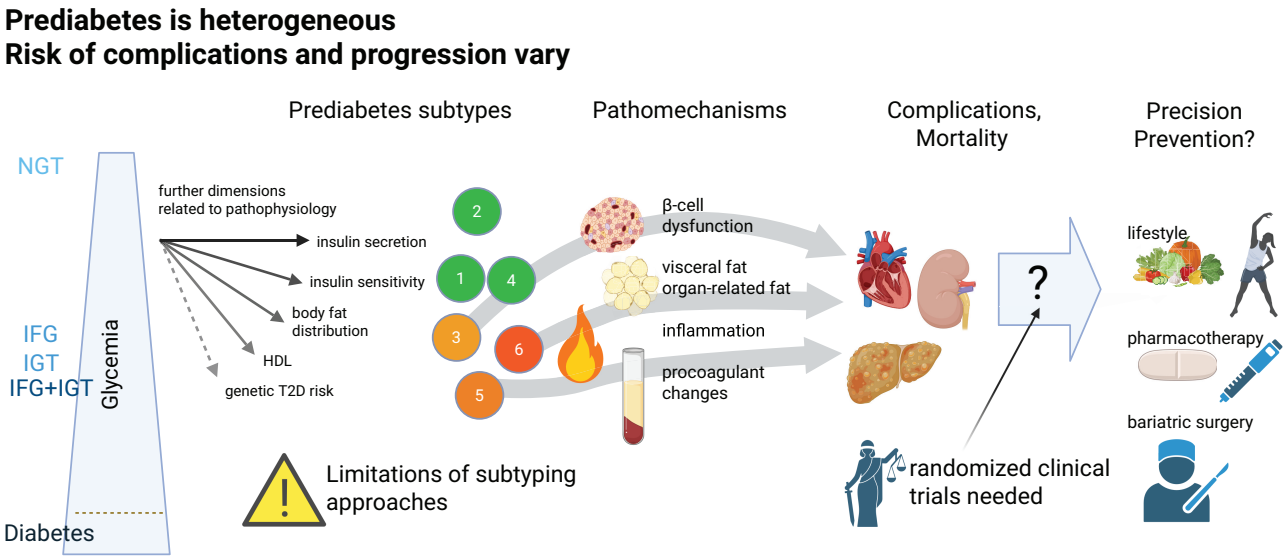
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Beyond Glucose—Rethinking Prediabetes for Precision Prevention

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IFG, impaired fasting glucose; IGT, impaired glucose tolerance; NGT, normal glucose tolerance; T2D, type 2 diabetes.

ARTICLE HIGHLIGHTS

- **Why did we undertake this study?**
  Prediabetes is heterogeneous, and current glycemic criteria do not capture variable risks for diabetes and complications.
- **What is the specific question we wanted to answer?**
  What are the implications of prediabetes subtypes with distinct biological profiles and risk trajectories, identified with multivariable, data-driven clustering approaches?
- **What did we find?**
  Subtypes of prediabetes highlight different pathophysiological features and stratify the risk of complications.
- **What are the implications of our findings?**
  Subtyping could enable tailored interventions for high-risk individuals, yet widespread implementation is currently limited by multiple factors. Prospective trials are needed to validate subtype-directed prevention strategies and their feasibility in clinical practice.

Beyond Glucose—Rethinking Prediabetes for Precision Prevention

Robert Wagner,[1,2,3] Elizabeth Selvin,[4] Ratika Sehgal,[5] Katsiaryna Prystupa,[2,3] Shivani Misra,[6] Andreas Fritsche,[3,7,8] and Martin Heni[5,9]

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Prediabetes affects more than one-third of U.S. adults, yet represents a biologically heterogeneous state that is only partly captured by traditional glycemic categories (impaired fasting glucose, impaired glucose tolerance, or borderline elevated HbA_{1c}). Leveraging unsupervised clustering in comprehensively phenotyped cohorts has identified six reproducible prediabetes subtypes integrating insulin sensitivity, insulin secretion, visceral and hepatic fat, and genetic risk. Three high-risk subtypes (progressing prediabetes with fatty liver, progressing prediabetes with β-cell failure, and slow progressors with hyperinsulinemic insulin resistance) show distinct trajectories toward diabetes and unique complication patterns. For example, "slow progressors" develop albuminuria and face excess mortality, despite only modest glycemic deterioration over 10–15 years, showing that complications can arise before diabetes diagnosis. Recognizing these subtypes sharpens risk stratification and opens a path toward precision prevention. Intensive lifestyle modification and bariatric surgery offer the greatest glycemic benefit in the fatty liver subtype, whereas early pharmacologic β-cell protection may be required for the β-cell failure cluster. GLP-1–based therapies offer promising subtype-specific options and should be tested in randomized controlled studies. Future prediabetes intervention trials should move beyond diabetes incidence as the sole end point and systematically evaluate kidney, nerve, eye, and cardiovascular outcomes. While testing for long-term clinical end points might not be feasible in studies where individuals with prediabetes are recruited, the use of surrogate end points could facilitate the assessment of early complications. Such complication-focused, subtype-guided studies will determine whether early, tailored therapy can halt tissue damage and reduce the public health burden linked to prediabetes.

