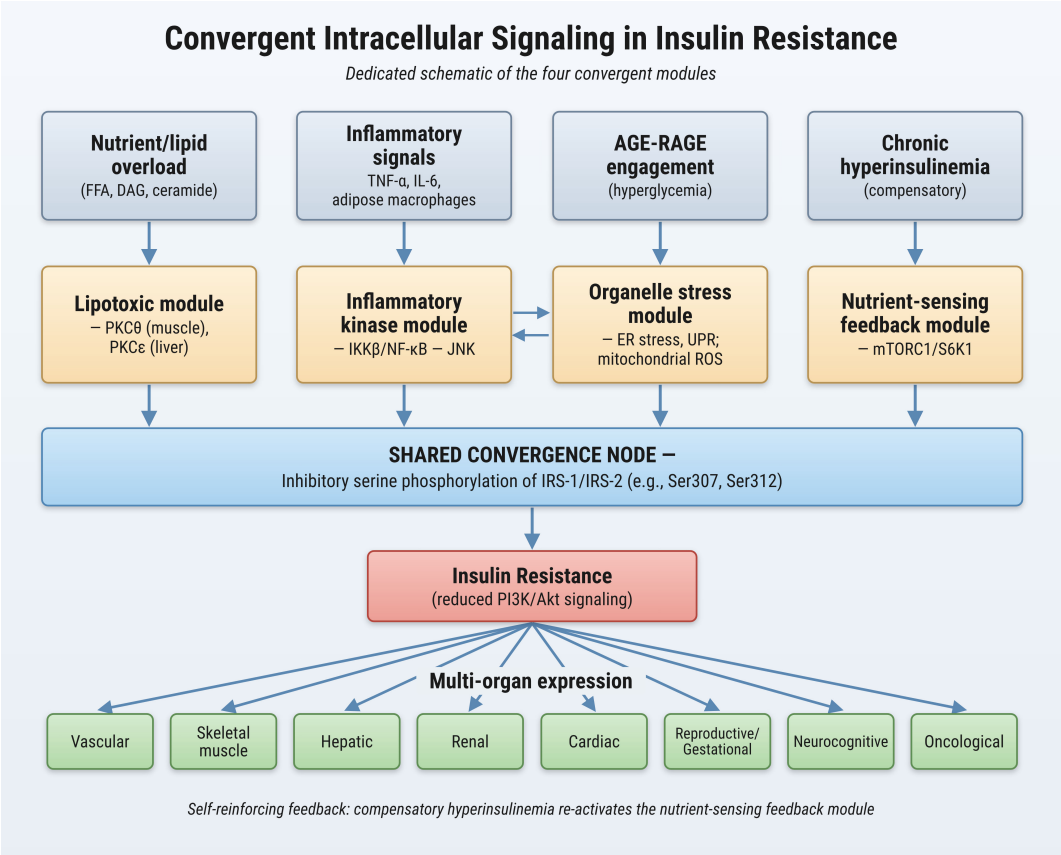


FIGURE 2
Convergent intracellular signaling in insulin resistance involves four triggers: nutrient/lipid overload, inflammatory signals, AGE-RAGE engagement, and chronic hyperinsulinemia. These activate four signaling modules (lipotoxic PKC, IKKβ/NF-κB, JNK, and mTORC1/S6K1) that lead to inhibitory serine phosphorylation of IRS-1/IRS-2, resulting in IR and organ-specific injury. A self-reinforcing feedback loop links hyperinsulinemia back to the nutrient-sensing module.

2 Epidemiology: the scale of the problem

Estimating IR prevalence is difficult because no universal diagnostic threshold exists. IR is common, potentially affecting more individuals than any single metabolic syndrome component. A 2025 systematic review found that globally, 26.5% of adults have HOMA-IR-defined IR, with regional estimates ranging from 26% to 30% (12). Earlier data indicated that around one in four U.S. adults over 20 met criteria for broader IR syndrome (13).

A modeling analysis estimated that 1.54 billion adults had metabolic syndrome by 2023, with prevalence increasing from 14.7% to 31.0% in women and from 9.0% to 25.7% in men (14). A global meta-analysis of over 28 million individuals reported prevalence between 12.5% and 31.4%, with the Americas and Eastern Mediterranean regions most affected (15). Since IR is the main driver, these figures may underestimate those in the cardiometabolic continuum before reaching diagnostic thresholds for diabetes, hypertension, or dyslipidemia.

Type 2 diabetes is a significant global health concern, with the IDF Diabetes Atlas estimating that 589 million adults aged 20–79 had diabetes in 2024, projected to reach 853 million by 2050, over 90% of which are type 2 cases (16, 17). Around 635 million adults have impaired glucose tolerance, and 488 million have impaired fasting glucose, increasing their risk. Notably, 43% of adults with diabetes, about 252 million, remain undiagnosed, emphasizing the need for improved identification methods beyond glycemic thresholds (17, 18).

3 Pathophysiology: how insulin resistance initiates the continuum

Insulin functions beyond glucose management, with two main signaling pathways that differ in actions and kinetics. The phosphatidylinositol 3-kinase (PI3K)/Akt pathway responds quickly to insulin, mediating acute metabolic effects like GLUT4 translocation and vasodilation, and is rapidly deactivated. In contrast, the mitogen-activated protein kinase (MAPK)/ERK pathway acts more slowly and persists longer, influencing mitogenic actions, cell growth, and prothrombotic gene expression over hours. Under normal conditions, these pathways are balanced, but in insulin-resistant states, the fast PI3K/Akt pathway becomes impaired. In contrast, the slower MAPK/ERK pathway may be preserved or enhanced by hyperinsulinemia (19). This leads to

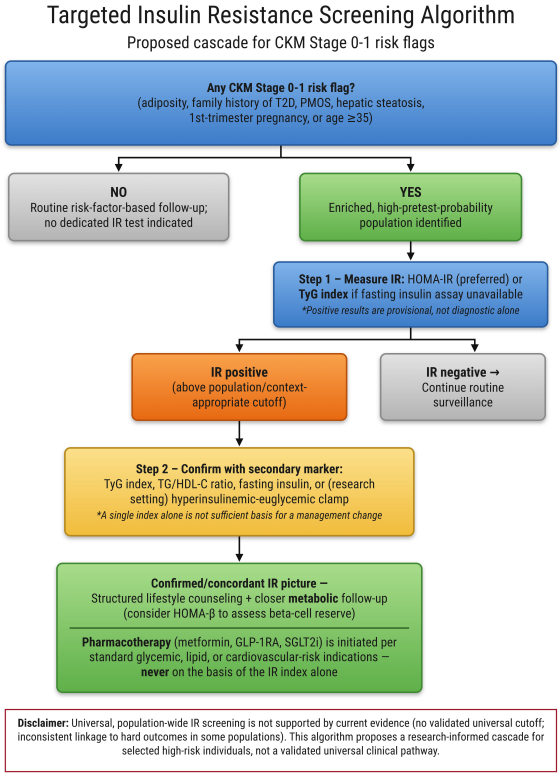


FIGURE 3
Proposed insulin resistance screening algorithm: individuals are assessed for CKM stage 0–1 risk flags (e.g., excess adiposity, family history of type 2 diabetes, PMOS, hepatic steatosis, first-trimester pregnancy, or age ≥35). Those with flags undergo HOMA-IR or TyG index testing; a positive result is confirmed with a secondary marker (TyG index, TG/HDL-C ratio, fasting insulin, or clamp in research settings) before triggering structured lifestyle counseling and closer metabolic follow-up. Pharmacotherapy is initiated per standard glycemic, lipid, or cardiovascular-risk indications, not based on the IR index alone. This targeted approach is preferred over population-wide screening, which lacks current evidence support. Created with Gemini AI.

increased vasoconstriction and inflammation, highlighting a selective defect in post-receptor insulin signaling that links IR to multiple organ injuries (as illustrated in Figure 1).

