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Closed-loop insulin therapy for outpatients with type 1 diabetes: a systematic review and meta-analysis

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Abstract

Objective: To evaluate the efficacy and safety of closed-loop insulin therapy in non-pregnant outpatients with type 1 diabetes.

Design: Systematic review and meta-analysis of randomised controlled trials

Data sources: Medline, Embase, Cochrane Library and grey literature through January 11th 2017

Eligibility criteria for selecting studies: Randomised controlled trials in non-pregnant outpatients with type 1 diabetes that compared any closed-loop delivery system with any type of insulin based therapy. Primary outcome was % of time that sensor glucose level was within the near normoglycaemic range (3.9 - 10 mmol/L). Secondary outcomes included % of time sensor glucose level was above 10 mmol/L, % of time sensor glucose level was below 3.9 mmol/L, overnight low blood glucose index, mean sensor glucose level, total daily insulin needs and HbA_{1c}. We used the Cochrane Collaboration Risk of Bias Tool to assess study quality.

Results: Thirty-four studies (792 participants) were included. Twenty-nine trials used a single-hormone closed-loop system, while eight trials assessed a dual-hormone closed-loop system. Percentage of time in near-normoglycaemic range (3.9 – 10.0 mmol/L) was significantly higher with closed-loop, both overnight (weighted mean difference 16.44%, 95% confidence interval 12.85 to 20.02) and throughout 24h (9.54%, 6.99 to 12.09). Closed-loop had a favourable effect on % of overall time with sensor glucose level above 10 mmol/L (−8.32%, −11.53 to −5.10) or below 3.9 mmol/L (−1.65%, −2.11 to −1.19) compared to control. Robustness of findings for the primary outcome was verified in a series of sensitivity analyses, including only trials at low risk of bias (11.98%, 8.99 to 14.96) or trials in unsupervised free-living conditions (10.82%, 8.03 to 13.62). Results were consistent in a subgroup analysis both for single-hormone and for dual-hormone closed-loop systems.

Conclusions: Closed-loop insulin systems are an efficacious and safe therapeutic approach for outpatients with type 1 diabetes.

Introduction

Despite significant advances in the treatment of type 1 diabetes, achieving good glycaemic control while avoiding hypoglycaemia remains a challenge both for patients across all age groups and healthcare providers. Insulin pump therapy and real-time continuous glucose monitoring (CGM) have been shown to improve glycated haemoglobin (HbA_{1c}) and reduce hypoglycaemia,[1] but they are dependent on user inputs, thus are prone to user error.

Closed-loop glucose control, also referred to as the artificial pancreas, is an emerging therapeutic option combining insulin pump and CGM to deliver insulin in a glucose-responsive manner as directed by a control algorithm. Glucagon can also be delivered in a similar glucose-responsive fashion as accommodated by dual-hormone closed-loop systems. Several closed-loop systems have been developed and their safety and efficacy have been evaluated in many studies showing promising results. A previous systematic review provided an overview of trials published until 2014,[2] however, a meta-analysis of closed-loop systems in the outpatient setting has not yet been published. Notably, the FDA has recently approved the first closed-loop system for use by people with type 1 diabetes over 14 years of age, based on a safety outpatient study.[3]

The aim of this systematic review and meta-analysis is to summarise and critically appraise all existing evidence on the clinical efficacy and safety of closed-loop insulin delivery systems for management of type 1 diabetes in the outpatient setting.

Methods

This systematic review and meta-analysis is based on a pre-specified protocol (**appendix 1**) and reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement (**appendix 2**).[4]

Search strategy and selection criteria

We searched MEDLINE, EMBASE, and Cochrane Database of Systematic Reviews (CDSR) and Central Register of Controlled Trials (CENTRAL), from inception to January 11th 2017. Our search strategy was based on search terms describing the intervention (Closed-loop system) in addition to a filter for randomised trials. We omitted terms related to type 1 diabetes to avoid missing potentially relevant studies.[5 6] We used search terms that had been identified from initial scoping searches, target references and browsing of database thesauri (**appendix 3**). We imposed no restrictions based on language or publication status. We also searched ClinicalTrials.gov and sought for additional studies from snowballing of included records.

We included randomised controlled trials in non-pregnant adults, children, and adolescents with type 1 diabetes in the outpatient setting (including hotel, diabetes camp or free-living conditions), irrespective of trial design (parallel or cross-over) or duration of intervention, that compared any closed-loop delivery system with any type of insulin based therapy, including multiple daily injections (MDI), insulin pump therapy, sensor-augmented insulin pump therapy (SAP), or sensor-augmented insulin pump with threshold suspend feature.

Patient involvement

No patients were involved in definition of the research question or the outcome measures, and interpretation or writing up of results. Data relating to the impact of the intervention on participants' quality of life were not extracted. Where possible, results of this systematic review and meta-analysis will be disseminated to the patient community or individual patients and families through the investigators of this meta-analysis.

Data extraction

References identified were imported into a reference management software (Endnote, Clarivate Analytics,

Philadelphia, USA) for de-duplication. Potentially eligible records were exported to Covidence™ (Covidence, Veritas Health Innovation Ltd, Melbourne, Australia) for screening. Three reviewers (E.B., E.A. and K.K.) working independently, screened all records in duplicate, and disagreements were arbitrated by a senior team member (A.T.). Initially, records were screened at title and abstract level, and potentially eligible studies were assessed in full text.

In case multiple records of a single study were retrieved, we collated data from all records, and utilised data from the report with the longest duration of follow-up. We extracted data for study and participant baseline characteristics, interventions, comparators and clinical outcomes in duplicate (E.B., E.A. and T.K.), using an electronic, pilot-tested, data extraction form (**appendix 4**). Disagreements were resolved by consensus or following discussion with a senior reviewer (A.T.).

Outcomes

The primary outcome was % of time that sensor glucose level was within the near normoglycaemic range (3.9 - 10 mmol/L). Secondary outcomes included % of time sensor glucose level was above 10 mmol/L, % of time sensor glucose level was below 3.9 mmol/L, overnight low blood glucose index, mean sensor glucose level, total daily insulin needs and HbA_{1c}. When available, we extracted data both for overall (24h) and overnight periods (as defined in each individual study).

Statistical analysis

We conducted meta-analyses when data were available for at least two studies. We calculated weighted mean differences (WMD) with 95% confidence intervals (CI), using an inverse-variance weighted random effects model. For trials reporting only median and interquartile range (IQR), we retrieved mean and variance values from authors of original reports or used appropriate formulas to calculate mean and variance, making no assumption on the distribution of the underlying data.[7] We combined data both from parallel group and cross-over studies. Finally, for crossover studies that reported their results as parallel group trials, we used appropriate methodology to impute within-patient differences.[8]

We conducted pre-specified subgroup analyses based on the mode of use (overnight or 24h) and type of closed-loop delivery system (single- or dual-hormone). We did a series of a priori decided sensitivity analyses for the primary outcome, excluding trials at unclear or high risk of bias, trials recruiting people in diabetes camps, or trials with supervised use of closed-loop system. We assessed statistical heterogeneity by means of the chi-square-based Cochran Q test and the I^2 statistic, with P values < 0.10 and $I^2 > 50\%$ representing high heterogeneity, respectively. Regarding HbA_{1c}, we synthesized only data from trials with at least 8 weeks' duration per intervention. All analyses were undertaken in RevMan 5.3 (Nordic Cochrane Centre, Copenhagen, Denmark) and STATA 13.0 (Stata Corporation, Texas, USA).

Assessment of risk of bias

Quality assessment was undertaken in duplicate by two independent reviewers (E.B. and E.A.), and disagreements were resolved by consensus or arbitrated by a third reviewer (A.T.). We used the Cochrane Collaboration Risk of Bias Tool to assess risk of bias for the primary outcome for individual studies. For crossover studies we also assessed a series of methodological challenges that are related to this specific design (appropriateness of cross-over design, carry-over effects, unbiased data).[9] We used results to provide an evaluation of the overall quality of the included studies (**appendix 5**) to inform a sensitivity analysis including only trials at overall low risk of bias. We explored risk of bias across studies, both visually using a funnel plot, and formally utilising Egger's statistical test.[10] In case of

significant publication bias, we used the trim and fill method as a sensitivity analysis, to provide an adjusted estimate of the meta-analysis.[11]

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The guarantor had full access to all the data in the study, and had final responsibility for the decision to submit for publication.

Results

Characteristics of included studies

The study selection process is depicted in **Figure 1**. Our search retrieved 9,488 records. Of these, 74 reports qualified for inclusion in our systematic review. After juxtaposing different reports that referred to the same study, data from 32 publications describing 34 trials (792 participants) were used to inform our systematic review.[12-43] One trial did not report data for outcomes assessed and was not included in the meta-analysis.[37]

Study and participants' baseline characteristics are shown in **Table 1**. The vast majority of included trials utilised a crossover design,[12-27 30 32-43] whereas only three trials were of parallel design.[28 29 31] In twenty-eight trials duration was less than four weeks,[12-22 24 26-31 33-41] whereas in the remaining six trials it ranged from eight to thirty weeks.[23 25 32 42 43] Thirteen trials recruited children or adolescents,[16 19 20 23 30 31 34-37 40 41 43] eleven trials recruited adults,[13-15 18 22 24-26 35 42 43] while ten trials recruited a mixed population.[12 17 21 27-29 32 33 38 39] In sixteen trials closed-loop was used overnight,[14 15 20 21 23 25 27 30 32-34 37-39 42 43] while in the remaining eighteen trials closed-loop was used throughout 24 hours.[12 13 16-19 22 24 26 28 29 31 35 36 40 41 43] Twenty-nine trials compared a single-hormone closed-loop system (mostly with sensor augmented pump therapy),[12 14-17 19-34 37-43] while eight trials assessed dual-hormone closed-loop systems in comparison mainly to conventional insulin pump therapy.[13 18 20-22 35 36] Among trials evaluating single hormone closed-loop systems, nine trials used the DiAs platform,[14-16 19 24 25 27 28 31] eight trials used the Florence algorithm,[23 26 37 40-43] four trials used the MD-Logic algorithm,[12 32-34] and five trials used the Medtronic closed-loop.[17 29 30 38 39] Most of the trials used a model predictive control algorithm,[18-26 35-37 40-43] six trials used a proportional integral derivative algorithm,[13 17 29 30 38 39] four trials used a fuzzy logic algorithm,[12 32-34] while the rest of the trials used other algorithms or did not provide relevant details.[14-16 27 28 31] Finally, eleven trials were held in a diabetes camp or a guesthouse,[19 20 24 27-31 34-36] while in twenty-three trials subjects were at home.[12-18 21-23 25 26 32 33 35 37-43] Only in a small subset of trials were subjects using closed-loop unsupervised under free-living conditions,[12 23 26 40-43] while the remaining studies either used remote monitoring or did not provide relevant details. Participants' mean age and HbA_{1c} at baseline ranged across studies from 12.0 to 47.0 years and from 7.0% to 8.6%, respectively.

Risk of bias assessment results

Risk of bias for the primary outcome is presented in **appendices 6** and **7**. Most studies were deemed at high risk for bias due to incomplete outcome data, because either they reported median instead of mean values or reported results that required extensive use of imputation methods to be used in meta-analyses. Both visually and formally, there was no evidence of publication bias for percentage of overall time near normoglycaemia (P=0.247). However, there was significant publication bias (P=0.010) for percentage of overnight time spent in near normoglycaemia, and visual inspection of the counter-enhanced funnel plot suggested that small negative studies were missing (**appendix 8**). Nevertheless, the adjusted meta-analytic estimate following use of the trim and fill method remained in favour of the

closed-loop (weighted mean difference 12.52%, 95% confidence interval 8.90 to 16.13, P<0.001).

Primary outcome

Compared with control, use of closed-loop was associated with increased percentage of overall time (24h) spent in near normoglycaemia (3.9 – 10.0 mmol/L) (9.54%, 95% confidence interval 6.99 to 12.09). This effect was consistent both for trials using closed-loop overnight (7.80%, 6.06 to 9.54), or throughout 24h (10.46%, 6.58 to 14.34) (**Figure 2**). This favourable effect was more evident on the percentage of time spent in near normoglycaemia overnight (16.44%, 12.85 to 20.02), and was consistent both when closed-loop was used either only overnight (17.15%, 13.26 to 21.04) or throughout 24h (15.67%, 9.19 to 22.16) (**Figure 3**).

Secondary outcomes

Use of closed-loop had a favourable effect on time spent in hyperglycaemia (> 10 mmol/L) during the whole day which was decreased by 8.32% (5.10 to 11.53) both in trials where closed-loop was used only overnight (−6.51%, −9.42 to −3.60), and in trials using closed-loop throughout 24h (−8.62%, −12.41 to −4.84) (**Figure 4**). Similarly, time spent at glucose concentrations higher than 10.0 mmol/L overnight was also decreased compared to control (−12.99%, −16.73 to −9.25), both in trials that used closed-loop either only overnight (−10.85%, −14.61 to −7.09), or throughout the day (24h) (−15.44%, −23.12 to −7.76) (**appendix 9**).

Overall time spent at glucose concentrations lower than 3.9 mmol/L over a period of 24h was also decreased compared to control (−1.65%, −2.11 to −1.19) (**Figure 5**). Results were consistent for overnight time spent at concentrations lower than 3.9 mmol/L (−2.54%, −3.13 to −1.94) (**appendix 10**). Consistently, use of closed-loop was associated with a decrease in overnight low glucose blood index (−0.42, −0.56 to −0.27).