PREDIABETES IS A HETEROGENOUS STATE OF INCREASED DIABETES RISK

Prediabetes refers to an intermediate stage of dysglycemia along the continuum from normal glucose metabolism toward diabetes (1). The concept of prediabetes emerged in the 1970s with the definition of a threshold of 140 mg/dL (7.8 mmol/L) for the 2-h postchallenge glucose level on a 75-g oral glucose tolerance test, derived from community-based studies showing a higher diabetes risk above this threshold (1). This was extended by a complementary definition based on fasting glucose (110 mg/dL), which is currently still in use by the World Health Organization but had been widened by the American Diabetes Association to 100 mg/dL. HbA_{1c}-based definitions have been added subsequently (American Diabetes Association, 5.7%–6.4%; International Expert Committee, 6.0%–6.4%). These differing definitions only hint at the substantial biological diversity hidden beneath the label of prediabetes, which encompasses a broad spectrum of pathophysiology and cardiometabolic risk. Recognition of this heterogeneity has spurred efforts to delineate subphenotypes that share

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coherent mechanisms and therefore carry distinct risks of diabetes and its complications.

INTEGRATIVE TRAIT ANALYSIS WITH DATA-DRIVEN CLUSTERING: BEYOND GLUCOSE LEVELS

Data-driven clustering algorithms enable interrogation of patterns in traits that co-occur early in the natural history of diabetes. This approach groups individuals based on shared profiles across multiple traits, exposing interactions overlooked in traditional one-trait-at-a-time analyses. In uncovering natural groupings within the data, clustering allows for the approximation of subtypes reflecting biological processes. Although some granularity is sacrificed, the resulting subtypes have the potential to improve understanding of pathophysiology, sharpen risk stratification, and spotlight targeted intervention opportunities.

With application to a well-phenotyped heterogeneous cohort at high risk of type 2 diabetes (T2D), clustering revealed interrelationships among metabolic, anthropometric, and genetic markers all of which were selected based on their relevance to T2D pathophysiology (2). These variables encompassed not only glucose but also other metabolically relevant traits, including glycemic and insulinemic responses during oral glucose tolerance tests (OGTTs), insulin sensitivity, insulin secretion, body fat distribution, and genetic susceptibility to T2D. Given the continuous nature of metabolic changes preceding diabetes onset and the difficulty of defining a priori meaningful glycemic thresholds, these data-driven analyses were conducted in populations enriched with, but not limited to, individuals with dysglycemia. The resulting subtypes of prediabetes metabolism represent groups with comparable patterns across the underlying variables. While they provide a conceptual framework to understand metabolic heterogeneity as inferred from the set of underlying variables, estimation of subtype membership is inherently approximate and should not be interpreted as deterministic at the individual level.

APPROXIMATE SUBTYPES OF PREDIABETES

Three of the identified subtypes comprised individuals with mostly healthy metabolism and three with an increased overall risk of developing diabetes. (See Fig. 1.)

Low-risk Subtypes

Among the subtypes with mostly healthy metabolism, >80% of the participants had normal glucose regulation. One subtype comprised metabolically healthy individuals with obesity and one comprised metabolically healthy individuals with overweight, and one cluster had a lean and insulin sensitive phenotype. Of note, ~25% of the participants classified in the overweight and obesity, but metabolically healthy, subtypes fulfilled the definition of metabolic dysfunction–associated steatotic liver disease (MASLD).

High-risk Subtypes

Among the three high-risk subtypes with overall increased diabetes risk, two were especially prone to developing diabetes ("progressing prediabetes with fatty liver" and "progressing prediabetes with β-cell failure"), and both were associated with distinct risk profiles for cardiovascular and kidney complications. The "progressing prediabetes with β-cell failure" subtype featured the highest proportion of impaired glucose tolerance (IGT) and increased intima-media thickness, aligning with data on the specific association of IGT with cardiovascular risk (3).