This review highlights IR as a key theme but does not suggest it is the sole cause of cardiometabolic issues. Other significant factors include genetic susceptibility, chronic inflammation, mitochondrial dysfunction, gut microbiome metabolites, and neurohormonal dysregulation. In individual patients, one mechanism may be the primary driver, with IR serving as a secondary point of convergence. The case for measuring and targeting IR, discussed later, is based on its being an early, measurable, and modifiable factor, rather than the only upstream cause.

3.1 Convergent intracellular signaling: crosstalk between insulin, inflammatory, and stress pathways

The asymmetry between PI3K/Akt and MAPK/ERK pathways is the starting point for a larger signaling network. Research indicates that IR results from multiple interacting pathways that converge on shared downstream kinases, as described in the "critical nodes" model of insulin signaling (20). Four such convergent modules are well characterized (Figure 2). First, a lipotoxic module, driven by diacylglycerol- and ceramide-dependent activation of novel protein kinase C isoforms (PKCθ in skeletal muscle, PKCε in liver; discussed further in Sections 3.4 and 3.5), phosphorylates insulin receptor substrates (IRS) proteins at inhibitory serine residues rather than their normal tyrosine sites. Second, an inflammatory kinase module, centered on IκB kinase β (IKKβ)/NF-κB and c-Jun N-terminal kinase (JNK), is activated by TLR 4 sensing of saturated fatty acids and lipopolysaccharide, by TNF-α and IL-6 released from adipose tissue macrophages, and by advanced glycation end-product (AGE) engagement of the receptor for AGE (RAGE) (21). Third, an organelle-stress module, comprising endoplasmic reticulum stress and the unfolded protein response, together with mitochondrial oxidative stress, is triggered by nutrient and lipid overload and, in turn, activates JNK, linking this module back to the second. Fourth, a nutrient-sensing feedback module, centered on mechanistic target of rapamycin complex 1 (mTORC1) and its downstream effector S6 kinase 1, is activated by the same hyperinsulinemia that IR produces, creating a self-reinforcing loop in which the compensatory response to IR becomes an additional cause of it. Critically, these four modules do not act as independent, parallel insults: they converge on a shared final pathway, inhibitory serine phosphorylation of IRS-1 and IRS-2 (e.g., at Ser307, Ser312), which uncouples IRS from the insulin receptor and from PI3K regardless of which upstream module initiated the phosphorylation event (22). This convergence explains an observation that a single-pathway model cannot: genetically, environmentally, and metabolically distinct insults, obesity-associated inflammation, lipid

oversupply, organelle stress, and chronic hyperinsulinemia itself, all produce a remarkably similar biochemical phenotype of IRS-1/2 inhibition, because they funnel onto the same limited set of critical signaling nodes rather than acting through fully independent mechanisms (20, 22). This convergent-network model, rather than the receptor-proximal PI3K/Akt-versus-MAPK/ERK asymmetry alone, is the more complete mechanistic account of how the diverse upstream drivers discussed throughout this review—adiposity, dyslipidemia, inflammation, gut dysbiosis, and genetic susceptibility among them—all funnel toward the same IR phenotype before diverging again into the organ-specific mechanisms described in Sections 3.3-3.10.

Beyond these four convergent modules, IR can also arise through mechanisms operating outside the canonical IRS-1/2 serine phosphorylation node, further reinforcing the idea that no single pathway is sufficient to account for the syndrome. Adipose tissue acts as an endocrine organ that influences insulin sensitivity. With increasing adipose mass, leptin levels rise, but hypothalamic leptin resistance develops, blunting satiety signaling, increasing food intake, and worsening peripheral insulin action. In contrast, ghrelin levels decrease with increased adiposity (23). Resistance can also occur at the receptor level due to reduced insulin receptor numbers, mutations that affect ligand binding, or autoimmune antibodies that blunt the cellular response to normal insulin levels (24). Additionally, accelerated insulin degradation reduces hormone exposure, while GLUT-4 mutations can hinder glucose uptake despite intact signaling (25). These receptor-level, hormonal, and transporter-level mechanisms operate largely in parallel with the shared serine-phosphorylation convergence node described above; together, they illustrate that the four-module framework, while capturing the dominant convergent pathway, does not exhaust how insulin action can fail.

The convergent signaling network is influenced by upstream genetic, epigenetic, and post-transcriptional regulation, helping explain the wide variation in IR susceptibility among individuals subjected to similar metabolic insults. On the genetic side, genome-wide association and next-generation sequencing studies have implicated numerous loci in IR susceptibility, including PPARG, IRS1, IGF1, NAT2, GCKR, FTO, and TCF7L2, acting through diverse regulatory mechanisms (26, 27); the PPARG Pro12Ala variant, for example, was among the first common variants linked to altered fatty acid and energy metabolism and to lower type 2 diabetes risk. In contrast, low-frequency variants in genes such as TBC1D4 have been tied to reduced insulin sensitivity (28). Identified variants account for only a minority of IR heritability, highlighting that genetics alone cannot explain most cases and that gene-environment interaction is key to pathogenesis (29).

Epigenetic modification of insulin-pathway genes provides a second, reversible layer of regulation that links environmental exposure to signaling output. DNA methylation at regulatory sites in genes including INS, IRS1, IGF1, IGFBP1/2, and PPARG tracks with obesity and IR status; increased methylation of the insulin gene promoter, for instance, accompanies reduced insulin transcription under chronic overnutrition, while PPARG hypermethylation parallels reduced PPAR-γ protein expression and worsening dyslipidemia (30).

