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



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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, incidence of severe hypoglycaemia, 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 with data for 37 comparisons) were included. Twenty-eight comparisons assessed a single-hormone closed-loop system, while a dual-hormone closed-loop system was assessed in nine comparisons. Only nine studies were at low risk of bias. 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. The main limitations of current research evidence on closed-loop systems are related to inconsistency in outcome reporting, small sample size and short follow-up duration of individual trials.

## 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. Currently, insulin treatment strategies in type 1 diabetes include either multiple daily insulin injections (MDIs) or continuous subcutaneous insulin infusion (CSII) with an insulin pump. In 2008, the National Institute for Health and Care Excellence (NICE) concluded that CSII therapy had a favourable effect on glycated haemoglobin ($HbA_{1c}$) and incidence of hypoglycaemia in patients with type 1 diabetes.[1] Until recently, CSII therapy was mostly guided by self-monitoring of capillary glucose testing.[2] However, in recent years, insulin pumps are also used in conjunction with real-time continuous glucose monitoring (CGM), hence allowing the patient to manually modify the insulin infusion rate according to CGM values (sensor augmented pump therapy, SAP).[2 3] Lately, introduction of a low glucose suspend (LGS) feature allows for automatic pump suspension when a pre-programmed CGM threshold value is reached.[4]

Closed-loop glucose control, also referred to as the artificial pancreas, is an emerging therapeutic option combining insulin pump and CGM with a control algorithm to deliver insulin in a glucose-responsive manner (single-hormone closed-loop system). 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. An early pooled analysis included only four studies in an inpatient setting,[5] while an overview published in 2015 summarised existing data from RCTs until September 2014.[6] Finally, a recent meta-analysis summarised evidence from published trials of closed loop systems in outpatients with type 1 diabetes.[7] Notably, the U.S. Food and Drug Administration (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.[8]

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 is reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement (**appendix 2**).[9]

### 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.[10 11] 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 MDIs, insulin pump therapy without CGM or with blinded CGM, and SAP with or without LGS.

**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, incidence of severe hypoglycaemia, mean sensor glucose level, total daily insulin needs and $HbA_{1c}$. We also used overnight low blood glucose index as an additional outcome for assessing hypoglycaemia. Low blood glucose index is a weighted average of the number of hypoglycaemic readings with progressively increasing weights as glucose levels decrease and is associated with risk for hypoglycaemia and prediction of severe hypoglycaemic episodes.[12]

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), applying an inverse-variance weighted random effects model using the DerSimonian and Laird estimation method.[13] We also calculated 95% prediction intervals to estimate a predicted range for the true treatment effect in any one individual study.[14] In addition, to account for uncertainty related to heterogeneity estimates, we calculated 95% confidence intervals applying the Hartung Knapp correction method.[15] 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.[16] 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.[17]

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 $Tau^2$ and $I^2$ statistics. 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 in individual studies**

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).[18] 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.

**Assessment of risk of bias across studies**

We explored risk of bias across studies, both visually using a contour enhanced funnel plot, and formally utilising Egger's statistical test.[19 20] In case of evidence of small study effects, we used the trim and fill method as a sensitivity analysis, to provide an adjusted estimate of the meta-analysis.[21]

**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, 32 publications describing 34 trials (792 participants with data for 37 comparisons) were used to inform our systematic review.[22-53] One trial did not report data for outcomes assessed and was not included in the meta-analysis.[47]

Study and participants' baseline characteristics are shown in **Table 1**. The vast majority of included trials utilised a crossover design,[22-37 40 42-53] whereas only three trials were of parallel design.[38 39 41] In twenty-eight trials duration was less than four weeks,[22-32 34 36-41 43-51] whereas in the remaining six trials it ranged from eight to thirty weeks.[33 35 42 52 53] Thirteen trials recruited children or adolescents,[26 29 30 33 40 41 44-47 50 51 53] eleven trials recruited adults,[23-25 28 32 34-36 45 52 53] while ten trials recruited a mixed population.[22 27 31 37-39 42 43 48 49] In sixteen trials closed-loop was used overnight,[24 25 30 31 33 35 37 40 42-44 47-49 52 53] while in the remaining eighteen trials closed-loop was used throughout 24

hours.[22 23 26-29 32 34 36 38 39 41 45 46 50 51 53] Twenty-five trials compared a single-hormone closed-loop system (mostly with unblinded SAP therapy),[22 24 25 27 29 33-39 41 40 42-44 47-53] while six trials assessed dual-hormone closed-loop systems in comparison mainly to insulin pump therapy (consisting of CSII combined with a blinded CGM system).[23 26 28 45 46] Additionally, three studies evaluated both a single-hormone and a dual-hormone system against control treatment (three-way cross-over trials).[30-32] Of note, in four studies assessing SAP therapy, the control comprised a SAP combined with an LGS feature.[27 39 48 49] Among trials evaluating single hormone closed-loop systems, nine trials used the DiAs platform,[24-26 29 34 35 37 38 41] eight trials used the Florence algorithm,[33 36 47 50-53] four trials used the MD-Logic algorithm,[22 42-44] and five trials used the Medtronic closed-loop.[27 39 40 48 49] Most of the trials used a model predictive control algorithm,[28-36 45-47 50-53] six trials used a proportional integral derivative algorithm,[23 27 39 40 48 49] four trials used a fuzzy logic algorithm,[22 42-44] while the rest of the trials used other algorithms or did not provide relevant details.[24-26 37 38 41] Seventeen closed-loop comparisons utilised the Dexcom G4® CGM sensor,[24-26 28-30 32 34 35 37 38 45 46 54] while an Enlite™ Sensor, a FreeStyle Navigator® or a Medtronic 4s sensor were used in the closed-loop systems in nine,[23 27 31 40 42-44 49] eight,[33 36 47 50-53] and one comparisons,[39] respectively. Type of CGM sensor wan not reported in two trials.[22 48] Of note, in 30 comparisons, type of CGM sensor was identical between closed-loop and control arms, one trial used a different sensor in the control arm,[39] and six trials did not report information for type of sensor used in the control arm.[22 25 26 38 41 48]

Finally, eleven trials were held in a diabetes camp or a guesthouse,[29 30 34 37-41 44-46] while in twenty-three trials subjects were at home.[22-28 31-33 35 36 42 43 45 47-53] Only in a small subset of trials were subjects using closed-loop unsupervised under free-living conditions,[22 33 36 50-53] 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**. Only nine studies were at low risk of bias. Most studies were deemed at high risk for bias, 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 small study effects for percentage of overall time near normoglycaemia (P=0.247). However, there was evidence of small study effects (P=0.010) for percentage of overnight time spent in near normoglycaemia, and visual inspection of the contour-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 closed-loop therapy (weighted mean difference 12.52%, 95% confidence interval 8.90 to 16.13, P<0.001).

**Primary outcome**

All meta-analysis results are presented as summary effect estimates for closed-loop versus control.

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) (overall effect estimate 9.54%, 95% confidence interval 6.99 to 12.09, $I^2$ 81%, $Tau^2$ 30.47, 25 studies). This effect was consistent both for trials using closed-loop overnight (7.80%, 6.06 to 9.54, 24%, 1.11, six studies), or throughout 24h (10.46%, 6.58 to 14.34, 85%, 58.04, 19 studies) (**Figure 2**). 95% confidence intervals for the overall effect estimate after applying the Hartung Knapp correction were 6.84 to 12.24, while 95% prediction intervals were -2.19 to 21.27. Of note, 95% prediction intervals were statistically

significant when closed-loop was used overnight (3.97 to 11.62) suggesting that closed-loop will be beneficial in at least 95% of the individual study settings when applied overnight, but not when applied throughout 24h (-6.14 to 27.06).

The favourable effect of closed-loop over control was more evident on the percentage of time spent in near normoglycaemia overnight (16.44%, 12.85 to 20.02, 76%, 54.78, 24 studies), and was consistent both when closed-loop was used either only overnight (17.15%, 13.26 to 21.04, 60%, 24.3, 12 studies) or throughout 24h (15.67%, 9.19 to 22.16, 83%, 105.48, 12 studies) (**Figure 3**), even when the Hartung Knapp correction was applied (**appendix 13**). Respective 95% prediction intervals calculated suggest that effect on time spent in near normoglycaemia overnight (95% prediction intervals 0.63 to 32.25) will be beneficial in at least 95% of the individual study settings when applied overnight (5.30 to 28.99), but not when applied throughout 24h (-8.37 to 39.71).

**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, 84%, 36.43, 17 studies) compared to control, both in trials where closed-loop was used only overnight (−6.51%, −9.42 to −3.60, 0%, 0.0, two studies), and in trials using closed-loop throughout 24h (−8.62%, −12.41 to −4.84, 86%, 45.87, 15 studies) (**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, 80%, 49.68, 19 studies), both in trials that used closed-loop either only overnight (−10.85%, −14.61 to −7.09, 70%, 21.96, 10 studies), or throughout the day (24h) (−15.44%, −23.12 to −7.76, 86%, 114.43, nine studies) (**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, 67%, 0,71, 23 studies) (**Figure 5**). Results were consistent for overnight time spent at concentrations lower than 3.9 mmol/L (−2.54%, −3.13 to −1.94, 54%, 1.06, 27 studies) (**appendix 10**). Data on incidence of severe hypoglycaemia (hypoglycaemia requiring third-party assistance) were available in 22 studies (559 patients). Overall, incidence of severe hypoglycaemia was low both in closed-loop (six episodes) and comparator (three episodes) arms. Use of closed-loop was also associated with a decrease in overnight low glucose blood index (−0.42, −0.56 to −0.27, 26%, 0.01, eight studies).

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, 83%, 0.28, 24 studies) (**Figure 6**). Results were more favourable for overnight mean sensor blood glucose levels (−0.84 mmol/L, −1.10 to −0.58, 79%, 0.39, 32 studies) (**appendix 11**). These findings were consistent with the effect of closed-loop on $HbA_{1c}$ (−0.26%, −0.38 to −0.13, 0%, 0.0, 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, 79%, 6.56, 12 studies) (**appendix 12**). 95% Hartung Knapp confidence intervals and prediction intervals for all outcomes are presented in **appendix 13**.

**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, nine studies) and for overnight (20.86%, 12.69 to 29.03, four studies) (**Figures 8 and 9**). 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, for all outcomes, results were consistent with those of the main analysis in a pre-specified subgroup analysis based on type of closed-loop utilised (single- versus dual-hormone closed-loop) (**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 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.[35 53 55] In total, our results reflect the progress made over the last decades of extensive research and development in this field.

### Strengths and limitations

Despite heterogeneity in interventions and comparators utilised, our systematic review provides the most valid and up-to-date overview on the field of artificial pancreas. An early pooled analysis of randomised controlled trials with closed-loop systems, published in 2011, included only four studies in an inpatient setting.[5] The effect of artificial pancreas in the outpatient setting was examined in a recent systematic review and meta-analysis.[7] However, validity and clinical interpretation potential of results were undermined by methodological decisions met regarding definition of outcomes, handling of median values, and exclusion of evidence from grey literature sources leading to missing a significant amount of the body of evidence (10 of 34 eligible studies).[56] Instead, the present meta-analysis incorporated a larger pool of eligible studies and assessed a broader variety of outcomes, focusing on outcome definitions that are considered most important in trials evaluating closed-loop systems.[54 57 58]

Composition of the review team ensured appropriate methodological and subject expertise, but also access to additional study data from individual studies.[33 36 50-53] To ensure internal validity of our conclusions we implemented current guidelines for the conduct and reporting of systematic reviews,[9] 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.

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.[59] 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,[38 39 41] 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.[54] 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.[60] 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. This could explain wide prediction intervals which included zero values for most outcomes in trials using CL for 24h, thus related findings should be interpreted with caution. On the contrary, there is strong evidence that overnight use of CL is beneficial for outcomes regarding time spent in near normoglycaemia or hypoglycaemia (95% prediction intervals excluding zero values) suggesting that this treatment effect can be expected in future patients.