Given the high hepatic lipid content of the "progressing prediabetes with fatty

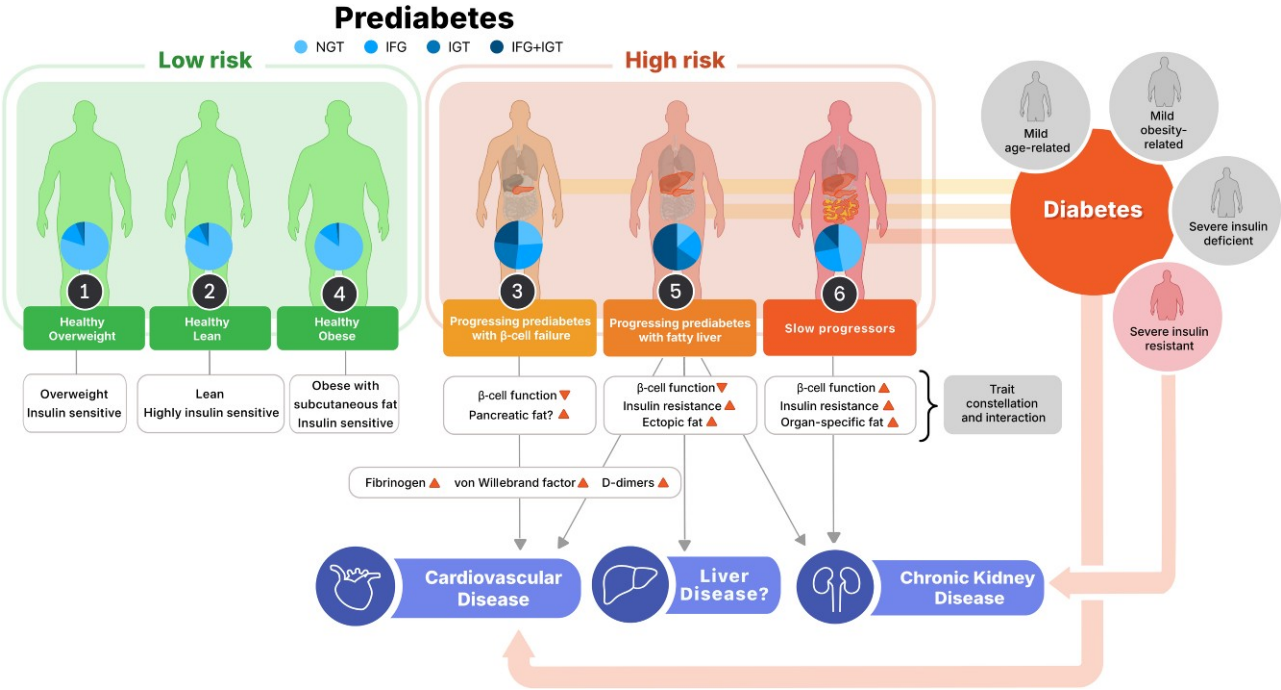


Figure 1—Distinct constellations of traits, including variations in insulin sensitivity, β-cell function, and organ-specific fat distribution, are seen among prediabetes subtypes. For these subtypes there are different trajectories toward diabetes, its subtypes, associated complications, and mortality. NGT, normal glucose tolerance.

liver" subtype, these individuals may be at elevated risk for developing liver fibrosis and cirrhosis, long-term complications also associated T2D.

Although for the third high-risk subtype heightened risk of diabetes was not demonstrated over a relatively short-term follow-up of 4 years, early signs of chronic kidney disease were detectable. Only after a long-term follow-up of 16 years, increased diabetes risk emerged. Given that >50% of those assigned to this subtype had impaired fasting glucose (IFG), IGT, or both but hyperglycemia did not imminently progress during follow-up, we term this subtype as "slow progressors." Despite the delayed diabetes development, overall mortality was highest for this subtype, even after confounders such as blood pressure, lipids, and smoking were controlled for. The dissociation of glycemic progression and the emergence of complications indicates that a specific interplay of subtype-inherent factors, together with intermediary hyperglycemia, can induce complications even in the absence of a rapid progression toward diabetes. This "slow progressor" subtype has important clinical implications, as these high-risk individuals who remain in a prolonged prediabetes state without imminently progressing to T2D may be overlooked, resulting in missed opportunities for a timely, targeted intervention to mitigate renal and cardiovascular disease.

A distribution similar to that of these prediabetes subtypes was observed in an East Asian cohort with use of a simplified set of variables, suggesting consistency and construct validity of this phenotype (4,5). This work identified a group similar to the "slow progressor" subtype, which, despite its moderate risk of progression to diabetes, was linked to an increased risk of chronic kidney disease and cardiovascular disease.

Hyperinsulinemic Insulin Resistance With Expansion of Visceral Fat: Key Features of the "Slow Progressor" Subtype

The "slow progressor" subtype is characterized by insulin resistance combined with hyperinsulinemia, occurring in the context of mild hyperglycemia and increased visceral adiposity. While, in theory, insulin resistance could be fully compensated for by adequately increased insulin secretion, this compensation is only partially achieved in this subtype. Understanding the biology behind these early changes in this subtype might yield important insights into the mechanisms driving this specific metabolic trajectory.

A classic explanation for the persistent slight increase of glucose in the context of insulin resistance is glucose allostasis—a hysteresis in glucose regulation that maintains modest hyperglycemia as a continuous stimulus to sustain chronically elevated insulin secretion (6,7).

In contrast to this traditional view, an alternative concept places insulin secretion at the start of a chain of events that lead to prediabetes (8). According to this hypothesis, insulin hypersecretion is a primary defect, which occurs independently of actual metabolic demand. The resulting hyperinsulinemia then induces secondary insulin resistance, which subsequently leads to elevated glucose levels (8,9). Indeed, in hyperinsulinemic states, independent from insulin sensitivity, often elevated rather than lower glucose levels are exhibited (10). This state of hyperinsulinemic insulin resistance may persist for years, without progressing to overt T2D (2). However, the chronically present hyperinsulinemia likely contributes to an increased risk of chronic kidney disease and elevated mortality, which was observed in the slow progressor subtype (11,12). Whether primary or secondary, hyperinsulinemia is a key step in the pathogenesis of T2D and there is some evidence to suggest that worse hyperinsulinemia may be associated with worse outcomes. For example, in youth, primary hyperinsulinemia in adolescents with obesity was associated with greater ectopic fat depots after follow-up (10). In youth with T2D hyperinsulinemia occurred to a far greater degree than in adult-onset T2D (13). Since the onset of T2D in youth and young adults is associated with a greater burden of adverse outcomes in comparison with onset in later life (14), severe hyperinsulinemia could be, in part, underlying this severe phenotype.

Adiposity Patterns in Specific Prediabetes Subtypes

In contrast to the "metabolically healthy obese" prediabetes subtype, primarily characterized by subcutaneous obesity, marked visceral obesity is seen for the slow progressor subtype and, to a lesser degree, also the two "progressing prediabetes" subtypes (Fig. 1). In addition, in the case of the "progressing prediabetes with fatty liver" subtype, with all individuals developing diabetes over a 10-year follow-up, excessively high (∼20%) mean hepatic triglyceride contents were seen.