Compared to control, use of closed-loop had a favourable effect on 24h mean sensor blood glucose, which was decreased by 0.51 mmol/L (0.27 to 0.76) (**Figure 6**). Results were more favourable for overnight mean sensor blood glucose levels (−0.84 mmol/L, −1.10 to −0.58) (**appendix 11**). These findings were consistent with the effect of closed-loop on HbA_{1c} (−0.26%, −0.38 to −0.13 compared to control, three studies) (**Figure 7**). Finally, there was no difference between closed-loop and control in the mean daily insulin needs (−0.23 IU, −2.07 to 1.61) (**Figure 8**).

Sensitivity and subgroup analyses

Results for the % of time spent in near normoglycaemia were similar in a sensitivity analysis including only trials at low risk of bias, both for 24h (11.98%, 8.99 to 14.96) and for overnight (20.86%, 12.69 to 29.03) (**appendices 12 and 13**). Similarly, results did not differ in a series of sensitivity analyses excluding trials that used closed-loop in diabetes camps or including only trials which used closed-loop in unsupervised patients in free-living conditions, both for 24h (10.66%, 8.63 to 12.69, and 10.82%, 8.03 to 13.62 respectively) (**appendices 14 and 15**) and for overnight time in near normoglycaemia (14.52%, 10.50 to 18.54, and 15.51%, 8.10 to 22.92 respectively) (**appendices 16 and 17**).

We also did a post hoc sensitivity analysis excluding trials comparing closed-loop systems with low glucose suspend systems, to explore their effect on hypoglycaemia. Both overall (24h) and overnight time spent at concentrations lower than 3.9 mmol/L was decreased compared to control (−1.74%, −2.26 to −1.23, and −2.60%, −3.27 to −1.93 respectively) (**appendices 18 and 19**).

Finally, in a pre-specified subgroup analysis based on type of closed-loop utilised (single- versus dual-hormone closed-loop), eight trials compared dual-hormone closed-loop mostly with insulin pump therapy, while the vast majority of twenty-eight eligible trials compared single hormone closed-loop with sensor augmented pump therapy. Results were consistent with those of the main analysis, for all outcomes (**Table 2**).

Discussion

Summary of key findings

Our data suggest that closed-loop therapy is associated with an increased percentage of time spent in normoglycaemia compared with control treatment, mainly due to its favourable effect during the overnight period. This was also verified by its effect both on hyperglycaemia and on hypoglycaemia. Results were robust both for single- and dual-hormone systems, and were consistent in all sensitivity analyses performed. Finally, this favourable effect was also evident in the relative reduction of mean blood glucose levels by 0.51 mmol/L, a finding consistent with a reduction of HbA_{1c} of at approximately 0.3% recorded in trials with a duration per intervention of more than eight weeks.[44 25 43] In total, our results reflect the progress made over the last decades of extensive research and development in this field.

Strengths and limitations

To the best of our knowledge, this is the first systematic review and meta-analysis evaluating the efficacy and safety of outpatient closed-loop systems use in type 1 diabetes. Despite heterogeneity in interventions and comparators utilised, our work provides the most valid overview on this field. Composition of the review team ensured appropriate methodological and subject expertise, but also access to additional study data from individual studies.[23 26 40-43] To ensure internal validity of our conclusions we implemented current guidelines for the conduct and reporting of systematic reviews,[4] and adhered to a pre-specified protocol with minimal deviations. We undertook a comprehensive search of multiple databases without imposing any restrictions based on language or publication type, and assessed quality of trials using valid methodological tools. Moreover, we synthesised existing data using appropriate methodology to account for inappropriate reporting and analysis methods utilised in some of the trials included. In addition, we conducted a range of sensitivity analyses excluding trials utilising remote monitoring or trials at high risk of bias to examine clinical relevance and robustness of our findings. Finally, we focused on outcomes that are considered most important in trials assessing closed-loop systems,[45] and used data only from randomised controlled trials ensuring maximum strength of evidence level.

We acknowledge several limitations both at the evidence and review level. Most trials had a small sample size, limiting the precision of our effect estimates. Despite using broad inclusion criteria, existing studies provide limited insight regarding clinically relevant sub-populations, such as people with increased hypoglycaemia burden, hypoglycaemia unawareness, gastroparesis, blindness, high HbA_{1c}, treated with corticosteroids, or from ethnic minorities.[46] Many trials were at high or unclear risk of bias due to sub-optimal reporting. In particular, most trials reported effect estimates for outcomes related to hypoglycaemia using median values and interquartile ranges, thus we had to impute mean and standard deviation values for use in meta-analyses. In addition, several crossover trials reported results as parallel group studies,[28 29 31] which also required use of imputation methods to allow synthesis of results.

Furthermore, we did not register our protocol at a publicly available database, and submitted it only for internal peer review. We focused on surrogate outcomes and did not extract evidence for specific patient-important outcomes, such as quality of life, incidence of ketoacidosis, or catheter occlusion. Instead, we adopted a more practical approach focusing on outcomes we expected to be most and best reported in trials.[45] Moreover, for missing or inappropriately reported data we refrained from contacting study authors other than those being members of the review group, but used appropriate methodology to impute data.[47] Finally, most analyses had a high degree of heterogeneity, which may be attributed to differences in CGM utilised, sensor accuracy and performance, compliance with closed-loop use in

the context of supervised and unsupervised settings, and comparators utilised in the context of availability or not of sensor glucose values during control therapy. Nevertheless, robustness of our results was verified in a series of sensitivity analyses mitigating some of these shortcomings.

Implications

Our study highlights a series of pitfalls in the conduct and reporting of closed-loop trials. Many trials had a short duration or were designed to assess the feasibility or safety, rather than long-term effectiveness. Despite existing guidance, we noted significant variation in outcomes assessed and metrics used.[48] It is important for research groups to report a minimum set of agreed outcome measures and respective metrics.[45] To ensure the clinical relevance and feasibility of this core outcome set, it is crucial that its development involves all key stakeholders, including patients, their families, clinicians, researchers, statisticians, methodologists, industry representatives, regulatory authorities and payers. To maximise yield of information and to facilitate analysis and synthesis of the totality of evidence, it may be important to agree on the use of a common individual patient data repository.[49 50] In order to enhance the external validity of evidence, it is recommended for future trials to broaden inclusion criteria and recruit more heterogeneous populations, including ethnic minorities.

The performance of current closed-loop systems could be enhanced by optimising system components. The use of novel insulin analogues with faster pharmacokinetics,[51] the development of room-temperature stable glucagon preparation and integration of closed-loop components in a single device could further enhance user experience, closed-loop utility, thus increase uptake. Future research may explore the potential differences between individual components (algorithms, CGMs) and determine their clinical relevance. It remains for upcoming trials to clarify the differences between single-hormone and dual-hormone systems, and explore the use of closed-loop in specific groups of people with type 2 diabetes, such as those with inpatient hyperglycaemia,[52] who may benefit from it. Finally, to support adoption, it is essential to assess cost-effectiveness to allow for reimbursement by various healthcare systems, and to ensure that adequate infrastructure exist.

Conclusions

Our systematic review and meta-analysis demonstrated that closed-loop systems are an efficacious and safe therapeutic approach for people with type 1 diabetes, leading to increased time within normoglycaemic range, and decreased time in hypo- and hyperglycaemia. The results were verified for all types of closed-loop and in all sensitivity analyses. Further research with rigorous studies, co-operation of research groups in terms of outcome reporting, and cost-effectiveness data are required to verify these findings and support adoption of closed-loop systems in clinical practice.

Contributors: EB, HT and AT conceived and designed the study. EB and EA did the scientific literature search. EB, KK, EA and AT did literature screening. EB, EA, TK and AT extracted data. EB, EA and AT did quality assessment of included studies. EB, TK, ABH, RH and AT did the analyses. EB, KK, HT, MT, TK, RH and AT wrote the first draft of the report. All authors contributed to interpretation and edited the draft report. AT is the study guarantor, had full access to all of the trial level data in the study, takes responsibility for the integrity of the data, and accuracy of the data analysis, and had the final responsibility to submit for publication.

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Competing interests

All authors have completed the ICMJE uniform disclosure at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; KK reports honoraria fees from Medtronic, Novo Nordisk and Sanofi, outside the submitted work; MT reports personal fees from Medtronic and Novo Nordisk, outside the submitted work; RH reports personal fees from Eli Lilly, Novo Nordisk, BBraun and Medtronic, grants from National Institute for Health Research Cambridge Biomedical Research Centre and Wellcome Strategic Award outside the submitted work, and reports patents and patent applications; AT reports honoraria fees from AstraZeneca, Boehringer Ingelheim and Novo Nordisk, outside the submitted work; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: Not required.

Data sharing: No additional data available.

The manuscript's guarantor affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

We attest that we have obtained appropriate permissions and paid any required fees for use of copyright protected materials.

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What is already known on this topic

Individual studies have demonstrated the safety and efficacy of closed-loop insulin systems in inpatients, patients under close monitoring or outpatients with type 1 diabetes.

Recently, the FDA approved the first closed-loop system for use by people aged 14 years and older with type 1 diabetes.

What this study adds

This meta-analysis documents that closed-loop therapy significantly improves glycaemic control while reducing the burden of hypoglycaemia in outpatients with type 1 diabetes.

Results are consistent for people using unsupervised closed-loop in free-living conditions, and both for single- and dual-hormone closed-loop systems.

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Identifier	Trial registration details	Setting	Population	CL	Comparator	Intervention duration	Patients (n)
Biester 2016[12]	NCT02636491	Home	Adults & adolescents	MD-Logic	SAP	24h	10
Blauw 2016[13]	NCT02160275	Home	Adults	Inreda Dual-hormone CL	Insulin pump therapy	24h	10
Brown 2015a[14]	NCT01939834 NCT02008188	House/Hotel	Adults	DiAs USS	SAP	Overnight	10
Brown 2015b[15]	R01DK085623	Home	NR	DiAs	SAP	Overnight	5
Chernavvsky 2016[16]	NCT01890954	Research house	Adolescents	DiAs USS	SAP	24h	16
De Bock 2015[17]	ACTRN12614001005640	Home	Adults & adolescents	Medtronic PID IFB	SAP + LGS	24h	8
El-Khatib 2016[18]	NCT02092220	Home	Adults	Dual-hormone CL	Insulin pump therapy or SAP	24h	39
Favero 2016[19]	NCT0260878	Diabetes camp	Children	DiAs	SAP	24h	30
Haidar 2015a[20]	NCT02189694	Diabetes camp	Adolescents	Single-hormone CL	Insulin pump therapy	Overnight	33
Haidar 2015b[20]	NCT02189694	Diabetes camp	Adolescents	Dual-hormone CL	Insulin pump therapy	Overnight	33
Haidar 2016a[21]	NCT01905020	Home	Adults & adolescents	Single-hormone CL	Insulin pump therapy	Overnight	28
Haidar 2016b[21]	NCT01905020	Home	Adults & adolescents	Dual-hormone CL	Insulin pump therapy	Overnight	28
Haidar 2017a[22]	NCT01966393	Home	Adults	Single-hormone CL	SAP	24h	23
Haidar 2017b[22]	NCT01966393	Home	Adults	Dual-hormone CL	SAP	24h	23
Hovorka 2014[23]	NCT01221467	Home	Adolescents	Florence	SAP	Overnight	16
Kovatchev 2014[24]	NCT01714505 NCT01727817 NCT01742741	Hotel/Guesthouse	Adults	DiAs SSM	SAP	24h	20
Kropf 2015[25]	NCT02153190	Home	Adults	DiAs SSM	SAP	Evening and night	32
Leelarantha 2014[26]	NCT01666028	Home	Adults	Florence	SAP	24h	17
Ly 2014[27]	NCT01973413	Diabetes camp	Adults & adolescents	DiAs USS	SAP	Overnight	20
Ly 2015a[29]	NCT02366767	Diabetes camp	Adults & adolescents	Medtronic PID IFB	SAP + LGS	24h	21
Ly 2015b[28]	NR	Diabetes camp	Adults & adolescents	DiAs	SAP	24h	16
Ly 2016a[31]	NCT02147860	Diabetes camp	Adolescents	DiAs USS	SAP	24h	33
Ly 2016b[30]	NR	Diabetes camp	Children & adolescents	Medtronic PID IFB	SAP	Overnight	21
Nimri 2014[32]	NCT01238406	Home	Adults & adolescents	MD-Logic	SAP	Overnight	24
Nimri 2016[33]	NCT01726829	Home	Children, adolescents &	MD-Logic	SAP	Overnight	75
Phillip 2013[34]	NCT01238406	Diabetes camp	Adolescents	MD-Logic	SAP	Overnight	54
Russell 2014a[35]	NCT01762059	Home & Hotel	Adults	Dual-hormone CL	Insulin pump therapy	24h	20
Russell 2014b[35]	NCT01833988	Diabetes camp	Adolescents	Dual-hormone CL	Insulin pump therapy	24h	32
Russell 2016[36]	NCT02105324	Diabetes camp	Preadolescents	Dual-hormone CL	Insulin pump therapy or SAP	24h	19
Schierloh 2015[37] †	NR	Home	Children	Florence	SAP	Overnight	15
Sharifi 2015[38]	NR	Home	Adults & adolescents	CL PID IFB	SAP + LGS	Overnight	11
Sharifi 2016[39]	NR	Home	Adults & adolescents	Medtronic PID IFB	SAP + LGS	Overnight	28

Tauschmann 2016a[41]	NCT01873066	Home	Adolescents	Florence	SAP	24h	12
Tauschmann 2016b[40]	NCT01873066	Home	Adolescents	Florence	SAP	24h	12
Thabit 2014[42]	NCT01440140	Home	Adults	Florence	SAP	Overnight	24
Thabit 2015a[43]	NCT01961622	Home	Adults	Florence	SAP	24h	33
Thabit 2015b[43]	NCT01778348	Home	Children & adolescents	Florence	SAP	Overnight	25

Table 1. Baseline characteristics of studies included in the systematic review. DiAs: Diabetes Assistant. USS: Unified Safety System. SAP: Sensor-augmented pump therapy. NR: Not Reported. MPC: Model Predictive Control. PID: Proportional Integral Derivative. IFB: Insulin Feedback. LGS: Low Glucose Suspend. CL: Closed Loop. SSM: Safety Supervision Module. †: not included in the meta-analysis.