**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.[61] It is important for research groups to report a minimum set of agreed outcome measures and respective metrics.[54 57 58] 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.[62 63] 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,[64] 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,[65] who may benefit from it. Moreover, the impact of artificial pancreas on quality of life and its effect on reducing patient burden should be

further explored,[66] considering that patients with type 1 diabetes and their carers have demonstrated a positive attitude towards closed-loop systems.[67-69] 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.

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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.

Findings of previous meta-analyses on closed-loop systems are limited mainly due to low number of studies incorporated and heterogeneous definitions of outcomes.

**What this study adds**

The totality of available evidence from randomised controlled trials 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.

The main limitations of current research evidence on closed-loop systems are related to inconsistency in outcome reporting, small sample size and short follow-up duration of individual trials.

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| Identifier | Trial registration details | Setting | Population | CL | Comparator | Intervention duration | Length of follow-up* | Patients (n) |
|---|---|---|---|---|---|---|---|---|
| **Biester 2016**[22] | NCT02636491 | Home | Adults & adolescents | MD-Logic | SAP | 24h | 2 days | 10 |
| **Blauw 2016**[23] | NCT02160275 | Home | Adults | Inreda Dual-hormone CL | Insulin pump therapy | 24h | 4 days | 10 |
| **Brown 2015a**[24] | NCT01939834 NCT02008188 | House/Hotel | Adults | DiAs USS | SAP | Overnight | 5 days | 10 |
| **Brown 2015b**[25] | R01DK085623 | Home | NR | DiAs | SAP | Overnight | 5 days | 5 |
| **Chernavvsky 2016**[26] | NCT01890954 | Research house | Adolescents | DiAs USS | Insulin pump therapy | 24h | 1 day | 16 |
| **De Bock 2015**[27] | ACTRN12614001005640 | Home | Adults & adolescents | Medtronic PID IFB | SAP + LGS | 24h | 5 days | 8 |
| **El-Khatib 2017**[28] | NCT02092220 | Home | Adults | Dual-hormone CL | Insulin pump therapy or SAP | 24h | 11 days | 39 |
| **Favero 2016**[29] | NCT0260878 | Diabetes camp | Children | DiAs | SAP | 24h | 3 days | 30 |
| **Haidar 2015a**[30] | NCT02189694 | Diabetes camp | Adolescents | Single-hormone CL | Insulin pump therapy | Overnight | 3 days | 33 |
| **Haidar 2015b**[30] | NCT02189694 | Diabetes camp | Adolescents | Dual-hormone CL | Insulin pump therapy | Overnight | 3 days | 33 |
| **Haidar 2016a**[31] | NCT01905020 | Home | Adults & adolescents | Single-hormone CL | Insulin pump therapy | Overnight | 2 days | 28 |
| **Haidar 2016b**[31] | NCT01905020 | Home | Adults & adolescents | Dual-hormone CL | Insulin pump therapy | Overnight | 2 days | 28 |
| **Haidar 2017a**[32] | NCT01966393 | Home | Adults | Single-hormone CL | SAP | 24h | 60 hours | 23 |
| **Haidar 2017b**[32] | NCT01966393 | Home | Adults | Dual-hormone CL | SAP | 24h | 60 hours | 23 |
| **Hovorka 2014**[33] | NCT01221467 | Home | Adolescents | Florence | SAP | Overnight | 3 weeks | 16 |
| **Kovatchev 2014**[34] | NCT01714505 NCT01727817 | Hotel/Guesthouse | Adults | DiAs SSM | SAP | 24h | 40 hours | 20 |
| **Kropf 2015**[35] | NCT02153190 | Home | Adults | DiAs SSM | SAP | Evening and night | 8 weeks | 32 |
| **Leelarantha 2014**[36] | NCT01666028 | Home | Adults | Florence | SAP | 24h | 8 days | 17 |
| **Ly 2014**[37] | NCT01973413 | Diabetes camp | Adults & adolescents | DiAs USS | SAP | Overnight | 5-6 days | 20 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Ly 2015a**[39] | NCT02366767 | Diabetes camp | Adults & adolescents | Medtronic PID IFB | SAP + LGS | 24h | 6 days | 21 |
| **Ly 2015b**[38] | NR | Diabetes camp | Adults & adolescents | DiAs | SAP | 24h | 5 days | 16 |
| **Ly 2016a**[41] | NCT02147860 | Diabetes camp | Adolescents | DiAs USS | SAP | 24h | 5 days | 33 |
| **Ly 2016b**[40] | NR | Diabetes camp | Children & adolescents | Medtronic PID IFB | SAP | Overnight | 1 day | 21 |
| **Nimri 2014**[42] | NCT01238406 | Home | Adults & adolescents | MD-Logic | SAP | Overnight | 6 weeks | 24 |
| **Nimri 2017**[43] | NCT01726829 | Home | Children, adolescents | MD-Logic | SAP | Overnight | 4 days | 75 |
| **Phillip 2013**[44] | NCT01238406 | Diabetes camp | Adolescents | MD-Logic | SAP | Overnight | 1 day | 54 |
| **Russell 2014a**[45] | NCT01762059 | Home & Hotel | Adults | Dual-hormone CL | Insulin pump therapy or SAP | 24h | 5 days | 20 |
| **Russell 2014b**[45] | NCT01833988 | Diabetes camp | Adolescents | Dual-hormone CL | Insulin pump therapy or SAP | 24h | 5 days | 32 |
| **Russell 2016**[46] | NCT02105324 | Diabetes camp | Preadolescents | Dual-hormone CL | Insulin pump therapy or SAP | 24h | 5 days | 19 |
| **Schierloh 2015**[47] † | NR | Home | Children | Florence | SAP | Overnight | 4 days | 15 |
| **Sharifi 2015**[48] | NR | Home | Adults & adolescents | CL PID IFB | SAP + LGS | Overnight | 5 days | 11 |
| **Sharifi 2016**[49] | NR | Home | Adults & adolescents | Medtronic PID IFB | SAP + LGS | Overnight | 4 days | 28 |
| **Tauschmann 2016a**[51] | NCT01873066 | Home | Adolescents | Florence | SAP | 24h | 7 days | 12 |
| **Tauschmann 2016b**[50] | NCT01873066 | Home | Adolescents | Florence | SAP | 24h | 3 weeks | 12 |
| **Thabit 2014**[52] | NCT01440140 | Home | Adults | Florence | SAP | Overnight | 4 weeks | 24 |
| **Thabit 2015a**[53] | NCT01961622 | Home | Adults | Florence | SAP | 24h | 12 weeks | 33 |
| **Thabit 2015b**[53] | NCT01778348 | Home | Children & adolescents | Florence | SAP | Overnight | 12 weeks | 25 |

**Table 1. Baseline characteristics of comparisons 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. *For cross-over trials, length of follow-up refers to the duration of each period, excluding wash-out period.

| Outcome | Number of studies (single/dual hormone) | Single hormone CL | Dual-hormone CL |
|---|---|---|---|
| % of overall time between 3.9 – 10.0 | 19/6 | 8.02 (5.25 to 10.80), 83%, 28.26 | 15.16 (10.68 to 19.63), 43%, 13.08 |
| % of overnight time between 3.9 – 10.0 | 16/8 | 13.88 (9.94 to 17.81), 75%, 43.86 | 22.84 (15.08 to 30.60), 74%, 88.82 |
| % of overall time > 10.0 mmol/L | 11/6 | −6.82 (−10.58 to −3.06), 86%, 33.29 | −11.58 (−18.17 to −4.99), 81%, 36.43 |
| % of overnight time > 10.0 mmol/L | 11/8 | −10.50 (−14.39 to −6.60), 73%, 27.68 | −17.21 (−25.58 to −8.85), 87%, 121.35 |
| % of overall time < 3.9 mmol/L | 18/5 | −1.39 (−1.84 to −0.93), 65%, 0.53 | −2.95 (−4.03 to −1.87), 30%, 0.45 |
| % of overnight time < 3.9 mmol/L | 20/7 | −2.15 (−2.74 to −1.57), 47%, 0.68 | −4.04 (−5.59 to −2.48), 47%, 1.93 |
| Overnight LBGI | 8/0 | −0.42 (−0.56 to −0.27), 26%, 0.01 | NE |
| Overall mean sensor glucose value (mmol/L) | 18/6 | −0.38 (−0.65 to −0.12), 82%, 0.23 | −0.90 (−1.48 to −0.32), 80%, 0.42 |
| Overnight mean sensor glucose value (mmol/L) | 24/8 | −0.67 (−0.94 to −0.39), 78%, 0.32 | −1.47 (−2.14 to −0.79), 80%, 0.72 |
| Overall daily insulin needs (IU) | 11/1 | −0.64 (−2.40 to 1.13), 77%, 5.58 | NE |

**Table 2**. Summary of subgroup meta-analyses results based on type of closed-loop utilised (single-hormone closed-loop studies mainly used sensor-augmented pump therapy as comparator; dual-hormone closed-loop studies mainly used insulin pump therapy as comparator). Values presented are weighted mean differences (95% confidence intervals), $I^2$, $Tau^2$ between closed-loop and comparator. CL: closed-loop. LBGI: low blood glucose index. 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 % 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.

**Figure 9**. 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.

**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, 4 |
| 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. | 5, 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, 5 |

| 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. | 4-5 |
| **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). | 6, 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. | 6-7, Figures 2-9, appendices 9-13 |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | 6, Figures 2-8, appendices 9-13 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | 6, appendix 8 |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | 7, Table 2, appendices 14-19 |
| **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). | 8 |
| 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). | 8-9 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 9 |
| **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. | 10 |

**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**

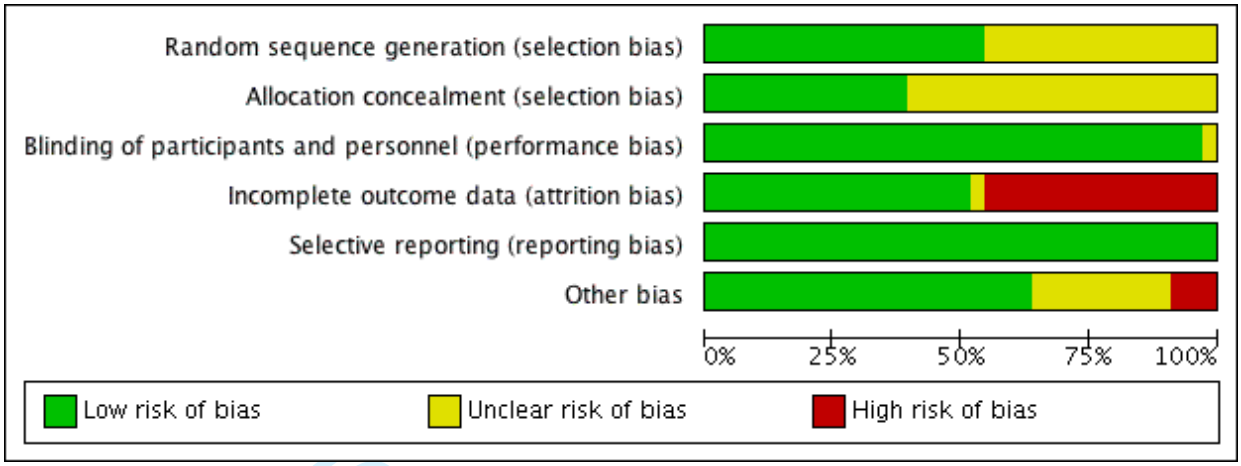
**Overall risk of bias assessment**

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

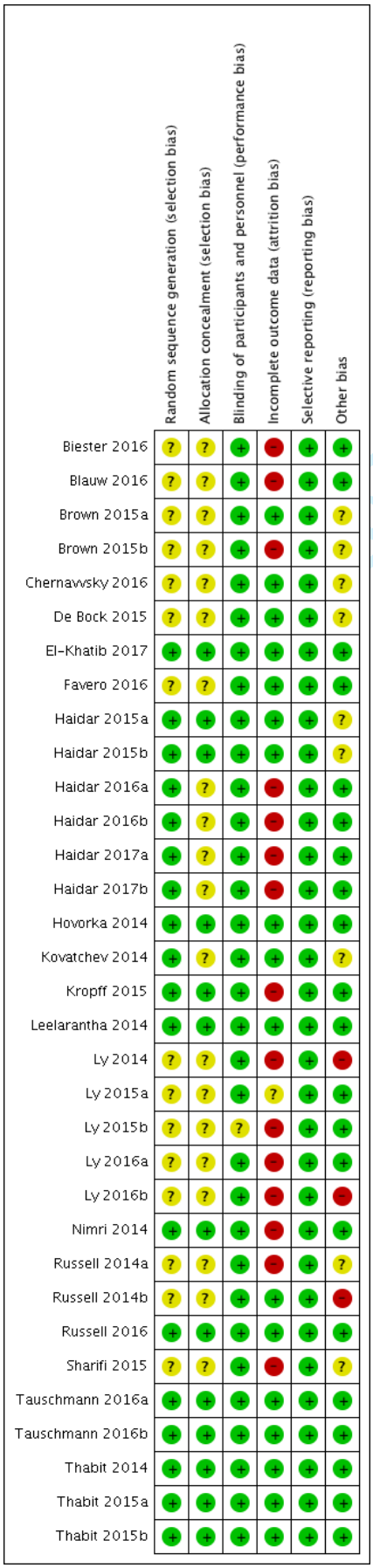
- Sequence generation (or randomised treatment order for cross-over studies)
- Allocation concealment
- Blinding
- Selective reporting
- Incomplete outcome data
- Other bias
  - Appropriateness of cross-over design (only for cross-over studies)
  - Carry-over effects (only for cross-over studies)
  -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