Recent findings have highlighted how organ fat depots are instrumental in defining disease risk. Lipid accumulation in the liver appears to play a crucial role in the metabolic progression to diabetes (15) and in promoting secondary organ damage, such as kidney disease (16). Mechanistic studies further highlight the adverse effects of organ-specific fat depots, such as renal sinus fat and pancreatic fat, especially when interacting with an insulin resistant environment (17).

These concomitant pathophysiologic phenotypes are particularly relevant for high-risk prediabetes subtypes marked by lipid accumulation patterns: a combination of increased hepatic lipid content and hyperglycemia amplifies cardiovascular risk, whereas hepatic lipid accumulation primarily affects liver health (18,19).

Data from a lifestyle intervention study suggest that hepatic lipid content also plays a critical role in impairing pancreatic insulin secretion, particularly in the most diabetes-prone "progressing prediabetes with fatty liver" subtype (20).

Inflammatory and Procoagulant Changes in the High-risk Subtype Possibly Contribute to Complications

The "progressing prediabetes with fatty liver" subtype also features a high inflammatory burden, which could mechanistically contribute not only to an increased cardiovascular risk but also to a higher incidence of distal sensorimotor polyneuropathy (21,22). Another study demonstrated that patients in the high-risk prediabetes subtypes have elevated levels of procoagulant markers including fibrinogen, von Willebrand factor, and D-dimers, indicating a coagulation profile that could also contribute to heightened cardiovascular risk (23).

Prediabetes Subtypes in Clinical Practice

In defining prediabetes subtypes, adiposity was assessed with MRI, a polygenic T2D risk score was applied for assessment of genetic predisposition, and glucose and insulin levels during OGTTs were used to measure glycemia, insulin

sensitivity, and insulin secretion. All of these are burdensome for routine use in clinical practice. A simplified application without MRI-derived features and genetics was used in the replication cohort, but an OGTT was still used to precisely assess insulin secretion, sensitivity, and glycemia.

Both the definition and the simplified approach of prediabetes subtyping have been implemented in a Web-based prediabetes subtype calculator, which is available for research use (https://cluster.apps.dzd-ev.org), to assign prediabetes subtypes for individuals without diabetes. While measures such as glycated hemoglobin or HOMA indices could theoretically serve as surrogates, many of these proxies may be insufficiently sensitive to detect important early changes in prediabetes (24–27).

OMICS Approaches

Emerging biomarker approaches, such as a large-scale assessment of plasma peptides using proteomics, already show promise in the identification of IGT (28), and urinary peptidomics has been successfully used in identification of the high-risk prediabetes subtypes (29). Information on characteristic proteome changes could also deepen our understanding of the biological background of the subtypes. Since the protein or metabolite features could be surrogates of key variables of multivariate prediabetes subtyping, the combination of a few subtype-specific biomarkers could ultimately replace the complex phenotyping currently confined to the research setting.

Limitations of Multivariable Approaches and Subtyping

While multivariable phenotyping to derive subtypes decomposing heterogeneity is a powerful concept, there are limitations to this approach. The reliance on costly and difficult-to-measure phenotypes can restrict the scalability and standardization of these procedures. Even simple measures that are available in low-resource settings, such as blood pressure or waist circumference, could be affected by substantial measurement unreliability (30). Furthermore, there are concerns regarding the large-scale feasibility and scalability of OGTTs. High intra-individual variability is seen with fasting glucose, but particularly postchallenge glucose, with a coefficient of variation of up to 13% (31).

With hard clustering methods, such as those used to define prediabetes subtypes, each individual is assigned to a single discrete cluster, even though the underlying variables are typically continuous. This rigid classification can misrepresent individuals with intermediate or overlapping phenotypes. To address this limitation, measures like normalized relative entropy have been proposed to quantify classification uncertainty within hard clusters (32,33). Alternatively, soft clustering techniques allow for individuals to be associated with multiple clusters in assigning probabilities of belonging to each cluster, thereby capturing phenotypic gradients more accurately. These methods have been applied in the context of diabetes subtypes (34), including analyses based on genetic traits (35). While soft clustering introduces additional complexity at the individual level, it is helpful for research purposes as it enables the identification and potential exclusion of individuals with ambiguous or mixed profiles from downstream analyses.

Another approach involves dimensionality reduction, which projects individual profiles onto a two-dimensional map of heterogeneity instead of assigning discrete subtypes (36). This strategy overcomes some of the rigidity of hard clustering and may better reflect biological variation.

However, temporal drift remains a challenge across all methods that rely on time-varying traits; for instance, ∼20% of individuals change diabetes subtype or position on the heterogeneity map over a 5-year period (37,38). The "metabolically healthy obesity" subtype could be especially prone to temporal drift: one study showed that almost 50% of individuals with obesity without metabolic syndrome developed metabolic syndrome over a follow-up of 12.2 years (39). This highlights that the change of underlying variables could lead to an altered risk situation over time. Relying mostly on genetic instruments such as polygenic risk scores in subtyping mitigates temporal drift but disregards environmental factors in addition to challenges with implementation on the patient level.

