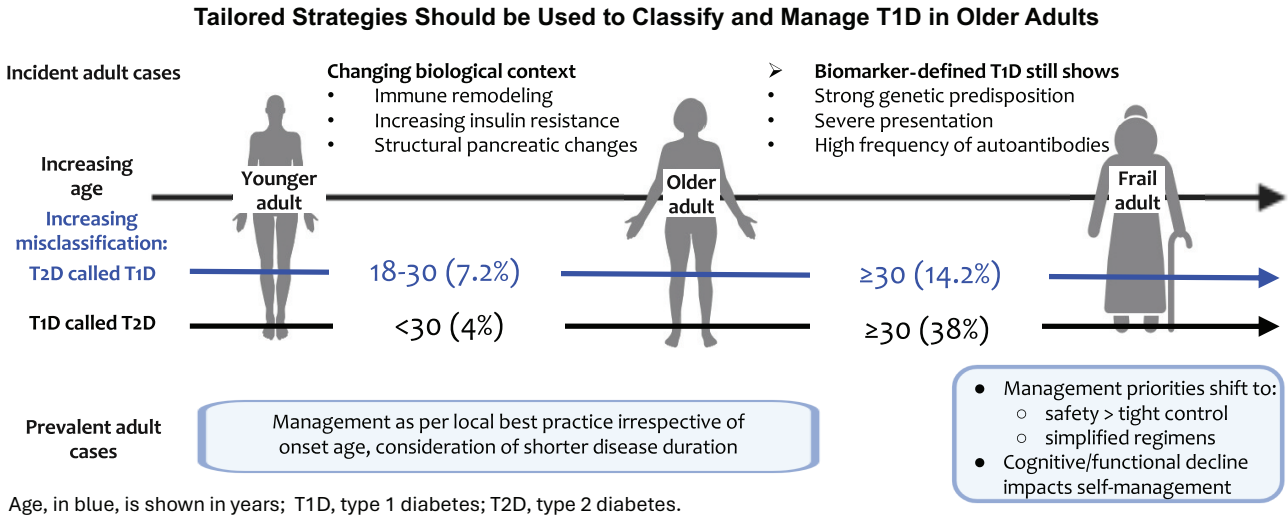
Diabetes Care
American Diabetes Association

Pathophysiology and Treatment of Type 1 Diabetes in Older Adults

Alessandra Petrelli, Nicholas J. Thomas, Suzy V. Hope, Loredana Bucciarelli, and Paolo Fiorina

Diabetes Care 2026;49(00):1–12 | https://doi.org/10.2337/dci25-0143



Age, in blue, is shown in years; T1D, type 1 diabetes; T2D, type 2 diabetes.

ARTICLE HIGHLIGHTS

- **Why did we undertake this study?**
  We undertook this study because type 1 diabetes diagnosed after age 30 years is common yet frequently misclassified, and the clinical needs of older adults remain insufficiently defined.
- **What is the specific question(s) we wanted to answer?**
  We sought to determine how age at onset and aging influence the biology and clinical course of type 1 diabetes and how these factors should inform classification, risk prediction, and management in adults and older individuals.
- **What did we find?**
  We found that age-related differences reflect a phenotype shaped by the biological context of autoimmunity and that much apparent adult heterogeneity results from misclassification in the absence of robust biomarkers.
- **What are the implications of our findings?**
  Our findings support biomarker-informed diagnostic pathways and age-tailored strategies for screening, prevention, and management.

Pathophysiology and Treatment of Type 1 Diabetes in Older Adults

Alessandra Petrelli,[1,2] *Nicholas J. Thomas,*[3,4] *Suzy V. Hope,*[3,5] *Loredana Bucciarelli,*[2,6] *and Paolo Fiorina*[6,7,8]

https://doi.org/10.2337/dci25-0143

This article highlights how age and type 1 diabetes interact to shape clinical onset and treatment, emphasizing the need for tailored strategies in classifying and managing type 1 diabetes across the lifespan, particularly in later life. This article represents an expert perspective based on selected literature. In considering type 1 diabetes in adults, distinction is needed between incident cases, where biological age influences underlying pathophysiology, and prevalent cases, capturing both adult-onset type 1 diabetes and long-standing childhood-onset type 1 diabetes in individuals reaching older age. Type 1 diabetes diagnosed after age 30 years presents diagnostic and management challenges. Diagnosis remains difficult due to high prevalence of type 2 diabetes and frequent misclassification. When adult-onset type 1 diabetes is rigorously defined, key clinical features, including progression from dysglycemia and early β-cell decline, more resemble those in younger individuals. Differences across ages are best interpreted as an age-related phenotype arising from the biological context in which autoimmunity occurs, immune remodeling, insulin resistance, and pancreatic changes, rather than distinct pathogenic mechanisms. While incidence of adult-onset type 1 diabetes is largely static, prevalence is increasing, especially among those ages ≥65 years, largely due to improved outcomes with declining mortality and disability-adjusted life-years. While type 1 diabetes management should not intrinsically alter with age, older adults face elevated risks of comorbidities, including frailty and cognitive and visual impairment, which can complicate management and impact glucose levels, particularly hypoglycemia risk; individualized glycemic targets are needed with a focus on safety and quality of life. Moving forward integrating adults into pre–type 1 diabetes screening and prevention efforts will be essential to refine prediction, reduce misclassification, and guide disease-modifying interventions.

Type 1 diabetes is an autoimmune disease mediated by autoreactive T cells that selectively destroy pancreatic β-cells, leading to insulin deficiency and hyperglycemia (1). Traditionally considered a disorder of childhood and early adulthood, type 1 diabetes is increasingly recognized in older adults, including individuals diagnosed after age 30 years (2). Throughout this article, we use the term "adult-onset type 1 diabetes" to refer to diabetes diagnosed after age 30 years, while reserving the term "older adults" with type 1 diabetes exclusively for individuals aged ≥65 years, in accord with American Diabetes Association definitions (3). In contrast to extensive research in pediatric and young adult populations, the epidemiology, progression, and management of type 1 diabetes in older adults remain largely underexplored. Classification of type 1 diabetes in adults increasingly relies on biomarker-based approaches. Among islet autoantibodies, GAD65 autoantibodies are predominant in

View Online Article

[1]*Department of Clinical Sciences and Community Health, Dipartimento di Eccellenza 2023-2027, University of Milan, Milan, Italy*
[2]*Pio Albergo Trivulzio, Milan, Italy*
[3]*University of Exeter, Exeter, U.K.*
[4]*Department of Diabetes and Endocrinology, Royal Devon University Healthcare NHS Foundation Trust, Exeter, U.K.*
[5]*Department of Healthcare for Older People, Royal Devon University Healthcare NHS Foundation Trust, Exeter, U.K.*
[6]*International Center for T1D, Pediatric Clinical Research Center Romeo ed Enrica Invernizzi, Dipartimento di Scienze Biomediche e Cliniche (DIBIC), University of Milan, Italy*
[7]*Division of Endocrinology, ASST Fatebenefratelli-Sacco, Milan, Italy*
[8]*Division of Nephrology, Boston Children's Hospital and Harvard Medical School, Boston, MA*

Corresponding author: Alessandra Petrelli, alessandra.petrelli@unimi.it, orPaolo Fiorina, paolo.fiorina@unimi.it

Received 12 December 2025 and accepted 4 April 2026

A.P. and N.J.T. contributed equally to this work.

adult-onset disease, whereas IA-2 and ZnT8 autoantibodies are more frequent in childhood-onset type 1 diabetes (4). In the context of a clinical suspicion of type 1 diabetes, the presence of islet autoantibodies shows very high specificity (typically >95% with modern assays), particularly when multiple autoantibodies are detected (5). However, in unselected adult populations with diabetes, the positive predictive value of single autoantibody positivity is limited, reflecting both the low prior probability of type 1 diabetes and the not insignificant rate of incidental autoantibody positivity in nonautoimmune diabetes (6). For this reason, multivariable diagnostic strategies integrating age at diagnosis, autoantibody status, HLA or type 1 diabetes genetic risk scores, BMI, and family history can improve discrimination between autoimmune and nonautoimmune diabetes in adults and reduce misclassification (2,5,7,8). In this article, we initially focus on the unique clinical, genetic, and immune features of type 1 diabetes diagnosed after age 30 years, with particular attention to where type 1 diabetes is defined by robust biomarkers, particularly the presence of multiple islet autoantibodies and loss of endogenous insulin secretion. We then discuss management of prevalent older adult type 1 diabetes cases irrespective of onset age. Here we highlight that while increasing age should not directly impact management, its association with comorbidities including frailty and cognitive impairment brings key therapeutic considerations relevant to this growing but underinvestigated population. This article is an expert opinion piece; references were selected based on the authors' expertise to highlight studies most relevant to the conceptual framework discussed.

PHENOTYPES OF ADULT-ONSET TYPE 1 DIABETES

Classification of Adult-Onset Type 1 Diabetes

Although type 1 diabetes incidence peaks during adolescence, it remains substantial across all early decades of life, and a considerable proportion of cases are diagnosed after age 30 years. However, much less is known about the characteristics of adult-onset disease, predominantly due to difficulties in robust case definition (2). This challenge of classifying diabetes grows with age, as type 2 diabetes becomes increasingly prevalent, lowering the prior likelihood that adult-onset diabetes is type 1 (5). While >90% of children with diabetes have an autoimmune form, the pattern is reversed in adults, where >90% have type 2. Adding further complexity, a nonobesity phenotype of type 2 diabetes is increasingly recognized in older age, likely reflecting age-related changes in body composition (e.g., sarcopenia and visceral adiposity) rather than low cardiometabolic risk (9). As in the general population, among adults with type 1 diabetes there is increasing prevalence of overweight and obesity, approaching population levels in several cohorts (10–12).