Histone modifications add a parallel layer: insulin-pathway components such as the insulin receptor, IRS1, Akt, and GLUT4 tend to be relatively deacetylated in insulin-resistant tissue. In contrast, others, including IRS2, FOXO1, JNK, and AMPK, tend to be relatively acetylated, a pattern consistent with a broader shift in chromatin accessibility at metabolic loci during IR development (30). A recent regulatory layer involves non-coding RNAs, such as microRNAs that modulate GLUT4 expression and influence gluconeogenesis and insulin secretion (30). Some non-coding RNAs and miRNAs affect insulin response differently across tissues. Particularly, miR-29 and miR-31 affect muscle and adipose tissue, while others, such as miR-375, regulate β-cell mass (30). Circulating non-coding RNAs are being explored as potential biomarkers for early dysglycemia. Long non-coding RNAs (e.g., H19, MALAT1) and circular RNAs (e.g., circHIPK3, circACC1) provide additional post-transcriptional control over glucose and lipid handling by acting as molecular sponges for microRNAs (30). Although their causal significance in humans is not fully established, these non-coding RNAs indicate a complex regulatory network involving genetic, epigenetic, and post-transcriptional mechanisms (30).

A specific molecular switch downstream of the insulin receptor helps explain why this PI3K/Akt-versus-MAPK/ERK asymmetry develops in the first place. The ubiquitous non-receptor tyrosine phosphatase SHP2 (encoded by PTPN11) is recruited to phosphotyrosine motifs on activated receptors and, once catalytically active, exerts opposite effects on the two branches: it dephosphorylates the p85-binding (Y-X-X-M) motifs on insulin receptor substrate-1 (IRS-1) and GAB1, thereby dampening PI3K/Akt signaling, while simultaneously relaying activation of the RAS/MAPK/ERK cascade (31). Tissue-specific mouse models reveal that the effects of SHP2 loss vary by cell type: in hepatocytes and macrophages, it improves glucose tolerance and reduces inflammation, whereas loss in skeletal muscle, pancreatic β-cells, or hypothalamic neurons impairs glucose uptake, insulin secretion, and energy balance (31). Human genetics offers the clearest evidence that SHP2 hyperactivation alone can produce IR in an intact organism: patients with Noonan syndrome, a RASopathy caused by activating germline PTPN11 mutations. Both the human syndromes and the mouse models show glucose intolerance and IR driven by macrophage-mediated inflammation, even with reduced adiposity. Allosteric SHP2 inhibitors, currently in early oncology trials, reverse this phenotype and improve liver fat in obese mice, suggesting SHP2 as a promising target for addressing both signaling and inflammation in IR (31, 32).

3.2 Adipose tissue mechanisms: the endocrine origin of the continuum

Adipose tissue is the largest endocrine organ, and its transition from insulin sensitivity to resistance indicates metabolic dysfunction (33). Insulin induces hepatic lipid synthesis and lipid accumulation in adipose tissue (33). Healthy adipose tissue expansion involves balanced growth in adipocyte number and size, with adequate vascularization. In contrast, pathological expansion leads to adipocyte hypertrophy, local hypoxia, and inflammation that disrupt insulin signaling. Visceral fat is more inflammatory and less

effective at buffering lipids than subcutaneous fat, thereby raising metabolic risk even at similar body mass index levels (33).

In IR, adipose tissue exhibits an altered adipokine profile—adiponectin falls while leptin, TNF-α, and IL-6 rise—producing a pro-inflammatory signature detectable before the onset of overt metabolic disease. Macrophages shift from the anti-inflammatory M2 to the pro-inflammatory M1 phenotype, and chronic endoplasmic reticulum stress and mitochondrial dysfunction perpetuate this cycle (33).

Impaired lipid buffering releases free fatty acids into the liver and muscles, making adipose insulin resistance a key causal factor. It is linked to polyendocrine metabolic ovarian syndrome, cardiovascular disease, and several cancers (33). Current insulin sensitizers, such as thiazolidinediones and GLP-1 receptor agonists, alongside new strategies targeting adipose function, present a favorable opportunity for early intervention (33).

The "adipose expandability hypothesis" presents a compelling explanation regarding the limitations of subcutaneous adipose tissue expansion. It posits that subcutaneous adipose tissue can only expand safely to a certain threshold. When this capacity is surpassed, any additional caloric surplus is directed towards visceral and ectopic fat depots, such as those in the liver, muscle, and pericardium. These regions are associated with increased inflammation and heightened insulin resistance. This phenomenon may elucidate why some individuals maintain metabolic health despite a high body mass index, while others develop insulin resistance at a normal weight. The key differentiator may reside in subcutaneous adipose tissue expandability rather than total adiposity.

3.3 Vascular and endothelial mechanisms

Endothelium-derived nitric oxide (NO), stimulated through insulin's PI3K/Akt/eNOS pathway, contributes to insulin-mediated glucose uptake in skeletal muscle by increasing capillary recruitment and blood flow (3). When this pathway is selectively impaired, unopposed MAPK-dependent signaling increases endothelin-1 production and upregulates adhesion molecules such as VCAM-1, ICAM-1, and PAI-1, favoring vasoconstriction, leukocyte adhesion, and a prothrombotic vascular surface (4, 6). Clinically, this translates into measurable endothelial dysfunction that precedes overt atherosclerosis and independently predicts incident heart failure, particularly in hypertensive patients, as well as new-onset diabetes and cardiovascular events through an illness-event pathway distinct from glycemia alone (7, 8). Reviews of vascular pathophysiology in the metabolic syndrome converge on the same conclusion: endothelial dysfunction and IR are mutually reinforcing, each amplifying the other in a self-sustaining cycle that begins before hypertension or dyslipidemia become clinically manifest (5, 6).

3.4 Skeletal muscle mechanisms

Skeletal muscle comprises 70-80% of insulin-stimulated glucose disposal, making it the largest reservoir of insulin sensitivity. Studies using magnetic resonance spectroscopy and stable-isotope tracers have shown that raising plasma fatty acid levels reduces insulin-stimulated glucose transport and glycogen synthesis within three to five hours, mirroring the defects observed in type 2 diabetics and their insulin-resistant relatives (34). Rather than the classical Randle glucose-fatty-acid cycle, in which fatty acid oxidation was proposed to raise intracellular glucose-6-phosphate and secondarily inhibit hexokinase (34), the dominant contemporary model implicates intramyocellular accumulation of diacylglycerol and long-chain acyl-CoAs, which activate novel protein kinase C isoforms (PKC-θ in muscle, PKCε in liver). These serine/threonine kinases phosphorylate insulin receptor substrate-1 (IRS-1) at inhibitory serine residues rather than its normal tyrosine sites, blunting downstream PI3K activation and reducing GLUT4 translocation to the cell membrane and glucose transport, the rate-controlling step in insulin-stimulated muscle glycogen synthesis (34). This diacylglycerol-protein kinase C-IRS-1 axis in the liver and muscle links ectopic lipid accumulation from obesity, lipodystrophy, or mitochondrial dysfunction to IR. The selective post-receptor defect highlights that skeletal muscle IR is a key contributor to whole-body IR, driving subsequent vascular, hepatic, renal, and cardiac injuries (34). Thus, the assessment of glucose uptake, as well as the processes of anabolism and catabolism within skeletal muscle, represents a strategic method for evaluating IR and the efficacy of pharmacological treatments.