A further limitation of subtyping approaches is that most studies to date have been conducted predominantly in populations of European ancestry and therefore findings might not necessarily be transferable for other populations. Ultimately, the clinical utility of subtype-based approaches must be validated in prospective efficacy trials, which are still lacking.

THE NEED FOR PRECISION INTERVENTIONS IN PREDIABETES

Lifestyle Intervention Is First-line Therapy in Prediabetes

In prediabetes, comprehensive lifestyle change—diet, exercise, and weight loss—remains first-line therapy, lowering diabetes incidence by roughly 60% in the Finnish Diabetes Prevention Study (DPS) and the U.S. Diabetes Prevention Program (DPP), outperforming metformin's ∼30% effect, with benefits persisting for more than a decade and modulated by baseline risk profiles (40–44). Subsequent lifestyle intervention trials also showed the feasibility of a baseline risk stratification by traits such as insulin sensitivity, insulin secretion, and fatty liver (45,46). Also, recent data from the DPP showed that a partitioned polygenic risk score of β-cell failure predicts future diabetes independent from the intervention (47), suggesting that for prediabetes subtypes featuring increased genetic risk such as "progressing diabetes with β-cell failure," novel treatment approaches should be considered. DPP participants had concomitant IFG and IGT, while mean fasting glycemia was even higher in the DPS, positioning these participants to a high-risk prediabetes subtype.

When the baseline characteristics of DPS and DPP participants (42,48) are entered into the prediabetes subtype calculator, the average participant profile in both studies aligns closely with the "progressing prediabetes with fatty liver" cluster, the subtype associated with the highest diabetes risk compared with other clusters. This underscores that different intervention strategies might be needed for more heterogenous prediabetes populations.

Intensive Weight Reduction Through Bariatric Surgery

Bariatric surgery has been shown to prevent diabetes in conjunction with severe obesity. From observational studies investigators have reported remission rates of >80% at 1 year and sustained normoglycemia in more than half of individuals over several years, with younger age and greater early postoperative weight loss as key predictors of success

(49,50). Compared with the "metabolically healthy obese" and slow progressor subtypes, the "progressing prediabetes with fatty liver" subtype benefited most from bariatric surgery in terms of improvement of insulin sensitivity and secretion (51). It also benefits from reduction of liver fat through lifestyle intervention, which results specifically in an improvement of insulin secretion in this subtype (20).

Mechanistic Implications on Subtype-Specific Therapy

Overall data suggest that prediabetes subtypes characterized by severe insulin resistance with fatty liver and/or visceral adiposity likely benefit most from intensive weight reduction strategies. However, whether the key alteration, dysfunctional insulin secretion, can be improved with weight loss in the "progressing prediabetes with β-cell failure" subtype remains an open question. This β-cell dysfunction–dominated subtype might require early pharmacological intervention either for β-cell protection or for insulin substitution.

The Potential of Pharmacologic Interventions

Long-term weight loss through diet and exercise can be difficult to sustain due to metabolic and hormonal adaptations that promote weight regain (52). While lifestyle intervention remains the cornerstone of prediabetes management, the role of pharmacological therapy is increasingly gaining interest, especially for high-risk subgroups (53,54).

Metformin

With metformin, the most widely studied and used drug in prediabetes, modest but consistent benefits have been shown in delaying diabetes onset, particularly in younger and more insulin resistant individuals (55).

α-Glycosidase Inhibitors, Thiazolidinediones, and Basal Insulin

Efficacy of other pharmacologic agents has also been demonstrated in phenotype-specific contexts. Substantial benefits of acarbose have been shown in individuals with IGT in both Western and Asian populations (56), while similar preventive effects were demonstrated for voglibose in a Japanese trial (57). Pioglitazone, a thiazolidinedione, preserved β-cell function and reduced diabetes incidence in the Actos Now for the prevention of diabetes (ACT NOW) trial among individuals with IGT (58). Daily insulin glargine was evaluated over a median of 6.2 years in the Outcome Reduction With Initial Glargine Intervention (ORIGIN Trial) (n = 12,537, ∼12% of whom had IFG or IGT). Tightening fasting glucose to ≤5.3 mmol/L lowered diabetes conversion from 31% to 25% with no effect on cardiovascular or cancer outcomes. However, severe hypoglycemia occurred more frequently, and participants gained median ∼1.6 kg weight. A microvascular benefit was observed only among those with baseline HbA_{1c} ≥6.4% (59,60). In the 2.7-year ORIGIN and Legacy Effects (ORIGINALE) follow-up, glycemic and vascular differences disappeared (61).

SGLT2 Inhibitors and GLP-1 Receptor Agonists

In individuals who in addition to prediabetes already suffered from heart failure or chronic kidney disease, sodium–glucose cotransporter 2 inhibitors (SGLT2i) were associated with 13%–32% reduced risk of new-onset T2D (62).

