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Clinical and laboratory characteristics of novel diabetes subgroups: A systematic review and meta-analysis

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Proper classification of diabetes enhances accurate diagnosis and tailored management, and recent researchers introduce an innovative subgroup classification for adult diabetes. This study aims to evaluate the attributes of these novel diabetes subgroups. We conducted a systematic search across MEDLINE, Embase, and the Cochrane Library, focusing on the characteristics of novel diabetes subgroups. These included mild age-related diabetes (MARD), mild obesity-related diabetes (MOD), severe insulin-resistant diabetes (SIRD), severe insulin-deficient diabetes (SIDD), severe autoimmune diabetes (SAID), severe insulin-deficient and insulin-resistant diabetes (SIDRD), and severe obesity-related and insulin-resistant diabetes (SOIRD). Our review included 19 studies comprising 59,915 cases: 2,603 (4.34%) SAID, 14,946 (25.94%) SIDD, 9,285 (15.50%) SIRD, 13,323 (22.24%) MOD, 19,465 (32.49%) MARD, 87 (0.15%) SIDRD, and 206 (0.34%) SOIRD cases. The SIDD subgroup exhibited a reduced homeostatic model assessment of β-cell function. Both SIDRD and SIDD subgroups demonstrated elevated levels of HbA1c. Subgroups SIRD and MARD had decreased eGFR levels, correlating with a higher incidence of nephropathy. The SIRD subgroup presented the most significantly altered lipid metabolism and the highest insulin resistance. Distinct clinical and laboratory characteristics among the diabetes subgroups reveal the necessity for diverse treatment strategies. Tailored approaches are essential to effectively manage the various diabetes subtypes.

Keywords Diabetes, Classification, Clinical characteristics, Meta-analysis, Systemic review

Diabetes represents a significant global public health issue[1]. Approximately 537 million individuals worldwide were affected by diabetes in 2021, with projections suggesting an increase to 643 million by 2030. This escalating trend burdens individuals and societies considerably, particularly in low- and middle-income countries[2]. Early diagnosis and proper diabetes management are crucial for preventing or delaying the onset of various complications[3,4].

The World Health Organization (WHO, 1999) recommends an etiological classification system for diabetes mellitus, which includes four categories: type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), specific types of diabetes mellitus, and gestational diabetes mellitus. In 2024, the American Diabetes Association introduced an additional category under recommendation 2.5 to help facilitate early treatment[5] for individuals with hyperglycemia. However, this classification primarily focuses on the presence of hyperglycemia, islet-directed antibodies, and atypical clinical presentations without considering the etiology and clinical prognosis of patients.

In 2018, Ahlqvist et al. proposed a novel classification system for diabetes subgroups based on six variables: age at diagnosis, body mass index (BMI), glutamate decarboxylase antibodies (GADA), hemoglobin A1c (HbA1c), homeostatic model assessment 2 estimates of β-cell function (HOMA2-B), and insulin resistance (HOMA2-IR)[6]. This system delineates diabetes into five subgroups: mild age-related diabetes (MARD), mild obesity-related diabetes (MOD), severe autoimmune diabetes (SAID), severe insulin-resistant diabetes (SIRD), and severe insulin-deficient diabetes (SIDD). This new subgroup system has been validated by subsequent studies[7–10]. In 2022, research conducted in China introduced two additional subtypes based on 2-h postprandial blood glucose levels in middle-aged and elderly individuals: severe obesity-related and insulin-resistant diabetes (SOIRD) and severe insulin-deficient and insulin-resistant diabetes (SIDRD)[11]. Patients classified within these

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novel subgroups exhibited distinct complication progression trajectories compared to those in traditional groups, potentially enabling the development of targeted therapeutic strategies to delay or reverse diabetes progression and its related end-organ damage[12]. Despite these advancements, the clinical and laboratory characteristics of these novel subgroups have yet to be comprehensively summarized. Furthermore, diabetic populations within the Chinese community may present distinct characteristics requiring clarification.

Therefore, we performed a systemic review and meta-analysis to describe the clinical characteristics of patients categorized under the novel diabetes subgroup system, with additional analysis of Chinese diabetic patients. Our objective was to provide evidence to guide different management approaches to patients with different types of diabetes under this novel diabetic subgroup classification system.

