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Quantification of insulin adherence in adults with insulin-treated type 2 diabetes: A systematic review

Jannie Toft Damsgaard Nørlev [a,b,*], Ole Hejlesen [a], Morten Hasselstrøm Jensen [a,c], Stine Hangaard [a,b]

[a] Department of Health Science and Technology, Faculty of Medicine, Aalborg University, Selma Lagerløfs Vej 249, DK-9260, Gistrup, Denmark
[b] Steno Diabetes Centre North Denmark, Sønder Skovvej 3E, DK-9000, Aalborg, Denmark
[c] Data Science, Novo Nordisk A/S, Vandtårnsvej 112, DK-2680, Søborg, Denmark

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ABSTRACT

Aims: This systematic review aims to identify current methods used for the assessment of insulin adherence in adults with insulin-treated type 2 diabetes. The primary goal is to offer recommendations for clinical practice to improve quantification of adherence.

Methods: The review was conducted in accordance with PRISMA 2020 and registered at PROSPERO (CRD42022334134). PubMed, Embase, CINAHL, and PsycINFO were searched on 15 November 2022 and included three blocks: Type 2 diabetes, insulin, and adherence. We considered primary full-text studies describing an assessment method and a threshold for assessment of insulin adherence in adults with insulin-treated type 2 diabetes.

Results: A final sample of 50 studies were included. Identified methods fell into four categories: self-report, pharmacy claims, inulin count, and data from an insulin pen device. Commonly reported methods included: The Morisky Medication Adherence Scale, the (adjusted) Medication Possession Ratio, and the Proportions of Days Covered. A threshold of <80% was used to define non-adherence in nearly half of the studies. Yet, several thresholds were reported.

Conclusions: Most available methods for assessing insulin adherence in adults with insulin-treated type 2 diabetes are severely limited in providing in-depth insights into timing, dosing size, injection patterns, and adherence behavior. However, recognizing diverse types of non-adherence is crucial, as they denote unique behavioral entities requiring targeted intervention. Employing insulin injection data (e.g., from a smart insulin pen cap) to underlie an assessment method is a potential new approach to objectively assess insulin timing and dosing adherence in adults with insulin-treated type 2 diabetes.

1. Introduction

Type 2 diabetes is a progressive chronic disease, and many adults diagnosed with type 2 diabetes will eventually require insulin therapy to achieve adequate glycemic control [1]. Addition of basal insulin to previous treatment is considered the standard way to initiate insulin therapy but numerous adults will also need bolus insulin to achieve glycemic targets [2]. Insulin regimes are complex and individualized [2]. To obtain the full benefit of insulin the adult must uphold a high level of adherence, meaning that the insulin use (timing and dosage) corresponds with agreed recommendations from a healthcare professional [3]. Yet, insulin non-adherence is very common in adults with type 2 diabetes. Consequently, this increases morbidity and mortality, hospitalizations, and healthcare costs [4].

Accurate assessment of insulin adherence is essential in medical research and clinical practice [5]; if insulin therapy fails to achieve the expected outcome, healthcare professionals may assume that the dosing scheme was erroneous unless presented with other information [5]. Hence, accurate, detailed, and high-quality assessment of adherence is a crucial prerequisite for enhancing adherence since healthcare professionals need to identify non-adherence to provide effective support and intervention [6]. In addition, insulin therapy comes with unique challenges related to correct dosing and timing [7]. Therefore, being able to recognize diverse types of non-adherence holds significance, as

* Corresponding author. Department of Health Science and Technology, Aalborg University, Selma Lagerløfs Vej 249, DK-9260, Gistrup, Denmark.
E-mail address: jadano@hst.aau.dk (J.T.D. Nørlev).

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distinct dosing irregularities signify unique behavioral entities requiring targeted intervention [8,9]. Nevertheless, there is no gold-standard method to assess insulin adherence and no consensual standard for what constitutes adequate insulin adherence [3]. As a result, the ability of healthcare professionals to recognize non-adherence is insufficient and their estimates of adherence level have been demonstrated to be very inaccurate [10].

Previous literature reviews have summarized research regarding methods to assess adherence in adults with diabetes [7,11]. Clifford et al. (2014) [7] reviewed methodologies used to assess medication adherence in adults with diabetes, while Stolpe et al. (2016) [11] identified methods to measure insulin adherence in adults with diabetes focusing on methods that could be considered as a quality measure suitable for public-facing performance programs. Yet, neither Clifford et al. [7] nor Stople et al. [11] distinguished between types of diabetes or provided practical conclusions for healthcare professionals in clinical practice. Moreover, despite the growing body of literature on adherence to insulin therapy in recent years (e.g., use of technology), these latest findings have not been considered in prior reviews, as the most recent review was published in 2016 [11].

Hence, considering the complexity involved in assessing insulin adherence in adults with insulin-treated T2D and the critical demand for accurate and detailed assessment, this systematic review aims to identify current methods used for the assessment of insulin adherence in adults with insulin-treated type 2 diabetes. The primary goal is to offer recommendations for clinical practice to improve quantification of adherence.

2. Methods

2.1. Study design

This systematic review was conducted and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement [12]. A comprehensive search protocol was PROSPERO-registered (CRD42022334134) on 20 May 2022, and published on Open Science Framework (for further details see https://osf.io/g4mdr/).

2.2. Eligibility criteria

Studies were considered if they included adults (age ≥18 years) diagnosed with type 2 diabetes and prescribed insulin therapy. There was no limitation to duration of type 2 diabetes, time treated with insulin, and insulin type or regimen. Studies that included mixed population (e.g., type 1 diabetes and type 2 diabetes) and/or mixed medication (e.g., oral hypoglycemic agents supplemented with insulin) without a transparent subgroup analysis or without clear statement of diabetes type and medication were excluded. Furthermore, at least one method to assess insulin adherence had to be clearly described and a threshold to define adherence ought to be reported. There was no restriction to intervention, outcome, study setting, or data source.

Primary peer-reviewed full-text studies published in English, Danish, Swedish, or Norwegian between 1 January 2012, and 15 November 2022, were considered. All study designs, except study protocols and animal research, were contemplated.

2.3. Information sources and search strategy

Initially, unstructured searches were performed in PubMed and EMBASE to identify relevant search terms and thus qualify the systematic search. The systematic search followed the unstructured searches. The systematic search was performed in PubMed, EMBASE, CINAHL, and PsycINFO on 21 May 2022. The search was rerun on 15 November 2022. The first author performed database searches assisted by a research librarian with expertise and experience in medical science and diabetes. Citation searches in SCOPUS and Web of Science as well as reference searches were applied to identify additional studies.