	Single hormone closed-loop	Dual-hormone closed-loop
% of overall time between 3.9 – 10.0 mmol/L	8.02% (5.25 to 10.80)	15.16% (10.68 to 19.63)
% of overnight time between 3.9 – 10.0 mmol/L	13.88% (9.94 to 17.81)	22.84% (15.08 to 30.60)
% of overall time > 10.0 mmol/L	−6.82% (−10.58 to −3.06)	−11.58% (−18.17 to −4.99)
% of overnight time > 10.0 mmol/L	−10.50% (−14.39 to −6.60)	−17.21% (−25.58 to −8.85)
% of overall time < 3.9 mmol/L	−1.39% (−1.84 to −0.93)	−2.95% (−4.03 to −1.87)
% of overnight time < 3.9 mmol/L	−2.15% (−2.74 to −1.57)	−4.04% (−5.59 to −2.48)
Overnight low blood glucose index (LBGI)	−0.42 (−0.56 to −0.27)	NE
Overall mean sensor glucose value	−0.38 mmol/L (−0.65 to −0.12)	−0.90 mmol/L (−1.48 to −0.32)
Overnight mean sensor glucose value	−0.67 mmol/L (−0.94 to −0.39)	−1.47 mmol/L (−2.14 to −0.79)
Overall daily insulin needs	−0.64 IU (−2.40 to 1.13)	NE

Table 2. Subgroup analysis based on type of closed-loop utilised (single closed-loop study applied mainly sensor-augmented pump therapy as comparator; dual-hormone closed-loop applied mainly conventional pump therapy as comparator). Values presented are weighted mean differences (95% confidence intervals). NE: Not estimable

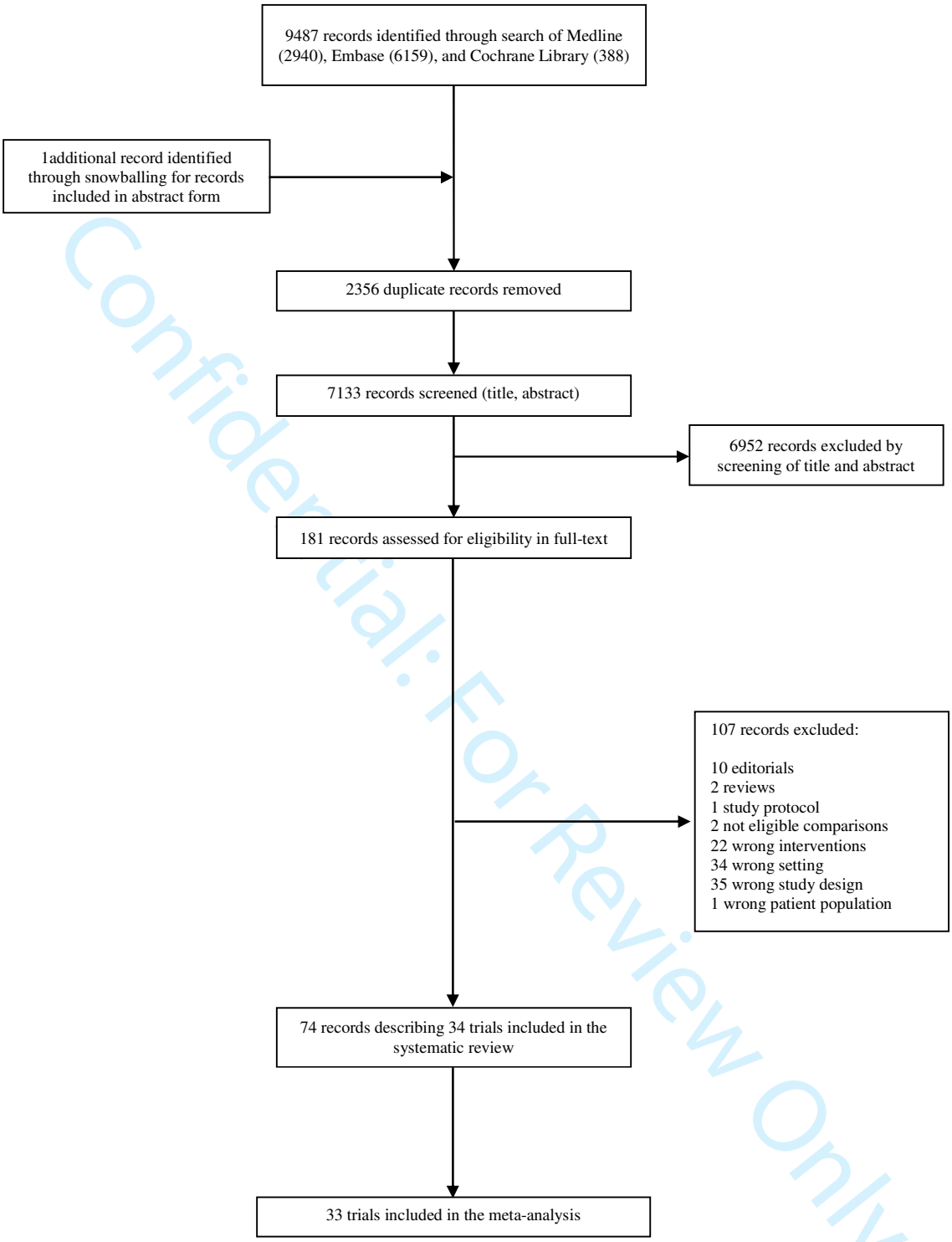


Figure 1. Flow diagram of study selection process.

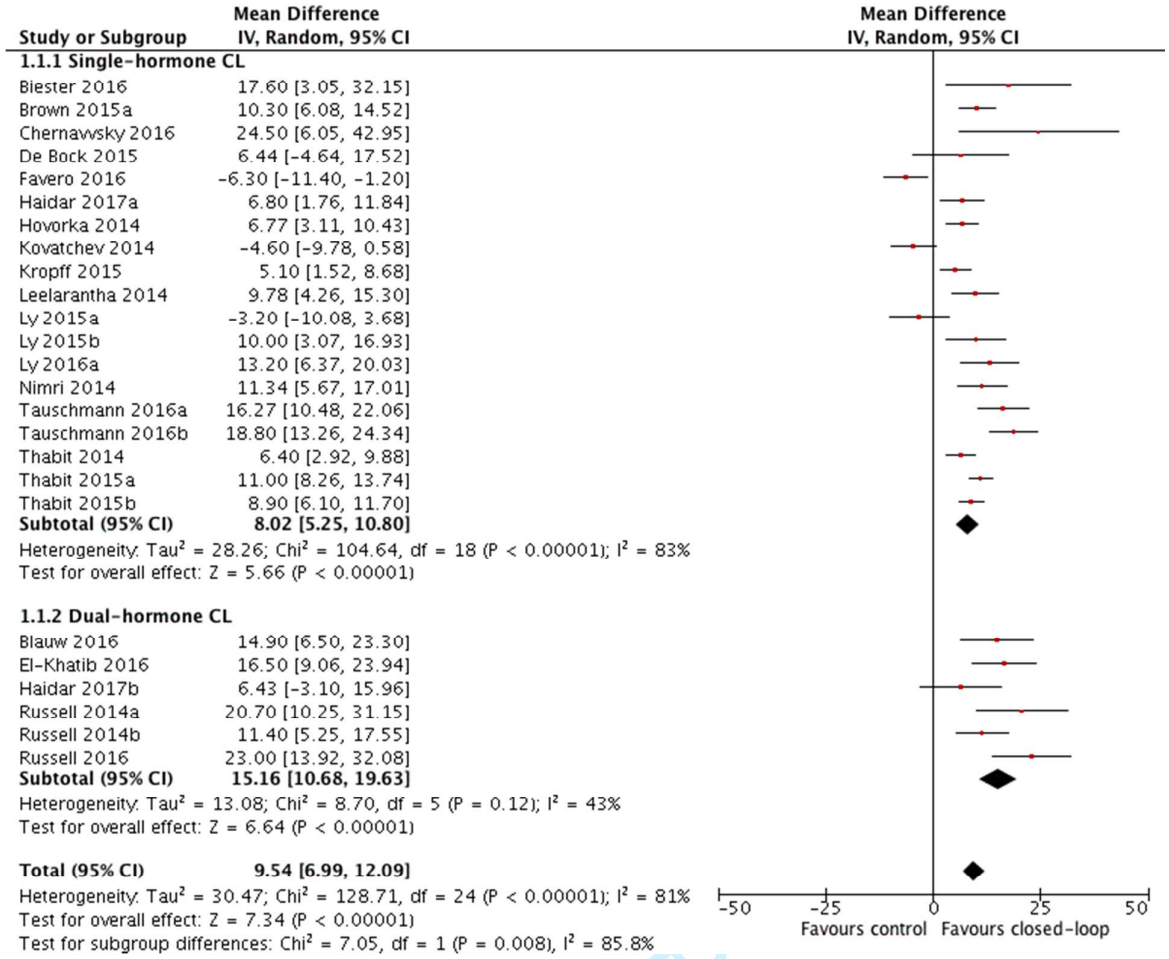


Figure 2. Weighted mean difference in % of overall time in near normoglycaemic range (3.9 – 10.0 mmol/L). Closed loop versus control treatment.

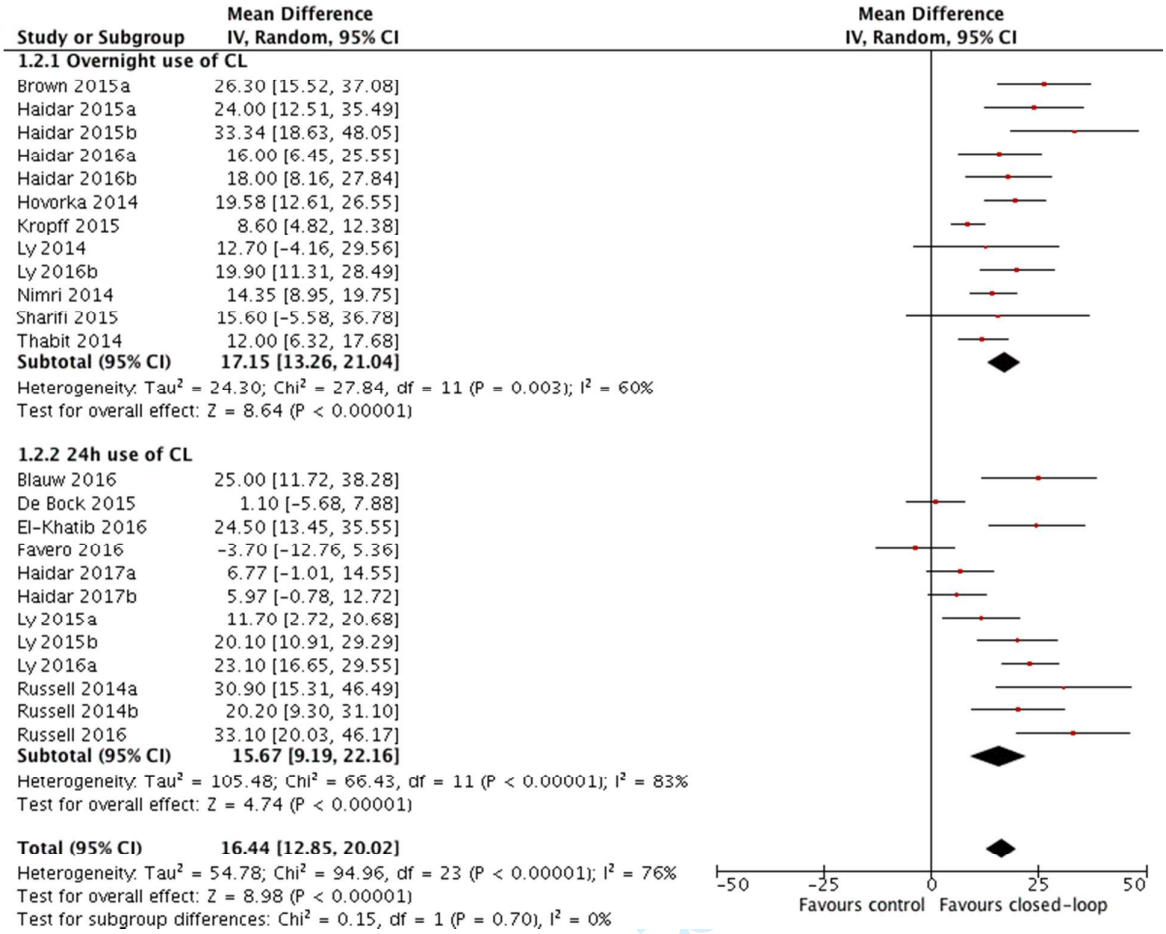


Figure 3. Weighted mean difference in % of overnight time in near normoglycaemic range (3.9 – 10.0 mmol/L). Closed-loop versus control treatment.