Reflecting these challenges, for many adults with autoimmune diabetes misclassification occurs, becoming more common with increasing onset age. For example, biomarker testing in a Scottish type 1 diabetes clinic resulted in reclassifying from type 1 to type 2 diabetes in the case of 7.2% of adults diagnosed between ages 18–30 years and 14.2% of those diagnosed at age ≥30 years (13). Conversely, a substantial proportion of autoimmune diabetes remains unrecognized at diagnosis, with ∼38% of individuals aged ≥30 years initially misclassified as having type 2 diabetes (14,15). Accurate type 1 diabetes classification is critical: in clinical practice to guide treatment and in research to define disease etiology. In cohorts of adults with clinically diagnosed type 1 diabetes, which include a mixture type 1 and misclassified 2 diabetes, characteristics will have been observed reflecting the mixture of the two disease etiologies.

Classification in adults can be enhanced by using biomarker definitions of type 1 diabetes. In this context, a biochemical diagnosis of type 1 diabetes should rely on the presence of multiple islet autoantibodies or compatible clinical characteristics confirmed by either single islet autoantibody positivity or evidence of severe insulin deficiency (e.g., low C-peptide levels). It has been shown that in adults islet autoantibodies are highly sensitive and specific for type 1 diabetes in the context of a clinical diagnosis (5). Accordingly, international guidelines now recommend confirmatory islet autoantibody testing in all adults with a clinical diagnosis of type 1 diabetes, with consideration of alternative diagnoses and noninsulin management if an individual is antibody negative (16). The importance of robust classification is increasingly critical as new disease-modifying immunotherapies for type 1 diabetes emerge. Additionally, glucagon-like peptide 1 receptor agonists and SGLT2 inhibitors are increasingly recommended as early therapies for type 2 diabetes because of their glycemic and cardiorenal benefits, but substantial caution continues to be advised regarding their safety in individuals with type 1 diabetes (17,18).

While islet autoantibodies are confirmatory in the context of a clinical diagnosis of type 1 diabetes, their predictive utility is reduced in unselected adults with diabetes. This reflects Bayes' theorem and the fact that the prior probability of type 1 diabetes among all adults with diabetes is low, meaning the positive predictive value of any imperfect test will also be low (5,6). In this setting, the prevalence of islet autoantibodies among those with nonautoimmune (type 2) diabetes will approximate that seen among control participants, equal to 1 − the assay specificity. For example, when cutoffs are defined at the 97.5th centile, ∼2.5% of individuals without autoimmune diabetes, including those with monogenic diabetes, test positive (5). Because nonautoimmune diabetes is ∼20 times more common than type 1 in adults, even highly specific assays yield a substantial proportion of "incidental positive" results, such that many single islet autoantibody–positive adults actually have nonautoimmune diabetes. This can help explain the intermediate phenotype of latent autoimmune diabetes in adults, which is most evident in older populations where the prior likelihood of a case of diabetes being type 1 diabetes is lowest. This diagnostic overlap is further highlighted by data-driven subclustering approaches in type 2 diabetes, where severe insulin-deficient diabetes (SIDD) closely resembles severe autoimmune diabetes (SAID), except for the absence of islet autoantibodies, underscoring the limitations of purely clinical classification in adults (19). Together, these findings reinforce that apparent heterogeneity across ages is best interpreted within an age-related phenotype model, shaped by the biological context in which autoimmunity occurs.

Accordingly, for the remainder of this article we focus on "conventional type 1 diabetes," here referring to autoimmune diabetes defined according to established clinical and biochemical criteria. Within this framework, we specifically examine how adult-onset disease may differ from childhood-onset type 1 diabetes. To help

interpret the heterogeneity observed in adult cohorts, Table 1 summarizes how the apparent clinical, genetic, immune, and metabolic features of adult-onset type 1 diabetes differ when cases are defined on the basis of conventional clinical criteria versus use of biomarker-based definitions.

Incidence and Prevalence of Type 1 Diabetes and Islet Autoimmunity in Older Adults

While incidence data in older adults remain limited and do not consistently show age-related increases, the prevalence of type 1 diabetes among individuals aged ≥65 years is rising. This increase likely reflects improved survival and long-term outcomes rather than a true rise in incident cases at older ages. Type 1 diabetes can develop at any age, and ∼42% of cases are diagnosed after age 30 years, representing <4% of all diabetes cases in people aged 30–60 years (2). While a sharp increase in type 1 diabetes incidence has been observed in young children (age <5 years) (20), recent data also point to a growing prevalence in individuals aged ≥65 years, with the highest rates reported among those aged 70–74 years (21). Between 1990 and 2019, the age-adjusted prevalence in this age-group rose by 28%, from 400 to 514 per 100,000, corresponding to an average annual increase of 0.86% (21). This growing prevalence of type 1 diabetes in adults and older adults underscores the need for the scientific and clinical community to reconsider current paradigms of care.

Clinical Phenotypes of Adult-Onset Type 1 Diabetes

At diagnosis, adults with adult-onset type 1 diabetes are often reported to have higher BMI and less severe features in comparison with children and younger adults, including lower HbA_{1c}, reduced weight loss, and lower rates of diabetic ketoacidosis (DKA) (4,22). However, as these cohorts rely on clinical diagnosis, there is risk of circularity: clinical features being used to both define and describe the disease. Studies with use of biomarker-based definitions are rare, but in those with long-standing type 1 diabetes defined by C-peptide deficiency or genetics, comparable clinical characteristics (BMI, sex, HbA_{1c}, insulin dose, DKA) have been shown regardless of onset age (2,14). Similarly, in newly diagnosed adult cohorts classified on the basis of two or more positive islet autoantibodies, presentation is typically severe, with weight loss in >80%, DKA in >20%, and osmotic symptoms in >90%, with no difference between those diagnosed at age ≤35 vs. >35 years (23).

Despite similar presentations, initial management varies by age, likely reflecting lower recognition of type 1 diabetes at diagnosis in older adults. Older adults are less likely to be admitted or started

Table 1—Conceptual framework illustrating how misclassification in clinically defined adult cohorts contributes to the apparent heterogeneity of adult-onset type 1 diabetes

Feature	Adult-onset T1D (clinical criteria)	Adult-onset T1D (biochemical definition)
Diagnostic definition	Clinical diagnosis based on clinician judgment or rapid insulin requirement	Presence of islet autoantibodies and/or severe insulin deficiency (low C-peptide)
Risk of misclassification	High, increasing with age	Low, but increasing with lower assay specificity
Islet autoantibodies	Variable; often single or absent due to inclusion of nonautoimmune diabetes	High prevalence. Multiple autoantibodies common
Predominant autoantibody	Apparent GAD65 predominance but heterogeneous	GAD65 predominant; IA-2A and ZnT8A less frequent than in childhood-onset T1D
T1D genetic risk (HLA/T1D GRS)	Reduced on average, reflecting loss of protective HLA and likely misclassification	Preserved T1D genetic susceptibility; protective HLA effects maintained
T2D genetic risk	Often elevated	Generally lower, though metabolic traits may contribute
BMI and insulin resistance	Often higher; reflects inclusion of nonautoimmune diabetes	Variable; insulin resistance acts as a modifier rather than a primary driver
Progression to insulin dependence	Heterogeneous; delayed insulin initiation common	Rapid and near-universal insulin requirement
β-Cell decline	Apparent slower decline reflects inclusion of nonautoimmune diabetes	Largely similar decline once dysglycemia develops
Immune phenotype	Poorly defined; confounded by misclassification	Age-related differences. Limited data in adults age ≥65 years
Pancreatic pathology	Not well characterized	Limited adult data. Insulitis generally less extensive than in children
Clinical management implications	Missed opportunities for noninsulin therapies where T2D is misclassified as T1D	Management aligned with that in autoimmune T1D, individualized on the basis of age, duration, and function
Implications for endotype definition	Apparent heterogeneity largely driven by misclassification	Supports an age-related phenotype; insufficient evidence for a distinct adult-specific endotype

GRS, genetic risk score; T1D, type 1 diabetes; T2D, type 2 diabetes; ZnT8A, ZnT8 antibodies.

on insulin at diagnosis, and more often noninsulin therapies are received (14,23). Early treatment failure with noninsulin agents and insulin requirement within 3 years are strongly predictive of diagnosis with underlying type 1 diabetes and should prompt autoantibody testing (16). Longitudinal studies with genetic or C-peptide criteria confirm that >85% of adults with type 1 diabetes require insulin within 1 year of diagnosis (2,14).

Age-Related Patterns of Autoimmunity and Clinical Presentation

Preclinical Autoimmunity and Early Progression to Diabetes Development

Type 1 diabetes develops over a prolonged preclinical phase marked by islet autoimmunity (25). Most childhood cases arise from autoimmunity initiated early in life, yet more than half of all type 1 diabetes diagnoses occur in adults, and the timing of seroconversion in this group remains uncertain. Because nearly all children with multiple autoantibodies progress by age 18 years, it follows that some adults must develop autoimmunity de novo later in life (26).