3.5 Hepatic mechanisms: the path to MASLD

In the liver, IR leads to a selective defect in which insulin fails to suppress gluconeogenesis but still stimulates *de novo* lipogenesis, resulting in continued glucose output and increased fat accumulation (35). Hepatic diacylglycerol accumulation activates protein kinase C epsilon, which directly impairs insulin receptor signaling, thereby mechanistically linking steatosis to IR, not merely statistically (35). The bidirectional relationship defines metabolic dysfunction-associated steatotic liver disease (MASLD), which requires hepatic steatosis and at least one cardiometabolic risk factor, often IR (36). MASLD affects around 30% of the global population and can progress to severe liver diseases, including cirrhosis and cancer (36). This makes the liver a key organ for early insulin resistance detection and a target for related damage.

Insulin's selective action in the liver—characterized by suppressed gluconeogenesis resistance alongside preserved lipogenic signaling—contributes to the distinctive dyslipidemia associated with insulin resistance. This condition is marked by increased VLDL triglyceride secretion, a greater presence of small dense LDL particles, and reduced HDL cholesterol levels. This lipid profile independently elevates cardiovascular risk, regardless of LDL cholesterol concentrations, and establishes a mechanistic link between hepatic insulin resistance and the vascular mechanisms described in Section 3.3.

3.6 Renal mechanisms

The kidney is responsive to insulin, which regulates podocyte integrity, sodium handling, and gluconeogenesis. A recent review (39) describes how, in IR states, homeostatic functions are disrupted, leading to glomerular hyperfiltration, proteinuria, sodium

retention, and progressive kidney injury. Compensatory hyperinsulinemia independently activates pro-growth and pro-fibrotic pathways that drive vascular dysfunction and fibrosis within the kidney itself (39). Analyses from RADAR/SONAR trials show that higher IR is associated with faster decline in estimated glomerular filtration rate and poorer outcomes among patients with type 2 diabetes and chronic kidney disease (CKD) (40). One large non-diabetic CKD cohort found no independent association between HOMA-IR and CKD progression, cardiovascular events, or mortality after adjustment, suggesting that this relationship may vary with the presence of diabetes and the IR index used (41, 42). As renal function declines, IR increases, creating a bidirectional loop where CKD worsens IR due to uremic toxins, inflammation, and vitamin D deficiency. In turn, IR accelerates CKD progression, highlighting the connection between kidney disease and the cardiometabolic continuum (43). IR and hyperinsulinemia activate the sympathetic nervous system, promote sodium retention by reducing Na+/K+-ATPase activity, and increase the glomerular filtration fraction. Concurrently, local activation of the renin-angiotensin-aldosterone system leads to mesangial dilation and podocyte remodeling, which interact with metabolic and inflammatory pathways (44).

3.7 Cardiac mechanisms

IR directly contributes to myocardial dysfunction by impairing insulin signaling in cardiomyocytes. This shifts substrate utilization from glucose to free fatty acid oxidation, increasing myocardial oxygen demand and leading to lipotoxicity, interstitial fibrosis, and diastolic dysfunction. These mechanisms are strongly linked to the development of heart failure with preserved ejection fraction (HFpEF), a rapidly growing cardiovascular issue within the CKM framework (44). The mutual reinforcement between IR and endothelial dysfunction predicts heart failure in hypertensive cohorts, linking a laboratory abnormality to a clinical outcome (7). Cardiac IR reduces GLUT4-mediated glucose transport into cardiomyocytes, leading to an energy-starved state in the failing, insulin-resistant heart. This inability to efficiently switch between glucose and fatty acid substrates impairs contractile efficiency and accelerates heart failure progression, whether with preserved or reduced ejection fraction (44).

3.8 Reproductive and gestational mechanisms

Pregnancy is a natural model of IR, and evidence shows that early gestational IR can identify women at higher risk for complications later, even before they become clinically apparent. A recent review highlights gestational IR as a double-edged sword. While a normal increase helps support the fetus, excessive IR—often worsened by pre-pregnancy overweight and excessive weight gain—can cause maternal complications like gestational diabetes and hypertension, along with long-term risks for the offspring (45). HOMA-IR measured as early as the first trimester predicts subsequent gestational diabetes in normal-weight and overweight or obese women, although its discriminative value is population and BMI-dependent. The index is not suitable for women of advanced maternal age (46). A case-control study of 375 women showed that first-trimester insulin resistance (HOMA-IR) was elevated in those who later developed preeclampsia, even before any clinical signs appeared, compared to matched controls (47). These findings highlight pregnancy as a key opportunity for targeted IR screening, given the low cost of tests, clear risk window, and established clinical pathways for positive results in obstetric care.

3.9 Neurocognitive mechanisms

The brain is an insulin-responsive organ, and increasing evidence suggests that cerebral IR may contribute to cognitive decline, leading to Alzheimer's disease being referred to as "type 3 diabetes" (48). Insulin supports neuronal glucose uptake, synaptic plasticity, and amyloid-β clearance through insulin-degrading enzyme. When neuronal PI3K/Akt signaling is impaired, due to factors crossing the blood-brain barrier or produced by activated microglia, this competition for insulin-degrading enzyme, along with decreased glucose uptake, leads to amyloid-β accumulation, tau hyperphosphorylation, neuroinflammation, and synaptic dysfunction (49). This review's central thesis highlights that peripheral IR and impaired glucose tolerance can be detected years before measurable cognitive decline. Additionally, midlife metabolic syndrome components, like HOMA-IR, independently predict dementia decades later. This suggests that cognitive impairment is a downstream effect of an early, silent process best identified through targeted screening, rather than waiting for irreversible neuronal injury to occur (48, 49). This mechanistic link has therapeutic relevance: GLP-1 receptor agonists, mentioned in Section 6 for their cardiorenal and hepatic benefits, cross the blood-brain barrier and improve neuronal insulin sensitivity. They are being investigated (e.g., in the EVOKE trial program) as disease-modifying approaches for early Alzheimer's disease, reinforcing the argument that IR-centered interventions benefit organs across the cardiometa bolic continuum, including the brain.

3.10 Oncological mechanisms

IR, known for its roles in various injuries (vascular, hepatic, renal, cardiac, reproductive, and neurocognitive), is now also recognized as an independent driver of carcinogenesis, linking the cardiometabolic continuum to cancer. A 2026 UK Biobank study used a nine-parameter predictor of insulin resistance (AI-IR), based on age, sex, race, body mass index, fasting plasma glucose, glycated hemoglobin, triglycerides, total cholesterol, and HDL cholesterol, to analyze data from 372,395 cancer-free participants. The study found that AI-IR outperformed BMI, metabolic syndrome, the TG/HDL-C ratio, and the TyG index in predicting diabetes (AUC 0.798). Additionally, it was independently associated with a significantly higher incidence of several cancers, including uterine, kidney, esophageal, pancreatic, colonic, and breast, along with nominal associations for six other types (50).