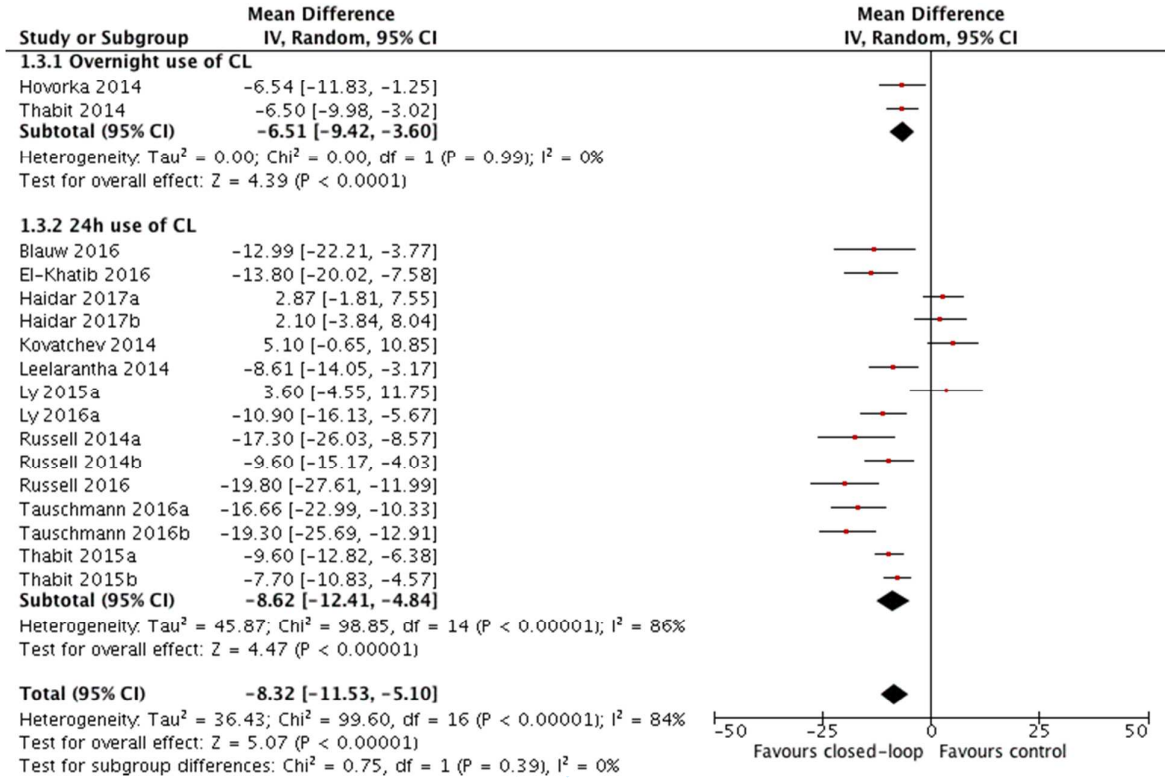


Figure 4. Weighted mean difference in % of overall time glucose was > 10.0 mmol/L. Closed-loop versus control treatment.

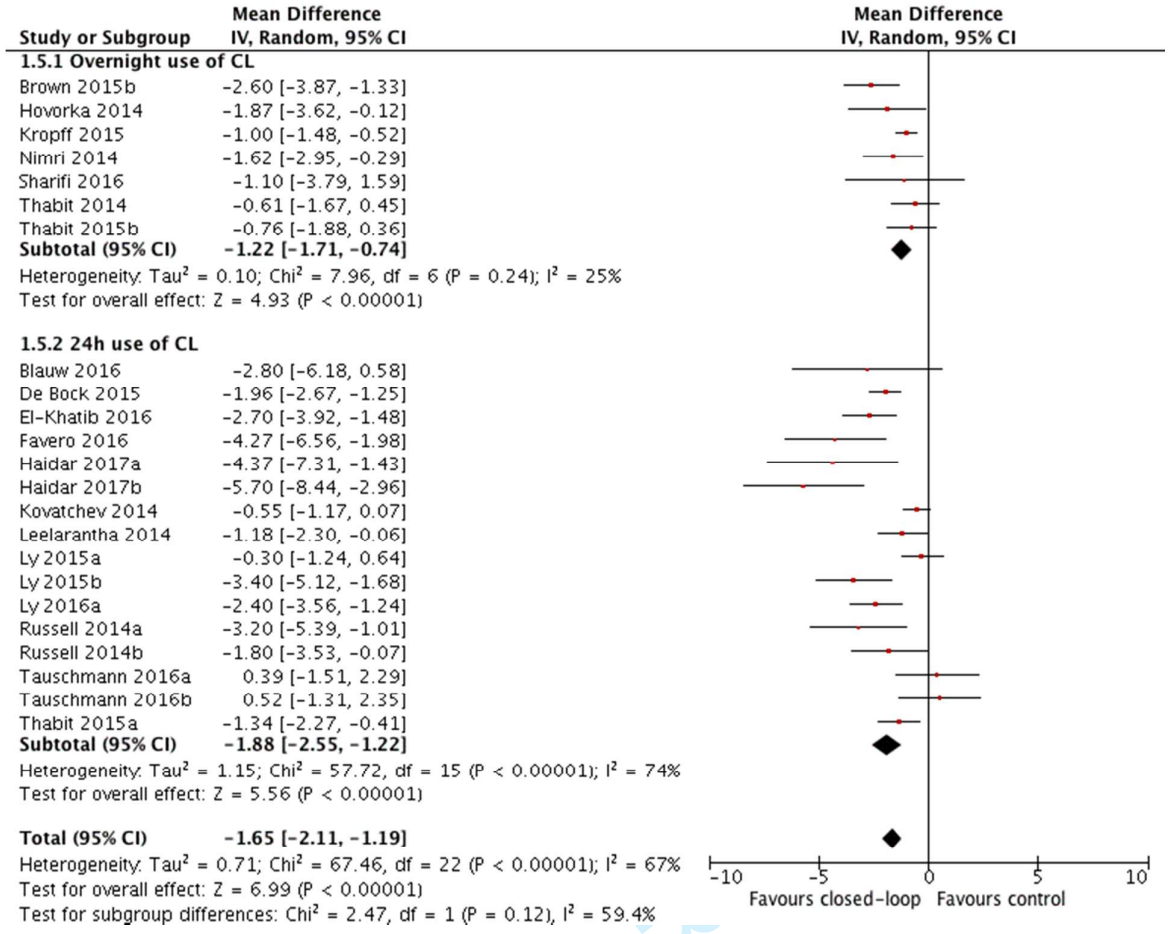


Figure 5. Weighted mean difference in % of overall time glucose was < 3.9 mmol/L. Closed-loop versus control treatment.

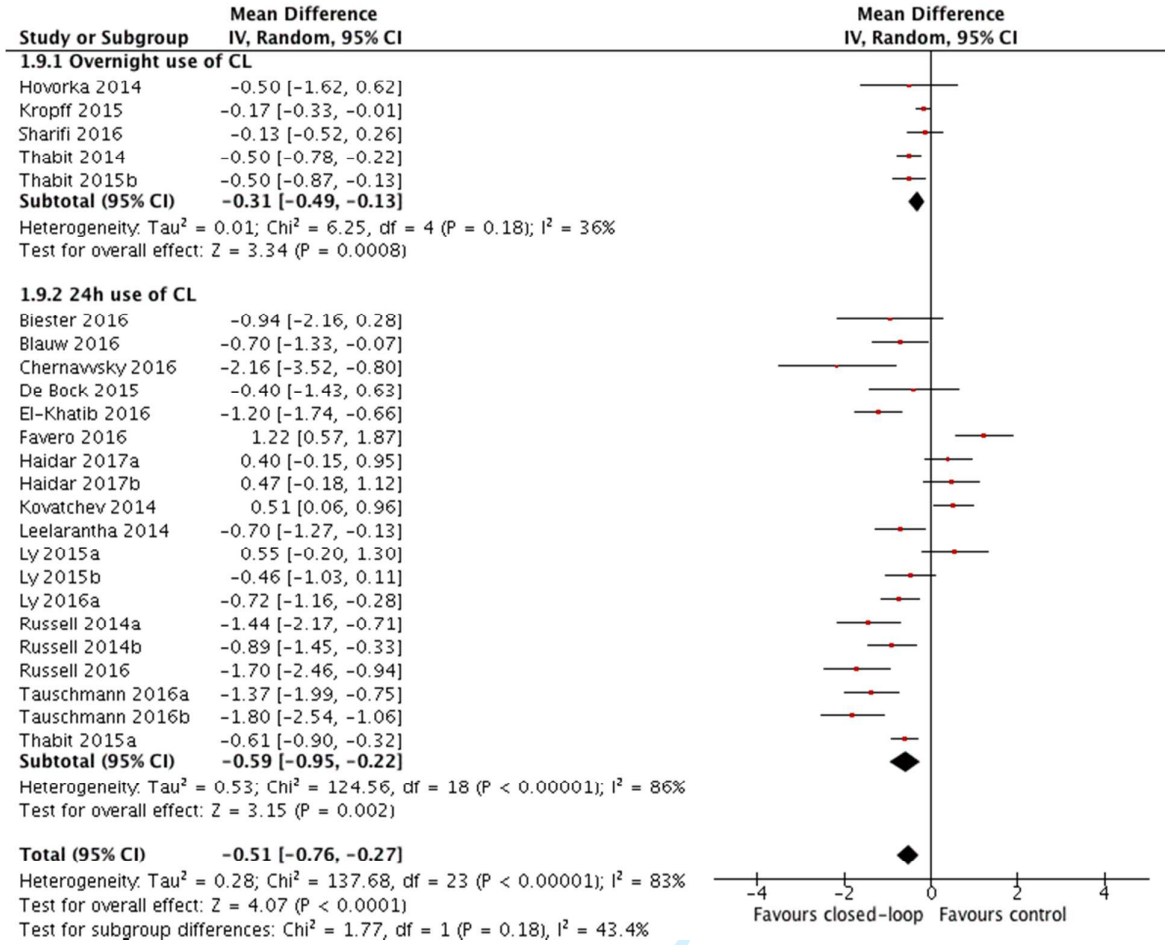


Figure 6. Weighted mean difference in overall mean sensor blood glucose (mmol/L). Closed-loop versus control treatment.

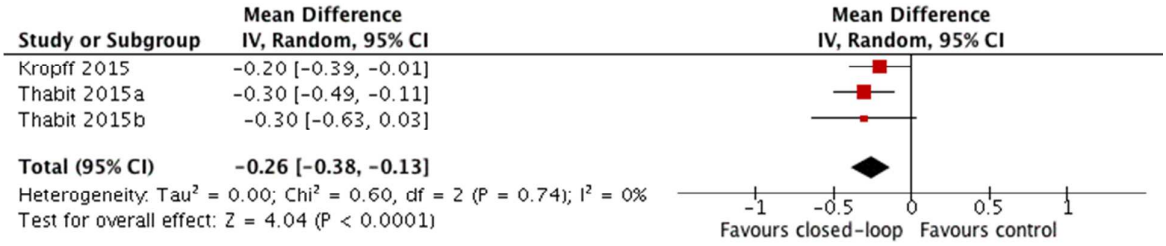


Figure 7. Weighted mean difference in change in HbA_{1c} (%). Closed-loop versus control treatment.

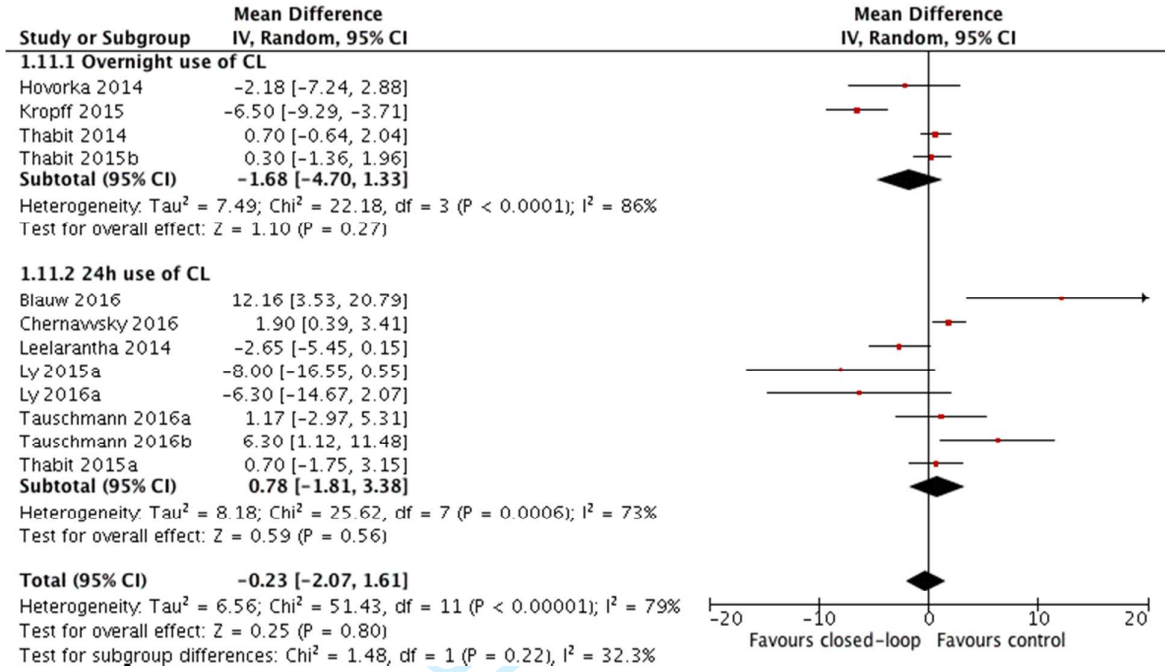


Figure 8. Weighted mean difference in overall daily insulin needs (IU). Closed-loop versus control treatment.