The systematic search comprised three blocks (keywords): type 2 diabetes, insulin, and adherence. Search terms included various synonyms, near-synonyms, acronyms, and spellings for all index terms and keywords. Different search functions were applied, including Boolean operators, abstract/title/keywords, phrase, truncation, thesaurus, free text, and advanced search. The search strategy was adapted for each database. Search strings are provided in Supplementary File.

2.4. Selection process

First, studies identified through the systematic searches were uploaded to RefWorks (ProQuest RefWorks, 2022) and duplicates were removed. Next, titles and abstracts were screened for assessment against eligibility criteria by the first author. The remaining studies underwent full-text review by the first author supported by a co-author (S.H.) with respect to the eligibility criteria of the review. Disagreement was resolved through discussion by the first author and a co-author (S.H.) or by inclusion of multiple co-authors. The reasons for exclusion of studies were recorded. Lastly, a final sample of studies was identified.

2.5. Data extraction

All studies in the final sample were read thoroughly by the first author and data were extracted using a standardized sheet in Microsoft Excel (2016). The extracted data included descriptions of methods to assess insulin adherence and thresholds. In addition, study characteristics (title, author(s), publication year, study design, study setting inclusive country, sample size), participant characteristics (age, sex), and information regarding type 2 diabetes and insulin therapy (duration, regimen/type of insulin, delivery device) were extracted. Co-authors were conferred during the extraction process.

2.6. Data synthesis

The identified methods to assess insulin adherence were categorized. This categorization guided the description of the results. A co-author (S.H.) validated the categorization. Data from all included studies were synthesized regardless of the number of times the method or threshold to assess insulin adherence was identified. Subsequently, all studies were summarized into an overview table with information on assessment methods, thresholds, and insulin use.

2.7. Risk of bias assessment

Critical appraisal tools from the Joanna Briggs Institute (JBI) were applied by study design to assess risk of bias [13]. The study design was determined using Andrews and Likis [14]. As JBI did not include a tool for descriptive cross-sectional studies an assessment tool from Downes M et al. [15] was used.

The first author assessed the included studies with support from co-authors. A scoring system inspired by Melo et al. (2018) [16] was established before the critical appraisal commenced as recommended by the JBI instructions. Co-authors were consulted when doubts regarding assessment and/or scoring occurred, and clarification was reached through discussion.

3. Results

As demonstrated by the flow diagram (Fig. 1), 7654 potentially relevant studies were identified and screened. Subsequently, 4862 studies were assessed based on title and abstract and 407 were eligible for full-text review. No additional studies were identified during citation and reference searches. A sample of 50 studies was included in the final dataset (Table 1).

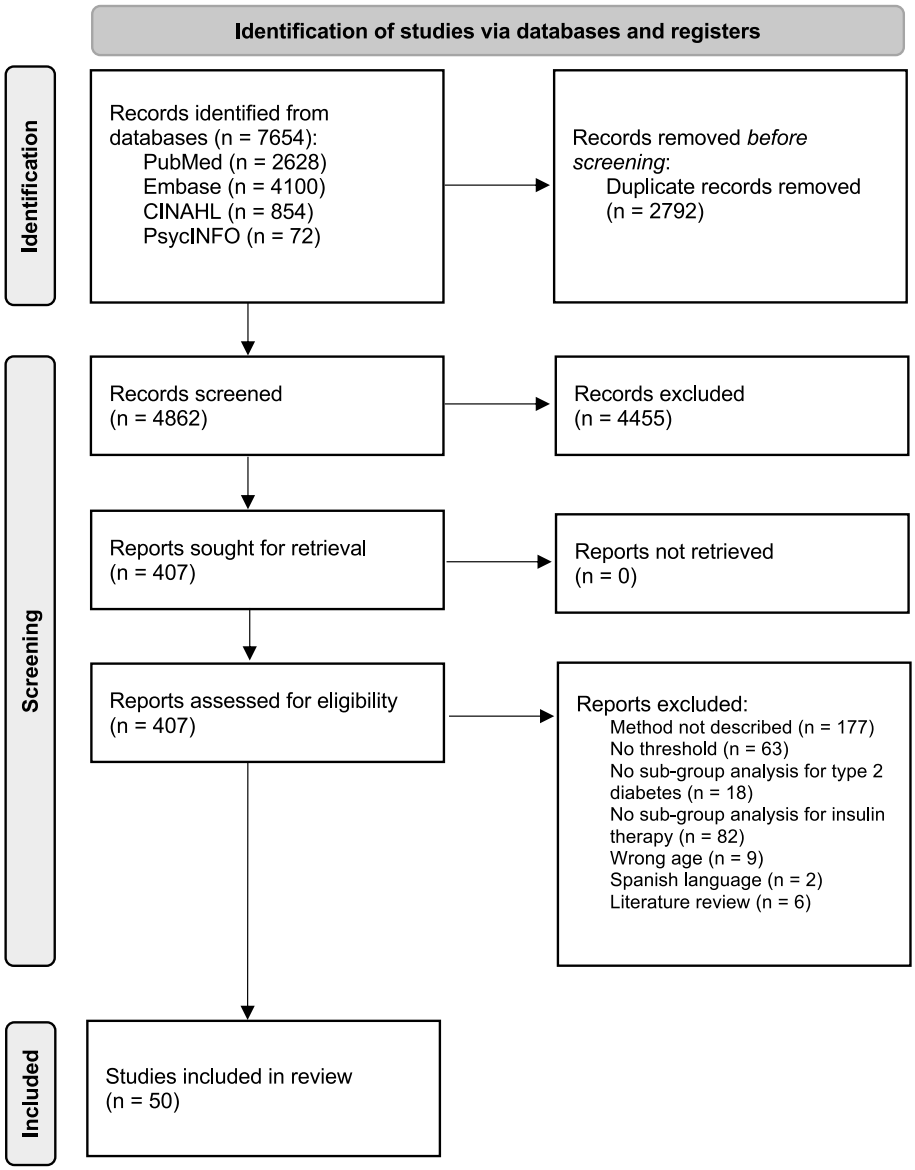

Fig. 1. Flow diagram of the systematic review process.

3.1. Study characteristics

Most studies used either a cross-sectional study design (n = 25) or a retrospective cohort design (n = 18). Half the studies reviewed were conducted in North America (n = 27), while the remaining studies were conducted in the Middle East (n = 6), Asia (n = 5), Europe (n = 5), South America (n = 4), or Africa (n = 2). One study was multinational.