Participants who were AI-IR-positive but free of diabetes had a 25% higher age- and sex-adjusted hazard of developing certain cancers (hazard ratio 1.25, 95% CI 1.20-1.31). This risk is similar to that from metabolic syndrome and the TG/HDL-C ratio, and greater than that indicated by body mass index or the TyG index,

supporting the idea that composite IR indices reveal pathophysiological risks that simple fat measurements overlook (50). The link between AI-IR and bronchial and lung cancer strengthened after accounting for body mass index, suggesting that glycemic and lipid factors, not just adiposity, play a role, and remained significant even after adjusting for smoking status. Conversely, skin cancer showed an inverse association with AI-IR, consistent with the established inverse relationship between body mass index and non-melanoma skin cancer (50). Given the cohort's age (40–69 years) and predominantly European ancestry, these findings strengthen the IR-centered continuum discussed in this review but require validation in more diverse populations before informing the targeted screening strategy in Section 8.

3.11 Examining the various causes of insulin resistance, the systemic factors that worsen it, and the importance of central regulation in this condition

This review emphasizes the model of adiposity-driven, or "primary metabolic," insulin resistance; however, it is important to note that the underlying pathophysiological mechanisms exhibit variability. Identifying its primary drivers has significant clinical implications for management. Immune-mediated insulin resistance can occur independently of excessive adiposity, particularly in chronic inflammatory and autoimmune diseases. Conditions such as rheumatoid arthritis and psoriasis are associated with insulin resistance that is disproportionate to body mass index, driven by circulating TNF-α, IL-6, and IL-17, all of which disrupt insulin receptor substrate signaling. This mechanism is analogous to the inflammation induced by adipose tissue macrophages discussed in Section 3.2, though it arises from systemic autoimmune activity rather than adipose tissue expansion.

Latent autoimmune diabetes in adults (LADA), characterized by the presence of glutamic acid decarboxylase antibodies (anti-GAD), represents a distinct category where autoimmune beta-cell destruction coexists with and may be exacerbated by peripheral insulin resistance. Furthermore, autoimmune thyroid disease, indicated by thyroglobulin antibodies (TgAb) and often associated with subclinical hypothyroidism, adversely affects insulin sensitivity by decreasing peripheral glucose disposal and altering lipid metabolism.

A third category, which is often underrecognized in clinical settings, is iatrogenic insulin resistance. Various agents induce this form of insulin resistance, including glucocorticoids, atypical antipsychotics (such as olanzapine and clozapine), protease inhibitors, and calcineurin inhibitors used post-transplantation. Each agent affects insulin resistance through distinct mechanisms, including induction of hepatic gluconeogenesis, dysregulation of hypothalamic appetite, interference with adipocyte differentiation, and direct toxicity to beta-cells. These potential causes of insulin resistance should be carefully considered when evaluating an abnormal insulin resistance index in patients lacking classical metabolic risk factors.

In addition to the four convergent signaling modules outlined in Section 3.1, several systemic neurohormonal axes contribute to the development of insulin resistance, each establishing its own reinforcing feedback loop. Activation of the renin-angiotensin-aldosterone system (RAAS), as discussed in the renal context in Section 3.6, also has systemic effects: angiotensin II diminishes insulin-stimulated glucose uptake in skeletal muscle by reducing microvascular perfusion and directly interfering with PI3K/Akt signaling pathways. Concurrently, aldosterone fosters inflammation and oxidative stress within adipose tissue. Overactivity of the sympathetic nervous system, frequently observed in obesity and sleep-disordered breathing, increases hepatic glucose output and free fatty acid mobilization through beta-adrenergic signaling, exacerbating insulin resistance in both hepatic and skeletal muscle tissues. Furthermore, chronic hypercortisolism—whether resulting from exogenous glucocorticoid therapy or endogenous sources such as chronic psychosocial stress and Cushing syndrome—promotes hepatic gluconeogenesis, visceral fat accumulation, and skeletal muscle proteolysis. These factors collectively worsen the insulin resistance phenotype through mechanisms that converge on the same IRS-1/2 serine phosphorylation node described in Section 3.1.

The central nervous system also regulates energy balance and influences peripheral insulin resistance. Hypothalamic signaling involving leptin and melanocortin is critical for regulating satiety and energy expenditure. Leptin resistance, as discussed in Section 3.2 in the context of peripheral adipose tissue, has a corresponding central component in which impaired hypothalamic leptin signaling leads to continued hyperphagia despite adequate or excess adipose mass. Additionally, mesolimbic dopaminergic reward pathways strongly influence food-seeking behavior, independent of metabolic needs. Notably, a reduction in the availability of striatal dopamine receptors has been associated with obesity and may contribute to the phenomenon of compulsive overeating. Moreover, serotonergic signaling plays a role in regulating both satiety and mood. At the same time, the central effects of GLP-1 receptor agonists on hypothalamic and brainstem appetite centers, distinct from the peripheral insulin-sensitizing effects discussed in Section 6, likely contribute to their effectiveness in the obesity-insulin resistance phenotype. This central regulatory axis remains relatively underexplored compared with the peripheral mechanisms highlighted throughout this review; however, it likely plays a significant role in the individual variability in susceptibility to insulin resistance noted in Section 3.1.

4 The cardiometabolic continuum reframed: from metabolic syndrome to CKM syndrome

The metabolic syndrome, focused on the clustering of abdominal obesity, hypertension, dyslipidemia, and hyperglycemia, has faced criticism for being a mere checklist of related issues. The American Heart Association introduced the CKM syndrome framework in October 2023 as a staged continuum to address these concerns (10).

Within this staged framework, Stage 0 involves no CKM risk factors and represents the primordial prevention window in which

subclinical IR, if present, is the earliest detectable deviation. Stage 1 is defined by excess or dysfunctional adiposity, with or without prediabetes or impaired glucose tolerance, and IR is the presumed mechanistic link to early glycemic abnormality. Stage 2 comprises measurable metabolic risk factors (hypertriglyceridemia, hypertension, metabolic syndrome, type 2 diabetes) or moderate-to-high-risk CKD, in which IR-driven endothelial, hepatic, and renal injury becomes clinically measurable. Stage 3 includes subclinical cardiovascular disease in the context of CKM risk factors, or very high-risk CKD, where chronic hyperinsulinemia and endothelial dysfunction contribute to subclinical atherosclerosis and myocardial remodeling. Stage 4 represents clinical cardiovascular disease, with or without kidney failure — the end-organ expression of a process that, mechanistically, began at Stage 0-1.

This staging system is actionable and moves away from the 2013 cardiovascular risk paradigm, which treated risk factors independently. The 2026 AHA/ACC/ADA/ASN guideline emphasizes dysfunctional adiposity and prediabetes as key modifiable stages, not just precursors to diabetes (11). Within this model, insulin resistance is posited as a central organizing principle rather than merely an incidental laboratory finding. The American Heart Association's conceptual framework for CKM syndrome identifies inflammation, oxidative stress, insulin resistance, and vascular dysfunction as interconnected processes that link dysfunctional adiposity to metabolic, renal, and cardiovascular damage (10). This review highlights IR as it is measurable and can be modified through four interconnected processes. However, this focus does not suggest that IR holds a uniquely privileged causal role within the AHA framework. This reframing prompts the question: Should IR be systematically measured in early preventive care, or should it continue to be identified opportunistically after glycemic or lipid thresholds are crossed?