Appendices

Appendix 1

Protocol

Closed-loop insulin therapy for type 1 diabetes: a systematic review and meta-analysis

Inclusion and exclusion criteria

Population

- Non-pregnant adults and children with type 1 diabetes, as defined in each individual study that were assessed in an outpatient setting (including hotel and diabetes camp settings) or under free-living conditions in their home and work environment.

Intervention

- Any closed-loop delivery system, defined as a system utilising a control algorithm, which autonomously increases and decreases insulin delivery based on real-time sensor glucose concentrations, assessed either during daytime, overnight period, or the day-and-night period.

Comparators

- Any type of insulin based therapy, including multiple daily injections (MDI), insulin pump therapy, sensor-augmented insulin pump therapy, sensor-augmented insulin pump with a low glucose suspend (LGS) feature.

Outcomes

Primary outcome:

Proportion of time that glucose level was within the near normoglycaemic range (3.9 - 10 mmol/l) (both overnight, and during a 24h period).

Secondary outcomes:

- % of time during day and night (24h) or night only that glucose level was below 3.9 mmol/l
- % of time during day and night (24h) or night only that glucose level was above 10 mmol/l
- area under the curve (AUC) of glucose < 3.5 mmol/l
- low blood glucose index (LBGI)
- Mean blood glucose levels
- HbA_{1c}
- Insulin amount administered

Study design

Randomised controlled trials, with parallel group or cross-over design, irrespective of duration of intervention.

Information sources

Search strategy

Search strategy based only on the intervention (Closed-loop system) and a filter for randomised trials, to avoid missing potentially relevant studies, as recommended in the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care and the Cochrane Handbook. We will use search terms that have been identified from initial scoping searches, target references and browsing of database thesauri (i.e. Medline

MeSH and Embase Emtree). We have developed search strategies specifically for each database based on the search features and controlled vocabulary of every individual bibliographic database. We will search the following databases and resources (via relevant interfaces):

- MEDLINE (PubMed)
- EMBASE (OvidSP)
- Cochrane Database of Systematic Reviews (CDSR) (Wiley Online Library)
- Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley Online Library)

We will also look for completed and on-going trials by searching the NIH ClinicalTrials.gov (http://www.clinicaltrials.gov/) trial registry.

We will impose no restrictions based on language or publication status. References identified will be imported in Endnote reference management software for de-duplication. Finally, we will export potentially eligible records to Covidence™ for further handling (screening and data extraction).

Study selection & data collection

All records will be screened via Covidence™, by two reviewers, working independently, and disagreements will be arbitrated by a senior team member. Initially, records will be screened at title and abstract level. Full texts for potentially eligible studies will be imported into Covidence™ and screened as described previously. Finally, we will extract data for the following variables: study and participant baseline characteristics, details for the interventions (i.e. single-hormone, algorithm utilised) and comparators, and clinical outcomes. Data will be extracted by two reviewers, using a piloted, data extraction form. Disagreements will be resolved by consensus or following discussion with a senior reviewer. For crossover studies that report their results as parallel group trials, we will use appropriate methodology to impute within-patient differences.

Study quality assessment

We will assess the methodological quality of included RCTs using the Cochrane Risk of Bias Tool. For crossover studies we will use a modified version to assess a series of methodological challenges that are linked with this specific design. We will use results for descriptive purposes to provide an evaluation of the overall quality of the included studies, but also to inform a sensitivity analysis. Quality assessment will be undertaken by two independent reviewers, and disagreements will be resolved by consensus or arbitrated by a third reviewer.

Data synthesis

Methods of analysis

We will combine data both from parallel group and cross-over studies if appropriate. We will calculate mean differences with 95% confidence intervals, using an inverse-variance weighted random effects model.

Subgroup analyses

Depending on accrued evidence, for the primary outcome we plan to conduct subgroup analyses based on mode of intervention (overnight or 24h use of closed-loop delivery system), and type of closed-loop (single vs dual-hormone closed-loop).

Sensitivity analyses

We will do sensitivity analysis for the primary outcome excluding trials at unclear or high risk of bias, trials conducted at other settings than home or hotel, and supervised trials.

Investigation of heterogeneity

We will assess presence of statistical heterogeneity by means of the chi-square-based Cochran Q test and the magnitude of heterogeneity by means of the I^2 statistic, with P values < 0.10 and $I^2 > 50\%$ respectively representing high heterogeneity. All analyses will be undertaken in Revman.

This protocol was submitted as a module assignment for the Systematic Review module for an MSc on Medical Research Methodology at Aristotle University Thessaloniki, and internally peer reviewed.

Appendix 2: PRISMA statement

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3, appendix 1
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 3
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4, appendix 4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4, appendix 5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	4
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	4

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	4
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	5, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	5, appendices 6-7
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	6, Figures 2-8, appendices 9-11
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	6, Figures 2-8, appendices 9-11
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	5, appendix 8
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	6, Table 2, appendices 12-19
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	7
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	7-8
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	8
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	9

Appendix 3

Search strategy

Embase (OvidSP)

#1. Artificial pancreas.mp. or exp artificial pancreas/
#2. exp bioartificial organ/
#3. (pancreas or insulin or diabet*).mp.
#4. 2 and 3
#5. exp bionics/
#6. 3 and 5
#7. bionic pancreas.mp.
#8. synthetic pancreas.mp
#9. artificial endocrine pancreas.mp.
#10. artificial beta cell*.mp.
#11. artificial b cell*.mp.
#12. artificial b-cell*.mp.
#13. closed-loop*.mp.
#14. 3 and 13
#15. closed loop*.mp.
#16. 3 and 15
#17. bioartificial pancreas.mp.
#18. bio-artificial pancreas.mp.
#19. 1 or 4 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 14 or 16 or 17 or 18
#20. (pump or delivery or release).mp.
#21. exp infusion pump/
#22. exp insulin infusion/
#23. 20 or 21 or 22
#24. glucose.mp.
#25. exp ambulatory monitoring/
#26. 24 and 25
#27. (monitor* or sensor* or sensing).mp.
#28. 24 and 27
#29. "sensed glucose".mp.
#30. (CGM or CGMS or glucosemeter or GlucoWatch or Guardian or Medtronic).mp.
#31. "freestyle navigator".mp.
#32. "glucose measurement".mp.
#33. exp blood glucose monitoring/
#34. 26 or 28 or 29 or 30 or 31 or 32 or 33
#35. (algorithm or computer or program* or modul* or controller or smartphone or tablet or "model predictive control" or MPC or "proportional-integral-derivative control" or "fuzzy logic" or FL).mp.

#36. 23 and 34 and 35
#37. 19 or 36
#38. crossover-procedure/ or double-blind procedure/ or randomized controlled trial/ or single-blind procedure/
#39. (random$ or factorial$ or crossover$ or cross over$ or cross-over$ or placebo$ or (doubl$ adj blind$) or (singl$ adj blind$) or assign$ or allocat$ or volunteer$).ti,ab,ot,hw.
#40. 38 or 39
#41. 37 and 40
#42. (letter or editorial or note).pt.
#43. animal/
#44. animal experiment/
#45. (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,ot,hw.
#46. or/43-45
#47. 42 or 46
#48. 41 not 47

Trial filter based on terms suggested by the Cochrane Handbook:

Lefebvre C, Manheimer E, Glanville J. Chapter 6: searching for studies. 6.3.2.2. What is in The Cochrane Central Register of Controlled Trials (CENTRAL) from EMBASE? In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org

COCHRANE

MeSH descriptor: [Pancreas, Artificial] explode all trees
MeSH descriptor: [Insulin Infusion Systems] explode all trees
MeSH descriptor: [Bionics] explode all trees
Exp blood glucose monitoring

MEDLINE (PubMed)

#1. Artificial pancreas [mh]
#2. Bioartificial Organs [mh] AND (pancreas [tw] OR insulin [tw] OR diabet* [tw])
#3. bionics [mh] AND (pancreas [tw] OR insulin [tw] OR diabet* [tw])
#4. “artificial pancreas” [tw]
#5. “bionic pancreas” [tw]
#6. “synthetic pancreas” [tw]
#7. “artificial endocrine pancreas” [tw]
#8. “artificial beta cell*” [tw]
#9. “artificial b cell*” [tw]
#10. “artificial b-cell*” [tw]

#11. closed-loop* [tw] AND (pancreas [tw] OR insulin [tw] OR diabet* [tw])

#12. “closed loop*” AND (pancreas [tw] OR insulin [tw] OR diabet* [tw])

#13. “bioartificial pancreas” [tw]

#14. “bio-artificial pancreas” [tw]

#15. OR/#1-14

#16. (pump [tw] OR delivery [tw] OR release [tw] OR Infusion Pumps, Implantable [mh] OR Insulin Infusion Systems [mh] OR Insulin/administration and dosage [mh])

#17. ((glucose [tw] AND Monitoring, Ambulatory [mh]) OR (glucose [tw] AND (monitor* [tw] OR sensor* [tw] OR sensing [tw])) OR "sensed glucose" [tw] OR CGM [tw] OR CGMS [tw] OR glucosemeter [tw] OR “freestyle navigator” [tw] OR GlucoWatch [tw] OR Guardian [tw] OR Medtronic [tw] OR Blood Glucose Self-Monitoring [mh] OR “glucose measurement” [tw])

#18. (algorithm [tw] OR computer [tw] OR program* [tw] OR modul* [tw] OR controller [tw] OR smartphone [tw] OR tablet [tw] OR “model predictive control” [tw] OR MPC [tw] OR “proportional-integral-derivative control” [tw] OR “fuzzy logic” [tw] OR FL [tw])

#19. AND/# 16-18

#20. #15 OR #19

#21. randomized controlled trial [pt]

#22. controlled clinical trial [pt]

#23. randomized [tiab]

#24. placebo [tiab]

#25. clinical trials as topic [mesh: noexp]

#26. randomly [tiab]

#27. trial [ti]

#28. #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27

#29. animals [mh] NOT humans [mh]

#30. #28 NOT #29

#31. #20 AND #30

Trial filter based on terms suggested by the Cochrane Handbook:

Lefebvre C, Manheimer E, Glanville J. Chapter 6: searching for studies. 6.4.11 Box 6.4b. Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision); PubMed format. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org

Appendix 4

Data extraction form

For every trial we extracted the following information:

Trial characteristics

- Identifier
- NCT
- Source
- Design
- Setting
- Population

Intervention characteristics

- Pump
- Sensor
- Algorithm
- Comparator
- Duration

Baseline characteristics

- Patients(n)
- Age (SD)
- Male (n)
- Weight (SD)
- BMI (SD)
- Diabetes duration (SD)
- Pump duration (SD)
- HbA_{1c} (SD)
- Daily insulin (SD)

We also extracted data (see below) for the following outcomes:

- % of overnight time glucose was between 3.9 – 10.0 mmol/l
- % of day and overnight time (24h) glucose was between 3.9 – 10.0 mmol/l
- % of overnight time glucose was below 3.9 mmol/l
- % of day and overnight time (24h) glucose was below 3.9 mmol/l
- % of overnight time glucose was above 10.0 mmol/l
- % of day and overnight time (24h) glucose was above 10.0 mmol/l
- Mean sensor blood glucose levels (24h)
- Mean sensor blood glucose levels (overnight)
- Change in HbA1c
- Insulin amount administered

CL arm pooled value

Mean

SD

Control arm pooled value

Mean

SD

Within pt diff (CL – Control intervention)

Mean

SD

Paired t test

p value

t value

We also extracted information for the following parameters for assessment of risk of bias for every individual trial:

- Sequence generation (or randomised treatment order for cross-over studies)
- Allocation concealment
- Blinding
- Dropout rate per arm/intervention period
- Type of analysis (ITT, per protocol) and method of imputation
- Selective outcome reporting
- Appropriateness of cross-over design
- Carry-over effects
- Unbiased data