Categorization of the methods used to assess insulin adherence. Identified methods to assess insulin adherence fell into four categories based on data source: self-report (n = 27, 53%), pharmacy claims (n = 19, 37%), insulin counts (n = 3, 6%), and insulin injection data recorded by a smart insulin pen cap (n = 1, 2%) (Fig. 2).

3.2. Insulin types assessed

Half the studies [17–42] reported information concerning the insulin type and regimen. Both basal insulin, bolus insulin, and a basal-bolus combination were reported. The remaining studies [43–66] did not report type of insulin. Studies using self-reported methods rarely reported on the insulin regimen, while most of the studies using pharmacy claims, insulin count and pen cap data did. In addition, if a participant used more than one type of insulin (e.g., basal and bolus) all types were assessed together when using self-reported methods, while each type of insulin was assessed separately when using pharmacy claims, insulin counts, and insulin pen cap data.

In 14 studies [18,20,23,25–31,33,36,37,41], both pens and vials were used for insulin administration, while pen only was used in four studies [40,42,60,64]. Most studies (n = 32) [17,19,21,22,24,32,34,35,38,39,43–59,61–63,65,66] did not report the device used to administer insulin.

3.3. Self-reported methods

In the 27 studies [17–24,43–61] that used self-reported methods to assess insulin adherence, fourteen different methods were used (Table 2). These methods included various approaches such as questionnaires [17–23,43–57,59], selected items from questionnaires [61], an interview [58], and simple questions [24,60].

In 21 [17,18,21–24,43,46,47,49–56,58–61] studies, insulin adherence was assessed by collecting data in the clinic (e.g., healthcare center, hospital, outpatient clinic), five studies [19,20,44,45,57] collected insulin adherence data via an online/web-based survey and one study [48]

Table 1
Study characteristics and overview of methods and thresholds used.

Reference	Study design	Assessment method information			Insulin information			
		Data source	Method	Threshold	Regimen	Before inclusion[a]	Device	Time using insulin[b]
Adisa & Fakeye 2013 [17]	Cross-sectional	Self-reported	• MMAS-4	<1: adherence ≥1: non-adherence	Basal premixed	No	NR	>3 months
Jarab et al. 2014 [43]	Cross-sectional	Self-reported	•MMAS-4	<1: adherence ≥1: non-adherence	NR	No	NR	NR
Mitchell et al. 2013 [44]	Cross-sectional	Self-reported	•Insulin adapted MMAS-4	0: high adherence	NR	No	NR	NR
Reach et al. 2013 [45]	Cross-sectional	Self-reported	•MMAS-4	<1: adherence ≥1: non-adherence	NR	No	NR	<5 years
Silva-Tinoco et al. 2022 [46]	Cross-sectional	Self-reported	• MMAS-4	≥3: adherence <3: non-adherence	NR	No	NR	NR
Pirdehghan & Poortalebi 2016 [47]	Cross-sectional	Self-reported	• MMAS-6	≥4: adherence ≤3: non-adherence	NR	No	NR	NR
Asheq et al. 2021 [48]	Cross-sectional	Self-reported	• Diabetes adapted MMAS-8	<6: low adherence 6-7: medium adherence 8: high adherence	NR	No	NR	NR
Bermeo-Cabrera et al. 2018 [18]	Cross-sectional	Self-reported	• MMAS-8	<6: poor adherence 6-7: moderate adherence 8: excellent adherence	Basal bolus basal-bolus	No	Pen Syringe	6 (3.3–10) years
Cummings et al. 2014 [49]	Cross-sectional	Self-reported	• MMAS-8	<6.0: low adherence ≥6.0: adequate adherence	NR	No	NR	NR
Javanmardifard et al. 2020 [50]	Cross-sectional	Self-reported	• MMAS-8	>6: desirable adherence	NR	No	NR	NR
Martinez-Perez et al. 2020 [51]	Cross-sectional	Self-reported	• MMAS-8	<6: low adherence 6-7: medium adherence 8: high adherence	NR	No	NR	NR
Saudi et al. 2021 [52]	Cross-sectional	Self-reported	• MMAS-8	<6: low adherence 6-7: medium adherence 8: high adherence	NR	No	NR	NR
Schaper et al. 2017 [19]	Cross-sectional	Self-reported	• Insulin adapted MMAS-8	≥3: non-adherence <3: adherence	Bolus	Yes	NR	NR
Stephenson et al. 2018 [20]	Cross-sectional	Self-reported	• MMAS-8	<6: low adherence 6-7: medium adherence 8: high adherence	Basal	Yes	Pen Syringe	Low adh: 7.0 ± 6.8 High adh: 7.8 ± 8.7
Osborn & Gonzalez 2016 [53]	Cross-sectional	Self-reported	• Insulin adapted MMAS-8	<8: non-adherence	NR	No	NR	NR
Azri et al. 2021 [21]	Cross-sectional	Self-reported	• IAQDM	≥80%: adherence <80%: non-adherence	Basal Bolus Premixed	No	NR	3 years
Aminde et al. 2019 [54]	Cross-sectional	Self-reported	• MCQ	<27: non-adherence ≥27: adherence	NR	No	NR	NR
Yong et al. 2022 [22]	Cross-sectional	Self-reported	• MCQ	<27: non-adherence ≥27: adherence	Basal Bolus	No	NR	6.5 ± 5,0 years

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Table 1 (*continued*)

Reference	Study design	Assessment method information			Insulin information			
		Data source	Method	Threshold	Regimen	Before inclusion[a]	Device	Time using insulin[b]
Halepian et al. 2018 [23]	Cross-sectional	Self-reported	• Adaption of Lu et al.'s questionnaire	0% = very poor adherence 20% = poor adherence 40% = fair adherence 60% = good adherence 80% = very good adherence 100% = excellent adherence	Basal-bolus Premixed Basal Basal-bolus Other	No	Pen Syringe	85.7 ± 89.5 months