A brief note on nomenclature is warranted, as terminology in this area has evolved rapidly. The term "cardiometabolic syndrome," once synonymous with metabolic syndrome, has been replaced by the American Heart Association's cardiovascular-kidney-metabolic (CKM) syndrome framework. This framework recognizes the kidney as a key organ system, rather than merely an incidental complication of diabetes or hypertension (1, 10, 11). Some authors refer to "cardiorenal metabolic syndrome" (CRMS) as a label for the same construct, representing the triad of cardiovascular, renal, and metabolic dysfunction linked by IR (44). A new concept, the cardiovascular-liver-metabolic (CLM) syndrome, has emerged, recognizing that MASLD shares upstream IR-driven pathophysiology with cardiovascular and renal diseases. This framework replaces the kidney with the liver as the third organ system, integrating MASLD with cardiovascular disease and type 2 diabetes into the cardiovascular-liver-metabolic multimorbidity (CLMM) phenotype (51). CKM, CRMS, and CLM/CLMM are overlapping, organ-specific lenses on the same IR-centered continuum described in Section 3, rather than competing terms. This review uses "CKM" as its primary framework, recognized in AHA policies and guidelines, while also acknowledging CRMS and CLM/CLMM as valid alternatives for hepatic outcomes.

5 Measuring insulin resistance: from the gold standard to clinically feasible surrogates

Methods to quantify IR range from complex, invasive procedures to simple indices from a fasting blood sample or anthropometric measurements. Understanding the merits and limitations of each is crucial for selecting the appropriate tool for clinical or research needs (52–54).

5.1 The hyperinsulinemic-euglycemic clamp

The hyperinsulinemic-euglycemic clamp, developed by DeFronzo and colleagues, remains the reference standard for quantifying whole-body insulin sensitivity (55, 56). A continuous intravenous insulin infusion maintains a fixed, high plasma insulin level, while a variable dextrose infusion keeps blood sugar normal; the required glucose infusion rate directly reflects tissue insulin sensitivity (55, 57). Its precision is unmatched, but its high cost, long duration, need for two IV catheters, and requirement for skilled operators make it unsuitable for routine clinical use; it will likely remain a research tool (58, 59).

5.2 HOMA-IR: performance, cutoffs, and limitations

The HOMA-IR model, calculated from a single fasting glucose and insulin measurement, is by far the most widely used clinical and epidemiological surrogate (60). The main weakness is the lack of a universally accepted cutoff, with thresholds ranging from 1.37 to 3.63 depending on factors such as population, age, sex, ethnicity, and validation method (61, 62; Table 1).

Despite this heterogeneity, HOMA-IR retains genuine clinical value in specific contexts: it reliably differentiates MASLD from non-MASLD at thresholds around 2.0-2.5 (63) and, among patients with established type 2 diabetes, higher HOMA-IR independently predicts future cardiovascular events even after adjustment for traditional risk factors (64). Its routine clinical applicability, however, remains limited by the requirement for insulin assays (65).

5.3 HOMA-β (HOMA2-%B): the complementary beta-cell function index

HOMA-IR is just one aspect of insulin dynamics. It uses fasting glucose and insulin values to calculate HOMA-β, which quantifies pancreatic beta-cell function as a percentage of that in a healthy population. Importantly, IR does not directly cause hyperglycemia if beta cells can adequately increase insulin secretion; type 2 diabetes arises when this response fails. Therefore, analyzing HOMA-β alongside HOMA-IR is essential. A normal HOMA-IR with low HOMA-β suggests a secretory defect, while a high HOMA-IR with maintained or elevated HOMA-β indicates compensated IR (66).

TABLE 1 Reported HOMA-IR cutoff values across selected validation studies. Sensitivity/specificity figures are as reported in the cited primary studies.

Population/ setting	Reported HOMA-IR cutoff	Performance/comment
Czech population, NGT vs. prediabetes	1.82	Sensitivity 0.60, specificity 0.66; not a reliable stand-alone screen (61)
Same cohort, diabetes threshold	3.63	Sensitivity 0.56, specificity 0.86; good specificity, insufficient sensitivity (61)
Thai women with PCOS (glucose intolerance)	>2.0	Sensitivity 84%, specificity 61%; reasonable first-step screen (62)
General adult literature	2.0–2.5 (up to 3.6 in some cohorts)	No consensus; population-specific (60)

Longitudinal data from a Chinese cohort studying type 2 diabetes progression showed that participants free of diabetes had a hyperbolic relationship between baseline HOMA2-%B and HOMA2-IR. In contrast, those who progressed to diabetes exhibited declining HOMA2-%B and rising HOMA2-IR, indicating that worsening beta-cell function, rather than just increasing IR, leads to hyperglycemia (67). In the Tehran Lipid and Glucose Study of 4,942 Iranian adults over 9.2 years, HOMA-B, HOMA-IR, HOMA-S, and fasting insulin were used to establish population-specific cutoffs for identifying the risk of type 2 diabetes (68). This confirmed the beta-cell index as a validated predictor rather than just a laboratory value. In kidney transplant recipients with type 2 diabetes, HOMA2-derived IR and beta-cell function assessed 1 year post-transplant are associated with long-term graft outcomes, highlighting their clinical importance (69).

This review highlights the need to measure IR before cardiometabolic problems arise. HOMA-β should be used alongside HOMA-IR, as both can be obtained from a single blood sample. This approach helps identify insulin-resistant individuals with declining beta-cell function who may need early intervention, while those who are well compensated may only require monitoring.

5.4 Emerging surrogate indices

Several composite indices from metabolic panels serve as practical alternatives to HOMA-IR, particularly the triglyceride-glucose (TyG) index. Calculated as the natural logarithm of the product of fasting triglycerides and fasting glucose divided by 2, TyG has shown sensitivity up to 96% and specificity up to 99% compared to HOMA-IR in a review of 15 studies with nearly 70,000 participants. However, the quality of evidence is rated low to moderate, and cutoff values vary (70–75). Large studies show that the TyG index independently predicts cardiovascular disease, stroke, myocardial infarction, and mortality in both diabetic and non-diabetic populations, with its predictive value increasing over time (71).

Indices such as METS-IR, eGDR, and HOMA-AD effectively assess insulin sensitivity (76, 77). In resource-limited settings without insulin assays, anthropometric measures (BMI, waist circumference, triglyceride-to-HDL ratio) correlate well with HOMA-IR (78, 79). Until recently, none of these surrogate indices had the prospective, outcome-driven validation needed for formal population screening; evidence was mainly cross-sectional or observational-cohort.