Although population-level data in adults remain limited, emerging evidence indicates that preclinical autoimmunity in adulthood is clinically relevant. In the population-based Autoimmunity Screening for Kids (ASK) study, 3.9% of adults tested positive for one or more islet autoantibodies and 0.6% for multiple autoantibodies, with GAD65 autoantibodies (GADA) predominating (27). In at-risk cohorts, up to one-half of the autoantibodies detected before age 50 years are first identified in adulthood (22). However, these data do not derive from prospective follow-up of autoantibody-negative adults, and the timing of seroconversion in adulthood therefore remains uncertain. Indirect evidence comes from longitudinal studies showing that ~50% of adults positive for multiple autoantibodies aged >20 years progress to stage 3 diabetes within 10 years (28), demonstrating that adult-onset islet autoimmunity carries substantial long-term risk. Although progression appears slower than in children, where ~50% progress within 5 years of seroconversion (29,30), the overall trajectory remains clinically meaningful.

Prospective studies (Diabetes Prevention Trial–Type 1 [DPT-1], Type 1 Diabetes TrialNet) consistently show faster progression from islet autoantibody positivity to stage 3 diabetes in children, with risk declining after age 20 years (31,32). However, once dysglycemia (stage 2) emerges, subsequent progression to stage 3 appears similar across age-groups (33). Importantly, these cohorts include few individuals >60 years of age, and direct evidence describing preclinical progression in older adults remains limited.

In adults, both the number and the specificity of autoantibodies remain strong predictors of progression: GADA, the most frequent autoantibody in adult-onset disease, is associated with slower progression to stage 3 type 1 diabetes, whereas IA-2 antibody (IA-2A) positivity confers consistently higher risk (31,34). Therefore, although the initiation of autoimmunity differs between adults and children, the later phases of preclinical progression (stage 2 → stage 3) are broadly similar across age-groups (35). Similarly, where type 1 is diagnosed robustly, age of onset appears to have limited impact on early postdiagnosis decline rate in C-peptide but adults and older children start from a far higher point, possibly reflecting recently reported differences in the underlying architecture of the very young pancreas (5,36,37) (Fig. 1). Although investigators for some earlier studies reported slower loss of β-cell function in recently diagnosed autoantibody-positive adults (38), recent analysis of other cohorts in the same study showed that type 2 diabetes genetic risk was associated with clinical progression only in adults positive for a single autoantibody (39), suggetsing potential for inclusion of some individuals whose diabetes does not have a type 1 etiology, but further clarification of observed differences between studies is needed.

Genetic and Autoantibody Features of Adult-Onset Type 1 Diabetes at Clinical Onset

Type 1 diabetes genetic predisposition decreases with increasing age of onset (7,12,21–28). Among adults with clinically diagnosed type 1 diabetes lower polygenic risk scores are seen, as well as reduced monozygotic twin concordance (40,41), and a diminished prevalence of high-risk HLA class II genotypes, particularly DR3-DQ2/DR4-DQ8, in comparison with childhood-onset cases (4,42–45). In these adult cohorts, the protective effect of DR15-DQ6 also appears attenuated (4,42–45). Genetic analyses further show increasing overlap with type 2 diabetes susceptibility loci in clinically diagnosed adult-onset cohorts, especially in older adulthood (46).

In contrast, when adult-onset type 1 diabetes is confirmed by autoantibody positivity, genetic risk appears far more stable across adult ages. Adult autoantibody-positive individuals maintain a preserved protective effect of DR15-DQ6 (23,47), and the modest reduction in type 1 diabetes genetic risk score relative to children is largely attributable to lower frequency of high-risk HLA class II genotypes rather than a fundamentally different genetic architecture (4,42–45). Importantly, among adults with a clinical diagnosis but who test negative for autoantibodies, markedly reduced type 1 diabetes genetic susceptibility is seen, a pattern not observed in children and strongly suggestive of nonautoimmune diabetes in a substantial proportion of these cases (48).

Autoantibody profiles at onset appear to differ substantially by age of diagnosis. Although several reports suggest lower autoantibody prevalence in adults than in children (4,49,50), many rely on clinical diagnostic criteria, where misclassification is common in older adults. When type 1 diabetes is defined by biochemical insulin deficiency (C-peptide <200 pmol/L), autoantibody positivity remains high (~80%) even in individuals age >30 years, although autoantibody measurement was performed after a longer diabetes duration in those diagnosed at younger versus older ages (26 vs. 13 years after diagnosis, respectively), a factor known to reduce detectable autoantibody positivity over time (14). Genetic analysis for 1,778 clinically diagnosed cases (After Diagnosis Diabetes Research Support System-2 [ADDRESS-2]) supports this: among clinically diagnosed cases in adults >30 years old who were antibody negative, 77% were genetically more consistent with type 2 diabetes, compared with 45% in those aged 18–30 years. After exclusion of misclassified cases, autoantibody positivity does not decline with older onset (48,51).

The type and number of autoantibodies also differ across ages. IA-2A positivity is common in children but far less frequent in adults, where GADA predominates across ethnic groups (22,50,52,53). Single autoantibody positivity is more common with older onset, 35% among adults vs. 19% in

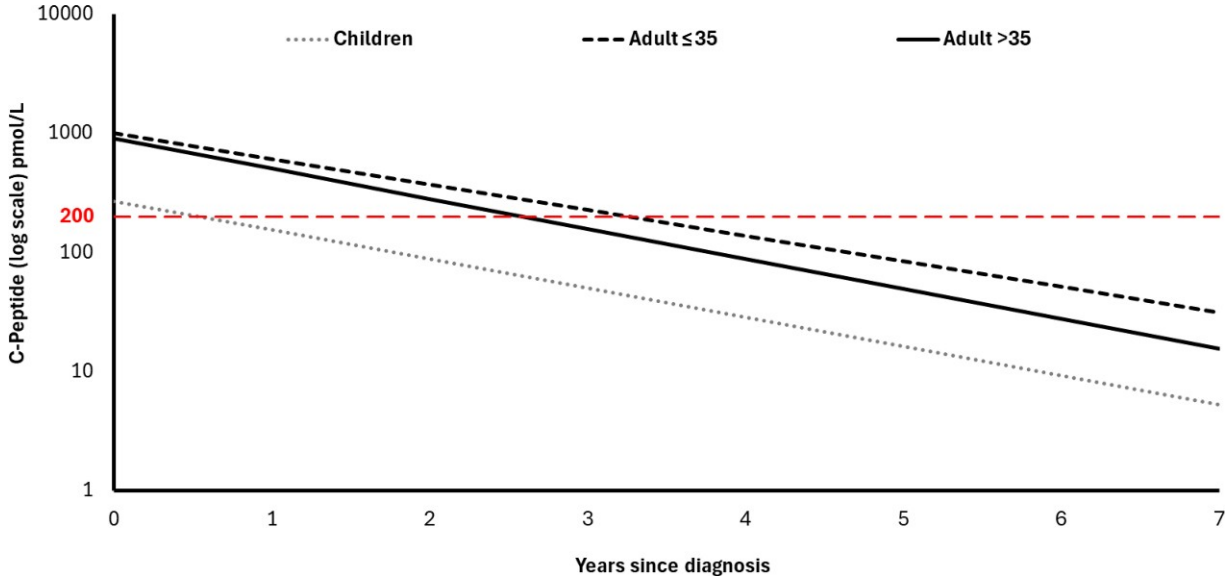


Figure 1—Type 1 diabetes progression rates defined by urine C-peptide–to–creatinine ratio as reported by Thomas et al. (23) in *Diabetes Care* (2023) and Shields et al. in *Diabetes Care* (2018) (24), highlighting the progression in a well-defined cohort of adult (age >35 years) type 1 diabetes in comparison with children and young adults (age ≤35 years).

children, and rises further among those diagnosed at >30 years of age (40% vs. 30% among those diagnosed at ≤30 years) (4,22,49,50,52).

Age-Related Modulation of Immune and Pancreatic Features of Adult-Onset Type 1 Diabetes

Nonspecific and Islet-Specific Immune Responses in Adult-Onset Type 1 Diabetes

The immunopathology of type 1 diabetes shows age-related variation between children and adults, reflecting differences in immune context rather than a fundamentally distinct process. In children, the immune response is typically characterized by strong activation of innate immune cells, including monocytes with increased cytokine secretion and enhanced HLA-DR expression early in the disease process (54,55). This is accompanied by a highly inflammatory adaptive response dominated by Th1 and Th17 activity and marked effector T-cell activation at disease onset (56–58).

In contrast, adult-onset disease develops within the same fundamental autoimmune framework but in the context of age-related immune remodeling shaped by immunosenescence and "inflammaging" (59). Regulatory control is diminished, with impaired Treg function and reduced checkpoint activity, and the immune repertoire shifts toward an expanded pool of memory and exhausted T cells (60,61). These changes occur alongside contraction of the naïve T-cell compartment, impaired B-cell and antigen-presenting cell function, and a proinflammatory cytokine milieu (62–64), creating a distinct immunological environment compared with the acute inflammatory response typically observed in children.

Antigen specificity also shows age-related patterns. In childhood-onset disease, insulin and proinsulin are the predominant T-cell targets (65,66), whereas in adult-onset disease, GAD65-reactive T cells are more frequently observed (56,67). Immunophenotyping studies, largely conducted in children and young adults, suggest differences in cytotoxic effector memory T-cell expansion at diagnosis, but comparable data in individuals aged ≥65 years are lacking.