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

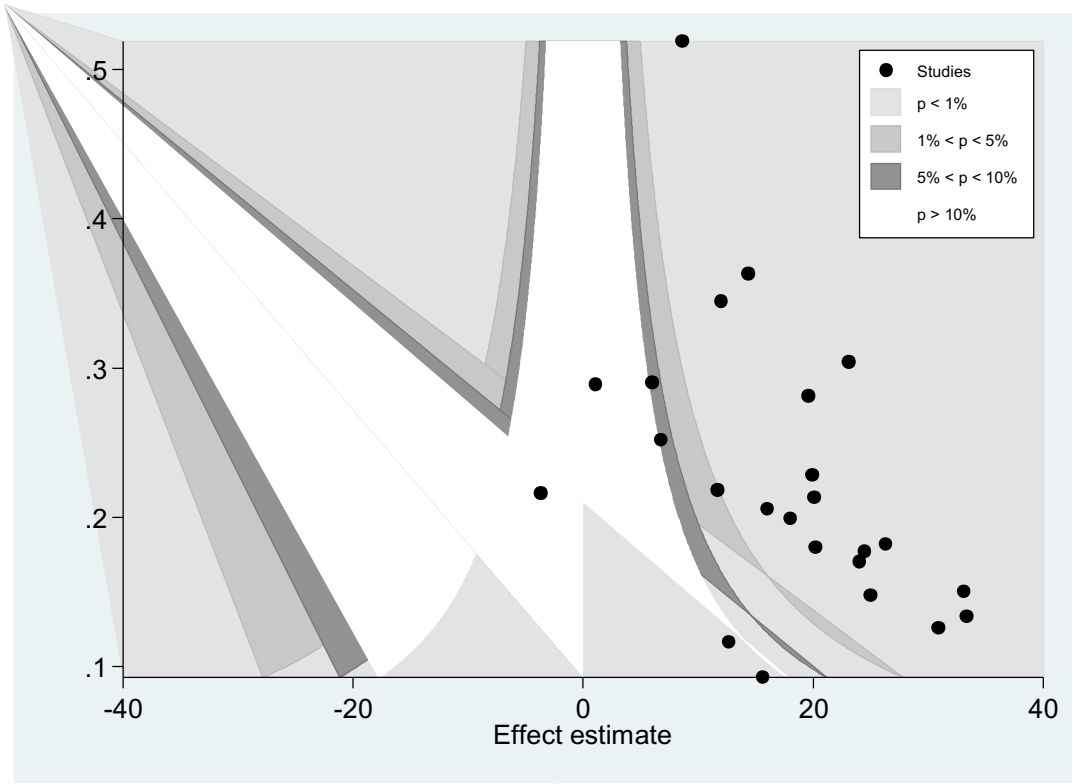
- If a study was considered at high risk of bias for any of the aforementioned domains, the study was characterised as "high risk study"
- If a study was considered at low risk of bias for all aforementioned domains, the study was characterised as "low risk study"
- In any other case the study was considered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



