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Precision prevention in type 2 diabetes

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Type 2 diabetes (T2D) affects hundreds of millions of people worldwide, leading to significant morbidity, complications, and premature death. As the global burden rises, there is an urgent need for effective prevention strategies. Pre-diabetes—the early stage of glycemic dysfunction—offers a critical window for intervention, particularly as individuals with prediabetes, respond better to preventive strategies than those with normal glucose levels.[1] However, current diagnostic criterial fail to capture the underlying pathophysiological heterogeneity or reliably predict progression to T2D[2]. A growing body of evidence suggests that "one-size-fits-all" prevention is insufficient. Understanding the heterogeneity of pre-diabetes is essential to identify those most likely to benefit from early, targeted interventions.[3] Phenotypic subtyping -classifying individuals by distinct risk profiles- offers a promissing step toward more pecise and effective prevention strategies.

Understanding and addressing T2D risk heterogeneity is now recognized as essential to advancing prevention and improving long-term outcomes. Global initiatives—such as the Precision Medicine in Diabetes Initiative (by the ADA and EASD),[3] and the NIDDK's working group on diabetes heterogeneity—underscore the need to move beyond traditional classifications toward more tailored approaches.

Over the past decade, efforts to subclassify T2D and pre-diabetes into distinct subtypes have accelerated.[4] Electronic health records (EHRs) have emerged as a powerful resource for characterizing heterogeneity in real-world clinical settings, enabling analysis of large, diverse populations through longitudinal, clinical, demographic, and laboratory data. This facilitates the integration of precision medicine into routine care.

The study by Washirasaksiri *et al*,[5] makes a valuable contribution to the growing field of precision prevention in T2D. Using EHRs, the authors applied a data-driven approach to identify pre-diabetes phenotypes in a Southeast Asian population and examined their associations with incident T2D, vascular complications, and mortality. This work represents an important step toward advancing tailored prevention strategies in globally diverse populations.

Six subphenotypes were identified using age, BMI, fasting glucose, HbA1c, HDL-C, and alanine aminotransferase. Subphenotypes characterized by obesity and dysmetabolism had the highest risk of progression to T2D, aligning with stablished links between obesity, insulin resistance, and beta-cell dysfunction. Notabily, Cluster 4—obese individuals with minimal glycemic deterioration—may reflect the "preclinical obesity" phenotype recently proposed by the Lancet Diabetes & Endocrinology Commission[6]. Elderly subphenotypes displayed the highest risk for cerebrovascular disease and macrovascular complications, along with moderately elevated risks for T2D, coronary artery disease, and mortality.

The analysis was conducted using EHR data from the outpatient clinic at Siriraj Hospital in Bangkok, Thailand. The phenotyping framework was adapted from a model previously described by Wagner *et al*,[2] with modifications to align with the local clinical context.

The primary strength of the study lies in its identification of clinically meaningful pre-diabetes subphenotypes in a real-world setting. By demonstrating the feasibility of applying and adapting an existing framework to a Southeast Asian population, the study offers important insights into phenotypic variation and disease progression in a region facing a growing burden of T2D. The use of EHR data enhances the generalizability and practical relevance of the findings, and the identification of a liver lipid-associated subtype—consistent with previous work[2]—further supports the applicability of the subgrouping framework across diverse populations.

This study highlights the potential of phenotypic subtyping to enhance risk stratification in pre-diabetes. However, its clinical utility is limited by several factors. The inherent variability of EHR data—including noise, missing

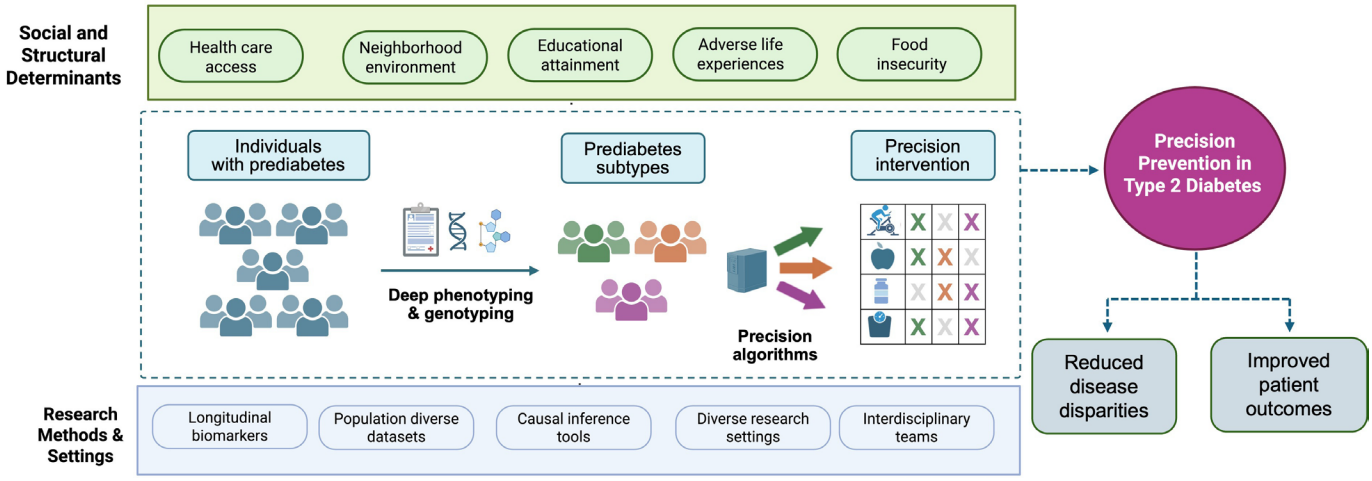

Figure 1 Framework for precision prevention in type 2 diabetes. Advancing subtype-specific prevention strategies requires integrating data across multiple levels—including molecular profiles, electronic health records, and environmental exposures. Social and structural determinants of health influence every stage of the framework and must be addressed to ensure equity and applicability. This approach should be supported by population-diverse datasets and validated across varied research settings using robust analytical methods.

values, and inconsistent documentation—may compromise the precision of phenotype classification. Additionally, the relatively short follow-up period restricts the ability to evaluate long-term outcomes such as complications and mortality. Most importantly, the phenotypes were defined based on baseline data alone, without accounting for changes in metabolic status over time—limiting insight into the dynamic biological processes that underlie disease progression.