Appendix 5

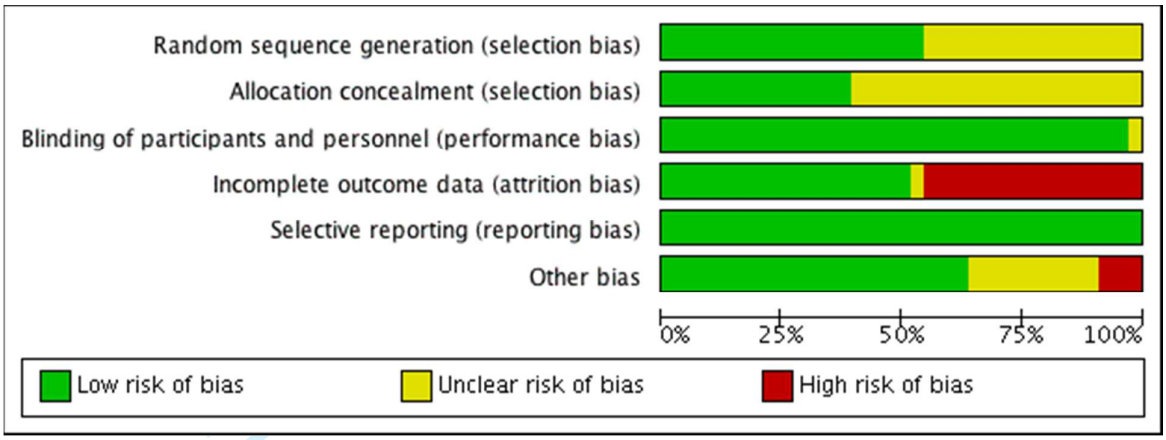
Overall risk of bias assessment

Key domains for assessment of risk of bias for the primary outcome

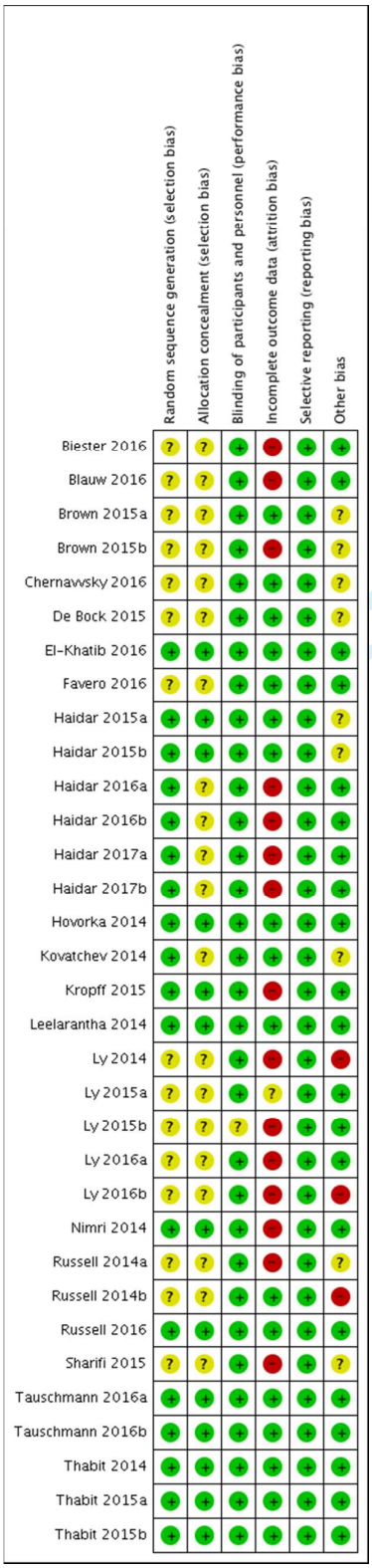
- Sequence generation (or randomised treatment order for cross-over studies)
- Allocation concealment
- Blinding
- Selective reporting
- Incomplete outcome data
- Other bias
  - Appropriateness of cross-over design (only for cross-over studies)
  - Carry-over effects (only for cross-over studies)
  - Unbiased data (only for cross-over studies)

The overall risk of bias was assessed in compliance with the following rules:

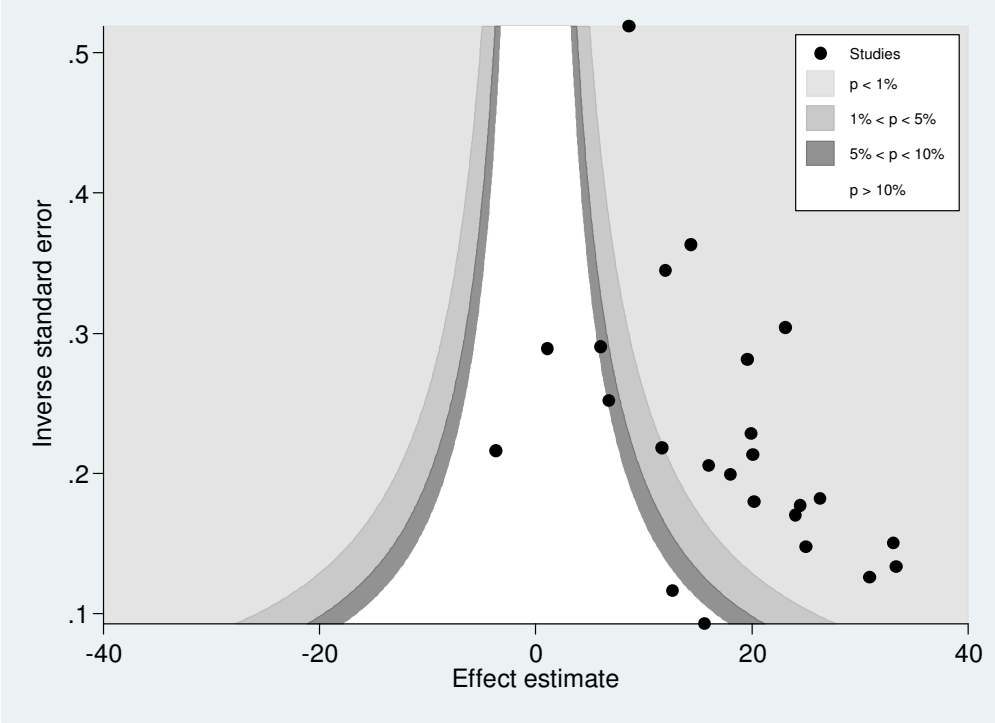
- If a study was considered at high risk of bias for any of the aforementioned domains, the study was characterised as "high risk study"
- If a study was considered at low risk of bias for all aforementioned domains, the study was characterised as "low risk study"
- In any other case the study was considered as "unclear risk study"



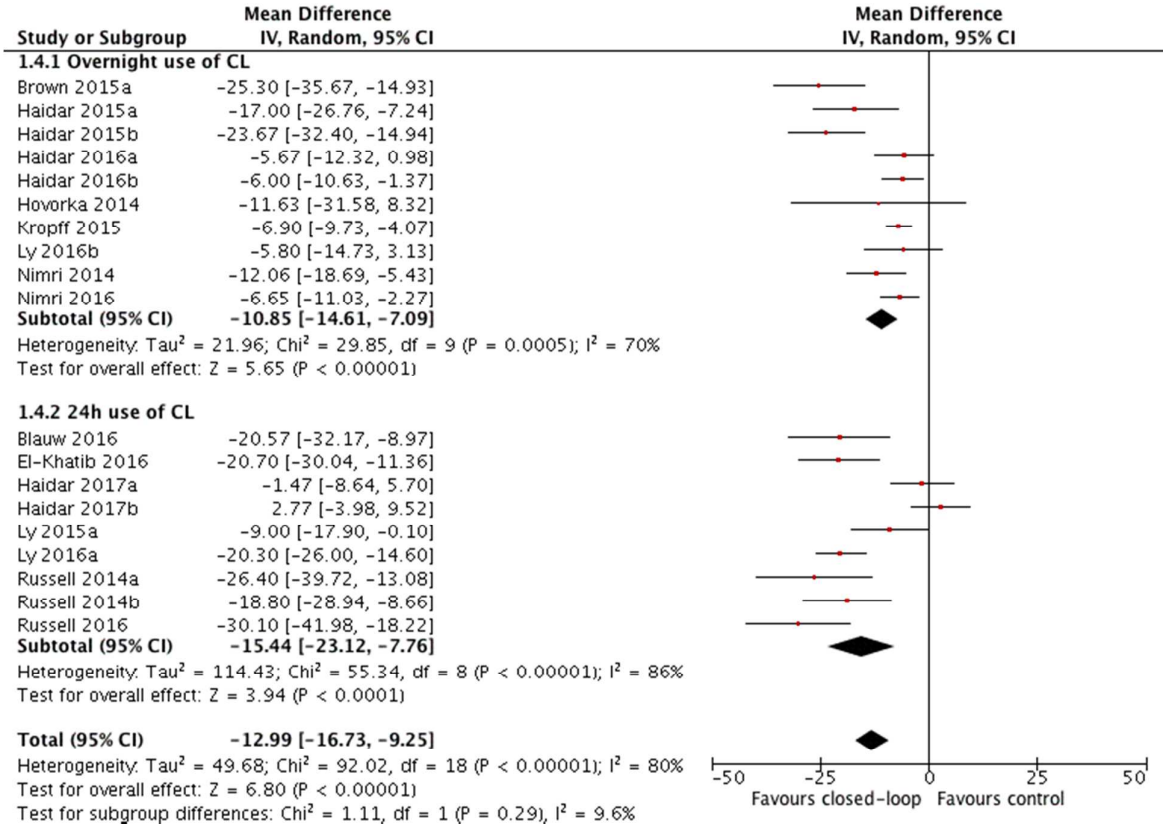
Appendix 6. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies



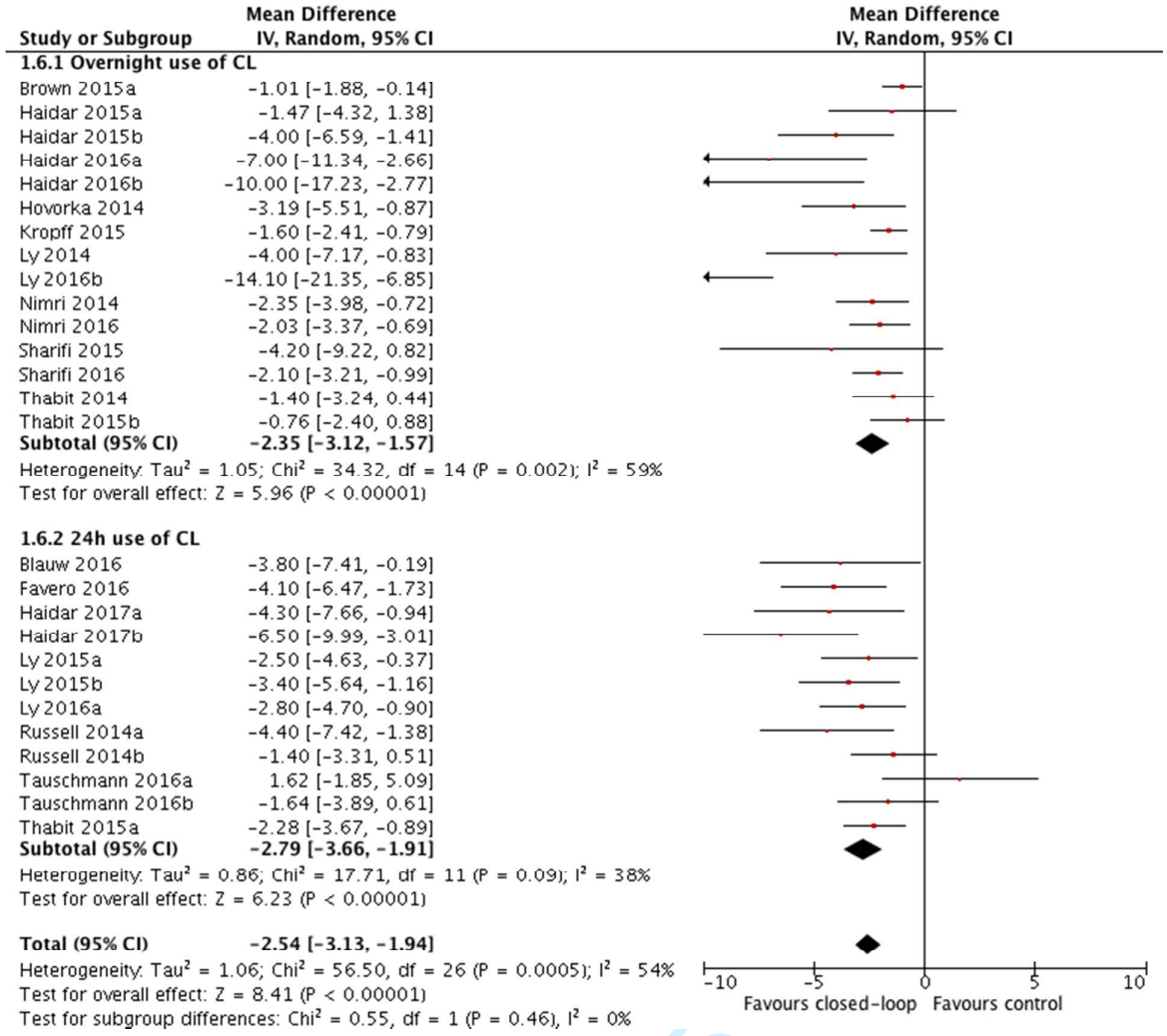
Appendix 7. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



