

Rising Insulin Resistance Trajectories and Cardiovascular Risk Beyond LDL-C Control: Reflections on a Two-Decade Population-Based Study

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SUMMARY OF KEY RESEARCH FINDINGS

This study, presented at the European Society of Cardiology (ESC) Congress 2026, asked whether the long-term pattern of insulin resistance identifies cardiovascular risk that persists once low-density lipoprotein cholesterol (LDL-C) is controlled.¹ In 4,051 adults from the population-based Tehran Lipid and Glucose Study, with at least three serial values of the homeostatic model assessment of insulin resistance (HOMA-IR) and free of cardiovascular disease (CVD), group-based trajectory modelling identified three patterns: low stable, moderate stable, and rising. Over a mean of 10.1 years after the index visit, 280 participants developed CVD. The rising pattern was associated with incident CVD both when LDL-C at index was controlled (odds ratio [OR]: 1.35; 95% CI: 1.07–1.77) and when it was not (OR: 1.52; 95% CI: 1.07–2.15), with no evidence of interaction by LDL-C status and little attenuation once LDL-C category and statin use were treated as time-varying

covariates. The authors concluded that a deteriorating trajectory of insulin resistance marks residual cardiovascular risk that LDL-focused prevention does not capture.

WHAT CHALLENGE DOES THIS ADDRESS?

Residual cardiovascular risk despite guideline-level LDL-C is well recognised, and insulin resistance is a strong candidate contributor: it is associated with incident CVD independently of conventional risk factors,² and it travels with atherogenic dyslipidaemia, hypertension, and dysglycaemia. Most supporting evidence, however, rests on insulin resistance measured once. A single value cannot separate a person whose HOMA-IR has been stable for a decade from one in whom it is climbing, and these two people plausibly do not face the same future. Trajectory analyses have begun to close that gap, linking a rising HOMA-IR pattern to incident CVD in a Korean cohort,³ but whether such a signal survives within people whose LDL-C already meets targets, with lipid control treated as time-updated rather than frozen at baseline, remained open. By fixing the trajectory period before the index visit and counting events afterwards, this study put that question on a defensible temporal footing.

RELEVANCE TO EUROPEAN PRACTICE

European prevention is organised around estimation and lipid control: the Systematic Coronary Risk Evaluation 2 (SCORE2) calculator anchors the 2021 ESC prevention guidelines, and neither the algorithm nor the downstream treatment pathway looks at insulin resistance.^{4,5} A patient whose LDL-C meets the 2019 European dyslipidaemia goals can therefore appear fully managed while their metabolic

state drifts year on year.⁶ In this cohort, that reassurance looked incomplete: risk graded upwards across joint phenotypes, peaking at a crude OR of 5.05 (95% CI: 3.10–8.20) for a rising trajectory with uncontrolled LDL-C against low stable with controlled LDL-C.¹

Transportability deserves a direct answer rather than a hopeful one. The Tehran Lipid and Glucose Study is a population-based West Asian cohort studied through a period of nutrition transition,⁷ with a substantial background burden of central obesity and dysglycaemia.⁸ Lipid-lowering practices across 1999–2011 predate current European treatment intensity, so controlled LDL-C here often reflects a naturally favourable profile rather than treatment to target, a phenotype distinct from the statin-treated European patient. Absolute risks will not transfer; SCORE2's regional recalibration is a reminder that they rarely do.⁵ More likely to travel is the relative pattern: an association consistent across strata, adjustment models, and time-varying lipid control. European cohorts holding serial insulin measurements are the natural place to test it.

WHAT ARE THE NEXT STEPS FOR THE RESEARCH?

Replication comes first, ideally in European cohorts with repeated fasting insulin and time-to-event modelling in place of the ORs reported here. The observational design cannot exclude residual confounding, and no interventional evidence yet shows that flattening a rising trajectory prevents events; insulin resistance is modifiable, but 'modifiable' and 'worth modifying for prevention' are different claims. HOMA-IR itself is an imperfect instrument, weighted towards fasting hepatic physiology rather than whole-body insulin sensitivity.⁹

Group-based trajectory modelling imposes discrete classes on continuous behaviour, and class membership carries assignment uncertainty. The definition of control, LDL-C below 100 mg/dL (2.6 mmol/L) at index, is more permissive than current ESC goals for patients at higher risk, so the residual-risk claim should be re-examined against stricter thresholds. Finally, serial insulin measurement is unrealistic in routine practice; simpler longitudinal surrogates deserve evaluation before trajectory-aware prevention can become more than an idea.

References

1. Esmaeili F et al. Associations of long-term insulin resistance trajectories with incident cardiovascular disease by LDL-C status, with time-updated lipid control: a two-decade population-based study. Abstract 89358. ESC Congress, 28–31 August, 2026.
2. Gast KB et al. Insulin resistance and risk of incident cardiovascular events in adults without diabetes: meta-analysis. *PLoS One*. 2012;7(12):e52036.
3. Lee JH et al. Associations of homeostatic model assessment for insulin resistance trajectories with cardiovascular disease incidence and mortality. *Arterioscler Thromb Vasc Biol*. 2023;43(9):1719–28.
4. Visseren FLJ et al.; ESC National Cardiac Societies; ESC Scientific Document Group. 2021 ESC guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J*. 2021;42(34):3227–337.
5. SCORE2 working group and ESC Cardiovascular Risk Collaboration. SCORE2 risk prediction algorithms: new models to estimate 10-year risk of cardiovascular disease in Europe. *Eur Heart J*. 2021;42(25):2439–54.
6. Mach F et al.; ESC Scientific Document Group. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J*. 2020;41(1):111–88.
7. Azizi F et al.; the Tehran Lipid and Glucose Study Group. Prevention of non-communicable disease in a population in nutrition transition: Tehran Lipid and Glucose Study phase II. *Trials*. 2009;10:5.
8. Azizi F et al. Prevalence of metabolic syndrome in an urban population: Tehran Lipid and Glucose Study. *Diabetes Res Clin Pract*. 2003;61(1):29–37.
9. Wallace TM et al. Use and abuse of HOMA modeling. *Diabetes Care*. 2004;27(6):1487–95.