Reference	Study design	Assessment method information			Insulin information			
		Data source	Method	Threshold	Regimen	Before inclusion*	Device	Time using insulin**
Reach et al. 2018 [55]	Cross-sectional	Self-reported	• Girerd questionnaire	<3 = adherence ≥3 = non-adherence	UC	No	NR	NR
Sagalla et al. 2020 [56]	Post hoc analysis	Self-reported	• Self-reported 3-tiem measure by Voils	>1 = non-adherence	NR	No	NR	NR
Unni et al. 2022 [57]	Cross-sectional	Self-reported	• MAR-scale	7 = adherence 0-6 = non-adherence	NR	No	NR	NR
Penaforte et al. 2017 [24]	Cross-sectional	Self-reported	• Single question	Yes = adherence No = non-adherence	Basal Bolus	No	NR	NR
Mukherjee et al. 2013 [58]	Cross-sectional	Self-reported	• Structered Interview	<80% = non-adherence	NR	No	NR	NR
Chen et al. 2019 [59]	Cross-sectional	Self-reported	• Self-reported regimen adherence factors questionnaire	<100% = non-adherence 100% = adherence	NR	No	NR	5.4 ± 4.6 years
Mashitani et al. 2013 [60]	Cross-sectional	Self-reported	• Straightforward questionnaire	1 = high adherence 2 = medium adherence 3-6 = low adherence	NR	No	Pen	NR
Trief et al. 2022 [61]	Prospective cohort	Self-reported	• 1 item SDSCA + 1 item adapted SDSAC	≥71.4% = adherence <71,4% = non-adherence	NR	No	NR	NR
Egede et al. 2012 [63]	Retrospective cohort	Pharmacy claims	• Traditional MPR	≥0.8/80% = adherence <0.8/80% = non-adherence	NR	No	NR	NR
Egede et al. 2014 [62]	Retrospective cohort	Pharmacy claims	• Traditional MPR	≥80% = adherence <80% = non-adherence	NR	No	NR	NR
Wei et al. 2014 [25]	Retrospective cohort	Pharmacy claims	• Traditional MPR • Adjusted MPR	≥0.8 = adherence <0.8 = non-adherence	Basal	Yes	Pen Syringe	NR
Zhang et al. 2014 [26]	Retrospective cohort	Pharmacy claims	• Traditional MPR • Adjusted PDC	≥0.8 = adherence <0.8 = non-adherence	Basal	Yes	Pen Syringe	UC
Stephenson et al. 2018 [27]	Retrospective cohort	Pharmacy claims	• Traditional MPR • Adjusted MPR • Hybrid MPR • Self-reported MPR	≥0.8 = adherence <0.8 = non-adherence	Basal	Yes	Pen Syringe	NR
Chandran et al. 2015 [64]	Retrospective cohort	Pharmacy claims	• Adjusted MPR	≥0.8 = adherence <0.8 = non-adherence	NR	No	Pen	NR
Eby et al. 2013 [28]	Retrospective cohort	Pharmacy claims	• Adjusted MPR	≥0.8 = adherence <0.8 = non-adherence	Bolus Premix	Yes	Pen Syringe	NR
Reynolds et al. 2015 [29]	Retrospective cohort	Pharmacy claims	• Adjusted MPR	≥0.8 = adherence <0.8 = non-adherence	Basal	Yes	Pen Syringe	Insulin-naïve
Slabaugh et al. 2015 [30]	Retrospective cohort	Pharmacy claims	• Adjusted MPR • Adjusted PDC	≥80% = adherence <80% = non-adherence	Basal	Yes	Pen Syringe	Insulin-naïve
Curtis et al. 2017 [65]	Retrospective cohort	Pharmacy claims	• Adjusted PDC	≥80% = adherence <80% = non-adherence	NR	No	NR	NR
Eby et al. 2020 [31]	Retrospective cohort	Pharmacy claims	• Adjusted PDC	≥80% = adherence <80% = non-adherence	Basal Basal-bolus	Yes	Pen Syringe	NR
Perez-Nieves et al. 2018 [32]	Retrospective cohort	Pharmacy claims	• Adjusted PDC	≥80% = adherence <80% = non-adherence	Basal	Yes	NR	Insulin-naïve

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Table 1 (*continued*)

Reference	Study design	Assessment method information			Insulin information			
		Data source	Method	Threshold	Regimen	Before inclusion*	Device	Time using insulin**
Pham et al. 2022 [33]	Retrospective cohort	Pharmacy claims	• Adjusted PDC	≥80% = adherence <80% = non-adherence	Basal	Yes	Pen Syringe	UC
Wright et al. 2022 [34]	Retrospective cohort	Pharmacy claims	• PDC	≥80% = adherence <80% = non-adherence	Basal	Yes	NR	NR
Zhou et al. 2018 [35]	Retrospective cohort	Pharmacy claims	• PDC	≥80% = adherence <80% = non-adherence	Basal	Yes	NR	UC
Chen et al. 2022 [37]	Retrospective cohort	Pharmacy claims	• PDC	≥80% = adherence <80% = non-adherence	Intermediate	Yes	Pen Syringe	NR
Hood et al. 2021 [36]	Retrospective cohort	Pharmacy claims	• PDC	≥80% = adherence <80% = non-adherence	Intermediate	Yes	Pen Syringe	NR
Taber et al. 2019 [38]	Retrospective cohort	Pharmacy claims	• PDC	≥80% = adherence <80% = non-adherence	Basal	Yes	NR	NR
Mcadam-Marx et al. 2022 [66]	Retrospective cohort	Pharmacy claims	• 60-day gap	A 60-day gap = non-adherence	NR	No	NR	NR
Horvat et al. 2018 [39]	Prospective cohort	Remaining insulin	• Count	90–105% = adherence <90% or >105% = non-adherence	Basal Bolus Intermediate	No	NR	NR
Patel et al. 2019 [40]	Post hoc analysis	Remaining insulin	• Count	≥80% = adherence <80% = non-adherence	Basal-bolus	Yes	Pen	Insulin-naïve
Machry et al. 2021 [41]	RCT	Remaining insulin	• Count	≥80% = adherence <80% = non-adherence	Basal Basal-bolus	Yes	Pen Syringe	Pen: 8.9 ± 8.9 years Syringe: 8.2 ± 8.7 years
Galindo et al. 2021 [42]	RCT, cross-over	Pen cap data	•Inuslin pen cap data	>85% of completed doses (missing 1 dose per week) = high adherence >60–85% of completed doses (missing 1–3 doses per week) = moderate adherence 15–60% of completed doses (missing 4–5 doses per week) = poor adherence <15% of completed doses (missing 6 doses per week) = non-adherence	Basal	Yes	Pen + smart cap	>3 months

MMAS = Morisky Medication Adherence Scale, IAQDM = Insulin Adherence Questionnaire for Diabetes Mellitus, MCQ = Medication compliance questionnaire, MAR-scale = The Medication Adherence Reasons, SDSCA = Summary of Diabetes Self-Care Activities, MPR = Medication Possession Ratio, PDC = Proportion of Days Covered. NR = Not reported, UC = Unclear.