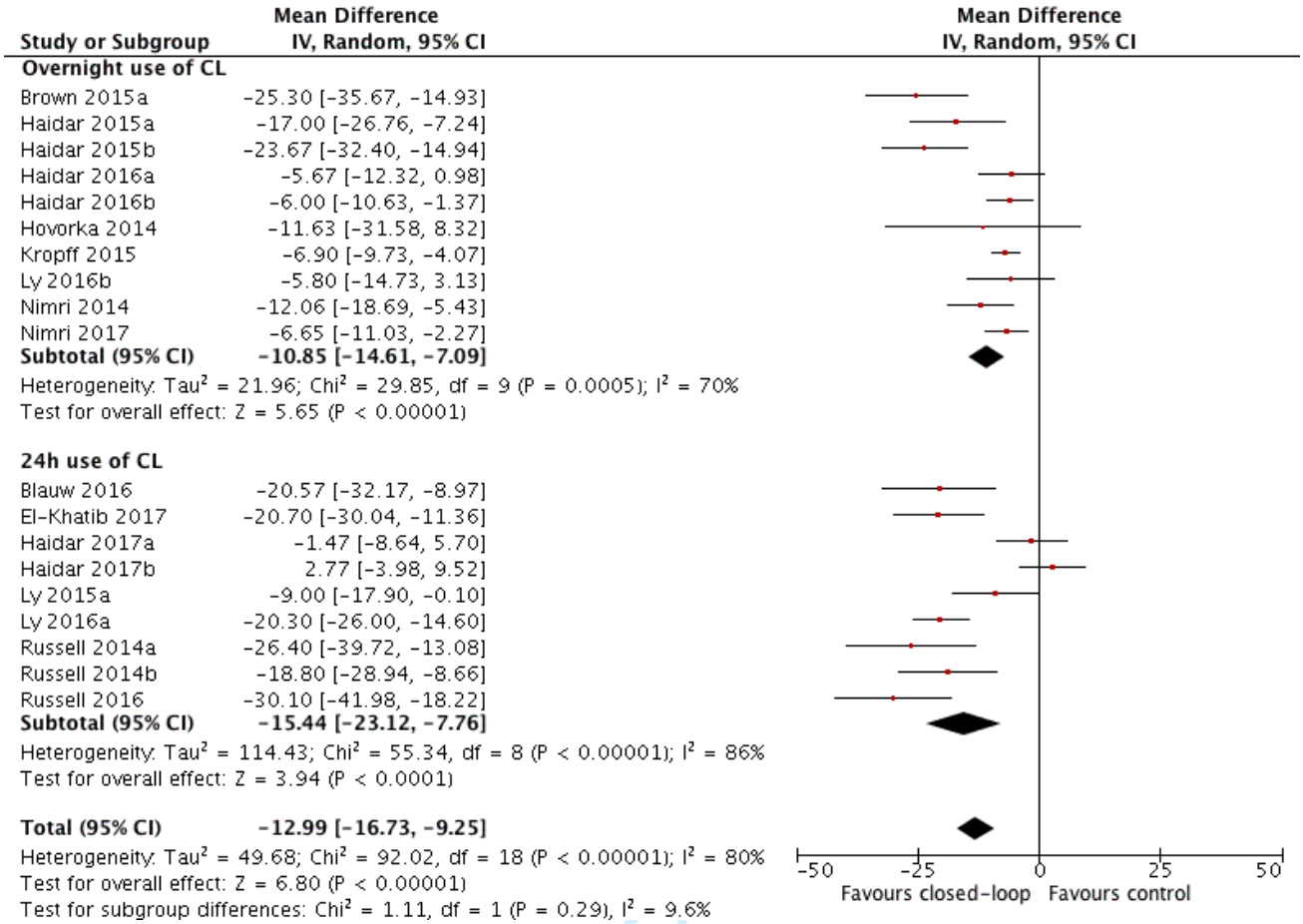

**Appendix 6**. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies



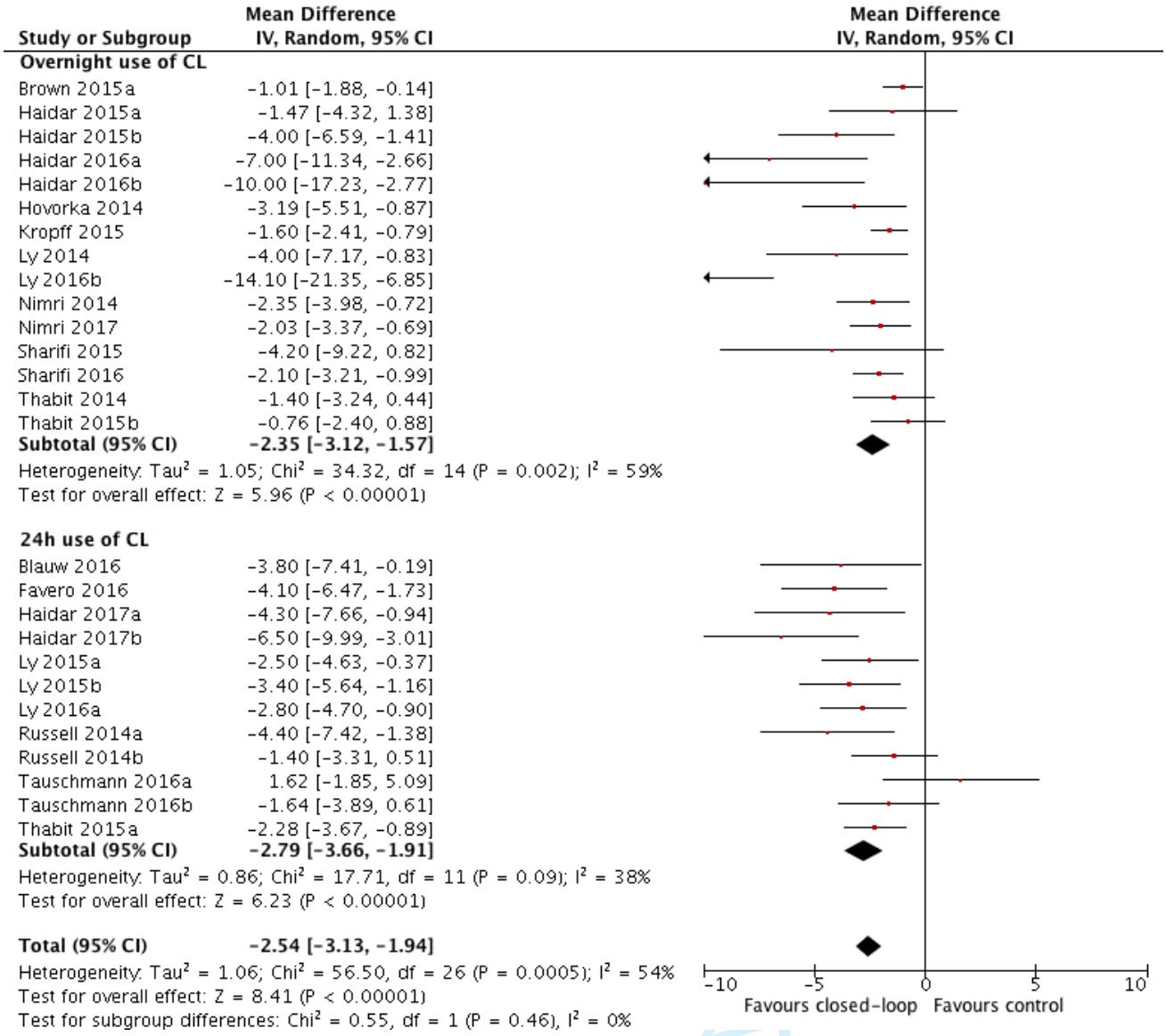

**Appendix 7**. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



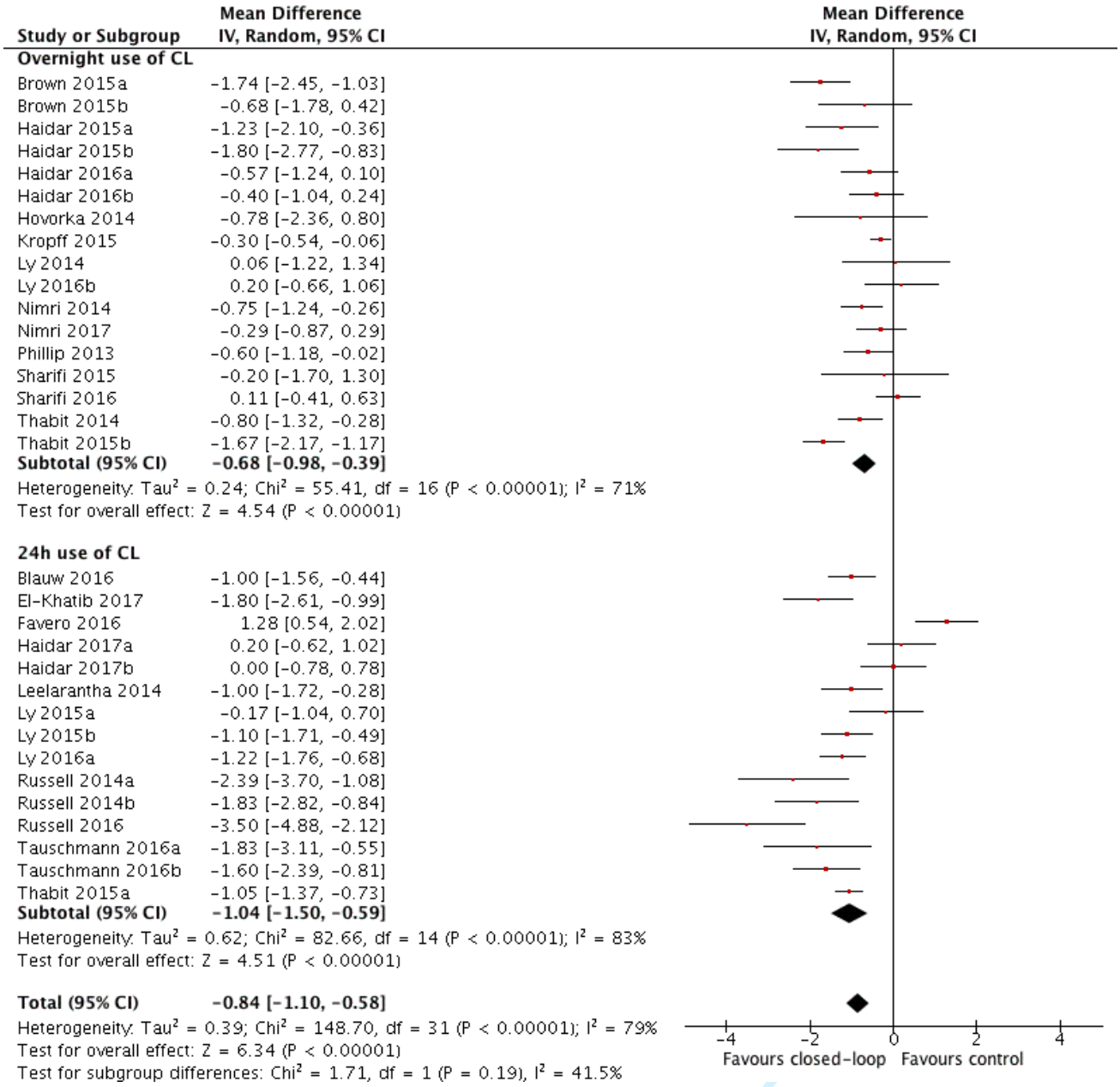

**Appendix 8**. Counter-enhanced funnel plot for studies assessing overnight time spent in near normoglycaemia.



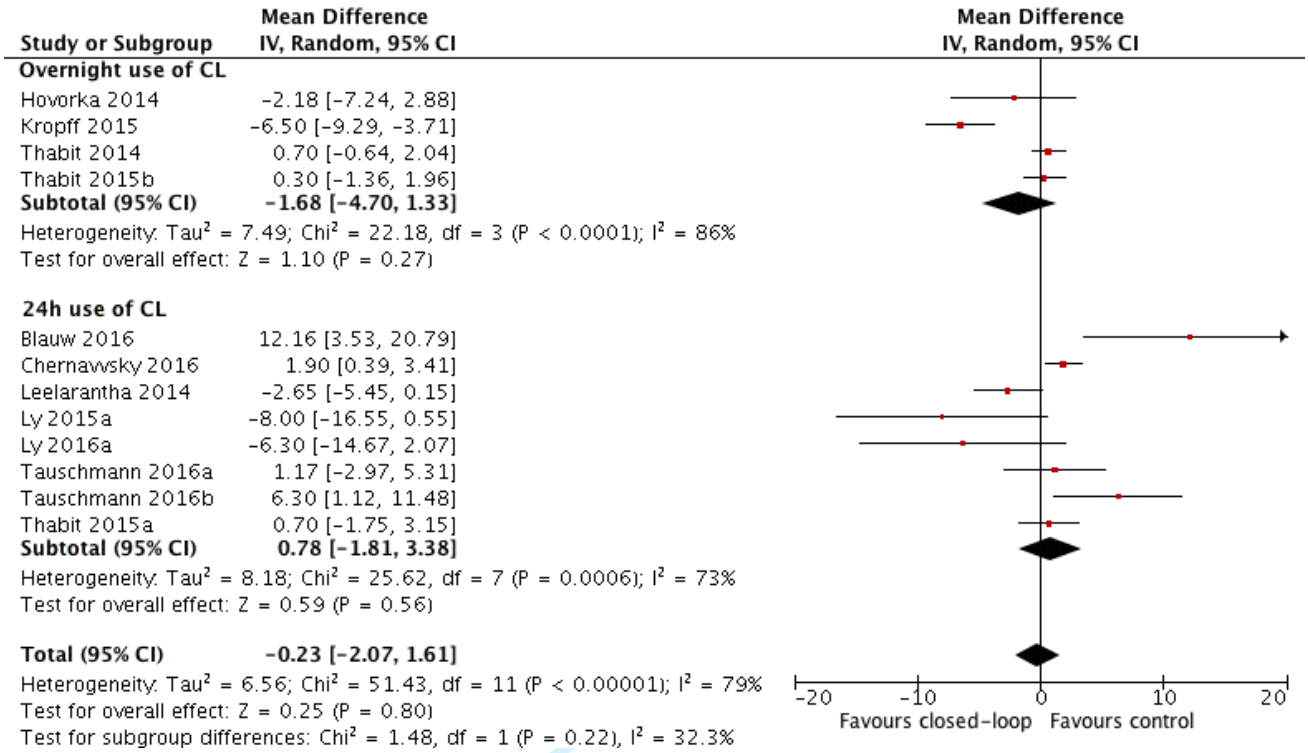

**Appendix 9**. Weighted mean difference in % of overnight time glucose was > 10.0 mmol/L. Closed-loop versus control treatment.