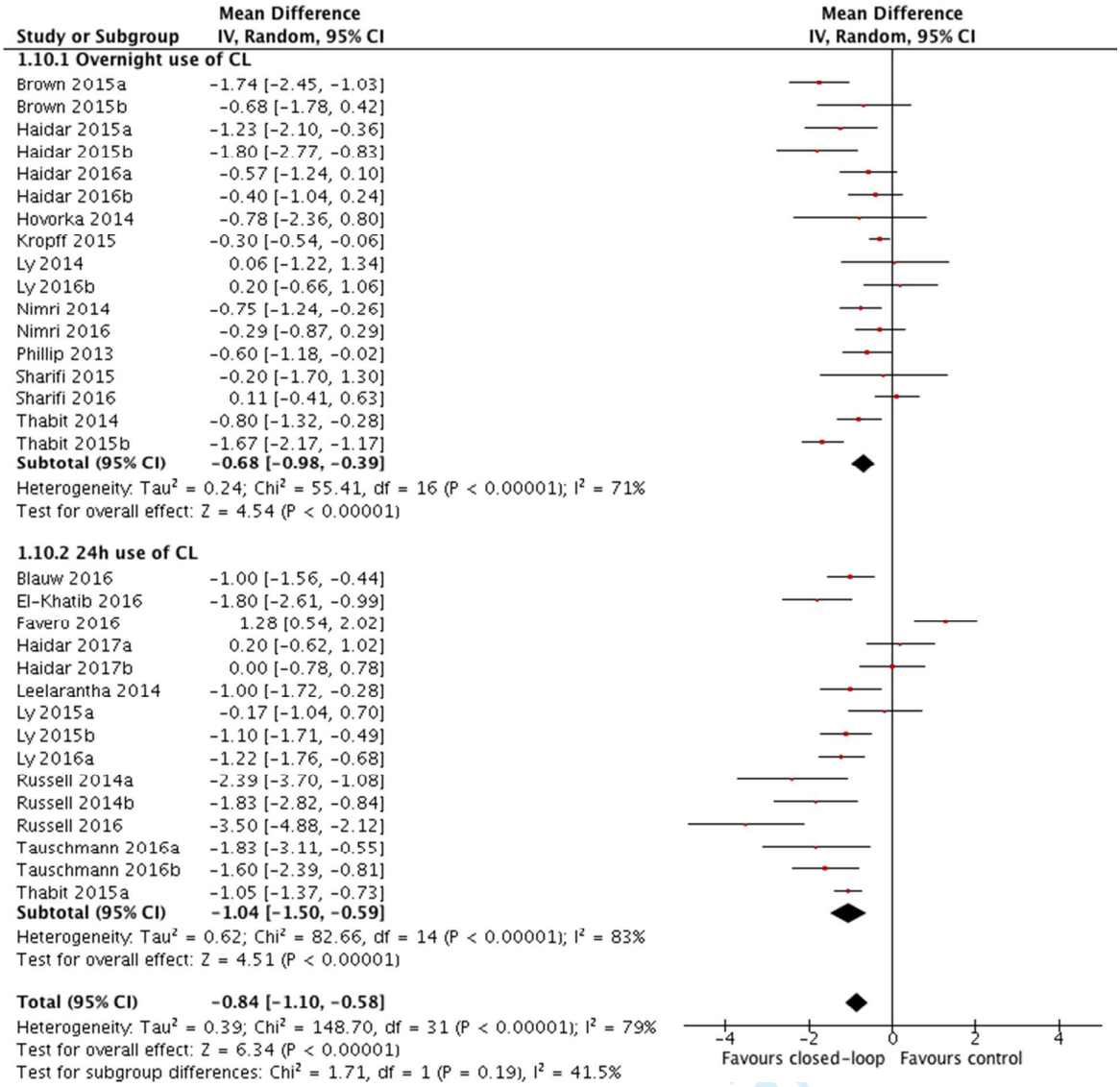
Appendix 8. Counter-enhanced funnel plot for studies assessing overnight time spent in near normoglycaemia.



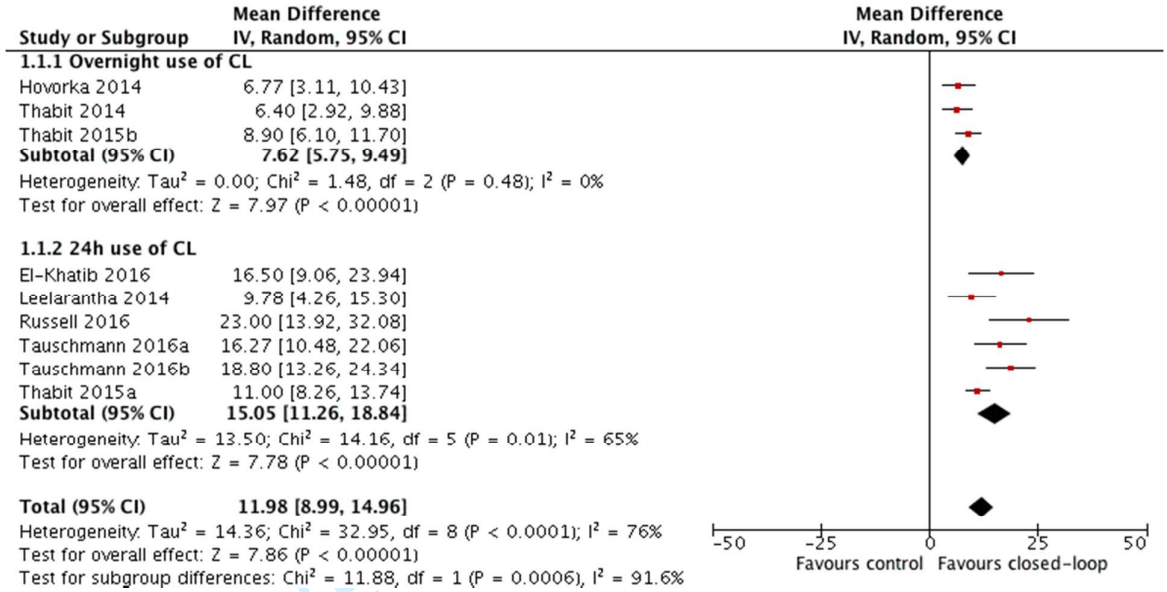
Appendix 9. Weighted mean difference in % of overnight time glucose was > 10.0 mmol/L. Closed-loop versus control treatment.



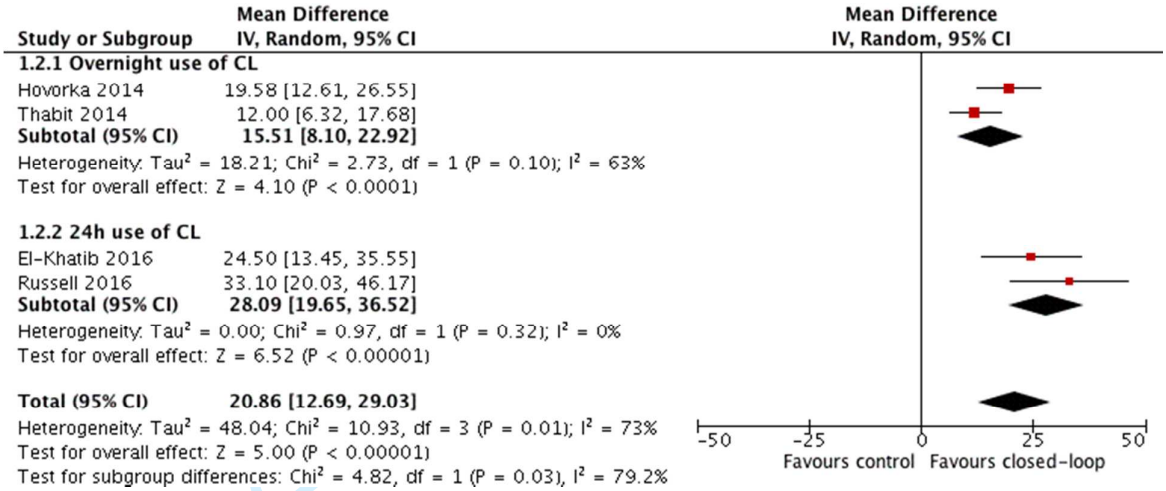
Appendix 10. Weighted mean difference in % of overnight time glucose was < 3.9 mmol/L. Closed-loop versus control treatment.



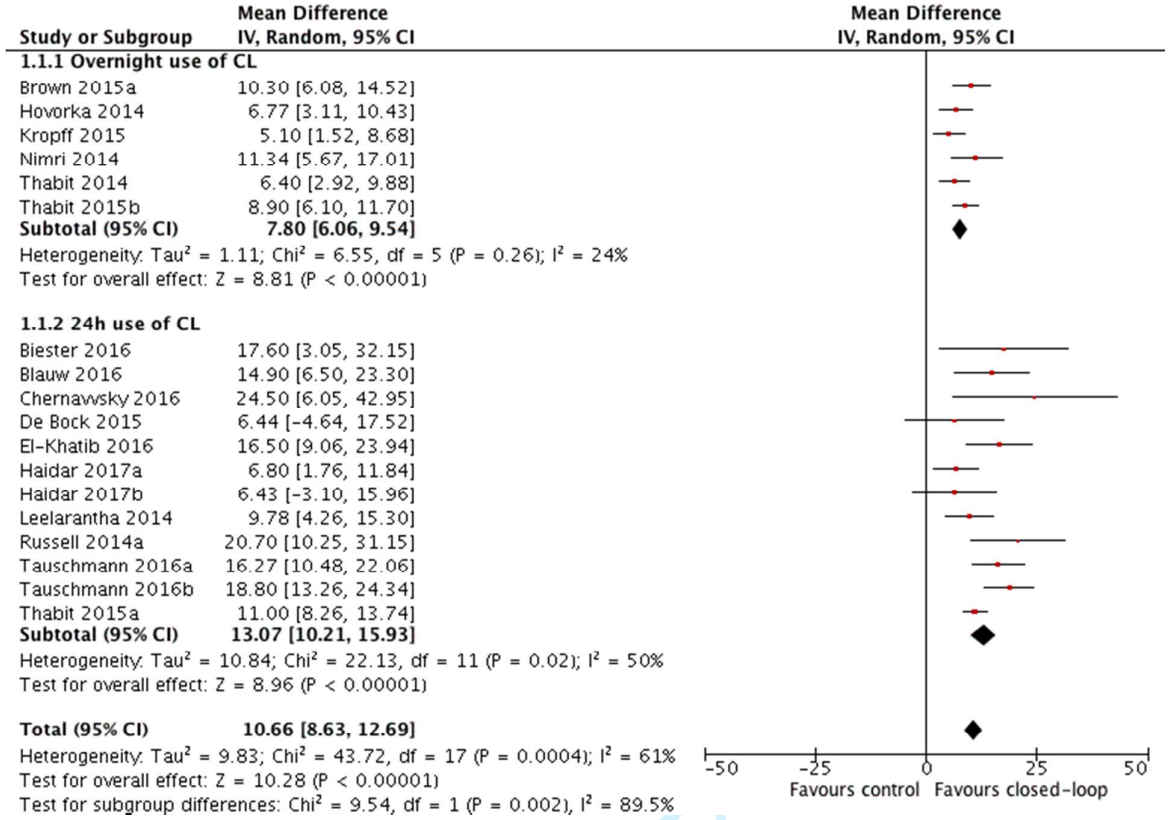
Appendix 11. Weighted mean difference in overnight mean sensor blood glucose (mmol/L). Closed-loop versus control treatment.



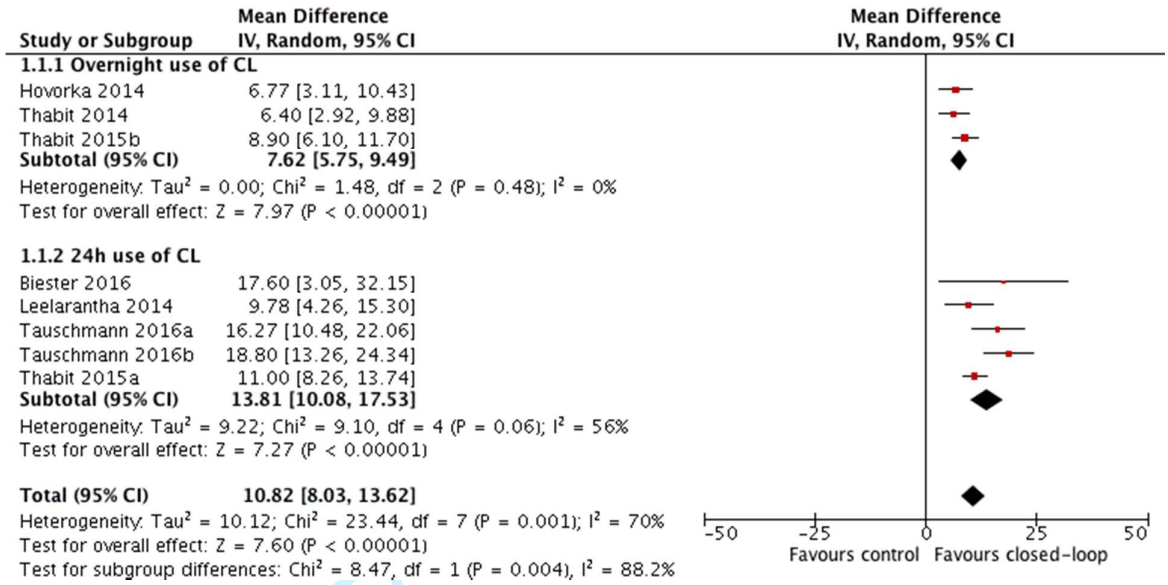
Appendix 12. Weighted mean difference in % of overall time in near normoglycaemic range (3.9 – 10.0 mmol/L). Closed-loop versus control treatment. Sensitivity analysis including only trials at low risk of bias.