Methods

Study protocol and registration

The study followed the preferred reporting items for systematic reviews and meta-analyses (PRISMA) checklist[13] and was registered at the International Prospective Register of Systematic Reviews (PROSPERO) with the registration number CRD42024604302.

Search strategy

Eligible studies were searched in the PubMed, Embase, and Cochrane Central Register of Controlled Trials from their inception until July 2024. A combined set of keywords was used, including "diabetes mellitus," "diabetes," "recent-onset," "novel," and "new." The strings for the database search are listed in the Supplementary Table S1.

Article eligibility criteria

The identified articles were included based on two selection criteria: (1) patient enrollment defined by a novel subgroup classification system for adult-onset diabetes and (2) patient categorization according to this classification system, which includes MARD, MOD, SAID, SIRD, SIDD, SOIRD, and SIDRD. Articles were excluded if they (1) lacked necessary data from original studies; (2) were letters, reviews, meeting abstracts, replies from authors, editorial comments, or case reports; or (3) were published in languages other than English. Only the article with the most comprehensive data was retained for duplicate publications.

Data retrieval

Two researchers independently extracted titles, abstracts, full texts, and relevant data from eligible articles using a standardized form in Microsoft Excel (Microsoft Corp. USA). Data collected included the first author's name, publication year, country of the study, number of patients, study design, and definitions of diabetes subtypes. Additionally, clinical characteristics such as age, sex, waist-to-hip ratio (WHR), BMI, fasting blood glucose (mg/dL), HbA1c, HOMA2-B, HOMA2-IR, total cholesterol (mg/dL), high-density lipoprotein (HDL)-cholesterol (mg/dL), low-density lipoprotein (LDL)-cholesterol (mg/dL), triglycerides (mg/dL), glomerular filtration rate (eGFR), and cystatin C were also documented. Any disagreements regarding article eligibility or content were resolved through open discussion within the research team.

Quality evaluation

The study quality and risk of bias assessment were conducted with the Newcastle Ottawa Scale (NOS)[14]. NOS has eight items within three domains based on the least risk of bias: (1) study group selection (four points), (2) group comparability (two points), and (3) exposure and outcome ascertainment (three points). The maximum score is 9. A study with a score of 7–9, 4–6, or 0–3 was deemed high quality, high risk, and very high risk of bias, respectively.

Statistical analysis

The effect estimate of interest was mean differences (MDs) and corresponding standard deviations. MDs from each study were combined by the random-effects mode[15]. The Cochran's Q test and Higgins's I^2 were applied to evaluate the heterogeneity of the study outcomes. An $I^2 > 50\%$ was considered a significant heterogeneity[16]. The Egger weighted regression and Begg rank correlation were used to evaluate the potential publication bias[17,18]. The study's robustness was evaluated by the sensitivity analysis to explore the potential impact of each study on the overall outcomes with the leave-one-out method, which deleted each study individually from the pooled analysis. All statistical analyses were performed in STATA 14.0 (Stata Corporation, Texas, USA). The statistically significant difference was considered for $P < 0.05$ in a two-sided test.

Results

Study selection

The search strategy and study selection process are detailed in Fig. 1. Initially, a total of 3,567 records were identified from three databases. After removing duplicates, 2,414 records remained. Subsequent reviews of titles, abstracts, and full texts led to the exclusion of studies due to incomplete information, the onset of diabetes before the age of 18 years, pregnancy or gestational diabetes, and secondary diabetes. Ultimately, 19 studies met al.l inclusion criteria and were selected for inclusion in the current meta-analysis[7–11,19–32].

Study characteristics

The characteristics of the 19 articles are listed in Table 1. There were 16 retrospective and three prospective studies from seven countries. Twelve studies included newly diagnosed diabetes. Diabetes was defined according to the WHO 1999 criteria, American Diabetes Association criteria, or European classification.