**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.

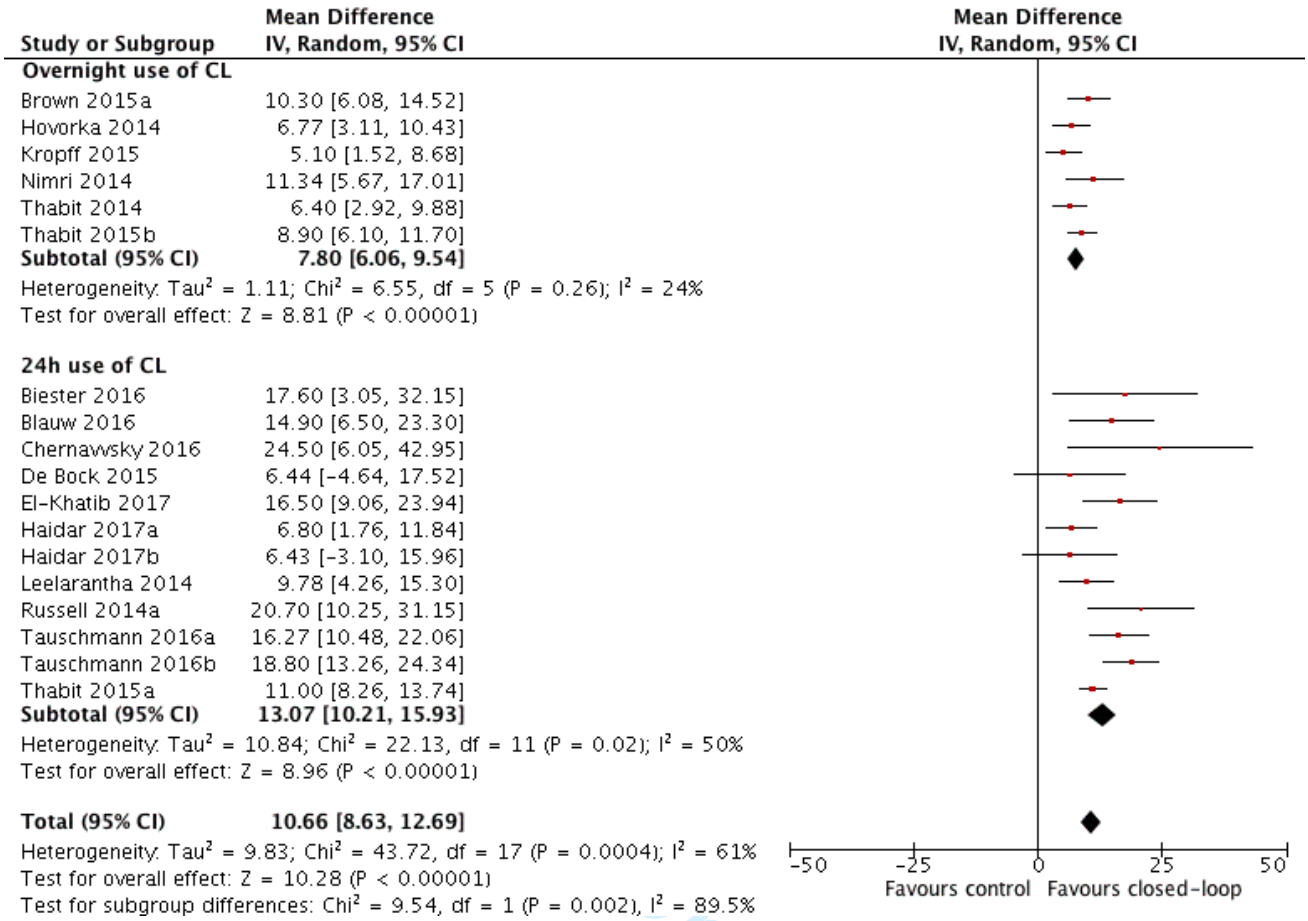



**Appendix 12**. Weighted mean difference in overall daily insulin needs (IU). Closed-loop versus control treatment.

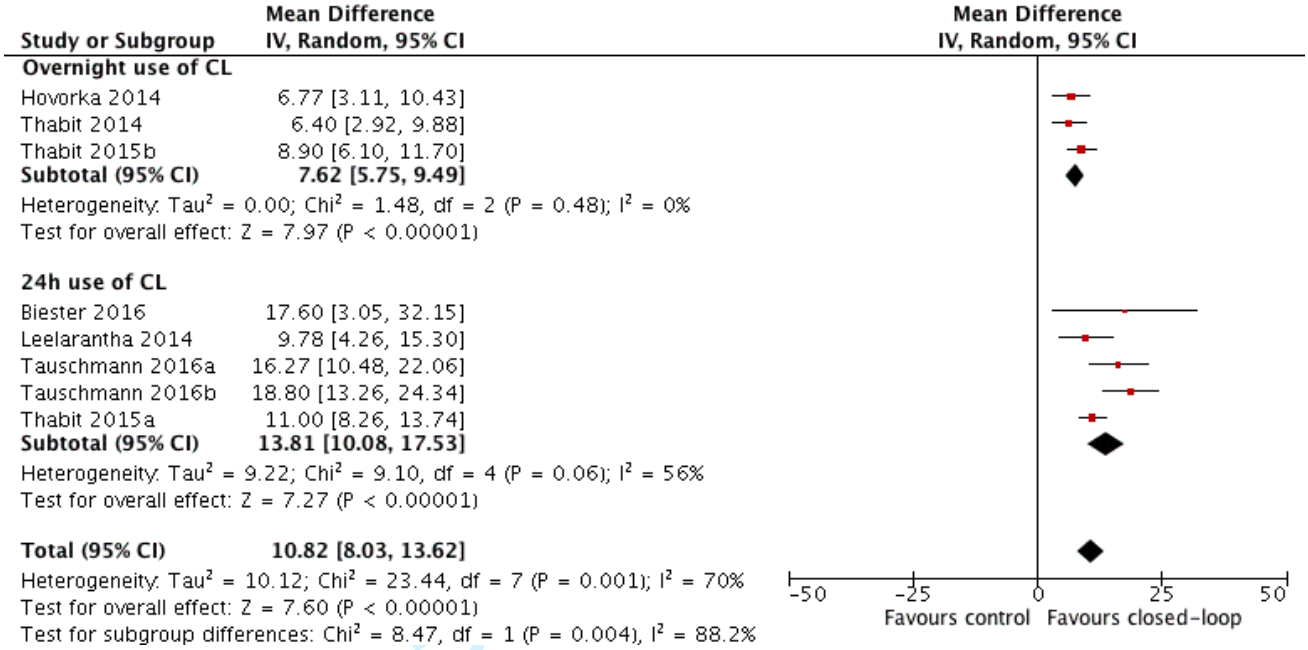
**Appendix 13.** Summary of findings of main analysis for all outcomes. Both overall effect estimates and subgroup effect estimates (based on overnight or 24h use of closed-loop system) between closed-loop and comparator are presented. BG: blood glucose. CIs: confidence intervals. CL: closed-loop. LGBI: low glucose blood index. NE: not estimable.

| Outcome | Number of studies | Effect estimate | Der Simmonian Laird 95% CIs | 95% Hartung-Knapp CIs | 95% Prediction intervals | $I^2$ (%) | $Tau^2$ |
|---|---|---|---|---|---|---|---|
| % of overall time between 3.9 – 10.0 mmol/L, Overall effect estimate | 25 | 9.54 | 6.99 to 12.09 | 6.84 to 12.24 | -2.19 to 21.27 | 81 | 30.47 |
| % of overall time between 3.9 – 10.0 mmol/L, Overnight use of CL | 6 | 7.8 | 6.06 to 9.54 | 5.26 to 10.34 | 3.97 to 11.62 | 24 | 1.11 |
| % of overall time between 3.9 – 10.0 mmol/L, 24h use of CL | 19 | 10.46 | 6.58 to 14.34 | 3.44 to 12.16 | -6.14 to 27.06 | 85 | 58.04 |
| % of overnight time between 3.9 – 10.0 mmol/L, Overall effect estimate | 24 | 16.44 | 12.85 to 20.02 | 12.91 to 19.97 | 0.63 to 32.25 | 76 | 54.78 |
| % of overnight time between 3.9 – 10.0 mmol/L, Overnight use of CL | 12 | 17.15 | 13.26 to 21.04 | 12.92 to 21.38 | 5.30 to 28.99 | 60 | 24.3 |
| % of overnight time between 3.9 – 10.0 mmol/L, 24h use of CL | 12 | 15.67 | 9.19 to 22.16 | 8.22 to 23.12 | -8.37 to 39.71 | 83 | 105.48 |
| % of overall time above 10.0 mmol/L, Overall effect estimate | 17 | -8.32 | -11.53 to -5.1 | -12.34 to -4.3 | -21.65 to 5.01 | 84 | 36.43 |
| % of overall time above 10.0 mmol/L, Overnight use of CL | 2 | -6.51 | -9.42 to -3.6 | -6.79 to -6.23 | NE | 0 | 0 |
| % of overall time above 10.0 mmol/L, 24h use of CL | 15 | -8.62 | -12.41 to -4.84 | -13.26 to -3.98 | -23.83 to 6.59 | 86 | 45.87 |
| % of overnight time above 10.0 mmol/L, Overall effect estimate | 19 | -12.99 | -16.73 to -9.25 | -17.46 to -8.52 | -28.39 to 2.41 | 80 | 49.68 |
| % of overnight time above 10.0 mmol/L, Overnight use of CL | 10 | -10.85 | -14.61 to -7.09 | -16.16 to -5.54 | -22.52 to 0.82 | 70 | 21.96 |
| % of overnight time above 10.0 mmol/L, 24h use of CL | 9 | -15.44 | -23.12 to -7.76 | -24.11 to -6.77 | -42.37 to 11.49 | 86 | 114.43 |
| % of overall time below 3.9 mmol/L, Overall effect estimate | 23 | -1.65 | -2.11 to -1.19 | -2.16 to -1.14 | -3.46 to 0.16 | 67 | 0.71 |
| % of overall time below 3.9 mmol/L, Overnight use of CL | 7 | -1.22 | -1.71 to -0.74 | -1.89 to -0.55 | -2.24 to -0.19 | 25 | 0.1 |
| % of overall time below 3.9 mmol/L, 24h use of CL | 16 | -1.88 | -2.55 to -1.22 | -2.1 to -0.34 | -4.29 to 0.53 | 74 | 1.15 |
| % of overnight time below 3.9 mmol/L, Overall effect estimate | 27 | -2.54 | -3.13 to -1.94 | -3.2 to -1.88 | -4.75 to -0.32 | 54 | 1.06 |

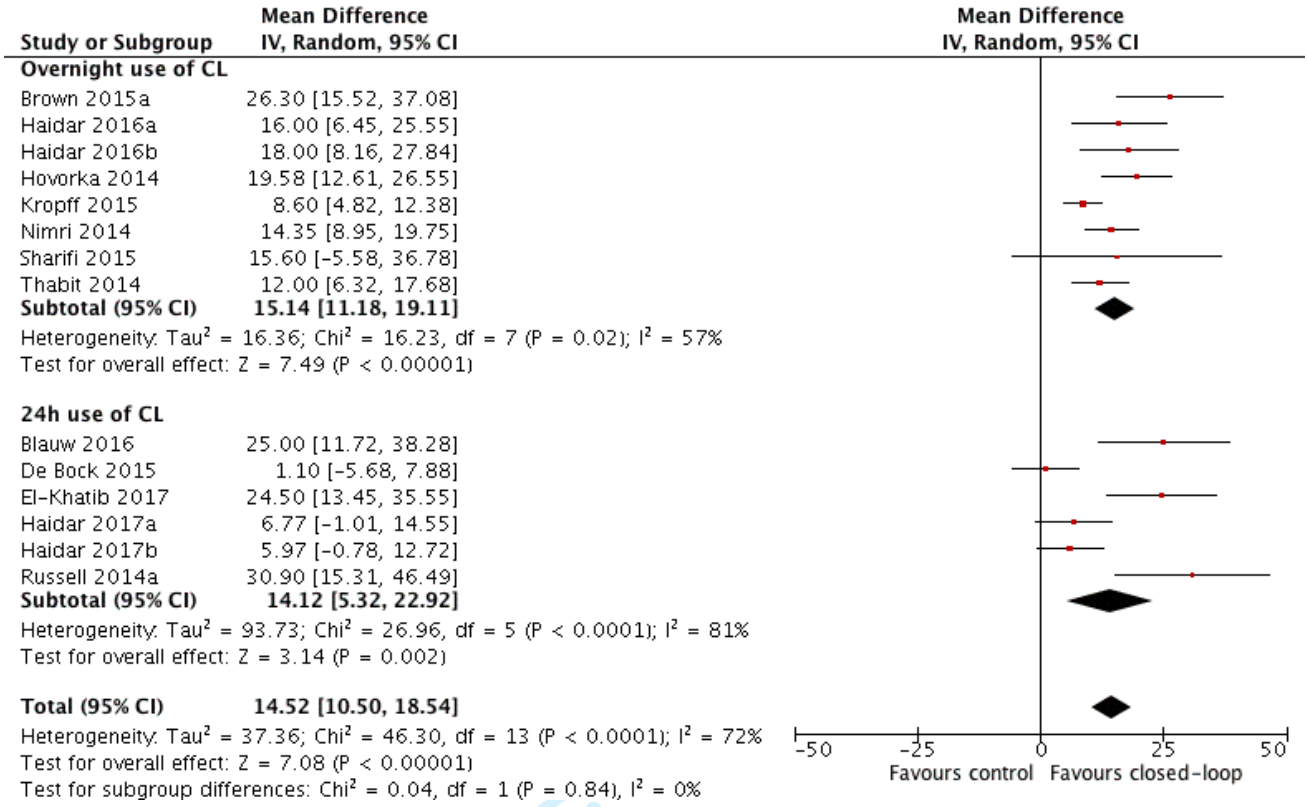
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| % of overnight time below 3.9 mmol/L, Overnight use of CL | 15 | -2.35 | -3.12 to -1.57 | -3.44 to -1.26 | -4.72 to 0.02 | 59 | 1.05 |
| % of overnight time below 3.9 mmol/L, 24h use of CL | 12 | -2.79 | -3.66 to -1.91 | -3.87 to -1.71 | -5.08 to -0.49 | 38 | 0.86 |
| Overnight LGBI, Overall effect estimate | 8 | -0.42 | -0.56 to -0.27 | -0.6 to -0.24 | -0.72 to -0.11 | 26 | 0.01 |
| Overnight LGBI, Overnight use of CL | 7 | -0.35 | -0.46 to -0.24 | -0.48 to -0.22 | -0.49 to -0.20 | 0 | 0 |
| Overnight LGBI, 24h use of CL | 1 | -1.07 | -1.64 to -0.5 | NE | NE | NE | NE |
| 24h Mean BG (mmol/L), Overall effect estimate | 24 | -0.51 | -0.76 to -0.27 | -0.79 to -0.23 | -1.63 to 0.61 | 83 | 0.28 |
| 24h Mean BG (mmol/L), Overnight use of CL | 5 | -0.31 | -0.49 to -0.13 | -0.56 to -0.06 | -0.74 to 0.12 | 36 | 0.01 |
| 24h Mean BG (mmol/L), 24h use of CL | 19 | -0.59 | -0.95 to -0.22 | -1.02 to -0.16 | -2.17 to 0.99 | 86 | 0.53 |
| Overnight Mean BG (mmol/L), Overall effect estimate | 32 | -0.84 | -1.1 to -0.58 | -1.07 to -0.61 | -2.14 to 0.46 | 79 | 0.39 |
| Overnight Mean BG (mmol/L), Overnight use of CL | 17 | -0.68 | -0.98 to -0.39 | -1 to -0.36 | -1.77 to 0.41 | 71 | 0.24 |
| Overnight Mean BG (mmol/L), 24h use of CL | 15 | -1.04 | -1.5 to -0.59 | -1.64 to -0.44 | -2.81 to 0.73 | 83 | 0.62 |
| 24h Total insulin delivered (IU), Overall effect estimate | 12 | -0.23 | -2.07 to 1.61 | -2.98 to 2.52 | -6.30 to 5.84 | 79 | 6.56 |
| 24h Total insulin delivered (IU), Overnight use of CL | 4 | -1.68 | -4.7 to 1.33 | -7.08 to 3.72 | -15.18 to 11.82 | 86 | 7.49 |
| 24h Total insulin delivered (IU), 24h use of CL | 8 | 0.78 | -1.81 to 3.38 | -3.3 to 4.86 | -6.93 to 8.49 | 73 | 8.18 |
| $HbA_{1c}$ | 3 | -0.26 | -0.38 to -0.13 | -0.41 to -0.11 | -1.10 to 0.58 | 0 | 0 |