Histopathological studies provide further evidence of age-dependent differences in pancreatic immune infiltration. Most histopathological data derive from children, adolescents, or young adults, and direct pancreatic evidence in individuals aged ≥65 years remains limited. Therefore, these observations are extrapolated to older ages with caution. In younger children (<7 years old), pancreatic lesions often display $CD20^{hi}$ B-cell–rich insulitis and broad antigen targeting, whereas in those diagnosed after age 13 years infiltrates are typically $CD20^{lo}$ and dominated by T cells and macrophages (68). Insulitis in adults also appears more focal and less extensive than in younger children (69–71). Notably, immune-cell infiltration of the exocrine pancreas has been described in adult-onset type 1 diabetes (72–74), and reduced circulating exocrine enzymes levels have been reported in adults with preclinical type 1 diabetes (75,76), although some markers show similar alterations across age-groups (77).

Taken together, these observations suggest that adult-onset type 1 diabetes develops within the same fundamental autoimmune framework described in childhood-onset disease, but in a biological context shaped by immune aging and pancreatic maturity. This environment may modulate the tempo and expression of autoimmunity, potentially through mechanisms such as bystander activation and epitope spreading (78). In addition, adult-onset disease arises in a mature pancreas, whereas childhood-onset autoimmunity affects an organ still undergoing growth and remodeling (36), which may contribute to quantitative rather than categorical differences in pathological patterns. Dedicated, age-stratified analyses of well-characterized pancreatic donor cohorts with detailed immune phenotyping will be essential to clarify whether specific immunopathological signatures differ meaningfully across the lifespan.

The Role of Insulin Resistance

Although β-cell autoimmunity is the defining feature of type 1 diabetes, insulin resistance acts as a clinically relevant disease modifier, with potentially greater impact in

adults. Proinflammatory cytokines such as IL-6 and TNF-α impair insulin signaling, promoting β-cell stress and apoptosis (79). Lifestyle-related factors, including weight gain, obesity, and physical inactivity, further exacerbate insulin resistance (80). Notably, direct measurement of insulin resistance using gold standard methods such as the hyperinsulinemic-euglycemic clamp has not been performed in individuals with preclinical type 1 diabetes, and current evidence is therefore largely indirect. Several prospective studies have shown that higher BMI and indices of insulin resistance are associated with progression to autoantibody development or symptomatic type 1 diabetes (81,82).

One conceptual framework for these observations is the accelerator hypothesis, which proposes that type 1 and type 2 diabetes lie on a continuum where genetic predisposition and metabolic stress converge to drive β-cell failure (83,84). However, an alternative interpretation is that insulin resistance may not directly accelerate autoimmunity and, rather, lowers the clinical threshold for hyperglycemia, thereby advancing the timing of type 1 diabetes onset in individuals with increased metabolic stress (85).

We performed a subanalysis of the TrialNet Pathway to Prevention Study (TNPTP) cohort (82) examining age-specific patterns of progression to stage 3 across tertiles of HOMA of insulin resistance (HOMA-IR) and Matsuda index (Fig. 2). In children (age <18 years), both markers showed a clear dose-response relationship: higher insulin resistance (higher HOMA-IR) or lower insulin sensitivity (lower Matsuda index) was strongly associated with increased progression risk. In young adults (18–30 years), this association was weaker and evident only in comparing the lowest with the highest tertile. In adults age >30 years, the pattern became binary, with increased risk confined to those in the highest HOMA-IR or lowest Matsuda tertile.

Population-level data indicate that overweight and obesity rates in type 1 diabetes mirror those of the general population (86,87). Thus, although overall adiposity is not disproportionately elevated in type 1 diabetes, a meaningful subset of adults, particularly in midlife, have excess BMI. Taken together, these observations suggest that insulin resistance in preclinical type 1 diabetes may advance the timing of clinical onset by lowering the β-cell functional reserve needed for symptoms to manifest, without clear evidence that it accelerates the underlying autoimmune process. In other words, insulin resistance appears to modulate when the disease becomes clinically evident—rather than how quickly it progresses biologically.

Age-Dependent Heterogeneity and the Proposed Concept of an "Aged" Type 1 Diabetes Phenotype

The endotype framework has been proposed to explain heterogeneity in type 1 diabetes across the lifespan (88,89). Early models distinguished an aggressive early-childhood form (endotype 1 [T1DE1]) from a slower, more indolent subtype appearing in adolescence and young adulthood (endotype 2 [T1DE2]) (90), and a more recent six-category schema (T1DE1–6) incorporates age at onset, immune and genetic features, C-peptide trajectories, and environmental exposures (91). Additional analytical approaches also suggest further subgrouping (92). However, multi-omics analyses in children have not identified distinct circulating endotypes, implying that divergence may emerge later in the disease course (93).

Within this context, a recurring constellation of clinical, immunological, genetic, and metabolic features has been described in adult-onset type 1 diabetes. These include lower genetic loading, greater environmental and metabolic pressures, immune remodeling, and structural pancreatic differences. Importantly, much of the supporting evidence derives from studies in adults <60 years old, and mechanistic data in individuals aged ≥65 years remain scarce.

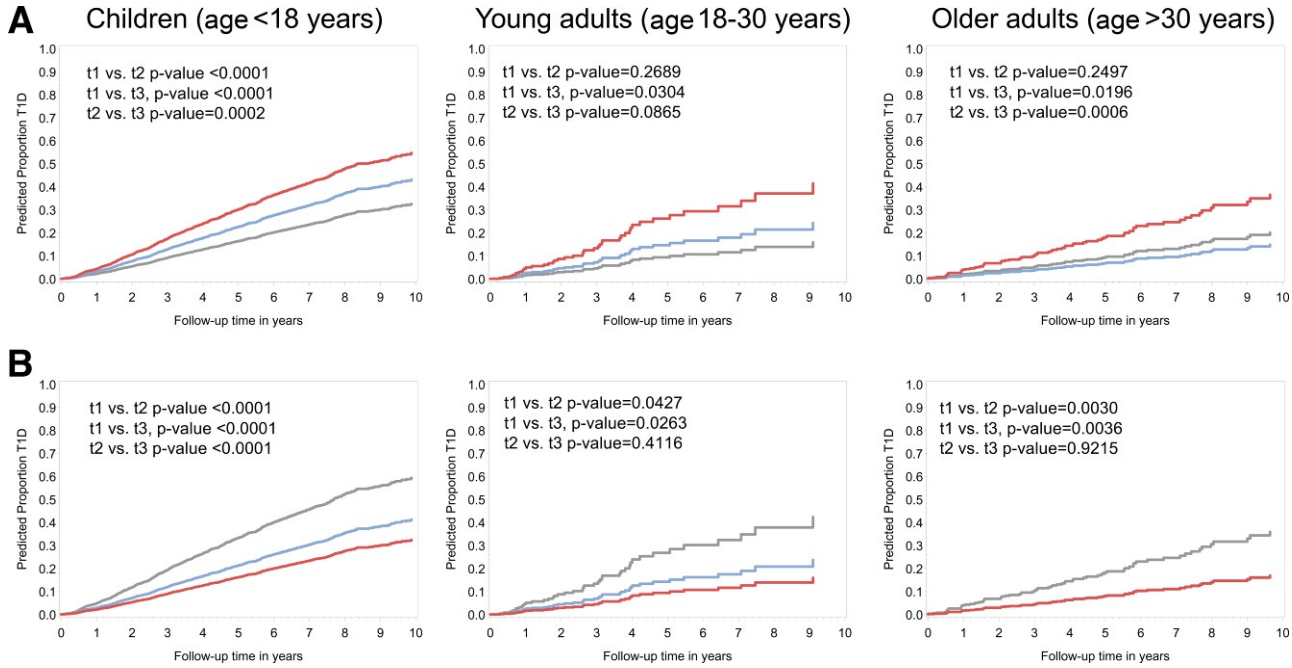


Figure 2—Predicted cumulative incidence of type 1 diabetes over time (years) by tertiles of baseline HOMA-IR (*A*) and Matsuda index (*B*) based on a Cox regression with adjustment for Index60 and age (curves based on median values of Index60 = 0.04). *A*: HOMA-IR tertile 1 (t1), gray; tertile 2, blue; tertile 3, red. *B*: Matsuda index tertile 1, gray; tertile 2, blue; tertile 3, red.

At present, these observations are best interpreted as representing an age-related phenotype within a continuous etiopathological spectrum rather than a distinct age-specific endotype. Moreover, part of the heterogeneity reported in adult cohorts likely reflects misclassification inherent to clinically defined populations. When adult-onset type 1 diabetes is rigorously defined using biochemical markers, many qualitative differences in comparison with childhood-onset disease become less pronounced, suggesting that age-related variation is largely quantitative rather than mechanistically distinct.

This conceptual distinction has clinical relevance. Adult-onset disease arises in a biological context shaped by immune remodeling, inflammaging, and greater insulin resistance, whereas individuals with long-standing childhood-onset disease who reach older age carry the cumulative consequences of prolonged β-cell loss and decades of insulin exposure. These differing biological trajectories help explain why age at onset and disease duration confer distinct vulnerabilities in later life, influencing risks of frailty, hypoglycemia, cognitive decline, and therapeutic priorities. Recognizing this continuum is essential to guiding individualized management strategies across the lifespan.