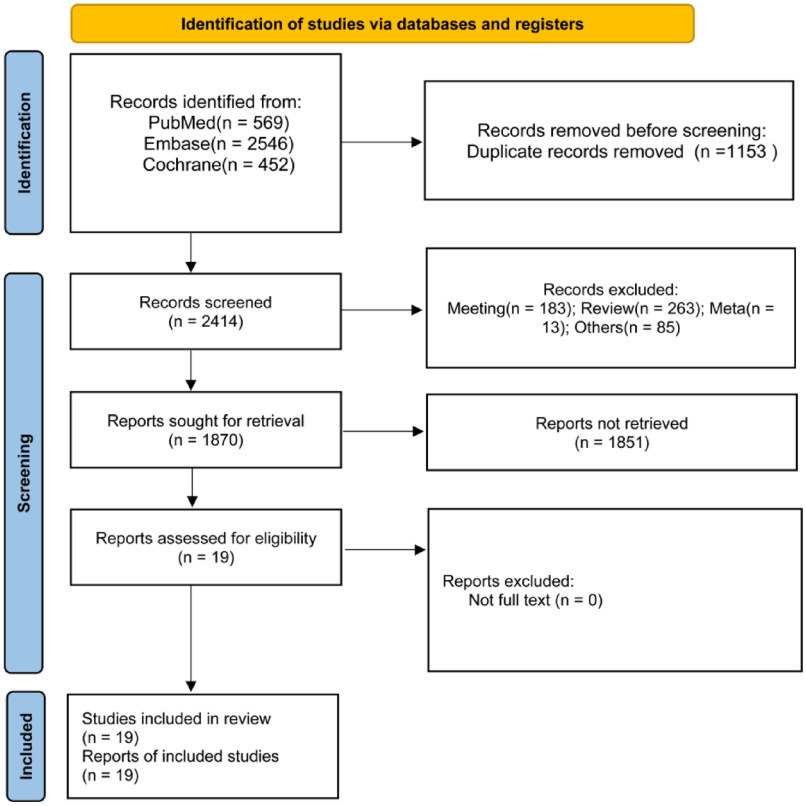

Fig. 1. Flow chart of the study selection.

Quality assessment

The quality assessment of the included studies is presented in Supplementary Table S2. All studies scored ≥ 6 (3 with 6 points and 16 with 7 points).

Characteristics of cases

A total of 59,915 cases were reported in these 19 studies. Among them, there were 2,603 (4.34%) SAID, 14,946 (25.94%) SIDD, 9,285 (15.50%) SIRD, 13,323 (22.24%) MOD, 19,465 (32.49%) MARD, 87 (0.15%) SIDRD, and 206 (0.34%) SOIRD cases. Male patients accounted for 55.27%, 64.03%, 57.79%, 52.30%, 59.53%, 60.90%, and 28.60% of SAID, SIDD, SIRD, MOD, MARD, SIDRD, and SOIRD cases, respectively.

In all included cases, the age was 50.14 (95%CI, 48.64 to 51.65; $I^2 = 100.0\%$, $P < 0.001$) years and the BMI was 27.54 (95%CI, 26.62 to 28.46; $I^2 = 100.0\%$, $P < 0.001$). The ages and BMI of each novel subgroup are shown in Fig. 2. In addition, the analysis results on WHR, FBG, HbA1c, HOMA2-B, HOMA2-IR, cholesterol, HDL, LDL, triglyceride, eGFR, and cystatin C are also shown in Fig. 2. The SOIRD had the most advanced age. The MOD had the highest BMI. The SIDD subgroup had a lower homeostatic model assessment of β-cell function. SIDRD and SIDD subgroups showed a high level of HbA1c. SIRD and MARD subgroups had a lower eGFR level, thus, a high incidence of nephropathy. The SIRD subgroup had the most significantly abnormal lipid metabolism and highest insulin resistance.

Characteristics of cases in China

Four studies reported cases in China, and the clinical characteristics of these cases are detailed in Supplementary Tables S3-S9. MARD and SIDD accounted for most cases. Notably, a higher percentage of males was observed in the SIDD subgroup. SAID cases were younger compared to other groups. Additionally, all subtypes exhibited lower levels of LDL cholesterol.

Publication bias

No publication bias was identified by Begg's ($P > 0.05$) and Egger's test ($P > 0.05$) in age, BMI, cystatin C, eGFR, FBG, HbA1c, HDL, HOMA2-B, HOMA2-IR, LDL, TC, triglyceride, and WHR analysis (Fig. 3).

Sensitivity analysis

The stability of the meta-analysis was examined using sensitivity analyses in each group. When any study was deleted, no fundamental change in the relevant pooled results was observed, indicating the stability of the meta-analysis (Supplementary Figure S1).