A 2026 study of 5,528 Chinese adults with CKM syndrome found that composite insulin resistance indices such as TyG-waist circumference (TyG-WC) and TyG-Chinese visceral adiposity index (TyG-CVAI) were strongly associated with cardiovascular disease. In contrast, eGDR showed an inverse association and had the highest discrimination (AUC 0.625). Incorporating these indices into machine-learning models slightly improved prediction (AUC up to 0.681) compared to covariate-only models (ΔAUC 0.04-0.07) (80). In a study of 371,207 UK Biobank participants without cardiovascular, hepatic, or metabolic diseases, who were followed for a median of 16.4 years, nine IR indices were associated with new cardiovascular-liver-metabolic multimorbidity (CLMM). TyG-waist-to-height ratio (TyG-WHtR) and TyG-waist circumference (TyG-WC) had the strongest associations with incident multimorbidity, with hazard ratios exceeding 2.0 per 1-SD increase, improving prediction beyond traditional risk factors (51). These studies provide the first large-scale evidence that composite TyG-derived indices, which include central adiposity and eGDR, can predict serious cardiometabolic events across CKM and CLM. Single indices only offer limited discrimination beyond established risk factors, which is relevant to the screening debate in Sections 7-9.

5.5 Non-insulin-based clinical and biochemical surrogate markers

An appealing category of surrogates uses lipid panels, anthropometric measurements, or physical exam findings, thereby avoiding the costs and variability of insulin immunoassays. Table 2 summarizes the principal non-insulin-based markers, their required inputs, reported diagnostic performance, and main limitations.

These markers complement HOMA-IR and the TyG index, not replace them. A fasting lipid panel (TG/HDL-C, LAP, VAI) can indicate IR risk when insulin assays are unavailable, and acanthosis nigricans can suggest a need for further low-cost evaluation, supporting the risk-stratified screening strategy in Section 8.

5.6 Biomarkers for injury to complementary organs that are currently used in clinical practice

Several organ-specific biomarkers currently used in routine clinical practice complement indices of insulin resistance (IR). These biomarkers support the IR-driven organ injury identified in Sections 3.3 to 3.10 and facilitate staging along the continuum discussed in Section 4. Within the cardiac domain, NT-proBNP and high-sensitivity troponin, already integrated into AHA subclinical heart failure criteria, correlate with the IR-mediated myocardial remodeling described in Section 3.7. In the renal domain, the urine albumin-to-creatinine ratio and cystatin C-based estimated

TABLE 2 Non-insulin-based clinical and biochemical surrogate markers of insulin resistance: inputs, reported diagnostic performance, and principal limitations.

Marker	Key inputs	Reported performance	Main limitation
TG/HDL-C ratio	Fasting triglycerides, HDL-C	Cutoffs ~2.53 (women)/2.8 (men); AUC 0.68–0.79 (82–86)	Less accurate in African-descent populations (87)
Visceral adiposity index (VAI)	Waist circumference, BMI, TG, HDL-C	AUC 0.65–0.735 (88–91)	Moderate discrimination vs. LAP/TyG
Lipid accumulation product (LAP)	Waist circumference, fasting TG	AUC 0.69–0.80 (88, 92)	Best regional data (Venezuela, Ghana) not yet globalized
TyG index (± BMI/waist circumference)	Fasting glucose, TG, ± BMI/WC	AUC up to 0.82–0.83 (88)	Cross-sectionally validated only; outcome trials pending
Serum uric acid	Single blood test	Correlates with waist circumference and TyG (90, 93)	Corroborating variable, not a stand-alone test
hs-CRP/ferritin	Blood test	Correlates with HOMA-IR and visceral adiposity (94, 95)	Affected by infection/alcohol; supportive only
Waist circumference/WHtR	Measuring tape only	AUC up to 0.93 (WC)/0.98 (WHtR) (96–99)	Reflects adiposity, not IR directly
Acanthosis nigricans	Visual inspection	Sensitivity ~73.5% (children); specificity 82–95% (darker skin/adults) (100–103)	Absence does not exclude IR.

glomerular filtration rate (eGFR) capture the glomerular and tubular injury, delineated in Section 3.6, and are endorsed by the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines for CKD risk stratification independent of IR status. In the hepatic domain, alanine aminotransferase, the Fibrosis-4 (FIB-4) index, and vibration-controlled transient elastography are employed to stage the MASLD spectrum introduced in Section 3.5. These organ-specific markers do not supplant IR indices; rather, they provide additional evidence of the downstream injuries that IR is posited to initiate. Consequently, combining an IR index with the relevant organ-specific marker is anticipated to yield more informative insights than either measure in isolation, particularly within the targeted and risk-stratified populations discussed in Section 8.

6 The case for routine screening: arguments in favor

Several converging lines of evidence support incorporating IR assessment into preventive practice, at least in defined risk groups:

IR can develop years before type 2 diabetes is diagnosed, with reduced insulin sensitivity detectable up to five years prior. Even with normal fasting glucose, blood pressure, and lipid levels, individuals may experience conditions such as endothelial dysfunction, hepatic steatosis, and renal hyperfiltration (2, 36, 39).

Diagnostic tools are inexpensive and part of routine care. HOMA-IR requires fasting glucose and insulin measurements, whereas the TyG index requires only a fasting lipid panel and glucose, both of which are typically included in standard metabolic screenings (70, 72).

Early diabetes interventions are highly effective, with the Diabetes Prevention Program demonstrating a 58% reduction in the incidence of type 2 diabetes through lifestyle changes over 3 years. Lasting benefits include a 43% reduction at 20 years in the Da Qing study, 43% at 7 years in the Finnish study, and 34% at 10 years in the DPP Outcomes Study (104, 105). These trials included participants with impaired glucose tolerance due to insulin resistance (IR), indicating that addressing IR earlier could offer a more effective treatment opportunity.

The CKM framework highlights the importance of Stages 0 and 1, characterized by dysfunctional adiposity and early glycemic issues associated with IR. Measuring IR directly could improve risk stratification at these early stages (1, 10, 11).

Effective, affordable interventions already exist. Metformin, the main insulin sensitizer, inhibits mitochondrial complex I and activates AMPK; its cardiovascular benefit in the UK Prospective Diabetes Study stemmed more from insulin-sensitizing effects than from glucose lowering alone (44). GLP-1 receptor agonists and SGLT2 inhibitors also improve insulin sensitivity alongside their glucose-lowering effects—for example, empagliflozin enhances vascular insulin sensitivity and muscle perfusion within 12 weeks (106), and both drug classes reduce cardiac, muscle, and liver fat (107). These pharmacological agents target various points within the IR pathway and are supported by clinical guidelines because of their established benefits for glycemic control, cardiovascular health, and renal function. An abnormal IR index may help identify individuals who could benefit from earlier, guideline-adherent consideration of these agents, rather than serving as an independent criterion for initiation.