CLINICAL MANAGEMENT OF TYPE 1 DIABETES IN OLDER ADULTS IRRESPECTIVE OF ONSET AGE

Of all people living with type 1 diabetes, 15% are aged ≥65 years and 2.8% ≥80 years (21,52). Chronological age alone should not guide clinical decision-making in later life. Many older adults retain good cognitive and physical function and should be offered best practice management. However, consideration is needed of interaction of current age, diagnosis age, disease duration, and comorbidities (2). Although evidence on the relationship between older age at onset and long-term outcomes remains limited, representing an important knowledge gap, individuals diagnosed with type 1 diabetes in adulthood typically reach older age with a shorter duration of disease and therefore have had less time to develop diabetes-related complications, although they may have accumulated other comorbidities unrelated to diabetes. In contrast, those with long-standing childhood-onset type 1 diabetes who are now reaching older age are more likely to present with comorbidities arising from prolonged insulin deficiency and lifetime exposure to hypoglycemia, particularly among those diagnosed before the advent of more modern diabetes management approaches (53). Type 1 diabetes self-management becomes increasingly complex in the presence of age-related comorbidities and a decline in physical and cognitive health, not least the ability to continue to independently self-manage. Although there is no universal definition of frailty, it is closely associated with these changes and can contribute to shifting treatment priorities.

In older adults with preserved functional status, management will largely follow local best practice. Therefore, the following section focuses on key considerations for older adult type 1 diabetes management where age-related comorbidities are present, summarizes current guidance, and highlights critical priorities for future research.

Impact of Frailty on Managing Type 1 Diabetes

Frailty is a highly heterogeneous concept, with individual circumstances and needs differing and evolving over time. Two distinct concepts of frailty exist:

1. Increased vulnerability to stressors because of decreased physiological reserve, causing limited capacity to maintain homeostasis (e.g., in type 1 diabetes managing hyperglycemia and avoiding hypoglycemia). Assessments incorporating this concept include the Fried Frailty Phenotype; the Fatigue, Resistance, Ambulation, Illnesses, and Loss of Weight (FRAIL) scale; and the Short Physical Performance Battery (94).
2. Accumulation of "deficits" that can lead to poor clinical outcomes, thus incorporating functional status (e.g., capacity for self-management). The Rockwood Clinical Frailty Scale, Lawton Instrumental Activities of Daily Living, and Barthel Index for Activity of Daily Living scores incorporate this concept (95).

There is not yet consensus on which tool(s) to use to identify frailty in type 1 diabetes, even though incorporation of frailty into management discussions and decisions is essential.

Cognitive Decline

Type 1 diabetes is a recognized risk factor for dementia, with a recent meta-analysis reporting ∼50% higher risk among those with type 1 diabetes compared with risk for those without diabetes (96). Cognitive decline can impact many aspects of diabetes management, e.g., absorbing new information or skills (such as incorporating alterations to insulin regimens or using continuous glucose monitoring [CGM] or pumps). Missed or mistakenly repeated insulin doses can occur in the context of cognitive impairment, and cognitive decline further complicates recognition and management of hypoglycemia. Dementia increases both the likelihood of hypoglycemia and the risk of serious consequences such as falls and fractures (53,97), while recurrent hypoglycemia can in turn further impair cognition (98). Finally, episodes of delirium may precipitate an acute deterioration in glycemic control, or, conversely, arise because of poor glucose regulation.

Physical Challenges

Declines in dexterity and vison and tremors may impair glucose checking, insulin administration, hypoglycemia treatment, sensor application, and use of CGM or pump controls (99), while hearing loss may compromise CGM alarm detection (100). Sarcopenia can impair insulin sensitivity, thus affecting insulin requirements, while also increasing risks associated with falls (101). Reduced mobility can add an additional risk in responding to hypoglycemia and affect attendance at appointments. Although remote reviews can reduce travel risks, communication challenges can make such interactions less constructive. Health care professionals should be aware of this and make proactive efforts to ensure reviews are high quality; how best to do this remains unclear (102).

Specific Management Considerations in the Context of Frailty

Glycemic Targets and Objectives of Management

Impaired counterregulation mechanisms with advancing age and longer disease duration add to the well-recognized risks of hypoglycemia in tight glycemic control. In older adults, hypoglycemia avoidance is often prioritized for safety reasons,

although patients long-standing appreciation of the value of tight glycemic control can sometimes be difficult to alter. Many aspects of frailty, physical or cognitive, may increase further risk of hypoglycemia. Although guidelines now recommend assessing frailty in older adults with diabetes, there is little consensus on the tools applied, with investigators in a recent scoping review finding that no studies specifically addressed frailty in type 1 diabetes (98,103), and no specific guidance for glucose targets in frail individuals with type 1 diabetes exists.

Most existing recommendations for modifications of targets in the context of frailty are focused on type 2 diabetes and consensus rather than evidence based (103). However, due to the lack of specific guidance for type 1 diabetes, these recommendations are often extrapolated to adults with type 1 diabetes. This represents a critical research gap, as glucose variability, and therefore the risks of DKA and hypoglycemia, is substantially greater in type 1 diabetes.

Where possible, glycemic targets should be discussed with patients and caregivers and individualized according to frailty, comorbidities, and hypoglycemia history. Some guidance suggests HbA_{1c} targets up to 8.5% (69 mmol/mol) for frail individuals, although higher levels may be required to avoid hypoglycemia (104).

Recent guidelines have advocated use of CGM in all adults with type 1 diabetes (105). In older adults uptake and use have been slower to establish but arguably may confer the greatest benefit, and use of CGM is likely to have a significant impact on the identifiable challenges and issues going forward. With increased uptake of CGM in this population, expert discussions have moved more toward consideration of the concepts of "time in range" and avoidance of hypoglycemia rather than HbA_{1c} targets per se (106). Given high glucose variability in many people with type 1 diabetes, this approach may ultimately be safer but still carries the risks of hyperglycemia, including dehydration, infection, and DKA. Ketone testing is often recommended when capillary blood glucose exceeds 15 mmol/L, and clear guidance is needed for result interpretation and management (104). However, incorporating additional self-management steps can be challenging at any stage of life, and particularly in the context of frailty. Establishing patient priorities and incorporating into research use of patient-reported outcome measures are also vital, and again, underresearched, in frailty.

Insulin Regimens

For reasons previously discussed, traditional multiple daily injections or continuous subcutaneous insulin infusion regimens can become unachievable in the context of frailty. Nutritional intake is frequently variable or poor, which also makes insulin dosing additionally challenging. Evidence to guide simplified insulin strategies in frail individuals is scarce, leaving decisions to clinician experience, patient preference, and practical considerations such as once- or twice-daily community nursing visits. Expert opinion suggests approaches such as reducing bolus doses so that most insulin is basal and giving fixed bolus doses after meals to mitigate for unfinished food (104). Although sometimes necessary, managing severe insulin deficiency when an individual is on once-daily basal insulin alone is extremely challenging: hyperglycemia is common, and frequent glucose monitoring and snacks are often required to prevent hypoglycemia.

Technology

Many international guidelines advocate for CGM use for older adults with type 1 diabetes, and limited data suggest that it can reduce hypoglycemia, improve well-being, and lessen diabetes-related distress (98,103). Sharing CGM data with health care staff enables remote reviews, reduces hospital visits, and can improve glycemic management. However, effective data sharing depends on access to appropriate technology. Many systems require manual downloads or automatic cloud upload via a smartphone, tools that some older or frail adults may not own or be comfortable using. Additionally, Wi-Fi may be unavailable in residential facilities, and mobile data coverage can be unreliable, particularly in rural areas, limiting the feasibility of remote monitoring.

Smart insulin pens can support patients and caregivers in the management of type 1 diabetes via recording insulin administration in real time, helping to prevent missed or duplicate doses. Retrospective dosing data can aid in interpreting unexpected episodes of hypo- or hyperglycemia. Additionally, some devices can be integrated with dosing algorithms to further optimize insulin management.

Insulin pumps may be a potential option for managing type 1 diabetes in the context of frailty. Pump technology has advanced from stand-alone pumps through sensor-augmented devices to automated insulin delivery (AID) systems, currently favored given their improved glycemic outcomes. While some studies of AID systems include older adults, frail participants are almost universally excluded (104). Potential challenges of AID use in older adults include risk of device removal in the context of cognitive impairment and the exclusive use of rapid-acting insulin, which increases vulnerability to rapid-onset DKA if insulin delivery is interrupted. Robust evidence on the benefits, risks, and cost-effectiveness of AID in older adults, particularly those living with frailty, is urgently needed. Long-duration diabetes or cognitive impairment may also reduce individuals' confidence in AID systems, leading to difficulties in trusting automated algorithms and a greater tendency to override them. It remains unclear whether standalone pumps or sensor-augmented pump therapy may be preferable in such situations, or whether efforts should instead be focused on supporting adaptation to AID systems (102).

Support With Daily Diabetes Management

Long-standing (often >50 years) self-management of a highly complex condition cannot easily be transferred to others, and understandably significant fear and anxiety may exist around potentially relinquishing self-care as physical or cognitive frailty develops (102). Family members or carers can have limited knowledge of type 1 diabetes management, including sick day rules. District nurse visits may not always coincide with meals (e.g., to support with insulin administration), and are usually limited to twice or even once daily, further restricting management options. In care homes, challenges include limited staff awareness of type 1 diabetes or technologies, involvement of multiple caregivers, and the need for care plans that support recognition and management of hypoglycemia and DKA (104,107).