Study, year	Country	Study design	Type of diabetes	Definition of diabetes	Exclusion
Zaharia et al., 2019	Germany	Prospective	Diabetes duration < 1 year	American Diabetes Association criteria	Diabetes of other causes, exocrine pancreas, and gestational diabetes, pregnancy, and acute or severe chronic heart, hepatic, renal, or psychiatric diseases
Li et al., 2020	China	Retrospective	Diabetes duration < 1 year	WHO 1999 criteria	Pregnancy or gestational diabetes; acute diseases that would interfere with glucose metabolism; malignancies; clinically suspected of being diagnosed as other specific types of diabetes
Anjana et al., 2020	India	Retrospective	Diabetes duration < 1 year	American Diabetes Association criteria	NA
Tanabe et al., 2020	Japan	Retrospective	Diabetes duration < 10 months	Fasting plasma glucose > 126 mg/dL, random plasma glucose > 200 mg/dL, but in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, or A1c > 6.5% (48 mmol/mol).	Patients with secondary diabetes, patients with diabetes onset before age 18 years
Huang et al., 2021	China	Retrospective	NA	American Diabetes Association	With incomplete information
Xiong et al., 2021	China	Retrospective	NA	European classification in Chinese populations	Patients diagnosed with type 1 diabetes; latent autoimmune diabetes in adults; patients with newly diagnosed diabetes mellitus; patients with missing data for clustered variables.
Ratter-Rieck et al., 2021	Germany	Retrospective	NA	European classification in Chinese populations	
Wang et al., 2021	China	Prospective	Newly diagnosed	FPG ≥ 7.0 mmol/L (126 mg/dL) and/or 2hPG ≥ 11.1 mmol/L (200 mg/dL) during OGTT and/or HbA1c ≥ 6.5%	Self-reported diabetes or use of diabetes medications
Fedotkina et al., 2021	Ukraine	Retrospective	Newly diagnosed	American Diabetes Association	Data values for BMI, HOMA2-B, and HOMA2-IR with more than three standard deviations
Herder et al., 2021	Germany	Retrospective	Diabetes duration < 1 year	American Diabetes Association	Any secondary forms of diabetes; poor glycemic control (HbA1c > 9.0% [75 mmol/mol]); current pregnancy; acute or severe chronic cardiac, hepatic, renal, or psychiatric diseases; active cancer; anemia; and acute infections, leukocytosis, immunosuppressive therapy, autoimmune diseases, and infection with HIV
Landgraf et al., 2022	Germany	Retrospective	NA	Clinical diagnosis	NA
Peng et al., 2022	China	Retrospective	Newly diagnosed	American Diabetes Association	Secondary diabetes, extreme outliners, leptin, and resistin levels
Prasad et al., 2022	India	Retrospective	NA	Clinical diagnosis	Type 1 diabetes, diagnosis before 20 years of age, history of ketoacidosis, continuous insulin treatment since diagnosis, fibrocalculous pancreatic diabetes, or fulfilling criteria for monogenic diabetes
Saatmann et al., 2022	Germany	Prospective	Diabetes duration of < 12 months, aged 18–69 years	American Diabetes Association	Diabetes of other causes; pregnancy; acute or severe chronic heart, hepatic, renal, or psychiatric diseases; or immunosuppressive treatment.
Song et al., 2022	China	Retrospective	Newly diagnosed	WHO 1999 criteria	(1) active infection, (2) serious other systemic diseases, (3) receiving glucocorticoid, (4) diagnosed as gestational diabetes and other special types of diabetes, (5) incomplete relevant clinical data.
Wang et al., 2022	Singapore	Retrospective	Diabetes duration of less than 5 years	Type 2 diabetes was diagnosed by the attending physicians after excluding type 1 diabetes and diabetes attributable to specific causes. Type 1 diabetes was diagnosed as a sustained requirement for insulin treatment within 1 year after diabetes diagnosis without measurement of GAD antibody.	Patients with cancer and autoimmune disease on active treatments and those with HbA1c > 12% (108 mmol/mol)
Li et al., 2023	China	Retrospective	Newly diagnosed	WHO 1999 criteria	(1) Patients who had received regular antidiabetic treatment or regular lipid-lowering treatment; (2) Patients who had a disease duration of more than 1 year; (3) Type 1 diabetes, gestational diabetes, and other special types of diabetes; (4) Acute severe complications of diabetes; (5) Patients with severe infections, severe cardiac, hepatic, or renal dysfunction, or tumors; (6) Pregnant and lactating women.
Wang et al., 2024	China	Retrospective	Newly diagnosed	American Diabetes Association	NA
Werkman et al., 2024	Netherlands	Retrospective	Newly diagnosed and already diagnosed	WHO 1999 criteria	Individuals with missing values in the variables needed for clustering and subsequently those with outliers (> 3 standard deviations from the mean) in these variables.