[a] Regimen was defined before inclusion as an inclusion criteria (yes/no).

[b] Values are mean ± SD or median (interquartile range).

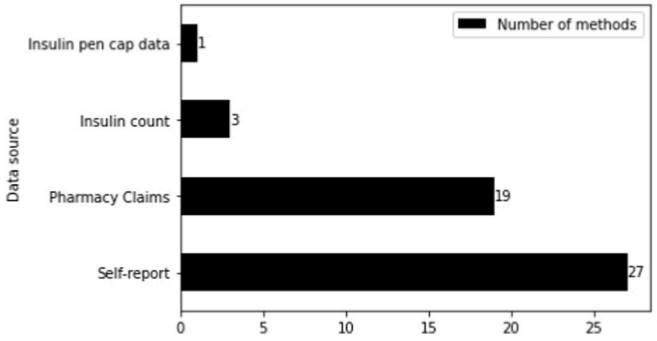

Fig. 2. Grouping of identified methods (four categories).

administered the questionnaire both online and in the clinic. The length of the self-reported methods varied (from one to 34 items); ranging from single items to questionnaires with several domains elucidating different aspects of adherence.

Two studies [21,23] assessed insulin adherence using methods validated for assessment of adherence to insulin therapy (IAQDM and Adaptions of Lu et al.'s questionnaire).

The *Morisky Medication Adherence Scale (MMAS)* was the most repeatedly used self-report measure (n = 15). The MMAS reflects ways adherence can occur. Both the original 4-item version (n = 5) [17,43–46] and the later developed 8-item version (n = 9) [18–20,48–53] were used. Pirdehghan and Poortalebi [47] used a self-modified 6-item version. The original generic version of the questionnaire was the most frequently used [17,18,20,43,45–47,49–52], while three studies [19,44,53] adapted the questionnaire to insulin therapy and Asheq et al. [48] adapted it to diabetic medication.

The *Medication Compliance Questionnaire (MCQ)* was used in two studies [22,54]. The MCQ is a generic seven-item questionnaire assessing patients' intentional and unintentional non-adherence to medication and reasons hereto during the last two months.

Aside from the MMAS and the MCQ, six other questionnaires were identified. Three of these were insulin-specific and included: 1) *the comprehensive Insulin Adherence Questionnaire for Diabetes Mellitus (IAQDM)* [21] asking about monitoring of insulin and blood sugar, self-adjustment of insulin therapy and insulin injection, 2) *Adaption of Lu et al.'s questionnaire* [23] asking about the frequency, percentage, and rating response of insulin use, and 3) *the Self-Reported Regimen Adherence Factors Questionnaire* [59] measuring recommended and actual weekly performance in maintaining an insulin-administration regimen. The three remaining questionnaires were generic and included 1) *The Medication Adherence Reasons Scale* [57] which established the overall extent of non-adherence and the specific reasons for non-adherence, 2) *the French Girerd Questionnaire* [55], and 3) *a self-reported measure by Voils* [56].

Most commonly, the questionnaires were self-administered. However, in Osborn and Gonzalez [53], given high rates of limited literacy skills, research assistants read self-report items and response options aloud to all participants. In Reach et al. [55] a question was explained to the participant if needed.

Two studies [24,60] assessed insulin adherence by asking a single insulin-specific question. Penaforte et al. [24] asked if insulin was taken according to the prescription and Mashitani et al. [60] asked how often insulin injections were omitted in the past month. Trief et al. [61] asked about taking recommended insulin doses by combining one item from the *Summary of Diabetes Self-Care Activities (SDSCA)* and one item from an adapted SDSCA. Lastly, Mukherjee et al. [58] used a pre-designed, pre-tested, structured interview schedule. Based on the patient's answers an adherence score was calculated.

3.4. Pharmacy claims data

Nineteen studies [25–38,62–66] used methods based on pharmacy claims data to provide estimates of insulin adherence, including the Medication Possession Ratio (MPR), derivations of the MPR, the Proportion of Days Covered (PDC), adjusted PDC and days gap. In fifteen studies [28,29,31–38,62–66] insulin adherence was calculated using one method, while the remaining four studies [25–27,30] used two or more methods. In all studies, except one [66], non-adherence was defined by a threshold of <80% (or 0.8).

Medication Possession ratio (MPR): The traditional MPR, used in five studies [25–27,62,63], was defined as the ratio of days for which a medication is supplied to the total days in a specified time interval. It was calculated by dividing the total days' supply of all filled claims for insulin in the study period by the number of days in the study period. Two studies [62,63] used a study period of 90 days, while the remaining three studies [25–27] used 1 year period (or 365 days). Because all days' supplies are included, even when early refills occur or an adult switches medications within the same class, the ratio of days' supply to days in the study period can potentially be > 1.0.

In seven studies [25–30,64] an insulin-adjusted MPR was used to account for the customization of insulin dosing (such as package size, carbohydrate intake, physical activity, body mass, illness, and insulin resistance), which induces variation in time between insulin refills. For example, an adult who required less insulin may have utilized their "30-day" supply of insulin over a 45-day period. The insulin-adjusted MPR was estimated separately for each insulin type used and calculated by multiplying the traditional MPR by an adjustment factor (the ratio of the average number of days between refills of the insulin type divided by the average recorded days' supply for the insulin type). All studies using the insulin-adjusted MPR had a study period of 1 year (or 365 days).

Three studies [25–27] used both the traditional MPR and the insulin-adjusted MPR and found that when using the adjusted MPR, adults appeared to be more adherent, compared with when MPR was used.

Stephenson et al. [27], assessed insulin adherence using four different types of MPR: traditional MPR, the insulin-adjusted MPR, the self-Reported MPR, and a hybrid MPR. The self-reported MPR was calculated by dividing the patient survey data for the number of 30-day pharmacy fills in the past 12 months by the number of days in the study period. The hybrid MPR integrated the patient's self-reported insulin doses and accounted for the actual number of insulin units dispensed over the study period, thus estimating the extent to which patients were able to administer their dispensed insulin dose for the study period based on their individual dose. For versions of the MPR, the study period was 365 days.

The proportion of days covered (PDC): Ten studies [30–38,65] assessed insulin adherence using the Proportion of Days Covered (PDC). The PDC and MPR are related in that the days' supply from pharmacy claims are used to calculate adherence for both, but they differ in their approach to determining days' supply. While MPR was based on the total days' supply for the study period, the PDC was based on the total number of covered days during the study period, regardless of the number of available prescriptions claims on any single day. Each day in the study period was individually evaluated for coverage by insulin, and the PDC could not exceed 1. The PDC was calculated for each type of insulin (e.g., basal and bolus).