7 The case against routine screening: limitations and counterarguments

The arguments above must be weighed against equally substantial limitations:

1. No IR index, including HOMA-IR, has a globally validated, population-independent cutoff, with thresholds varying significantly across studies, ethnicities, ages, and reference methods (61, 62). A shifting "positive" threshold based on the tested population yields inconsistent results for mass screening.

2. Even with optimized cutoffs, sensitivity remains low. In the Czech validation cohort, the cutoff for distinguishing normal glucose tolerance from prediabetes showed only 60% sensitivity, while the diabetes cutoff had 56% sensitivity, despite good specificity. The authors concluded that HOMA-IR "cannot currently be recommended as a reliable tool for IR screening" (61). Insulin immunoassays are not well standardized for clinical use, which limits comparison across cohorts and remains a barrier to the routine clinical use of fasting insulin measurements (81).
3. Outcome data linking IR indices to clinical endpoints are inconsistent. In a large non-diabetic CKD cohort, HOMA-IR was not linked to CKD progression, cardiovascular events, or mortality after adjusting for confounders (41). Surrogate markers and actual outcomes often don't align, underscoring a caution in evidence-based medicine: correlation doesn't imply a change in outcomes. Poorly validated tests, like creatine kinase screening in psychiatric admissions, can yield false positives without influencing management (108).
4. No randomized controlled trial has confirmed that lifestyle or pharmacological interventions based on the IR index yield better long-term cardiometabolic outcomes than standard triggers like impaired glucose tolerance. Studies such as the DPP used glycemic criteria, leaving the IR-triggered screening strategy a hypothesis rather than a proven fact.
5. Population-wide screening with a moderately sensitive, poorly specific test can lead to unnecessary costs and anxiety. A better approach is to identify high-risk individuals—those with excess adiposity, a family history, or abnormal lipid levels—using tests such as the oral glucose tolerance test.

8 Toward a balanced position: targeted rather than universal screening

Universal IR screening is not supported as a preventive test due to unvalidated cutoffs and inconsistent outcomes (41, 42). A targeted strategy suggests measuring IR with HOMA-IR or the TyG index in high-risk individuals (CKM Stage 0-1) such as those with excess adiposity, a family history of type 2 diabetes, PMOS, or hepatic steatosis (1, 10, 63, 70). Age ≥35 years is an independent risk marker for targeted assessment of insulin resistance, emphasizing the role of age in diabetes screening guidelines (109). In this age group, a high pretest probability and a positive test result lead to beneficial outcomes, such as lifestyle counseling and improved metabolic follow-up. Evidence supports early intensive lifestyle changes (104, 105). The CKM guideline advises against testing insulin sensitivity in the general population, focusing instead on early, reversible stages linked to adiposity and glycemic risk markers, which IR indices can refine (11). Targeted screening for diabetes and prediabetes in high-risk groups is more cost-effective than universal screening, especially with effective treatment. This emphasizes prioritizing high-risk populations. A summary is presented in Figure 3 (110, 111).

Since May 2026, polycystic ovary syndrome (PCOS) has been renamed polyendocrine metabolic ovarian syndrome (PMOS) by international consensus, highlighting its nature as a systemic endocrine-metabolic disorder. This review uses PMOS, with PCOS noted for reference since much of the literature predates the change (112). A study of 200 women with PMOS based on Rotterdam criteria found that 57.5% had HOMA-IR values ≥2.01, indicating a need for targeted IR screening. IR varied by phenotype: 69.6% in "complete" phenotype A (mean HOMA-IR 3.59) and 26.1% in "ovulatory" phenotype C (mean HOMA-IR 2.05). Notably, phenotype A had a shorter syndrome duration, suggesting a link between IR severity and phenotypic features. HOMA-IR correlated with blood pressure, pulse rate, and waist-to-hip ratio, and the authors proposed a "vicious cycle" involving ovarian androgen excess and hyperinsulinemia that contributes to a cardiometabolic continuum (113).

9 Research gaps and future directions

- Standardize HOMA-IR cutoffs across ethnicities, age groups, and assay platforms through large, multi-ethnic clamp-validation studies instead of population-specific derivations.
- Trials testing whether IR-guided intervention reduces type 2 diabetes, cardiovascular events, CKD progression, or MASLD progression compared to glycemia-guided intervention.
- Formal cost-effectiveness and diagnostic-yield analyses comparing targeted IR screening in CKM Stage 0–1 populations against current opportunistic detection.
- A comparison of HOMA-IR with TyG, METS-IR, and other surrogates for predicting outcomes is necessary. Although the 2026 cohorts (CHARLS and UK Biobank) have assessed TyG indices for cardiovascular and metabolic outcomes, further validation against renal and hepatic endpoints, as well as HOMA-IR, is required (51, 80).
- Examine the discordance between IR indices and hard renal outcomes in non-diabetic CKD cohorts to assess if it reflects a lack of causal effect or a limitation of HOMA-IR as a measurement tool.
- Organ-on-chip adipose tissue models replicate insulin resistance by demonstrating impaired Akt phosphorylation, reduced GLUT4 translocation, and dysregulated lipolysis. They help detect pharmacological reversals and complement animal models by enabling mechanism discovery and drug screening for insulin resistance therapies (114).

10 Discussion and conclusion

IR is a key factor leading to vascular, hepatic, renal, and cardiac injuries within the cardiometabolic continuum, as recognized in the cardiovascular-kidney-metabolic syndrome framework (1–8, 10, 11, 35–38). Measurement tools range from a reliable but impractical research gold standard to inexpensive surrogate indices that are insufficiently standardized for universal population screening (55, 61, 70). The evidence supports a graded, risk-stratified approach rather than a simplistic binary response. Routine IR testing in the general population lacks justification; however, targeted assessment of individuals identified at early stages of the cardiometabolic continuum is feasible and warrants further investigation as a potential component of individualized risk assessment. This is particularly relevant when combined with evidence-based lifestyle interventions. Whether such an approach independently improves disease trajectory beyond standard risk-factor-triggered care awaits confirmation through outcome-driven trials. Prioritizing trials that directly evaluate IR-guided interventions is essential to address existing evidence gaps.

Author contributions

AG: Visualization, Formal analysis, Writing – review & editing, Supervision, Writing – original draft, Conceptualization. JD: Writing – review & editing, Writing – original draft, Validation, Formal analysis, Supervision, Data curation. GC: Conceptualization, Writing – original draft, Visualization, Writing – review & editing.

Funding

The author(s) declared that financial support was not received for this work and/or its publication.

Conflict of interest

The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declared that generative AI was used in the creation of this manuscript. Generative artificial intelligence was used in the preparation of this manuscript. Figures 1, 2, and the screening-algorithm schematic in Figure 3, were generated using Google Gemini (Gemini 2.5, Google LLC, accessed 2026) and subsequently reviewed and edited by the authors to verify factual and terminological accuracy against the data and concepts presented in the text. The generative AI tool was not used for drafting, analyzing, or interpreting the scientific content of the manuscript, and is not credited as an author. The authors take full responsibility for the accuracy and originality of all figures.

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