Table 1. Characteristics of included studies. BMI, body mass index; FPG, fasting plasma glucose; GAD, glutamic acid decarboxylase; HbA1c, hemoglobin A1c; HIV, human immunodeficiency virus; HOMA2-B, homeostatic model assessment of β-cell function; HOMA2-IR, homeostatic model assessment of insulin resistance; NA, not available; OGTT, oral glucose tolerance test; WHO, World Health Organization.

Fig. 2. Forest plots of characteristics of cases. (**A**) ages; (**B**) body mass index; (**C**) waist-to-hip ratio; (**D**) fasting blood glucose; (**E**) HbA1c; (**F**) homeostatic model assessment of β-cell function; (**G**) homeostatic model assessment of insulin resistance; (**H**) total cholesterol; (**I**) high-density lipoprotein; (**J**) low-density lipoprotein; (**K**) triglyceride; (**L**) glomerular filtration rate; (**M**) cystatin C.

Discussion

Patients with diabetes can have various pathogenesis changes[33]. A deeper understanding of the etiology of diabetes can enhance disease diagnosis and management and facilitate the prediction of diabetes-related complications. In 2018, Ahlqvist et al. acknowledged the heterogeneous causes of diabetes and introduced a new classification system for adult-onset diabetes[6]. This system enhances our understanding of the differences among patients with various diabetes subtypes, advancing personalized diabetic care. However, the clinical characteristics of these novel subgroups have not been clearly defined. Our current study represents the first systematic review and meta-analysis to summarize the clinical characteristics of these novel diabetes subgroups. By comprehensively analyzing 19 articles, we have delineated the differences in the metabolomic and proteomic signatures of the seven subgroups, reinforcing the idea that diabetes patients exhibit diverse etiologies and require targeted treatment approaches.

In the past, the names and definitions of diabetes have changed a few times. The terms T1DM and T2DM were coined in 1955[34]. In the 1970 s, identifying autoimmuno antibodies to pancreatic β-cells created a new term for autoimmune T1DM[35,36]. However, up to now, no definition can classify all patients into either T1DM or T2DM[37–39]. Several models have been proposed, including the All New Diabetics In Scania (ANDIS) study in 2021[40] and the one by Ahlqvist et al. in 2018[6] ANDIS was a large diabetes cohort study[40] to study diabetes