The traditional PDC was used in five studies [34–38] and was calculated as the (percentage of) unique days covered by any insulin divided by the number of days in the study period. The reported study period varied between 6 months and 12 months. The remaining studies [30–33,65] used an adjusted PDC to account for the customization of insulin dosing. Slabaugh et al. [30], Eby et al. [31], and Pham et al. [33] multiplied PDC by an adjustment factor calculated as the median time between specific insulin claims divided by the median days' supply

Table 2
Methods based on self-reported data.

Author	Method	Items, n	Threshold	Recall period	Setting	Wording	Validated for insulin therapy	Type of insulin assessed	Type
Adisa & Fakeye, 2013 [17]	MMAS-4	4	<1: adherent ≥1: non-adherent	–	In clinic	Generic	No	Basal Premixed	Questionnaire
Jarab et al., 2014 [43]	MMAS-4	4	<1: adherent ≥1: non-adherent	–	In clinic	Generic	No	NR	Questionnaire
Reach et al., 2013 [45]	MMAS-4	4	<1: adherent ≥1: non-adherent	–	Online	Generic	No	NR	Questionnaire
Silva-Tinoco et al., 2022 [46]	MMAS-4	4	<3: non-adherent ≥3: adherent	–	In clinic	Generic	No	NR	Questionnaire
Mitchell et al. [44]	Adapted MMAS-4	4	0: high adherence	–	Online	Insulin specific	No	NR	Questionnaire
Asheq et al. [48]	MMAS-8	8	<6: low 6-7: medium 8: high	–	Online In clinic	Diabetes	No	NR	Questionnaire
Bermeo-Cabrera et al. [18]	MMAS-8	8	<6: poor 6-7: Moderate 8: Excellent	–	In clinic	Generic	No	Basal Bolus Basal-bolus	Questionnaire
Cummings et al. [49]	MMAS-8	8	<6.0 = low adherence ≥6.0 = adequate adherence	–	In clinic	Generic	No	NR	Questionnaire
Javanmardifard et al. [50]	MMAS-8		>6: desirable adherence	–	In clinic	Generic	No	NR	Questionnaire
Martinez-Perez et al. [51]	MMAS-8	8	<6: low 6-7: Medium 8: high	–	In clinic	Generic	No	NR	Questionnaire
Saudi et al. [52]	MMAS-8	8	<6: low 6-7: Medium 8: high	–	In clinic	Generic	No	NR	Questionnaire
Stephenson et al. [20]	MMAS-8	8	<6: low 6-7: Medium 8: high	–	Online	Generic	No	Basal	Questionnaire
Schaper et al. [19]	Adapted MMAS-8	8	≥3: non-adherence <3: adherence	–	Online	Insulin specific	No	Bolus	Questionnaire
Osborn & Gonzalez [53]	Adapted MMAS-8	8	<8: non-adherence	–	In clinic	Insulin specific	No	NR	Questionnaire
Pirdehghan & Poortalebi [47]	MMAS-6	6	≥4 (4–6): adherent ≤3: (0–3) non-adherent	–	In clinic	Generic	No	NR	Questionnaire
Azri et al. [21]	IAQDM	34	≥80%: adherence <80%: non-adherence	2 months	In clinic	Inuslin specific	Yes	Basal Bolus Premixed	Questionnaire
Aminde et al. [54]	MCQ	7	<27: non-adherence ≥27: adherence	1 month	In clinic	Generic	No	NR	Questionnaire
Yong et al. [22]	MCQ	7	<27: non-adherence ≥27: adherence	1 month	In clinic	Generic	No	Basal Bolus Basal-bolus Premixed	Questionnaire
Halepian et al. [23]	Adaption of Lu et al.'s questionnaire	3	0% = very poor, 20% = poor, 40% = fair, 60% = good, 80% = very good, and 100% = excellent.	1 month	In clinic	Insulin	Yes	Basal Basal-bolus Other	Questionnaire
Reach et al. [55]	Girerd questionnaire	6	Adherent: <3 positive answers Non-adherent: ≥3	NR	In clinic	Generic	No	UC	Questionnaire
Sagalla et al. [56]	Self-reported measure by Voils	3	>1: non-adherent	7 days	In clinic	Generic	NR	NR	Questionnaire
Unni et al. [57]	MAR-scale	20	7: adherent 0-6: non-adherent	7 days	Online	Generic	No	NR	Questionnaire
Penaforte et al. [24]	Single question	1	Yes: adherence No: non-adherent	NR	In clinic	Insulin	NR	Basal Bolus	Single item
Mukherjee et al. [58]	Structured Interview	NR	<80%: non-adherent	NR	In clinic	NR	NR	NR	Interview
Chen et al. [59]	Self-reported regimen adherence factors questionnaire	NR	<100%: non-adherence 100%: adherence	NR	In clinic	Insulin	NR	NR	Questionnaire
Mashitani et al. [60]	Straightforward questionnaire	1	1: high adherence 2: medium 3-6: low adherence	1 month	In clinic	Insulin	NR	NR	Questionnaire
Trief et al. [61]	1 item from SDSCA and 1 item from adapted SDSCA	2	≥71.4%: adherence <71,4%: non-adherence	7 days	In clinic	Insulin	No	NR	Single items

MMAS = Morisky Medication Adherence Scale, IAQDM = Insulin Adherence Questionnaire for Diabetes Mellitus, MCQ = Medication compliance questionnaire, MAR-scale = The Medication Adherence Reasons, SDSCA = Summary of Diabetes Self-Care Activities. NR = Not reported, UC = Unclear.

Table 3
Summary of critical appraisal for analytical cross-sectional studies (using JBI checklist).