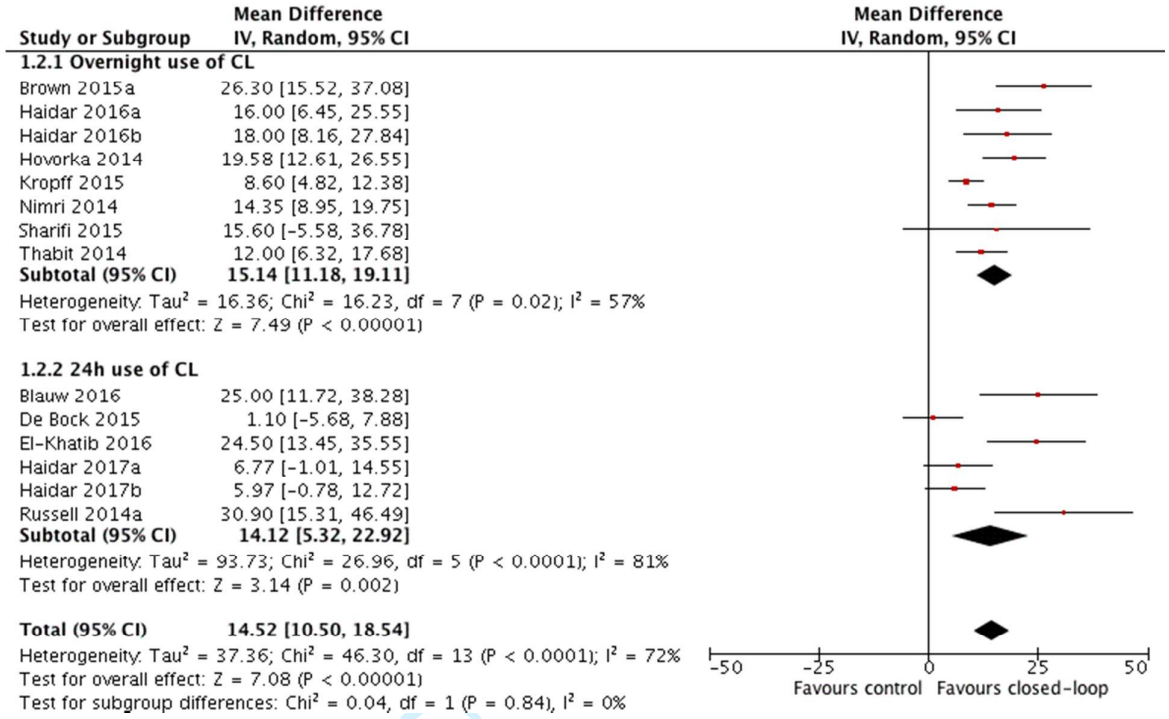
Appendix 13. Weighted mean difference in % of overnight time in near normoglycaemic range (3.9 – 10.0 mmol/L). Closed-loop versus control treatment. Sensitivity analysis including only trials at low risk of bias.



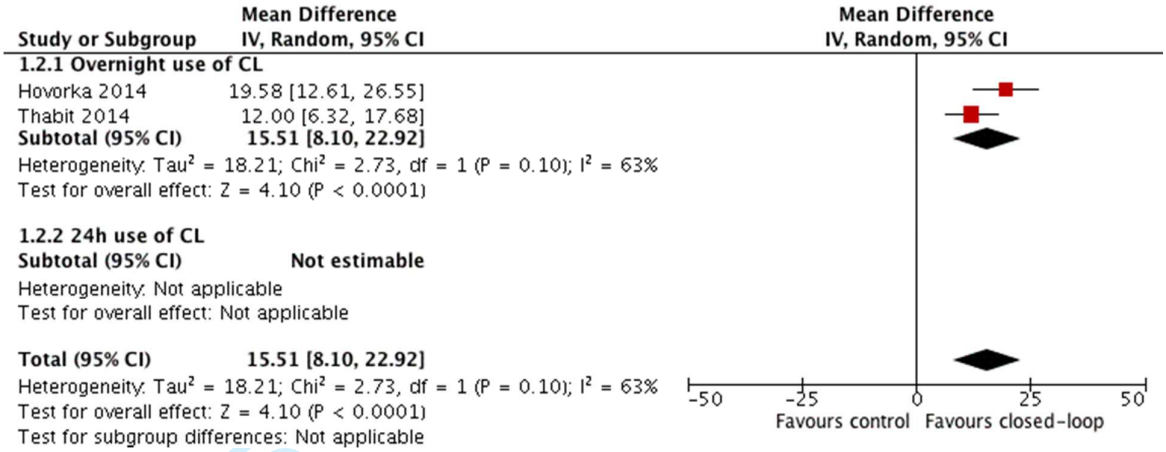
Appendix 14. Weighted mean difference in % of overall time in near normoglycaemic range (3.9 – 10.0 mmol/L). Closed-loop versus control treatment. Sensitivity analysis excluding trials recruiting patients in camps.



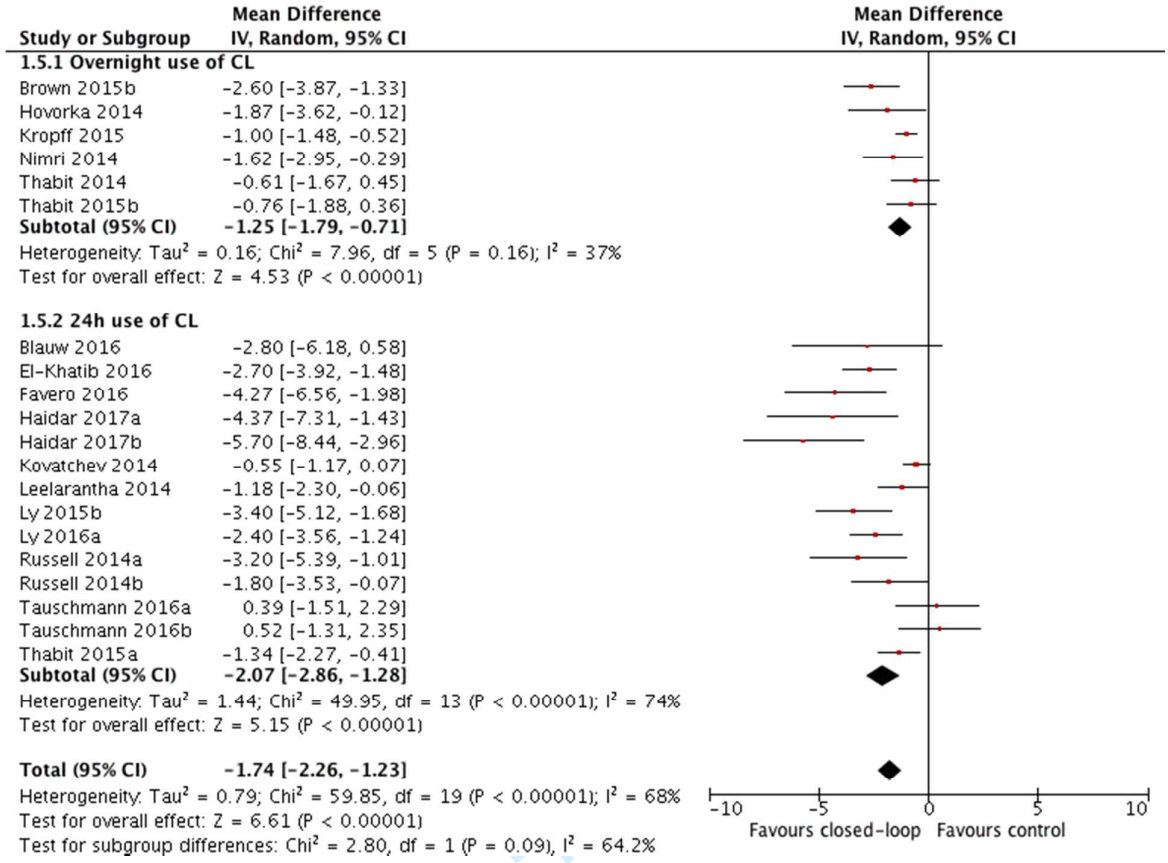
Appendix 15. Weighted mean difference in % of overall time in near normoglycaemic range (3.9 – 10.0 mmol/L). Closed-loop versus control treatment. Sensitivity analysis including only trials recruiting unsupervised patients in free-living conditions.



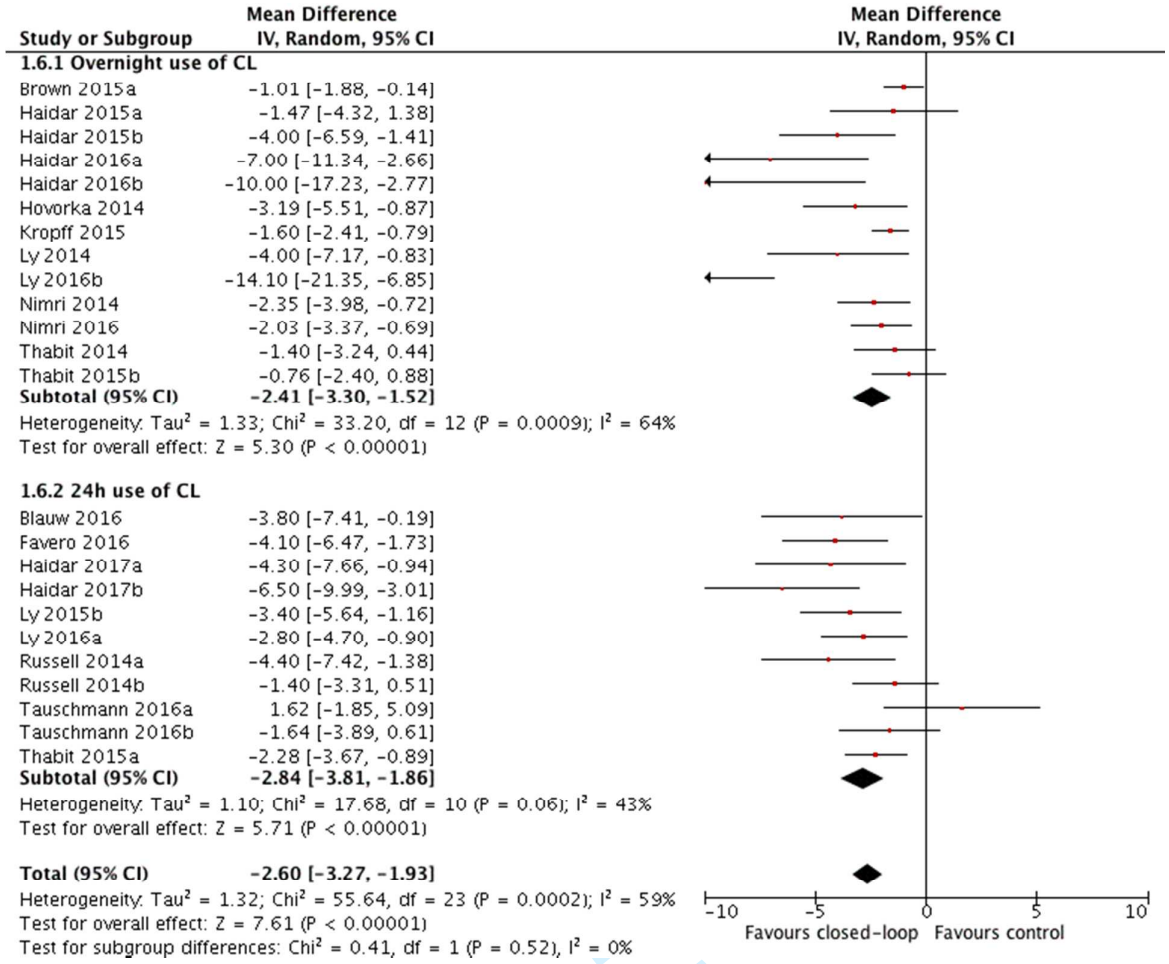
Appendix 16. Weighted mean difference in % of overnight time in near normoglycaemic range (3.9 – 10.0 mmol/L). Closed-loop versus control treatment. Sensitivity analysis excluding trials recruiting patients in camps.



Appendix 17. Weighted mean difference in % of overnight time in near normoglycaemic range (3.9 – 10.0 mmol/L). Closed-loop versus control treatment. Sensitivity analysis including only trials recruiting unsupervised patients in free-living conditions.



Appendix 18. Weighted mean difference in % of overall time glucose was < 3.9 mmol/L. Closed-loop versus control treatment. Sensitivity analysis excluding trials comparing closed-loop systems with low glucose suspend (LGS) systems.



Appendix 19. Weighted mean difference in % of overnight time glucose was < 3.9 mmol/L. Closed-loop versus control treatment. Sensitivity analysis excluding trials comparing closed-loop systems with low glucose suspend (LGS) systems.