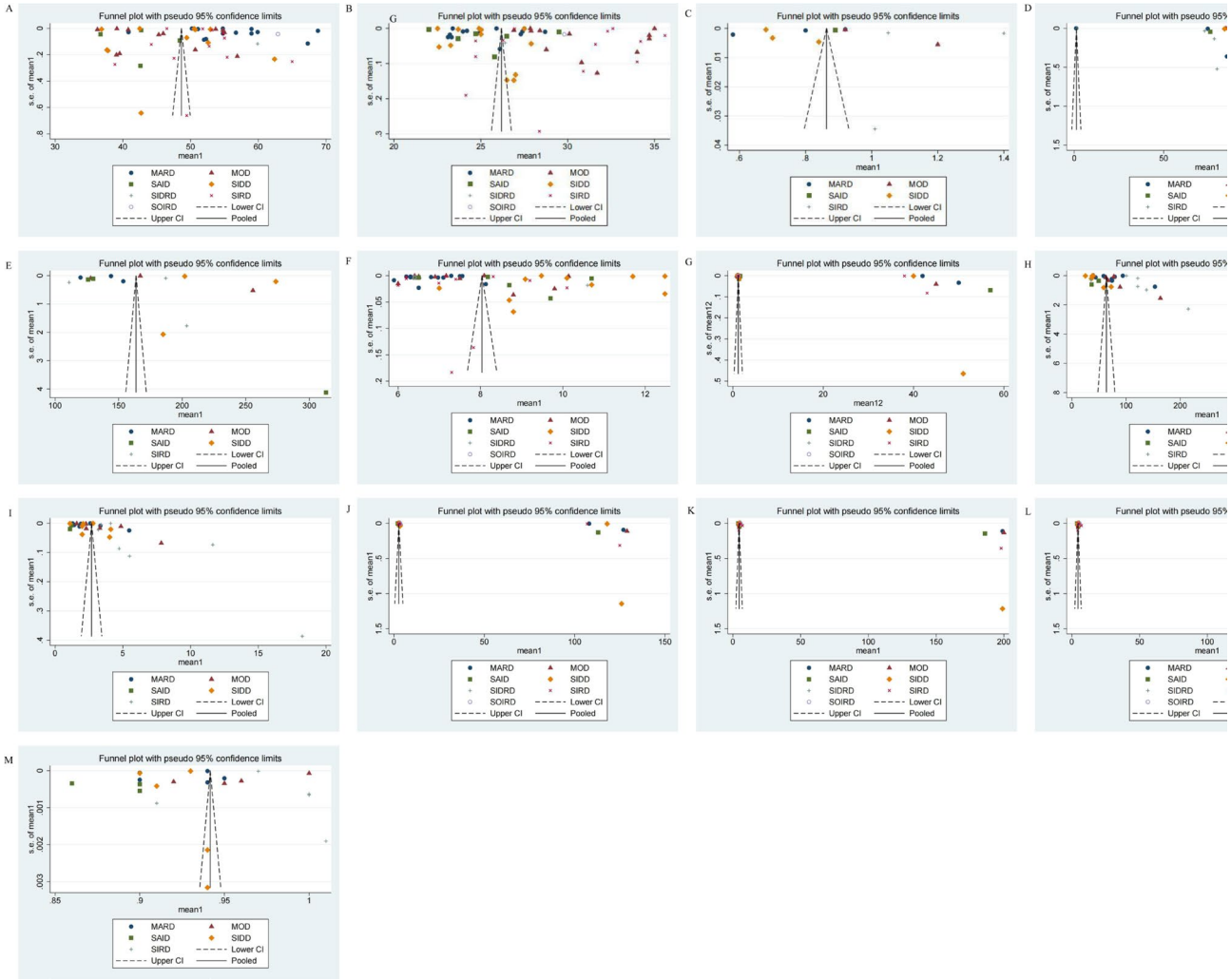

Fig. 3. Funnel plots of outcomes. (**A**) age; (**B**) body mass index; (**C**) cystatin C; (**D**) glomerular filtration rate; (**E**) fasting blood glucose; (**F**) HbA1c; (**G**) high-density lipoprotein; (**H**) homeostatic model assessment of β-cell function; (**I**) homeostatic model assessment of insulin resistance; (**J**) low-density lipoprotein; (**K**) total cholesterol; (**L**) triglyceride; (**M**) waist-to-hip ratio.

heterogeneity in all newly diagnosed diabetes regardless of their types. In the subtypes proposed by Ahlqvist et al.,[6] a data-driven approach based on several clinical variables was used to classify diabetes patients. These variables included age at diabetes onset, decarboxylase antibody, HbA1c, BMI, HOMA2-B, and HOMA2-IR. The key question of the novel diabetes subgroups is whether and to what extent this subgroup system could be generalized to other patient populations. Several studies on identifying the new subtypes were recently published in the Chinese population, confirming their robustness[20,21,41]. Similar efforts are underway in other populations, including India and Germany[9,10,23].

The diabetes subtypes identified by these five variables showed various clinical characteristics, disease progression, complications, treatment responses, and outcomes[6,41–43]. The presence of decarboxylase antibodies defines the SAID subgroup, thereby including antibody-positive diabetes patients who used to be included in T1DM. In our study, the SAID subgroup accounted for 4.34% of adult individuals. For adults with phenotypic risk factors overlapping with T1DM, including young age at diagnosis, unexplained weight loss, a complication such as ketoacidosis, rapid progression to insulin therapy, and a standardized islet autoantibody test are recommended for diabetes classification. In addition, MARD and SIDD were the two predominant subgroups. MARD has the highest incidence. SIDRD and SOIRD were less common. The insulin indices could aid in identifying the SIDD subtype that had a lower homeostatic model assessment of β-cell function, suggesting that the insulin deficiency should be addressed and treated early in this subgroup of patients[44].