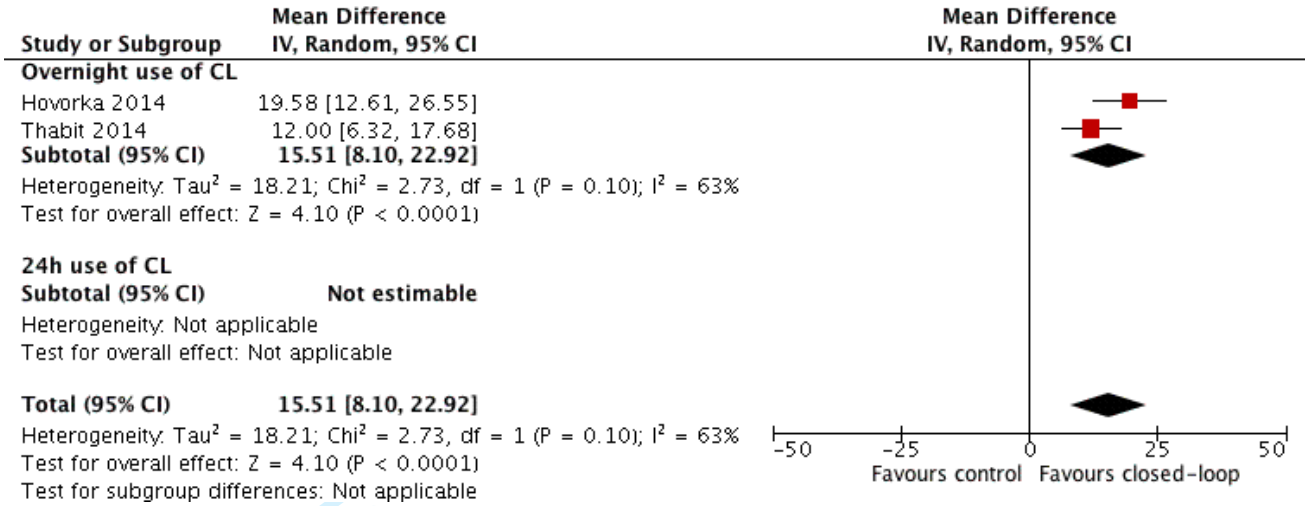

**Appendix 14**. Weighted mean difference in % of overall time in near normoglycaemic range (3.9 – 10.0 mmol/L). Closed-loop versus control treatment. Sensitivity analysis excluding trials recruiting patients in camps.



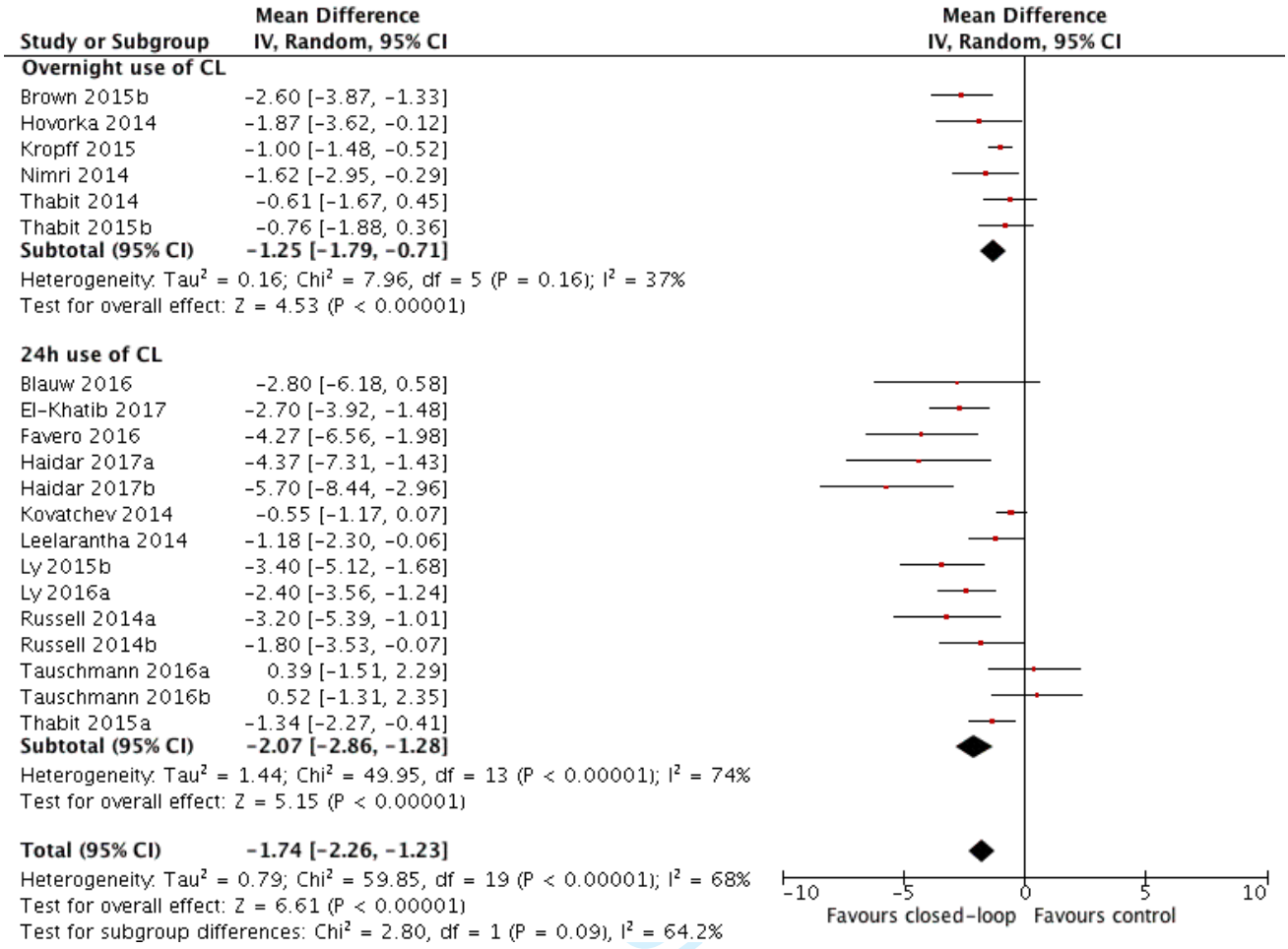

**Appendix 15**. Weighted mean difference in % of overall time in near normoglycaemic range (3.9 – 10.0 mmol/L). Closed-loop versus control treatment. Sensitivity analysis including only trials recruiting unsupervised patients in free-living conditions.



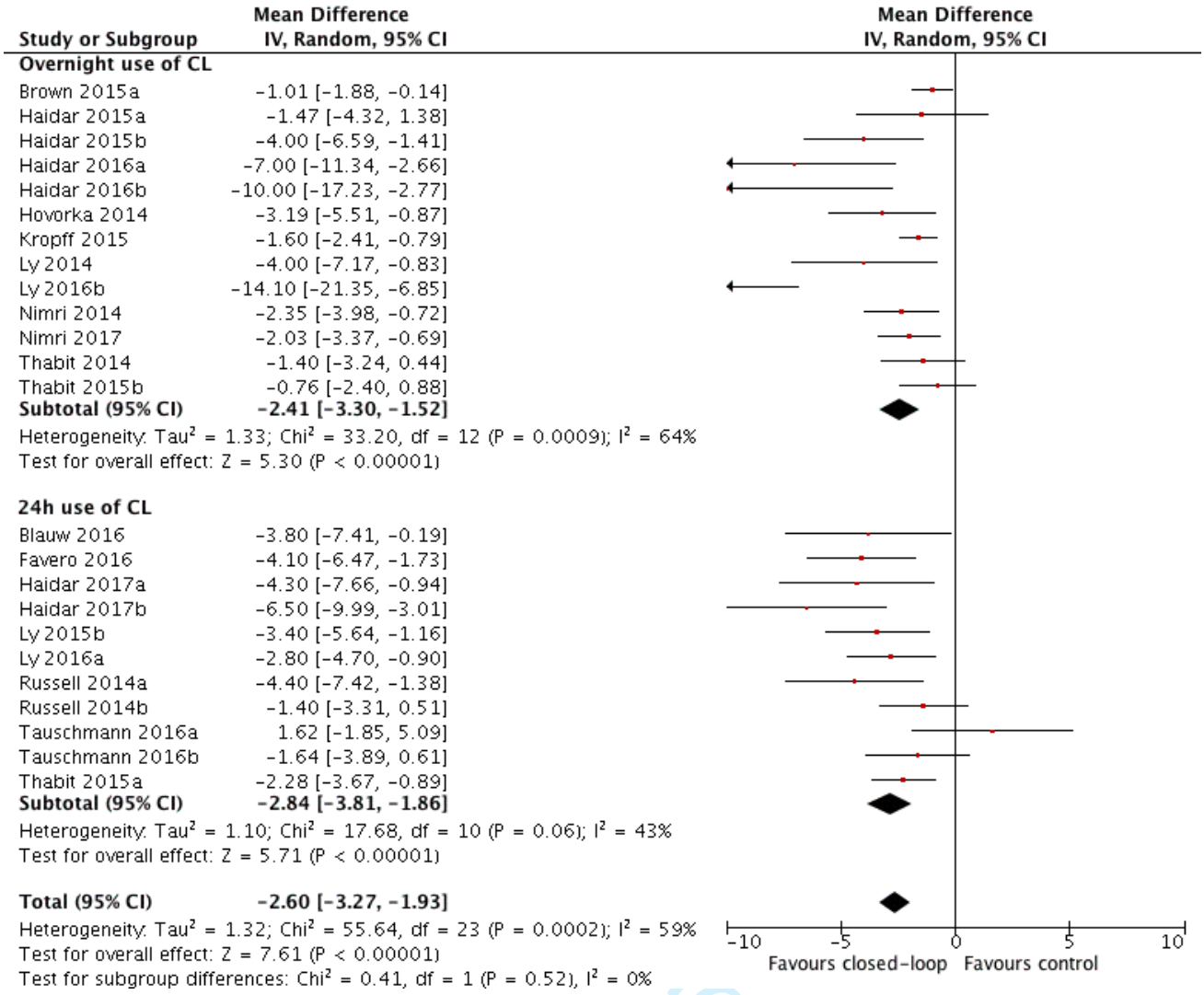

**Appendix 16**. Weighted mean difference in % of overnight time in near normoglycaemic range (3.9 – 10.0 mmol/L). Closed-loop versus control treatment. Sensitivity analysis excluding trials recruiting patients in camps.