Secondary Prevention of Related Risks

The comorbidity and complication risk associated with type 1 diabetes makes polypharmacy common. This carries potential harms, including drug interactions, side effects, reduced adherence, and, in older adults, increased risk of falls (108). Regular medication review and deescalation where possible are therefore essential; e.g., antihypertensive therapies affecting the

Table 2—Considerations for management of type 1 diabetes in older adults in specific scenarios

Situation	Unmet need
Frailty	A simple, effective screening and assessment tool to identify individuals with frailty and enable personalized care
Glucose targets	Frailty-specific type 1 diabetes glycemic targets balancing risks of DKA and hypoglycemia while incorporating patient priorities
Insulin regimens	Optimal Alternative insulin regimens, particularly for when insulin is administered by a caregiver
Glucose monitoring	Optimization of supervision and response to CGM data when required
AID	Safe use of AID systems and mitigation strategies, including role of combinations with low-dose basal insulin
Diabetes care provision	Training and support for caregivers and optimal approaches to remote diabetes care delivery
Impact of age of onset	Understanding distinct management needs in older adults with long-standing childhood-onset type 1 diabetes vs. in the case of later-onset disease

renin-angiotensin system can exacerbate hypoglycemia by increasing insulin sensitivity (109). Evidence suggests no additional benefit from lowering systolic blood pressure <140 mmHg, while diastolic levels <70 mmHg are associated with increased mortality. Statins are generally indicated in older adults with type 1 diabetes, though their use should be reconsidered when life expectancy is limited (110). Considerations and key research priorities for managing type 1 diabetes in older adults across specific clinical scenarios are summarized in Table 2.

CONCLUSIONS

Type 1 diabetes diagnosed after age 30 years is increasingly recognized yet remains substantially less well defined than its childhood-onset counterpart. Across epidemiology, genetics, immune mechanisms, and clinical presentation, evidence indicates age-related variation during the preclinical phases, with more convergent features once individuals reach stage 2. Adult-onset type 1 diabetes develops within a biological context shaped by immune remodeling, inflammaging, metabolic stress, and structural pancreatic changes, suggesting a constellation of features consistent with an age-related phenotype. The question of whether this represents a discrete endotype or the late-life expression of broader disease heterogeneity remains unresolved. Current evidence does not support the definition of a discrete adult- or older adult–specific endotype. Instead, many reported differences across ages appear to arise from the interaction of immune aging, metabolic modifiers, and frequent misclassification in clinically defined adult cohorts.

Importantly, age at onset and disease duration represent distinct dimensions that shape vulnerability later in life. Individuals with adult-onset type 1 diabetes reach older age with a shorter duration of autoimmune disease but greater influence of metabolic modifiers such as insulin resistance, whereas those with childhood-onset disease aging into later life carry the cumulative consequences of decades of insulin deficiency and hypoglycemia exposure. These differing trajectories have direct implications for risks of frailty, cognitive decline, and functional impairment and should inform individualized management strategies.

While frailty and multimorbidity represent important challenges in older adults, many people aged ≥65 years years with type 1 diabetes remain cognitively intact and functionally independent, achieving good outcomes, particularly with the support of modern diabetes technologies. Clinical management should therefore be guided not by chronological age alone but by the interaction of current age, age at onset, disease duration, comorbidities, and functional status. Consensus on a tool to recognize frailty in type 1 diabetes is urgently needed to aid clinical management as well as for consistency in research approaches for this understudied population.

The prospect of pre–type 1 diabetes screening in adults is under active discussion (111,112). While expert consensus (113) supports population-based screening in children, how and whether to extend this strategy to adults remains uncertain. Screening in older adults could help prevent symptomatic onset and improve understanding of preclinical disease, but key questions remain regarding optimal timing, expected benefit, and implementation. The preclinical course in this population is poorly defined, and the balance of benefit and risk is likely to vary depending on frailty, comorbidities, and life expectancy. Careful evaluation of cost-effectiveness and psychological impact is essential before widespread adoption.

Given the substantial burden and frequent misclassification of diabetes in adults, prioritizing the development and validation of diagnostic algorithms that accurately distinguish type 1 from type 2 diabetes is essential, as is designing prevention and disease-modifying trials specifically tailored to adults across the lifespan. Addressing these gaps will be critical to advancing precision prediction, prevention, and care across the lifespan. Furthermore, despite growing recognition of adult-onset and older adult type 1 diabetes, substantial knowledge gaps remain in both disease pathogenesis and clinical management. Closing these gaps should be a priority to inform evidence-based classification, optimize care strategies, and guide future therapeutic and preventive interventions in this expanding population.

Acknowledgments. The authors acknowledge David Cuthbertson, Health Informatics Institute, University of South Florida, Tampa, FL, for providing the data shown in Fig. 2.

Funding. A.P. is supported by Breakthrough T1D (1-FAC-2025-1632-A-N) and The Leona M. and Harry B. Helmsley Charitable Trust (G-2507-08409). N.J.T. is supported by a University of Exeter National Institute for Health and Care Research Clinical Lectureship Match funding scheme, funded by a philanthropic donation by the Gillings Foundation.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Handling Editors. The journal editors responsible for overseeing the review of the manuscript were Steven E. Kahn and Jennifer B. Green.

References

1. Bluestone JA, Herold K, Eisenbarth G. Genetics, pathogenesis and clinical interventions in type 1 diabetes. Nature 2010;464:1293–1300