Patients in the SIDRD and SIDD subgroups exhibited high levels of HbA1c at diagnosis and commonly progressed more rapidly to requiring insulin therapy compared to other subgroups. This progression aligns with their frequent insulin deficiency and ketoacidosis at diagnosis. Consequently, patients within these subgroups should receive frequent mealtime and basal insulin injections daily or continuous subcutaneous insulin infusion to effectively manage their glucose levels.

Dennis et al. demonstrated that baseline eGFR could predict the time required for progression to chronic kidney disease in patients with T2DM[45]. Consistent with this, our study found lower eGFR levels and a higher incidence of nephropathy in the SIRD and MARD subgroups. This finding aligns with prior research indicating that diabetic nephropathy and end-stage renal disease are frequently observed in patients with SIRD. When determining treatment options, it is essential to consider renal benefits and improved outcomes while also minimizing the risk of hypoglycemia and reducing cardiovascular events. The recently proposed concept of cardiovascular-kidney-metabolic (CKM) syndrome by the president of the American Heart Association in 2023 reveals the importance of clinically recognizing these patients as part of the CKM subset[46]. Therefore, SGLT-2 inhibitors or GLP-1 receptor agonists are preferred for glycemic management in these patients[47].

Some previous studies found that male sex, FBG, total cholesterol, and triglyceride were associated with diabetic retinopathy[48,49]. In our study, the SIRD subgroup had the most significantly abnormal lipid metabolism, with the highest serum triacylglyceride, high total cholesterol, and low HDL cholesterol. Abnormal lipid level is a risk factor for cardiovascular disease and can worsen diabetes-related complications. Therefore, SGLT2 inhibitors and/or GLP-1 receptor agonists should be recommended in these patients for glycemic management and cardiovascular risk reduction[50].

SIRD was reported to have high insulin resistance and secretion. In this study, patients with SIRD had the highest HOMA2-B and HOMA2-IR. The treatment plan should focus on minimizing insulin resistance and increasing insulin sensitivity using thiazolidinediones and metformin.

The novel subgroup classification system facilitates the development of more personalized treatment strategies by targeting the relationship between antihyperglycemic medications and the etiology of diabetes[12]. With this classification, patients at higher risk for rapid disease progression should receive more aggressive treatment at diagnosis to prevent organ damage. The novel SAID subgroup, which includes T1DM, predominantly requires insulin therapy; this explains the more frequent insulin use observed in our study's SAID group. Dennis et al. reported that subtypes differed in glycemic response, noting a particular benefit from thiazolidinediones in SIRD patients and sulfonylureas in MARD patients[45]. Insulin therapy was also extensively used in these two subgroups.

Our study has several limitations. Firstly, important demographic information such as race and ethnicity was missing from the retrieved articles, limiting our ability to perform detailed subgroup analyses based on these demographics. Secondly, the included studies were predominantly conducted in two countries (China, $n = 4$ and Germany, $n = 3$), potentially leading to over-representative results of these regions. Additionally, there was high heterogeneity (I^2 value of 75 to 100%) in the gender ratio across different studies. We also only reviewed studies published in English, which could introduce biases in our analysis. Furthermore, factors such as environmental and genetic influences on diabetes development and progression were not considered in this study, which might affect the comprehensiveness and representativeness of our findings. Finally, it remains uncertain whether these novel diabetes subgroups classified in the current study represent distinct, fixed pathological entities or dynamic stages along a continuum of the disease progression. Prospective longitudinal studies are required to clarify the stability of these subgroups over time and to determine whether transitions between subgroups occur with disease progression or in response to interventions.

In conclusion, our systematic review and meta-analysis is the first to summarize the clinical characteristics of the novel diabetes subgroups. The findings reveal that patients in different subgroups differ in clinical presentations and their risks of diabetes-related outcomes, revealing the need for personalized treatment approaches. Future studies should further explore the diverse characteristics and treatment strategies for different diabetes subtypes to enhance patient outcomes.

Data availability

All authors had access to the raw data. The corresponding author had complete authority over the data and its submission for publication.

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Author contributions

NA and JL Developed the conception of the review, designed the methodology, participated in data collection, manuscript drafting and data analysis and approved the final manuscript. JY and SJ Participated in designing and editing and finally approved the manuscript. QW and JD Participated in data collection, analyzing, editing and finally approved the final draft.

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Declarations

Competing interests

The authors declare no competing interests.

Ethics approval

Not applicable.

Patient consent

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Additional information

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