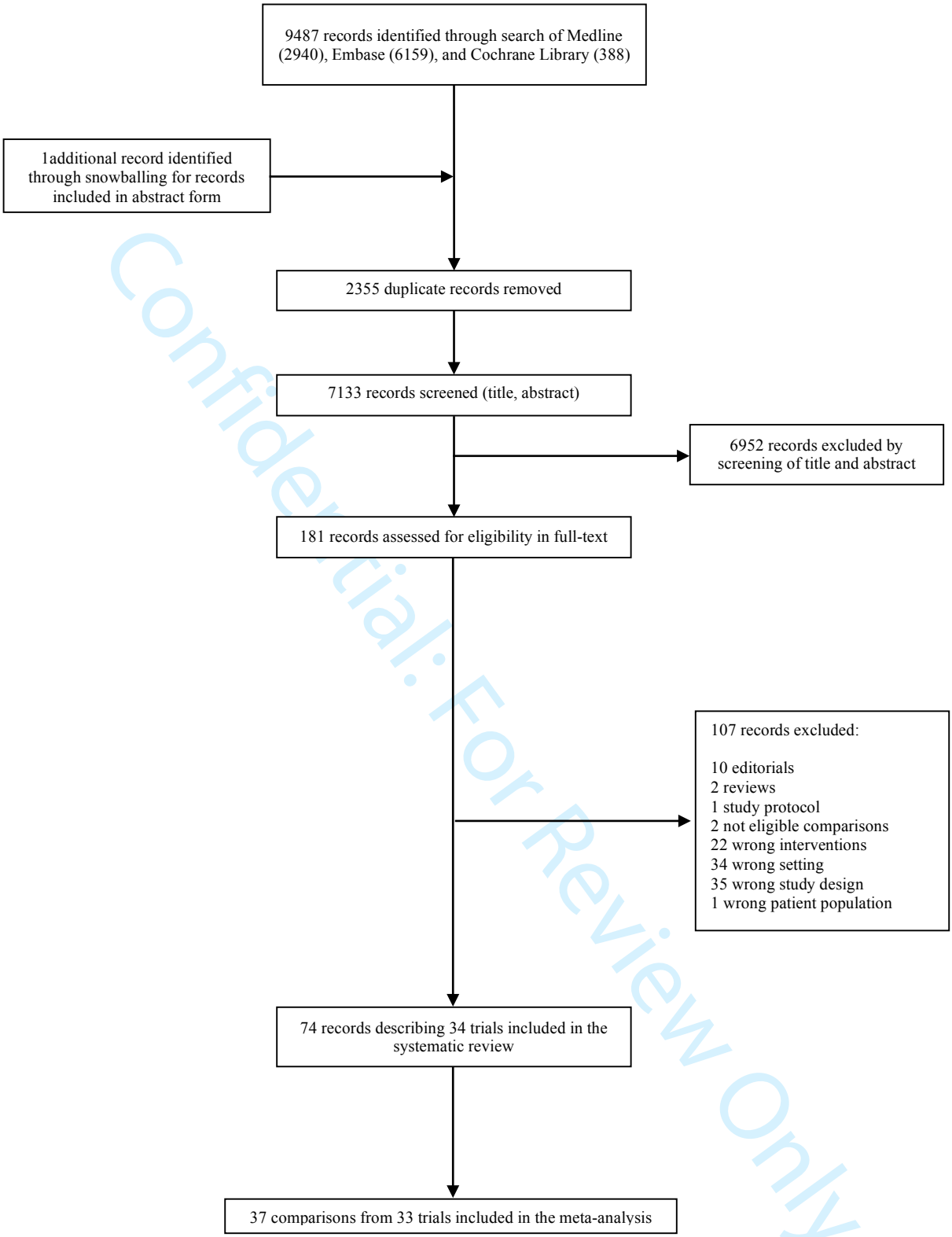

**Appendix 17**. Weighted mean difference in % of overnight time in near normoglycaemic range (3.9 – 10.0 mmol/L). Closed-loop versus control treatment. Sensitivity analysis including only trials recruiting unsupervised patients in free-living conditions.

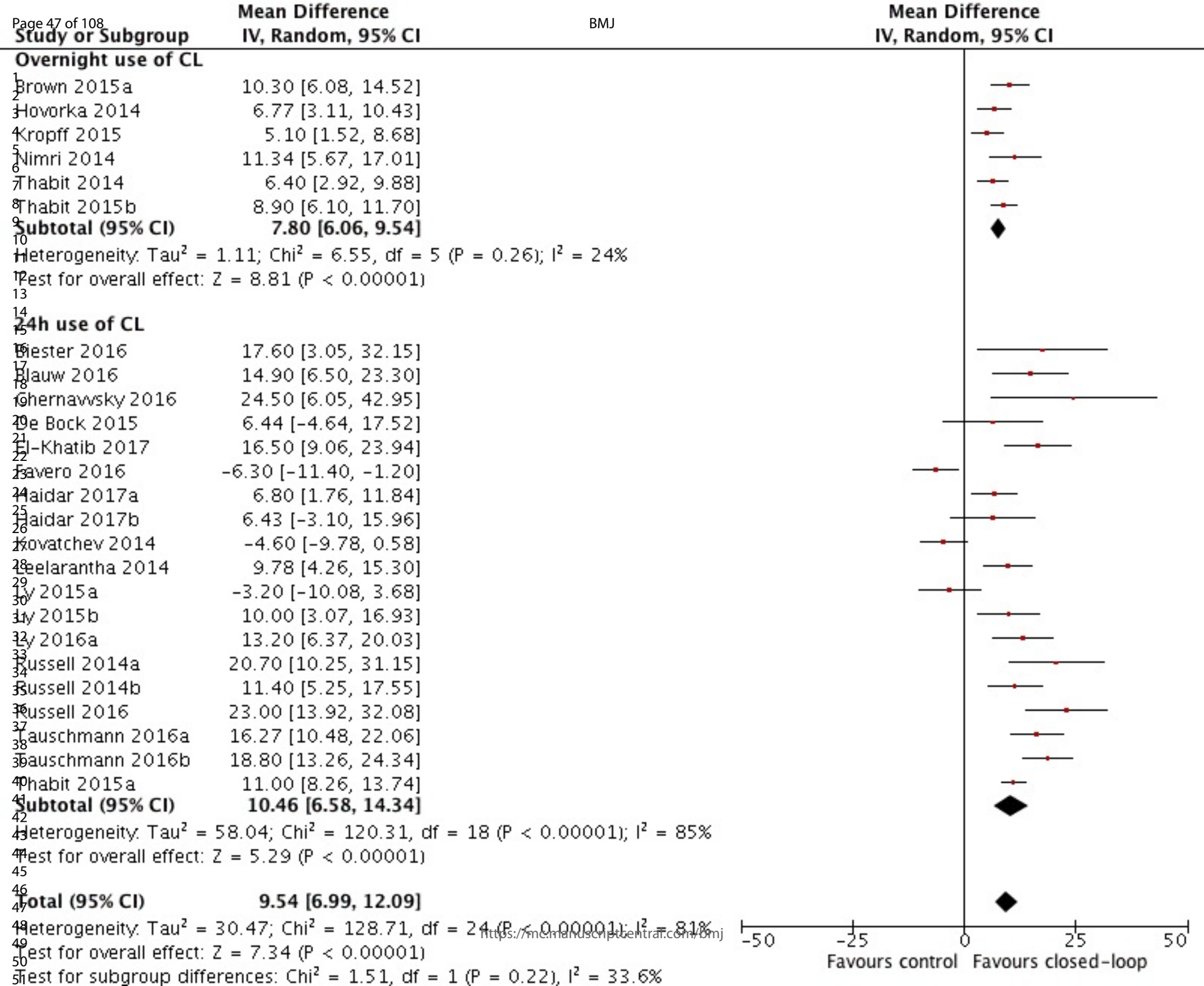


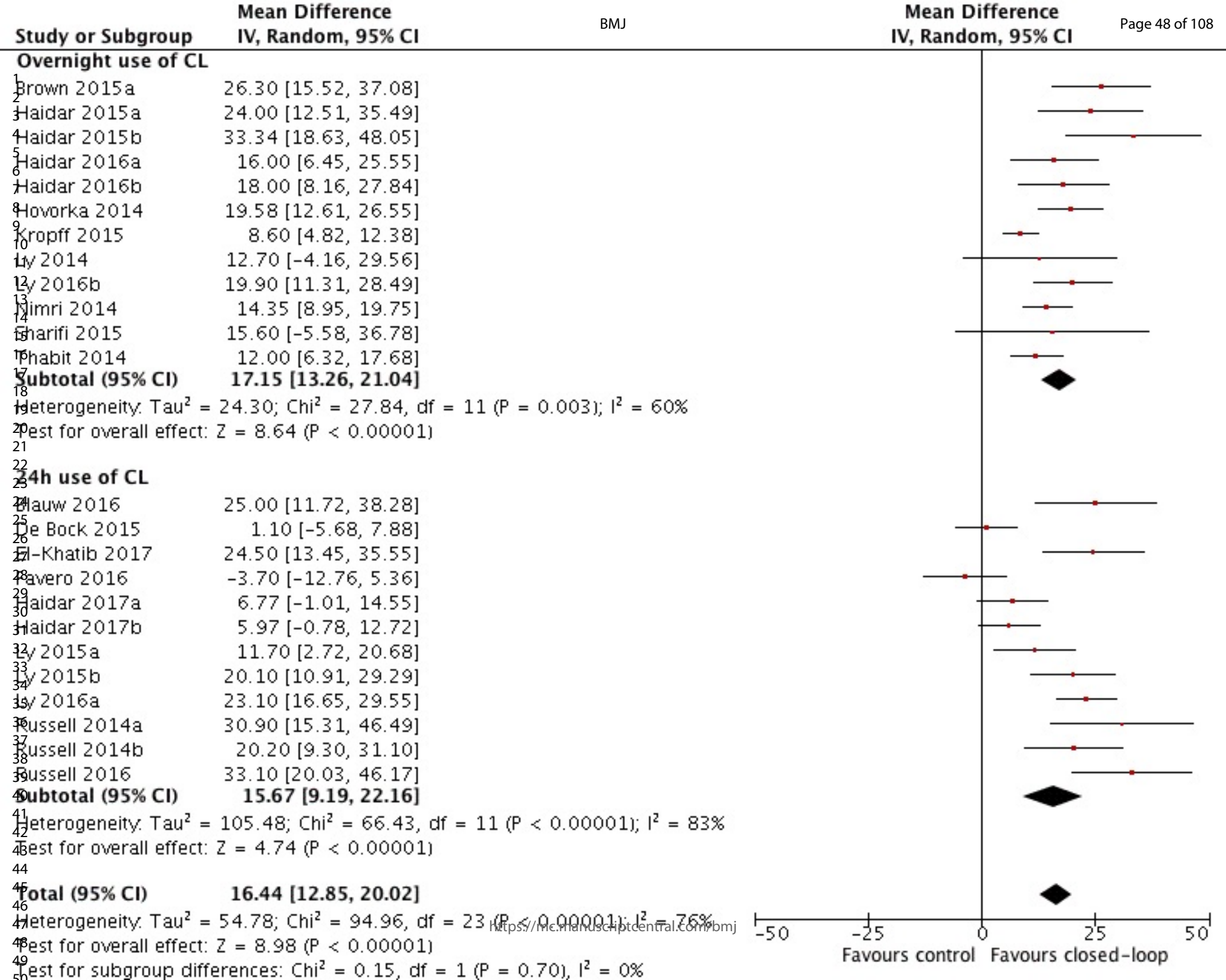

**Appendix 18**. Weighted mean difference in % of overall time glucose was < 3.9 mmol/L. Closed-loop versus control treatment. Sensitivity analysis excluding trials comparing closed-loop systems with low glucose suspend (LGS) systems.