More recently, superior effects of GLP-1 receptor agonists (GLP1RA) on weight loss, glycemic control, and cardiovascular risk profiles have been demonstrated. Trials such as A Phase 2 Study of Once-Weekly LY3437943 Compared With Placebo in Participants Who Have Obesity or Are Overweight With Weight-Related Comorbidities and Semaglutide Treatment Effect in People with obesity (STEP) 10 suggest that these agents, when added to lifestyle intervention, may offer a more effective strategy for individuals with high-risk phenotypes (54,63). In a cohort of individuals with obesity of whom 40% had prediabetes, with the GLP-1/GIP coagonist tirzepatide a 92% reduction of diabetes incidence over 176 weeks was seen, and this reduction was still at 88% after 17 weeks of the discontinuation of therapy (64). In addition, combination therapy with SGLT2i and GLP1RA was efficacious in the prevention of heart failure and vascular events, which could project a similar effect augmentation for their combination in prediabetes (65). Of note, GLP1RA showed potential to improve β-cell function in the severe insulin-deficient diabetes cluster (66), suggesting their potential in improving β-cell function also in the "progressing diabetes with β-cell failure" subtype of prediabetes.

Given the elevated risk of renal disease in the slow progressors, SGLT2i would qualify as early intervention for this subtype, independent of glycemic benefits. Similarly, while data on specific alteration of detrimental body fat compartments are still lacking, a potential reduction of renal sinus fat by GLP1RA and similar drugs could yield long-term risk reduction for renal complications.

Other Compounds

Efficacy of resmetirom, a novel thyroid hormone receptor-β agonist, has been demonstrated in reducing hepatic fat content and improving markers of liver fibrosis in individuals with noncirrhotic MASLD and steatohepatitis (67). Given that the majority of individuals in two of the three high-risk prediabetes subtypes had MASLD ("progressing prediabetes with fatty liver" 100% and slow progressor 75%) (2), and that hepatic lipid content appears to be involved in β-cell dysfunction in the former subtype (20), resmetirom may hold promise for improvement of β-cell function, and prevention of T2D, as well as its hepatic complication in at least one of these high-risk subtypes.

Balancing Efficacy, Side Effects, Treatment Adherence, and Costs

Bariatric and pharmacologic approaches could be options for individuals classified into high-risk prediabetes subtypes who do not reach their treatment goals with intensive lifestyle intervention alone (45). However, weight loss might not be effective for all individuals (68). In a retrospective evaluation of individuals with obesity who received GLP1RA, 17.8% were nonresponders, showing that therapy response varies (69). Of note, the glycemic efficacy of GLP1RA was lower in individuals with T2D characterized by low β-cell function, suggesting that a subset of persons could show a limited response to these agents in prediabetes as well (70). On the other hand, GLP1RA also exert rapid effects in improving insulin sensitivity and fasting and postprandial glucose, which are independent of weight loss (71).

While bariatric surgery is highly effective in achieving substantial and sustained weight loss and diabetes prevention, it carries risks including surgical complications, micronutrient deficiencies, and the need for lifelong nutritional monitoring, which limits its widespread applicability in the general population with prediabetes.

Most pharmacologic treatment options such as metformin, acarbose, GLP1RA,

and GLP1RA plus GIP receptor agonists predominantly have transient gastrointestinal side effects that tend to regress after therapy initiation. Interestingly, discontinuation patterns suggest that metformin might be less tolerated in Asians, compared with Europeans, while the inverse holds for acarbose (72).

For metformin, an increased risk of lactic acidosis seems to be confined to those with underlying conditions such as advanced renal and acute disease (73). For thiazolidinediones, overall weight gain, even when this affects subcutaneous fat depots and increases insulin sensitivity, is a serious limitation (74). Importantly, while major long-term safety concerns have not been confirmed for GLP1RA, increased relative risk of conditions with very low background risk such as that of nonarteritic anterior ischemic optic neuropathy may emerge in the long term and could be difficult to refute (75). Treatment with GLP1RA may also be associated with reduction in muscle mass, raising concerns about a potential risk of sarcopenia, particularly with long-term use; the clinical consequences of such changes remain insufficiently understood and warrant further investigation (76). In addition to potential side effects, the willingness to initiate and adhere to pharmacologic treatment in the context of prediabetes is influenced by several factors, including the asymptomatic nature of the condition, the low awareness of future health risks, and general attitudes toward long-term medication use (43,77).

The broader use of pharmacologic intervention in prediabetes can be also limited by cost, accessibility, and the need for more evidence to define the risk-benefit and cost-effectiveness profiles in this setting. While metformin could be underused for diabetes prevention, given consistent data on its cost-effectiveness (78), there are currently no convincing studies on the cost-effectiveness of SGLT2i and GLP1RA/GIPRA. Despite their efficacy, preliminary results of a microsimulation model in U.S. adults with prediabetes and obesity did not support cost-effectiveness of GLP1RA treatment from the perspective of a health care system (79).

Given the limited cost-effectiveness of applying pharmacologic prevention broadly, routine pharmacotherapy for all individuals with prediabetes is neither warranted nor practical. Instead, identifying individuals with prediabetes who are at highest risk for diabetes and its complications, and matching them with targeted interventions, should be the priority. Pharmacologic treatment may be appropriate for selected high-risk groups failing lifestyle measures—which still requires prospective validation. In parallel, prospective validation of subtype-specific risk and treatment response in diverse populations—along with frameworks that are accessible to nonendocrine specialties such as primary care, cardiology, gastroenterology, and women's health—will be essential to ensure real-world clinical utility and equitable implementation.