2. Thomas NJ, Jones SE, Weedon MN, Shields BM, Oram RA, Hattersley AT. Frequency and phenotype of type 1 diabetes in the first six decades of life: a cross-sectional, genetically stratified survival analysis from UK Biobank. Lancet Diabetes Endocrinol 2018;6:122–129
3. American Diabetes Association Professional Practice Committee. 13. Older adults: Standards of Care in Diabetes—2025. Diabetes Care 2025; 48(Suppl. 1):S266–S282
4. Sabbah E, Savola K, Ebeling T, et al. Genetic, autoimmune, and clinical characteristics of childhood- and adult-onset type 1 diabetes. Diabetes Care 2000;23:1326–1332
5. Thomas NJ, Jones AG. The challenges of identifying and studying type 1 diabetes in adults. Diabetologia 2023;66:2200–2212
6. Jones AG, McDonald TJ, Shields BM, Hagopian W, Hattersley AT. Latent autoimmune diabetes of adults (LADA) is likely to represent a mixed population of autoimmune (type 1) and nonautoimmune (type 2) diabetes. Diabetes Care 2021; 44:1243–1251
7. Lynam A, McDonald T, Hill A, et al. Development and validation of multivariable clinical diagnostic models to identify type 1 diabetes requiring rapid insulin therapy in adults aged 18-50 years. BMJ Open 2019;9:e031586
8. Lynam AL, Dennis JM, Owen KR, et al. Logistic regression has similar performance to optimised machine learning algorithms in a clinical setting: application to the discrimination between type 1 and type 2 diabetes in young adults. Diagn Progn Res 2020;4:6
9. Bradley D, Hsueh W. Type 2 diabetes in the elderly: challenges in a unique patient population. J Geriatr Med Gerontol 2016;2:14
10. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in underweight and obesity from 1990 to 2022: a pooled analysis of 3663 population-representative studies with 222 million children, adolescents, and adults. Lancet 2024;403: 1027–1050
11. Van der Schueren B, Ellis D, Faradji RN, Al-Ozairi E, Rosen J, Mathieu C. Obesity in people living with type 1 diabetes. Lancet Diabetes Endocrinol 2021;9:776–785
12. Lalanne-Mistrih M-L, Bonhoure A, Messier V, et al. Overweight and obesity in people living with type 1 diabetes: a cross-sectional analysis of the BETTER registry. Diabetes Metab Res Rev 2024;40:e3837
13. Foteinopoulou E, Clarke CAL, Pattenden RJ, et al. Impact of routine clinic measurement of serum C-peptide in people with a clinician-diagnosis of type 1 diabetes. Diabet Med 2021;38:e14449
14. Thomas NJ, Lynam AL, Hill AV, et al. Type 1 diabetes defined by severe insulin deficiency occurs after 30 years of age and is commonly treated as type 2 diabetes. Diabetologia 2019; 62:1167–1172
15. Muñoz C, Floreen A, Garey C, et al. Misdiagnosis and diabetic ketoacidosis at diagnosis of type 1 diabetes: patient and caregiver perspectives. Clin Diabetes 2019;37:276–281
16. Holt RIG, DeVries JH, Hess-Fischl A, et al. The management of type 1 diabetes in adults. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2021;44:2589–2625
17. Medicines and Healthcare products Regulatory Agency. GLP-1 Receptor Agonists: Reports of Diabetic Ketoacidosis When Concomitant Insulin Was Rapidly Reduced or Discontinued. GOV.UK, 2019. Accessed 15 January 2026. Available from https://www.gov.uk/drug-safety-update/glp-1-receptor-agonists-reports-of-diabetic-ketoacidosis-when-concomitant-insulin-was-rapidly-reduced-or-discontinued
18. Musso G, Saba F, Cassader M, Gambino R. Diabetic ketoacidosis with SGLT2 inhibitors. BMJ 2020;371:m4147
19. Ahlqvist E, Storm P, Käräjämäki A, et al. Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables. Lancet Diabetes Endocrinol 2018;6:361–369
20. Mayer-Davis EJ, Lawrence JM, Dabelea D, et al.; SEARCH for Diabetes in Youth Study. Incidence trends of type 1 and type 2 diabetes among youths, 2002-2012. N Engl J Med 2017;376:1419–1429
21. Yang K, Yang X, Jin C, et al. Global burden of type 1 diabetes in adults aged 65 years and older, 1990-2019: population based study. BMJ 2024;385: e078432
22. Niechcial E, Rogowicz-Frontczak A, Piłaciński S, et al. Autoantibodies against zinc transporter 8 are related to age and metabolic state in patients with newly diagnosed autoimmune diabetes. Acta Diabetol 2018;55:287–294
23. Thomas NJ, Hill AV, Dayan CM, et al.; StartRight Study Group. Age of diagnosis does not alter the presentation or progression of robustly defined adult-onset type 1 diabetes. Diabetes Care 2023;46:1156–1163
24. Shields BM, McDonald TJ, Oram R, et al. C-peptide decline in type 1 diabetes has two phases: An initial exponential fall and a subsequent stable phase. Diabetes Care 2018; 41:1486–1492
25. Insel RA, Dunne JL, Atkinson MA, et al. Staging presymptomatic type 1 diabetes: a scientific statement of JDRF, the Endocrine Society, and the American Diabetes Association. Diabetes Care 2015; 38:1964–1974
26. Gillespie KM, Long AE. What have slow progressors taught us about T1D-mind the gap! Curr Diab Rep 2019;19:99
27. Pauley ME, Simmons KM, Dong F, et al. Prevalence of islet autoantibodies in adults without diabetes. J Endocr Soc 2025;9:bvaf095
28. Urrutia I, Martinez R, Calvo B, et al.; Collaborative Working Group. Risk for progression to type 1 diabetes in first-degree relatives under 50 years of age. Front Endocrinol (Lausanne) 2024; 15:1411686
29. Ziegler AG, Rewers M, Simell O, et al. Seroconversion to multiple islet autoantibodies and risk of progression to diabetes in children. JAMA 2013;309:2473–2479
30. Rewers M, Agardh D, Bennett Johnson S, et al.; TEDDY Study Group. Unfolding the mystery of autoimmunity: The Environmental Determinants of Diabetes in the Young (TEDDY) study. Diabetes Care 2025;48:1125–1135
31. Bosi E, Boulware DC, Becker DJ, et al.; Type 1 Diabetes TrialNet Study Group. Impact of age and antibody type on progression from single to multiple autoantibodies in type 1 diabetes relatives. J Clin Endocrinol Metab 2017;102:2881–2886
32. Bingley PJ, Wherrett DK, Shultz A, Rafkin LE, Atkinson MA, Greenbaum CJ. Type 1 Diabetes TrialNet: a multifaceted approach to bringing disease-modifying therapy to clinical use in type 1 diabetes. Diabetes Care 2018;41:653–661
33. Templeman EL, Ferrat LA, Parikh HM, et al.; Type 1 diabetes TrialNet Study Group. Development and recalibration of a multivariable type 1 diabetes prediction model for type 1 diabetes across multiple screening studies. BMC Med 2025;23:433
34. Sims EK, Cuthbertson D, Ferrat LA, et al. IA-2A positivity increases risk of progression within and across established stages of type 1 diabetes. Diabetologia 2025;68:993–1004
35. Ferrannini E, Mari A, Monaco GSF, Skyler JS, Evans-Molina C. The effect of age on longitudinal measures of beta cell function and insulin sensitivity during the progression of early stage type 1 diabetes. Diabetologia 2023;66:508–519
36. Marcovecchio ML, Hendriks AEJ, Delfin C, et al.; INNODIA consortium. The INNODIA Type 1 Diabetes Natural History Study: a European cohort of newly diagnosed children, adolescents and adults. Diabetologia 2024;67:995–1008
37. Murrall K, Luckett T, Lekka C, et al.; EXE-T1D Consortium. Small things matter: lack of extraislet β cells in type 1 diabetes. Sci Adv 2025;11: eadz2251
38. Hao W, Gitelman S, DiMeglio LA, Boulware D, Greenbaum CJ; Type 1 Diabetes TrialNet Study Group. Fall in C-peptide during first 4 years from diagnosis of type 1 diabetes: variable relation to age, HbA_{1c}, and insulin dose. Diabetes Care 2016; 39:1664–1670
39. Templeman EL, Ferrat LA, Thomas N, et al. Contrasting adult and pediatric populations in a cohort of at-risk relatives in the T1D TrialNet Pathway to Prevention Study. Diabetes Care 2025; 48:1571–1580
40. Redondo MJ, Yu L, Hawa M, et al. Heterogeneity of type I diabetes: analysis of monozygotic twins in Great Britain and the United States. Diabetologia 2001;44:354–362
41. Kumar D, Gemayel NS, Deapen D, et al. North-American twins with IDDM: genetic, etiological, and clinical significance of disease concordance according to age, zygosity, and the interval after diagnosis in first twin. Diabetes 1993;42:1351–1363
42. Howson JMM, Rosinger S, Smyth DJ, Boehm BO; ADBW-END Study Group; Todd JA. Genetic analysis of adult-onset autoimmune diabetes. Diabetes 2011;60:2645–2653
43. Petrone A, Galgani A, Spoletini M, et al. Residual insulin secretion at diagnosis of type 1 diabetes is independently associated with both, age of onset and HLA genotype. Diabetes Metab Res Rev 2005;21:271–275
44. Tait BD, Harrison LC, Drummond BP, Stewart V, Varney MD, Honeyman MC. HLA antigens and age at diagnosis of insulin-dependent diabetes mellitus. Hum Immunol 1995;42:116–122
45. Graham J, Kockum I, Sanjeevi CB, et al. Negative association between type 1 diabetes and HLA DQB1*0602-DQA1*0102 is attenuated with age at onset. Swedish Childhood Diabetes Study Group. Eur J Immunogenet 1999;26: 117–127
46. McKeigue PM, Spiliopoulou A, McGurnaghan S, et al. Persistent C-peptide secretion in type 1 diabetes and its relationship to the genetic architecture of diabetes. BMC Med 2019;17:165
47. Thomas NJ, Dennis JM, Sharp SA, et al. DR15-DQ6 remains dominantly protective against