Reference	1	2	3	4	5	6	7	8	Risk of bias
Adisa & Fakeye (2013) [17]	+	+	+	+	+	–	–	+	Low
Aminde et al. (2019) [54]	–	+	–	+	+	+	+	+	Low
Asheq et al. (2020) [48]	–	+	–	–	+	+	+	–	moderate
Azri et al. (2021) [21]	+	–	–	+	+	+	+	+	Low
Bermeo-Cabrera et al. (2018) [18]	+	+	–	+	+	+	+	+	Low
Chen et al. (2019) [59]	+	+	+	+	+	+	–	+	Low
Cummings et al. (2014) [49]	–	–	+	+	UC	+	+	+	Moderate
Halepian et al. (2018) [23]	+	+	–	–	–	+	–	+	Moderate
Jarab et al. (2014) [43]	+	+	+	+	+	UC	+	+	Low
Javanmardifard et al. (2020) [50]	+	+	+	+	–	–	+	–	Moderate
Martinez-Perez et al. (2020) [51]	+	+	–	+	NA	NA	–	NA	Moderate
Mashitani et al. (2013) [60]	–	+	+	+	+	+	–	+	Low
Mitchell et al. (2013) [44]	–	+	+	+	–	–	–	–	High
Mukherjee et al. (2013) [58]	+	+	+	+	+	UC	–	+	Low
Osborn & Gonzalez (2016) [53]	+	+	+	+	NA	NA	+	NA	Low
Penaforte et al. (2017) [24]	+	+	–	+	–	–	–	–	High
Pirdehghan & Poortalebi (2016) [47]	+	–	+	+	UC	UC	–	+	Moderate
Reach et al. (2013) [45]	+	–	–	–	+	+	+	+	Moderate
Reach et al. (2018) [55]	–	+	+	+	+	+	+	+	Low
Saudi et al. (2021) [52]	+	+	+	–	+	–	+	–	Moderate
Schaper et al. (2017) [19]	+	–	–	–	+	+	–	+	Moderate
Silva-Tinoco et al. (2022) [46]	+	+	+	+	+	+	+	+	Low
Stephenson et al. (2018) [20]	+	–	–	+	–	–	+	–	High
Yong et al. (2022) [22]	+	+	+	+	+	+	+	–	Low

UC = Unclear, NA = Not Applicable, + = Yes, and – = No.

Table 4
Summary of critical appraisal for descriptive cross-sectional studies (using AXIS Appraisal Tool for Cross-Sectional Studies).

Reference	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	Risk of bias
Unni et al. (2022) [57]	+	+	–	+	–	–	–	–	–	–	–	+	–	–	+	+	+	+	–	+	High

+ = Yes, and – = No.

Table 5
Summary of critical appraisal for cohort studies (using JBI checklist).

Reference	1	2	3	4	5	6	7	8	9	10	11	Risk of bias
Chandran et al. (2014) [64]	NA	NA	+	–	–	+	7	+	NA	NA	–	High
Chen et al. (2022) [37]	NA	NA	+	–	–	+	–	+	NA	NA	+	Moderate
Curtis et al. (2017) [65]	NA	NA	+	+	+	+	–	+	NA	NA	+	Low
Eby et al. (2013) [28]	+	+	+	+	+	+	+	+	NA	NA	+	Low
Eby et al. (2020) [31]	+	+	UC	+	+	+	+	+	+	NA	+	Low
Egede et al. (2012) [63]	NA	NA	+	+	+	+	+	+	+	+	+	Low
Egede et al. (2014) [62]	NA	NA	+	+	+	–	+	+	UC	–	+	Moderate
Hood et al. (2021) [36]	+	+	+	+	+	+	–	+	NA	NA	+	Low
Horvat et al. (2018) [39]	+	+	+	+	UC	–	–	+	–	–	–	High
Mcadam-Marx et al. (2022) [66]	NA	NA	+	–	–	+	–	+	NA	NA	UC	High
Pham et al. (2022) [33]	+	+	+	+	+	+	–	+	+	NA	+	Low
Perez-Nieves et al. (2018) [32]	NA	NA	+	+	+	+	–	+	NA	NA	+	Low
Reynolds et al. (2015) [29]	+	+	+	UC	+	+	+	+	NA	NA	–	Low
Slabaugh et al. (2015) [30]	+	+	+	+	+	+	+	+	NA	NA	+	Low
Stephenson et al. (2018) [27]	UC	UC	–	+	+	+	–	+	NA	NA	+	Moderate
Taber et al. (2019) [38]	NA	NA	+	+	+	+	+	UC	UC	–	–	Moderate
Trief et al. (2022) [61]	NA	NA	–	+	+	–	–	+	–	–	+	High
Wei et al. (2014) [25]	+	+	+	+	+	+	–	+	+	+	+	Low
Wright et al. (2022) [34]	+	+	+	–	+	+	–	+	–	+	+	Low
Zhang et al. (2014) [26]	+	NA	NA	+	+	+	+	+	NA	NA	+	Low
Zhou et al. (2018) [35]	+	+	+	–	+	+	–	+	NA	NA	+	Low

UC = Unclear, NA = Not Applicable, + = Yes, and – = No.

Table 6
Summary of critical appraisal for RCT studies (using JBI checklist).

Reference	1	2	3	4	5	6	7	8	9	10	11	12	13	Risk of bias
Galindo et al. (2021) [42]	+	+	+	–	–	–	+	UC	UC	+	–	+	–	High
Machry et al. (2021) [41]	+	+	+	–	–	–	+	UC	+	+	–	+	+	Moderate
Patel et al. (2019) [40]	UC	UC	UC	–	–	UC	+	UC	+	+	–	+	+	High
Sagalla et al. (2022) [56]	UC	UC	UC	–	–	UC	UC	UC	UC	+	–	+	+	High

UC = Unclear, NA = Not Applicable, + = Yes, and – = No.

reported on prescriptions claims for insulin. Curtis et al. [65] calculated PDC using the average number of days between fills for an insulin prescription. Perez-Nieves et al. [32] adjusted for the possibility that insulin may not be used in a method consistent with the days' supply field in a claims database. The study period was either reported as 12 months or 3 years.

60-day gap: As the only study McAdam-Marx et al. [66] used a 60-day gap in insulin supply during the 12-month study period as a measure of insulin adherence. A gap in therapy began the day the insulin supply should have run out per the reported number of days supply dispensed. If a 60-day gap was identified, the patient was considered non-adherent.

3.5. Insulin count

In three studies [39–41], insulin adherence was assessed by insulin counts either at home visits or visits at a clinic. The insulin adherence rate was calculated by dividing the amount of insulin used by the expected amount of insulin to be used, according to the medical records, over the number of days between the respective visits. The result was multiplied by 100 to get the percentage rate.

Different thresholds were used to define adequate adherence. Two of the studies [40,41] defined adherence as taking ≥80% of the insulin and taking <80% as non-adherent. The third study [39] classified patients as adherent when 90–105% of the prescribed insulin was injected, whereas patients who took <90% or >105% were classified as non-adherent.