Beyond Just Preventing Diabetes

Beyond merely delaying the onset of overt diabetes, the aim of prevention should be to mitigate the earliest signs of organ damage. Accumulating evidence shows that clinically relevant end-organ injury often begins during prediabetes and the highest morbidity/mortality does not always coincide with the highest glycemic risk (2). Among the major intervention studies, only the long-term extensions of the DPP (Diabetes Prevention Program Outcomes Study [DPPOS]) and the Da Qing study included systematically examining microvascular outcomes; even there, aggregate benefit emerged only after 15 years and remained modest (55,80). Given that people in the slow progressor subtype category already display elevated urinary albumin–to–creatinine ratios before meeting diagnostic criteria for diabetes, future trials should incorporate complication-related end points in addition to (or even instead of) diabetes incidence. However, it would take decades to look at "hard" end points such as cardiovascular risk in unstratified prediabetes, unless only very high-risk individuals are included in such trials. Therefore, a more sensitive strategy will be to incorporate subclinical end points that capture tissue injury long before clinical events become apparent. Renal markers (like urinary albumin–to–creatinine ratio), ophthalmic imaging (improved scalability with artificial intelligence–based evaluation), quantitative sensory testing for peripheral neuropathy, and use of cardiac biomarkers could indicate impeding end-organ damage and make such studies feasible. Accordingly, future studies should *1*) include stratification of people with prediabetes by validated risk phenotypes, *2*) be adequately powered to detect subclinical or intermediate end points and *3*) retain long-term surveillance for definitive clinical events. Such designs would align outcome measures with the biological goals—arresting or reversing injury at its inception—while maintaining practical feasibility and statistical power within realistic trial horizons.

COMPARING PREDIABETES AND DIABETES: SUBTYPES, PROGRESSION, AGE, AND ETHNICITY

Subtypes have also been identified in diabetes. Ahlqvist et al. (81) proposed a widely studied classification of adult-onset diabetes subtypes, which has since been replicated across diverse populations (82). While some individuals in the slow progressors prediabetes subtype category develop diabetes after many years, more than half transition into the severe insulin-resistant diabetes subtype (2).

In a direct comparison between prediabetes and diabetes subtypes, among patients undergoing coronary angiography, mortality was increased for the high-risk prediabetes subtypes compared with the low-risk subtypes (22). However, for even the high-risk prediabetes subtypes mortality was lower than for most T2D clusters. Only for the "mild obesity-related" diabetes cluster was mortality lower, comparable with that of the high-risk prediabetes subtypes. This comparison emphasizes that while prediabetes carries significant health risks, T2D remains a more severe condition.

The clinical significance of prediabetes also varies markedly with age. In a prospective study of older individuals, prediabetes was highly prevalent, yet regression to normoglycemia or death occurred substantially more often than progression to overt diabetes (83). These findings suggest that the prognostic implications of prediabetes are age dependent and should be interpreted in the context of competing risks and life expectancy. Of note, aging is associated with increased HbA_{1c} levels, independently of glucose and insulin resistance, which could lead to a decreased diagnostic specificity of HbA_{1c} also in prediabetes (84).

Race and ethnicity can be associated with prediabetes risk factors, leading to

different distributions of subtypes across ethnically diverse cohorts. For example, East Asians appear to have lower insulin secretion relative to insulin sensitivity in comparison with individuals of European or African descent, suggesting a predisposition to insulinopenic phenotypes (85). In a large study involving nearly 5 million adults, investigators examined the interplay between obesity and ethnicity in modulating disparities in shaping prediabetes risk (86). Prediabetes was most prevalent among Asian adults, with high rates also seen among Hawaiian/Pacific Islander and Hispanic individuals and lower rates among Black American, American Indian/Alaska Native, and White individuals (86). While hepatic lipid content was the strongest factor explaining glycemic progression from normoglycemia to prediabetes and diabetes in a cohort of South Asians living in the U.S., hepatic fat, visceral fat, intramuscular fat, and epicardial fat, together with other risk factors, failed to explain the higher prevalence of prediabetes in this group than in other ethnicities (87,88). In contrast to this, lipodystrophy-like genetic variants conveying insulin resistance independent of body mass explained a large part of the increased diabetes risk in South Asians at a lower BMI, compared with individuals of European ancestry (89). Rooney et al. (90) reported global variations in prediabetes subtypes: IGT was most prevalent in North America and Europe, while IFG was predominant in Southeast Asia and India. In India, the prevalence of IFG was nearly three times higher than of IGT (91). This is particularly important to consider, as early diabetes prevention trials predominantly included individuals with IGT or combined IGT and IFG, often excluding those with isolated IFG (92). Such findings highlight the need for tailored interventions addressing heterogeneous risk factors in the progression from prediabetes to T2D.

These data highlight that multiple factors have to be considered (such as age, adipose distribution, liver fat, and other risk factors that characterize the underlying phenotype) in evaluating the need for intervention in prediabetes. While targeted strategies for high-risk individuals are warranted, diabetes itself should remain the primary clinical focus due to its greater overall burden of disease and complications, and long-term health care impact. This perspective challenges the rationale for aggressively pursuing remission of prediabetes in all individuals. A more differentiated approach that is guided by individual risk defined according to age, comorbidities, and pathophysiologic hallmarks may help optimize resource allocation and clinical decision-making. Improving subphenotyping in prediabetes offers an opportunity for diabetes prevention. Balancing precision interventions in high-risk prediabetes with comprehensive treatment of diabetes could lead to better patient outcomes.