type 1 diabetes throughout the first five decades of life. Diabetologia 2021;64:2258–2265
48. Thomas NJ, Walkey HC, Kaur A, et al. The relationship between islet autoantibody status and the genetic risk of type 1 diabetes in adult-onset type 1 diabetes. Diabetologia 2023;66:310–320
49. Vermeulen I, Weets I, Asanghanwa M, et al.; The Belgian Diabetes Registry. Contribution of antibodies against IA-2β and zinc transporter 8 to classification of diabetes diagnosed under 40 years of age. Diabetes Care 2011;34:1760–1765
50. Luo S, Li X, Huang G, et al. Distinct two different ages associated with clinical profiles of acute onset type 1 diabetes in Chinese patients. Diabetes Metab Res Rev 2020;36:e3209
51. Eason RJ, Thomas NJ, Hill AV, et al.; StartRight Study Group. Routine islet autoantibody testing in clinically diagnosed adult-onset type 1 diabetes can help identify misclassification and the possibility of successful insulin cessation. Diabetes Care 2022;45:2844–2851
52. Rogowicz-Frontczak A, Pilacinski S, Wyka K, Wierusz-Wysocka B, Zozulinska-Ziolkiewicz D. Zinc transporter 8 autoantibodies (ZnT8-ab) are associated with higher prevalence of multiple diabetes-related autoantibodies in adults with type 1 diabetes. Diabetes Res Clin Pract 2018;146:313–320
53. Leslie RD, Evans-Molina C, Freund-Brown J, et al. Adult-onset type 1 diabetes: current understanding and challenges. Diabetes Care 2021;44:2449–2456
54. Bradshaw EM, Raddassi K, Elyaman W, et al. Monocytes from patients with type 1 diabetes spontaneously secrete proinflammatory cytokines inducing Th17 cells. J Immunol 2009;183:4432–4439
55. Arif S, Leete P, Nguyen V, et al. Blood and islet phenotypes indicate immunological heterogeneity in type 1 diabetes. Diabetes 2014;63:3835–3845
56. Arif S, Tree TI, Astill TP, et al. Autoreactive T cell responses show proinflammatory polarization in diabetes but a regulatory phenotype in health. J Clin Invest 2004;113:451–463
57. Kent SC, Chen Y, Bregoli L, et al. Expanded T cells from pancreatic lymph nodes of type 1 diabetic subjects recognize an insulin epitope. Nature 2005;435:224–228
58. McKinney EF, Lee JC, Jayne DRW, Lyons PA, Smith KGC. T-cell exhaustion, co-stimulation and clinical outcome in autoimmunity and infection. Nature 2015;523:612–616
59. Franceschi C, Garagnani P, Parini P, Giuliani C, Santoro A. Inflammaging: a new immune-metabolic viewpoint for age-related diseases. Nat Rev Endocrinol 2018;14:576–590
60. Wong FS, Wen L. A predictive $CD8^+$ T cell phenotype for T1DM progression. Nat Rev Endocrinol 2020;16:198–199
61. Yang K, Zhang Y, Ding J, Li Z, Zhang H, Zou F. Autoimmune CD8+ T cells in type 1 diabetes: from single-cell RNA sequencing to T-cell receptor redirection. Front Endocrinol (Lausanne) 2024;15:1377322
62. Cisneros B, García-Aguirre I, Unzueta J, et al. Immune system modulation in aging: molecular mechanisms and therapeutic targets. Front Immunol 2022;13:1059173
63. Moro-García MA, Alonso-Arias R, López-Larrea C. When aging reaches CD4+ T-cells: phenotypic and functional changes. Front Immunol 2013;4:107
64. Zhang H, Weyand CM, Goronzy JJ. Hallmarks of the aging T-cell system. FEBS J 2021;288:7123–7142
65. Durinovic-Belló I, Jelinek E, Schlosser M, et al. Class III alleles at the insulin VNTR polymorphism are associated with regulatory T-cell responses to proinsulin epitopes in HLA-DR4, DQ8 individuals. Diabetes 2005;54(Suppl. 2):S18–S24
66. Nakayama M, Beilke JN, Jasinski JM, et al. Priming and effector dependence on insulin B:9-23 peptide in NOD islet autoimmunity. J Clin Invest 2007;117:1835–1843
67. Danke NA, Yang J, Greenbaum C, Kwok WW. Comparative study of GAD65-specific CD4+ T cells in healthy and type 1 diabetic subjects. J Autoimmun 2005;25:303–311
68. Leete P, Willcox A, Krogvold L, et al. Differential insulitic profiles determine the extent of β-cell destruction and the age at onset of type 1 diabetes. Diabetes 2016;65:1362–1369
69. Richardson SJ, Pugliese A. 100 YEARS OF INSULIN: pancreas pathology in type 1 diabetes: an evolving story. J Endocrinol 2021;252:R41–R57
70. In't Veld P. Insulitis in human type 1 diabetes: the quest for an elusive lesion. Islets 2011;3:131–138
71. Wedgwood KCA, Richardson SJ, Morgan NG, Tsaneva-Atanasova K. Spatiotemporal dynamics of insulitis in human type 1 diabetes. Front Physiol 2016;7:633
72. Rodriguez-Calvo T, Ekwall O, Amirian N, Zapardiel-Gonzalo J, von Herrath MG. Increased immune cell infiltration of the exocrine pancreas: a possible contribution to the pathogenesis of type 1 diabetes. Diabetes 2014;63:3880–3890
73. Campbell-Thompson ML, Filipp SL, Grajo JR, et al. Relative pancreas volume is reduced in first-degree relatives of patients with type 1 diabetes. Diabetes Care 2019;42:281–287
74. Kattner N. Immune cell infiltration in the pancreas of type 1, type 2 and type 3c diabetes. Ther Adv Endocrinol Metab 2023;14:20420188231185958
75. Giovenzana A, Vecchio F, Cugnata F, et al. Exocrine pancreas function is impaired in adult relatives of patients with type 1 diabetes. Acta Diabetol 2022;59:473–479
76. Vecchio F, Messina G, Giovenzana A, Petrelli A. New evidence of exocrine pancreatopathy in pre-symptomatic and symptomatic type 1 diabetes. Curr Diab Rep 2019;19:92
77. Bakinowska L, Vartak T, Phuthego T, et al.; Action LADA Consortium; BOX Study Group. Exocrine proteins including trypsin(ogen) as a key biomarker in type 1 diabetes. Diabetes Care 2023;46:714–721
78. Yosri M, Dokhan M, Aboagye E, Moussawy MA, Abdelsamed HA. Mechanisms governing bystander activation of T cells. Front Immunol 2024;15:1465889
79. Shoelson SE, Lee J, Goldfine AB. Inflammation and insulin resistance. J Clin Invest 2006;116:1793–1801
80. Buscemi C, Randazzo C, Barile AM, et al. Factors associated with body weight gain and insulin-resistance: a longitudinal study. Nutr Diabetes 2024;14:21
81. Ferrara-Cook C, Geyer SM, Evans-Molina C, et al.; Type 1 Diabetes TrialNet Study Group. Excess BMI accelerates islet autoimmunity in older children and adolescents. Diabetes Care 2020;43:580–587
82. Petrelli A, Cugnata F, Carnovale D, et al. HOMA-IR and the Matsuda Index as predictors of progression to type 1 diabetes in autoantibody-positive relatives. Diabetologia 2024;67:290–300
83. Wilkin TJ. The accelerator hypothesis: weight gain as the missing link between type I and type II diabetes. Diabetologia 2001;44:914–922
84. Petrelli A, Giovenzana A, Insalaco V, Phillips BE, Pietropaolo M, Giannoukakis N. Autoimmune inflammation and insulin resistance: hallmarks so far and yet so close to explain diabetes endotypes. Curr Diab Rep 2021;21:54
85. Gale EAM. To boldly go–or to go too boldly? The accelerator hypothesis revisited. Diabetologia 2007;50:1571–1575
86. Foster NC, Beck RW, Miller KM, et al. State of type 1 diabetes management and outcomes from the T1D Exchange in 2016-2018. Diabetes Technol Ther 2019;21:66–72
87. Rawshani A, Sattar N, Franzén S, et al. Excess mortality and cardiovascular disease in young adults with type 1 diabetes in relation to age at onset: a nationwide, register-based cohort study. Lancet 2018;392:477–486
88. Battaglia M, Ahmed S, Anderson MS, et al. Introducing the endotype concept to address the challenge of disease heterogeneity in type 1 diabetes. Diabetes Care 2020;43:5–12
89. Evans-Molina C, Dor Y, Lernmark Å, et al. The heterogeneity of type 1 diabetes: implications for pathogenesis, prevention, and treatment-2024 Diabetes, Diabetes Care, and Diabetologia Expert Forum. Diabetologia 2025;68:1859–1878
90. Redondo MJ, Morgan NG. Heterogeneity and endotypes in type 1 diabetes mellitus. Nat Rev Endocrinol 2023;19:542–554
91. Weston CS, Boehm BO, Pozzilli P. Type 1 diabetes: a new vision of the disease based on endotypes. Diabetes Metab Res Rev 2024;40:e3770
92. Achenbach P, Hippich M, Zapardiel-Gonzalo J, et al.; DiMelli Study group and DPV Study group. A classification and regression tree analysis identifies subgroups of childhood type 1 diabetes. EBioMedicine 2022;82:104118
93. Codazzi V, Baldoni N, Scotti GM, et al. A multi-omics integration approach relying on circulating factors does not discern subtypes of childhood type 1 diabetes. Commun Med (Lond) 2025;5:201
94. Fried LP, Tangen CM, Walston J, et al.; Cardiovascular Health Study Collaborative Research Group. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001;56:M146–M156
95. Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173:489–495
96. Li L, Wong D, Fisher CA, et al. Increased risk of dementia in type 1 diabetes: a systematic review with meta-analysis. Diabetes Res Clin Pract 2025;222:112043
97. American Diabetes Association Professional Practice Committee. 7. Diabetes technology: *Standards of Care in Diabetes—2024*. Diabetes Care 2024;47(Suppl. 1):S126–S144
98. Golding JA, Yong EST, Hope SV, Wright JE, Levett TJ, Chakera AJ. Type 1 diabetes and frailty: a scoping review. Diabet Med 2024;41:e15344
99. Pfützner J, Hellhammer J, Musholt P, et al. Evaluation of dexterity in insulin-treated patients

with type 1 and type 2 diabetes mellitus. J Diabetes Sci Technol 2011;5:158–165
100. Mattishent K, Loke YK. Bi-directional interaction between hypoglycaemia and cognitive impairment in elderly patients treated with glucose-lowering agents: a systematic review and meta-analysis. Diabetes Obes Metab 2016;18:135–141
101. Milluzzo A, Quaranta G, Manuella L, et al. Sarcopenia in type 1 diabetes mellitus: a systematic review. Diabetes Res Clin Pract 2025;227:112399
102. Wylie TAF, Morris A, Robertson E, et al. Ageing well with diabetes: a workshop to co-design research recommendations for improving the diabetes care of older people. Diabet Med 2022; 39:e14795
103. Strain WD, Hope SV, Green A, Kar P, Valabhji J, Sinclair AJ. Type 2 diabetes mellitus in older people: a brief statement of key principles of modern day management including the assessment of frailty. A national collaborative stakeholder initiative. Diabet Med 2018;35:838–845
104. Brooks A, Chakera AJ. The challenge of managing type 1 diabetes in frail older people. Diabet Med 2019;36:453–456
105. American Diabetes Association Professional Practice Committee. 7. Diabetes technology: Standards of Care in Diabetes—2025. Diabetes Care 2025;48(Suppl. 1):S146–S166
106. Wilson A, Morrison D, Sainsbury C, Jones G. Narrative review: continuous glucose monitoring (CGM) in older adults with diabetes. Diabetes Ther 2025;16:1139–1154
107. Sinclair AJ; Task and Finish Group of Diabetes UK. Good clinical practice guidelines for care home residents with diabetes: an executive summary. Diabet Med 2011;28:772–777
108. Bispham JA, Hughes AS, Driscoll KA, McAuliffe-Fogarty AH. Novel challenges in aging with type 1 diabetes. Curr Diab Rep 2020;20:15
109. Morris AD, Boyle DI, McMahon AD, et al.; The Darts/Memo Collaboration. ACE inhibitor use is associated with hospitalization for severe hypoglycemia in patients with diabetes. DARTS/MEMO Collaboration. Diabetes Audit and Research in Tayside, Scotland. Medicines Monitoring Unit. Diabetes Care 1997;20:1363–1367
110. Kilvert A, Fox C. Diagnosis and management of diabetes in older people. Pract Diab 2017;34: 195–199
111. Phillip M, Achenbach P, Addala A, et al. Consensus guidance for monitoring individuals with islet autoantibody–positive pre-stage 3 type 1 diabetes. Diabetes Care 2024;47:1276–1298
112. Thomas N, Tatovic D, Jones A, Narendran P. Managing adults with screen-detected islet autoantibody positivity: a pragmatic framework. Lancet Diabetes Endocrinol 2025;13:980–986
113. Haller MJ, Bell KJ, Besser REJ, et al. ISPAD clinical practice consensus guidelines 2024: screening, staging, and strategies to preserve beta-cell function in children and adolescents with type 1 diabetes. Horm Res Paediatr 2024; 97:529–545