3.6. Insulin injection data from a smart insulin pen cap

Galindo et al. [42] assessed insulin adherence using insulin injection data from a smart insulin pen cap that tracked date, time, and dosage of each insulin injection. Mistiming was defined as the injection not given within 2h of the expected daily time of administration and dose omissions were defined as doses not recorded. Cumulative insulin adherence was defined as the proportion of expected injections completed, as captured by the number of weekly basal insulin doses administered. Participants were classified as non-adherent when completing <15% of doses (equivalent to missing 6 doses per week).

3.7. Risk of bias

The overall quality of the studies was generally high, with half of the studies (n = 25, 50%) achieving "low risk of bias" fourteen studies (28%) achieved "moderate risk", while the remaining eleven studies achieved "high risk" when using Critical Appraisal Tools (Tables 3–6).

4. Discussion

This systematic review identified various methods used to assess insulin adherence in adults with insulin-treated type 2 diabetes. Most frequently used were self-reported methods, followed by methods using pharmacy claims data. Insulin count and smart insulin pen cap data were much less frequently used.

The widespread use of self-reported methods points towards the convenience of these methods, especially questionnaires; they are non-invasive and easily implemented in the clinical setting, they require minimal effort to complete, and clinicians can offer direct feedback [3,5]. Nevertheless, self-reported methods rely on patient recall and candid responses, exposing the self-reported methods to overestimation of insulin adherence [9]. Therefore, self-reported methods generally are considered an inaccurate method for assessment of insulin adherence [5].

In contrast, methods based on pharmacy claims can provide information on whether a patient obtained the prescribed quantity of insulin over a given time. Yet, a limitation of these methods is that they do not directly measure insulin-injection behavior, rather they measure insulin-collecting behavior because the data source does not contain information on whether the correct insulin dose was injected [64,67]. This challenge is also present when assessing insulin adherence using insulin count; insulin count does not reveal whether insulin dosing and timing were correct or if a patient discarded insulin prior to the count [68].

Moreover, as demonstrated by three of the included studies [25–27] and in line with Stolpe et al. [11] traditional methods using pharmacy claims fall short when applied to insulin because of the individualized dosing regimens. Several of the included studies attempted to account for shortcomings in the calculation of adherence by creating an adjustment factor and applying it to the traditional methods. However, Stephenson et al. [27] indicated that while traditional pharmacy claims-based methods underestimated adherence the adjusted methods overestimated adherence.

While self-reported methods and pharmacy-claims-based calculations are commonly employed in clinical practice, their ability to provide comprehensive insights into timing, dosing size, injection patterns, and adherence behavior is particularly limited [9,53]. Consequently, healthcare professionals who rely on these methods often find themselves making decisions based on assumptions [69]. This can result in the oversight of non-adherence in their patients, potentially resulting in suboptimal treatment and placing individuals at risk of developing complications [10,70,71]. Therefore, different assessment approaches are desired.

The results from this systematic review imply that utilizing insulin injection data from a smart insulin pen cap data [42] can address some of the methodological issues inherent in the assessment of insulin adherence. By using insulin injection data, it was possible to factor in timing, dosing, and type of insulin. This is supported by Munshi et al. [72] who demonstrated that adherence to insulin (dosing and timing) can be objectively assessed using a Bluetooth pen cap technology. Nevertheless, the utilization of insulin injection data in adherence assessment or quantification hasn't been described in detail. Therefore, research focusing on the way insulin injection data can be effectively used is needed.

Traditionally, medication non-adherence is generally defined as taking <80% of prescribed medications [62]. Sokol et al. showed that adherence levels of ≥80% were associated with a lower risk of hospitalization and lower costs of care for patients with diabetes [73]. Nevertheless, results from this review indicate no consensual standard regarding thresholds. Studies using the same method differed in their definition of adherence. For instance, the standard threshold for the MMAS-8 is ≥ 1 and for the MMAS-4 it is < 6. However, Silva-Tinoco et al. [46] defined non-adherence with a score of ≤3 (≥3: adherent) when using MMAS-4, and Schaper et al. [19] used a score of ≥3 for MMAS-8. The diverse use of thresholds challenges comparison of adherence levels in research. Yet, this may not be relevant in the clinic because adherence levels are not likely to be compared across methods.

There is a clear need for further research. The diverse approaches to assessing insulin adherence underline the fact that there is no gold-standard method and even when a similar approach was taken (e.g., self-report), it was used inconsistently, with for example, various self-report measures used, with no standard recall period, question content, response options, and threshold. The diverse approaches for assessing insulin adherence call for more standardized methods for quantification of adherence and this issue could be a viable topic for future research. However, employing insulin injection data is a promising methodology for quantifying insulin adherence and could close the gap that currently exists in insulin adherence assessment.

4.1. Limitations

The inadequate reporting of insulin type (basal/bolus) in the included studies complicated the overview and guidance for method selection. Validity of the review is weakened since mainly one reviewer undertook parts of the review process. To minimize the effect, a co-

author supported the full-text screening and co-authors were continuously consulted to clarify doubts during the review process. Furthermore, the systematic review was strengthened since the structured search was assisted by a research librarian with expertise and experience in medical science and diabetes, ensuring a thorough search. Although the broad search and comprehensive literature strengthen this systematic review, the search was still limited to English and Scandinavian languages, why relevant studies may have been overlooked.

5. Conclusions

This systematic review identified current methods for assessing insulin adherence in adults with insulin-treated type 2 diabetes. All methods were associated with assessment challenges varying in accuracy, complexity, and threshold. In addition, most available methods are severely limited in providing in-depth insights into timing, dosing size, injection patterns, and adherence behavior. However, recognizing diverse types of non-adherence is crucial, as they denote unique behavioral entities requiring individual evaluation. Therefore, future research should prioritize the development of a standardized adherence quantification method that offers comprehensive insights to healthcare professionals.

Employing insulin injection data (e.g., from a smart insulin pen cap) to underlie an assessment method is a potential new approach to objectively assess insulin timing and dosing adherence in adults with insulin-treated type 2 diabetes. This new methodology could close the gap that currently exists in insulin adherence assessment. However, further research is warranted.

Author contribution statement

All authors contributed to the study conception and design. J.T.D.N performed the search, analysis, and interpretation of results supported by S.H. J.T.D.N drafted the manuscript. All authors reviewed the results and approved the final version of the manuscript.

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Declaration of competing interest

M.H.J. is an employee of, and holds stock in, Novo Nordisk A/S. Apart from that, we declare that no conflicts of interest are associated with this publication and that Novo Nordisk A/S did not influence the research or its presentation.

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Appendix A. Supplementary data

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