CLINICAL CHALLENGES AND FUTURE DIRECTIONS

Despite improved understanding of heterogeneity, translating prediabetes subtypes into clinical practice remains challenging. Current diagnostic criteria for prediabetes rely exclusively on glycemic thresholds, which fail to capture the full spectrum of individual risk. This approach does not distinguish between low-risk individuals, who may require minimal clinical attention, and high-risk individuals, who could benefit from early, multifactorial interventions targeting metabolic, hepatic, and cardiovascular pathways.

In this review, we present a proof-of-concept framework that conceptualizes prediabetes as a multifactorial condition comprising biologically distinct subtypes. These subtypes offer a more refined understanding of underlying pathophysiology, potentially enabling improved risk stratification and personalized treatment strategies. While early findings are promising, and highlight the existence of a slowly progressing form of prediabetes that can directly lead to complications, the complexity of multivariable approaches—along with unresolved methodological questions regarding clustering techniques and the lack of prospective validation—does not

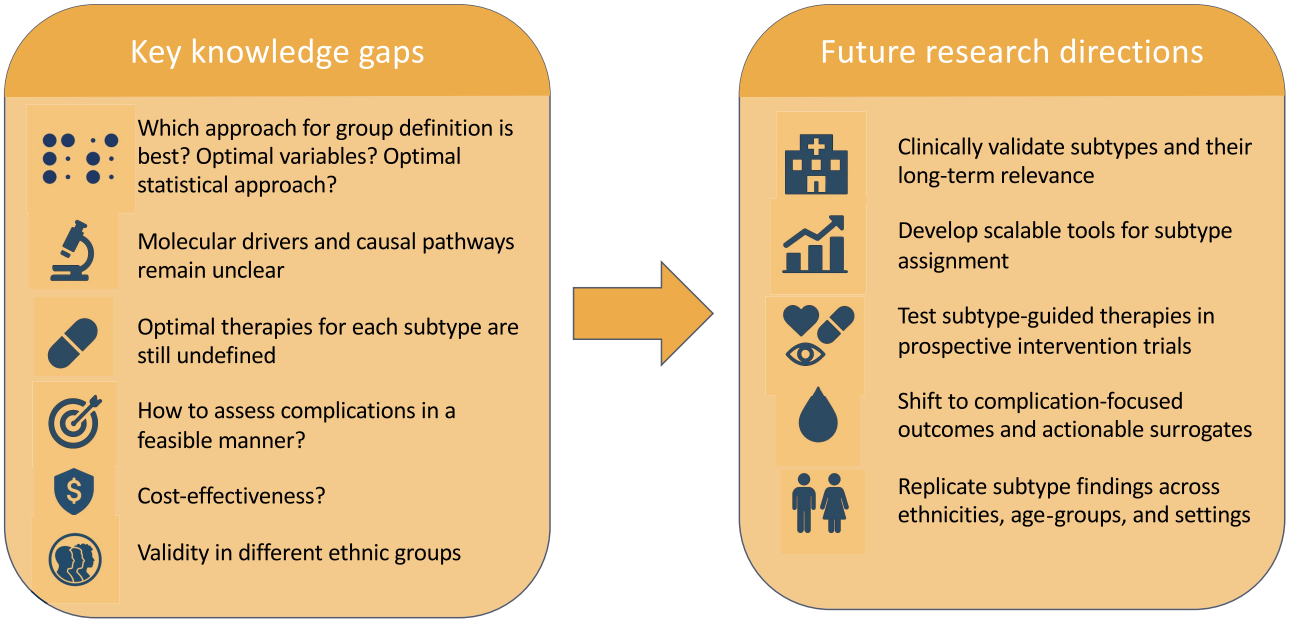


Figure 2—Key knowledge gaps and future research directions related to the subtypes of prediabetes.

currently justify a redefinition of prediabetes or diabetes itself. Glycemic thresholds remain practical, well-validated tools for population-wide screening, and any reclassification would require robust prospective evidence and broad clinical consensus.

Ultimately, the identification of practicable biomarkers that define phenotypes of prediabetes, alongside early indicators of organ damage, could support precision interventions at earlier stages. Such strategies would enable therapeutic approaches to extend beyond short-term glycemic control and instead focus on reducing long-term complications across multiple organ systems. Randomized clinical trials specifically designed to test subtype-directed interventions will be essential to validate this framework and may, in the long term, inform updates to diagnostic criteria and treatment guidelines (Fig. 2).

CONCLUSIONS

Prediabetes is increasingly recognized as a heterogeneous condition encompassing biologically distinct subtypes with varying risks for progression to T2D and associated complications. The framework presented in this article offers a conceptual basis for redefining prediabetes as a multifactorial disorder, with the potential to improve risk stratification and guide more personalized interventions. However, several challenges remain before these insights can be translated into clinical practice. Current glycemic thresholds remain the cornerstone of diagnosis due to their practicality and established predictive value, and any revision to diagnostic criteria would require rigorous validation and consensus. Moreover, the implementation of subtype-based approaches must overcome methodological complexities with demonstration of added clinical utility through prospective trials. Future efforts should be focused on understanding whether interventions for different subtypes result in the same or different outcomes. This could be facilitated through identifying robust biomarkers and early indicators of organ damage to support targeted prevention strategies. In moving beyond short-term glycemic end points, precision approaches to prediabetes management may inform treatment guidelines and public health strategies and ultimately reduce long-term complications. Moving from scientific discovery to implementation will require not only simplified classification tools but also integration into clinical workflows in primary care and specialty settings.

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