IMPLICATIONS AND FUTURE DIRECTIONS

Advancing toward actionable, subtype-specific prevention strategies will require the integration of multiple layers of information—including longitudinal, molecular, and environmental data—supported by diverse population datasets and robust analytical methods (figure 1).

Most clinical features used to define pre-diabetes subtypes are dynamic and influenced by disease progression and treatment, which can lead to shifts in cluster membership over time. While phenotypic clustering provides valuable insights into T2D risk heterogeneity, its utility is constrained when based solely on static, baseline measures. Incorporating longitudinal changes—including responses to interventions—could improve predictive performance by allowing subtypes to evolve with the individual's clinical profile.

To address the limitations of phenotype instability, high-throughput omics technologies—including genomics, proteomics, metabolomics, and host microbiome profiling—offer promising avenues to map molecular heterogeneity, uncover causal mechanisms, and identify therapeutic targets.[7] These molecular signatures may provide more temporally stable phenotypes and improve tracking of treatment responses. In parallel, genetic tools such as process-specific polygenic risk scores[7–9] hold potential for defining biologically informed subtypes that remain consistent over time and could complement longitudinal biomarker assessments in future precision prevention models.

Building on this, fully realizing the promise of precision prevention also requires a deeper understanding of the sources of interindividual variation in response to interventions. Although large randomized clinical trials have demonstrated that healthy lifestyle and dietary modifications can prevent or delay the onset of T2D, substantial variability exists in how individuals respond.[10] Phenotypic and genetic subtyping can help identify those who may require specific dietary or lifestyle adaptations to achieve meaningful risk reduction. For example, individuals with "preclinical obesity," such as those in cluster 4, may benefit from tailored lifestyle modifications, long-term monitoring, and early counseling[6]—an approach that aligns intervention intensity with risk level and enhances both clinical outcomes and cost-effectiveness.

While phenotypic and genetic subtyping can improve individual risk stratification, biological variation alone does not fully explain disparities in T2D outcomes. Environmental and social factors—including diet, physical activity, and social determinants of health (SDoH)—interact closely with biological profiles to shape disease risk and response to intervention. SDoH such as adverse life experiences, economic inequality, educational attainment, and neighborhood environments act as chronic stressors that contribute to systemic inflammation and exacerbate metabolic risk. Integrating these dimensions into predictive models is essential to ensure that advances in precision medicine reduce, rather than reinforce, existing health disparities.

Achieving precision prevention in T2D will require equitable, data-driven strategies grounded in interdisciplinary and methodologically rigorous science. This includes causal inference tools, advanced computational

tools, and robust study designs with expertise from epidemiology, endocrinology, bioinformatics, and implementation science. Validating phenotypic classifications across diverse contexts—observational studies, clinical trials, and real-world care—is essential to ensure their generalizability and clinical utility. Embedding this work in population-diverse datasets is critical to producing globally relevant insights. Building on this progress will require sustained efforts to translate our understanding of T2D heterogeneity into inclusive, actionable strategies that benefit to all populations. At the same time, while we pursue more personalized approaches, lifestyle modification and publich health interventions remain the foundation of diabetes prevention. Realizing the full potential of precision prevention will depend on collaborative efforts across disciplines and populations to ensure strategies are both effecive and equitable.

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REFERENCES

1 Bodhini D, Morton RW, Santhakumar V, *et al*. Impact of individual and environmental factors on dietary or lifestyle interventions to prevent type 2 diabetes development: a systematic review. *Commun Med (Lond)* 2023;3:133.
2 Wagner R, Heni M, Tabák AG, *et al*. Pathophysiology-based subphenotyping of individuals at elevated risk for type 2 diabetes. *Nat Med* 2021;27:49–57.
3 Tobias DK, Merino J, Ahmad A, *et al*. Second international consensus report on gaps and opportunities for the clinical translation of precision diabetes medicine. *Nat Med* 2023;29:2438–57.
4 Misra S, Wagner R, Ozkan B, *et al*. Precision subclassification of type 2 diabetes: a systematic review. *Commun Med (Lond)* 2023;3:138.
5 Washirasaksiri C, Borrisut N, Lapinee V. Identification of pre-diabetes sub-phenotypes for type 2 diabetes, related vascular complications and mortality. *BMJ Open Diab Res Care* 2025;1–12.
6 Rubino F, Cummings DE, Eckel RH, *et al*. Definition and diagnostic criteria of clinical obesity. *Lancet Diabetes Endocrinol* 2025;13:221–62.
7 Sevilla-González M, Smith K, Wang N, *et al*. Heterogeneous effects of genetic variants and traits associated with fasting insulin on cardiometabolic outcomes. *Nat Commun* 2025;16:2569.
8 Smith K, Deutsch AJ, McGrail C, *et al*. Multi-ancestry polygenic mechanisms of type 2 diabetes. *Nat Med* 2024;30:1065–74.
9 Suzuki K, Hatzikotoulas K, Southam L, *et al*. Genetic drivers of heterogeneity in type 2 diabetes pathophysiology. *Nature New Biol* 2024;627:347–57.
10 Knowler WC, Barrett-Connor E, Fowler SE, *et al*. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002;346:393–403.