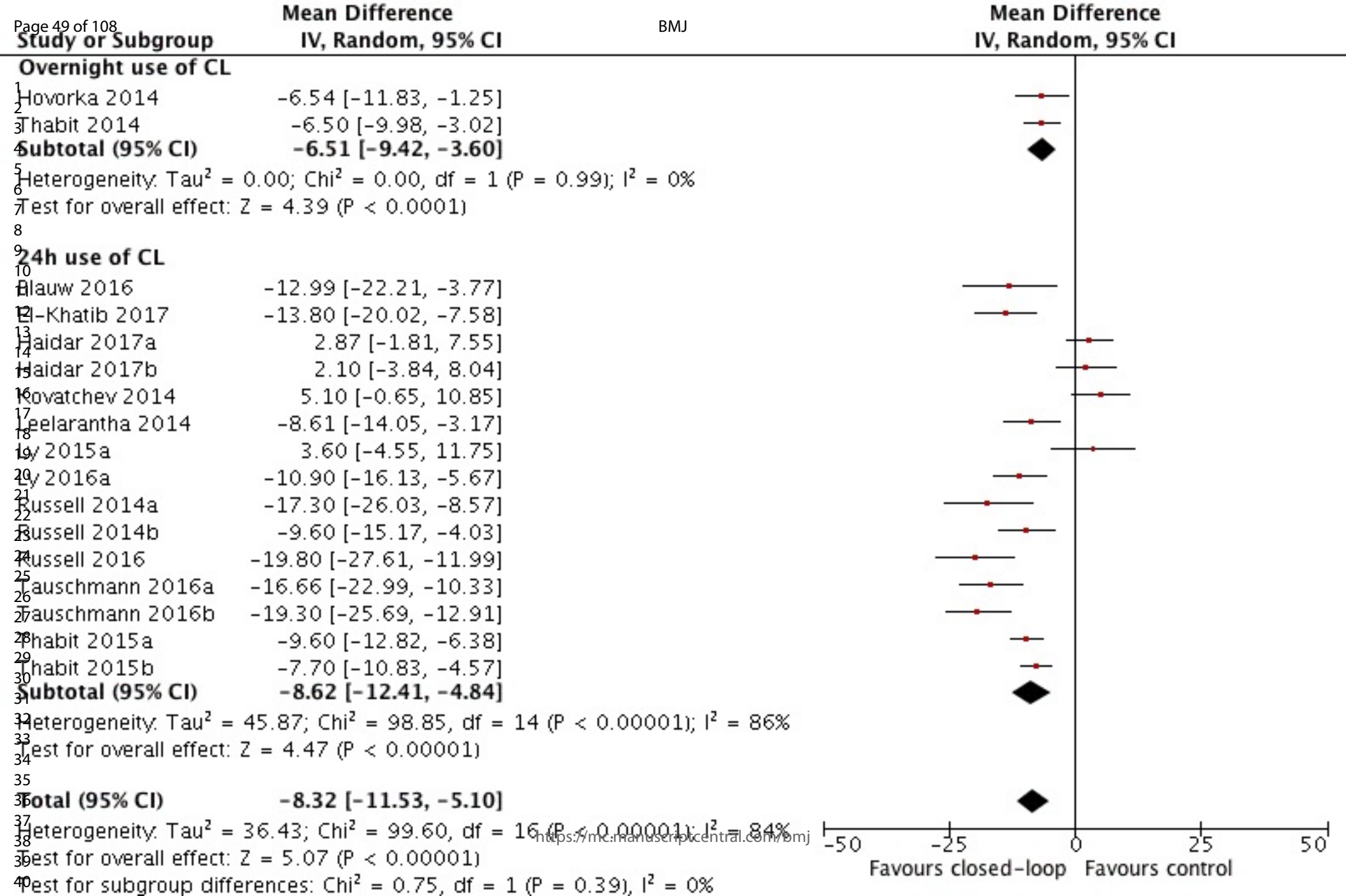


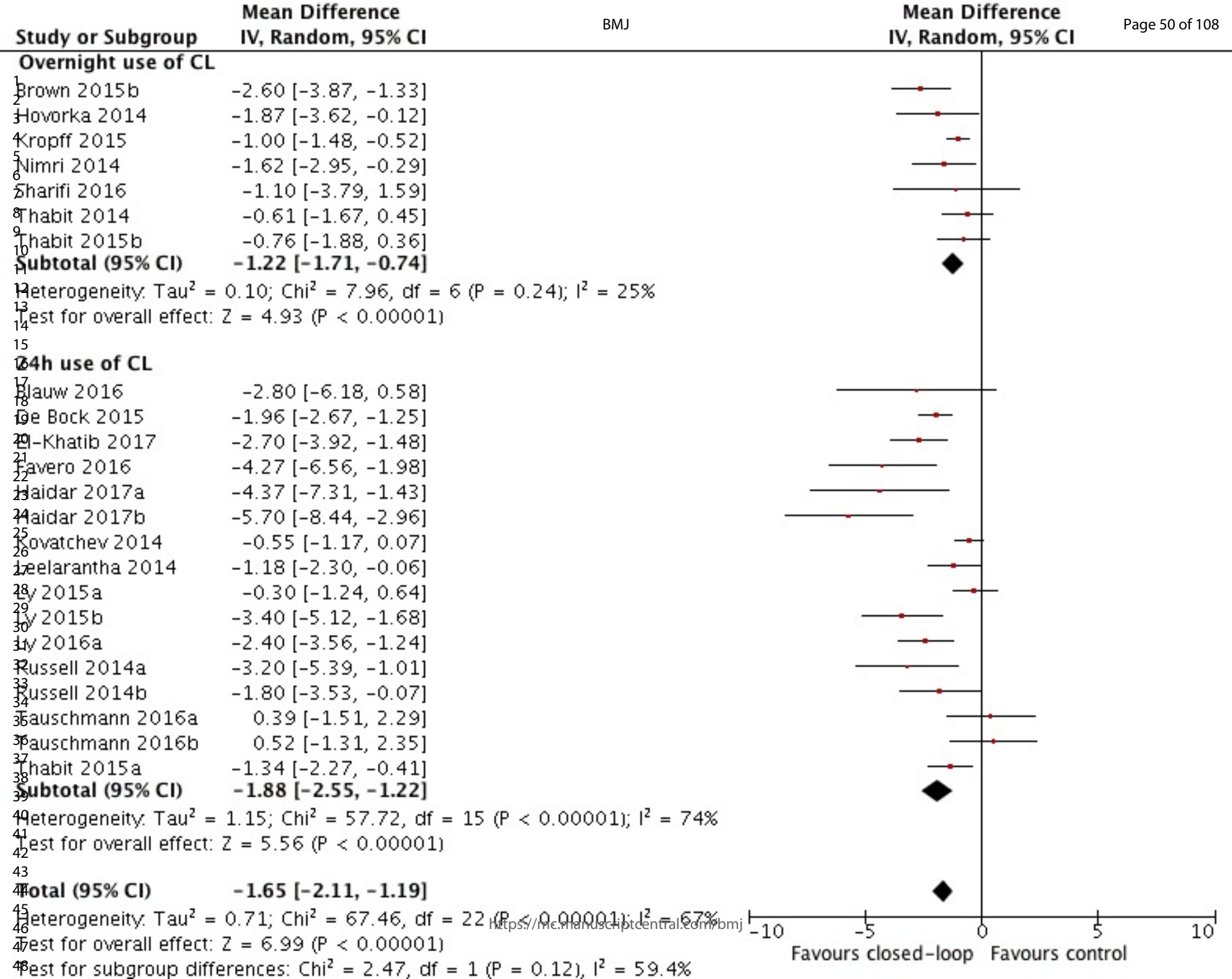

**Appendix 19**. Weighted mean difference in % of overnight time glucose was < 3.9 mmol/L. Closed-loop versus control treatment. Sensitivity analysis excluding trials comparing closed-loop systems with low glucose suspend (LGS) systems.

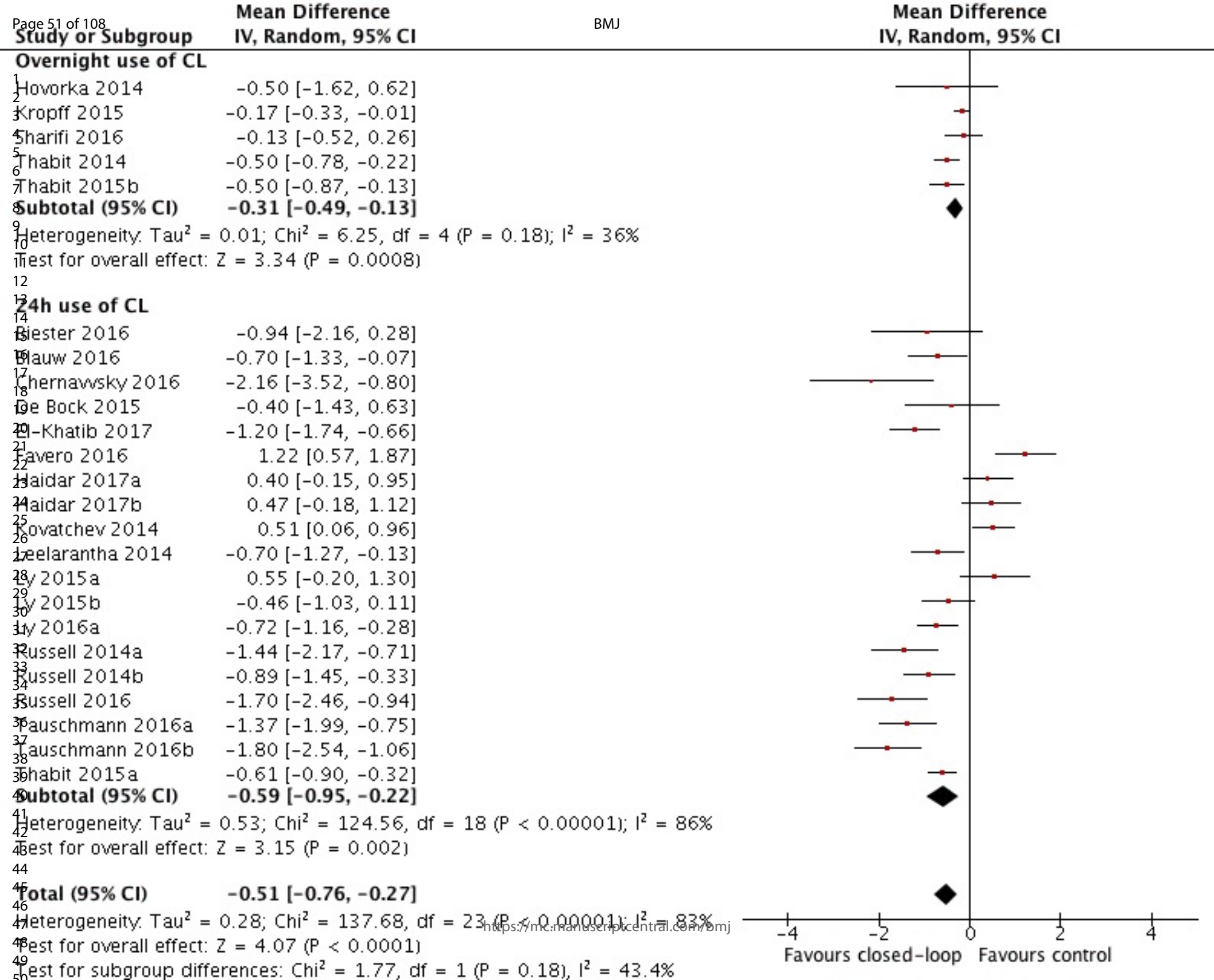








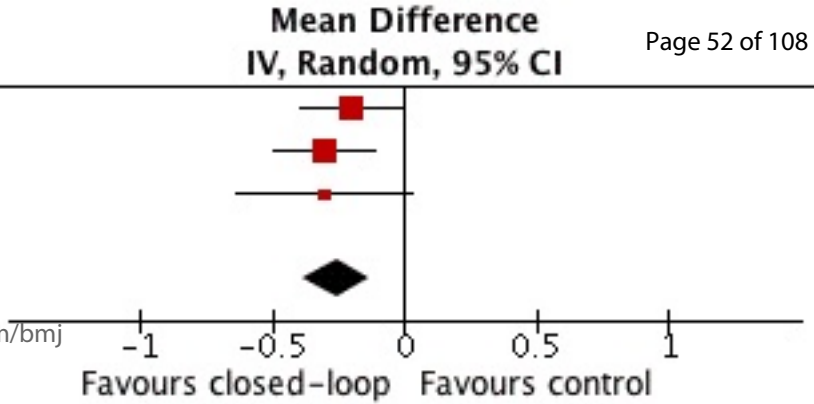


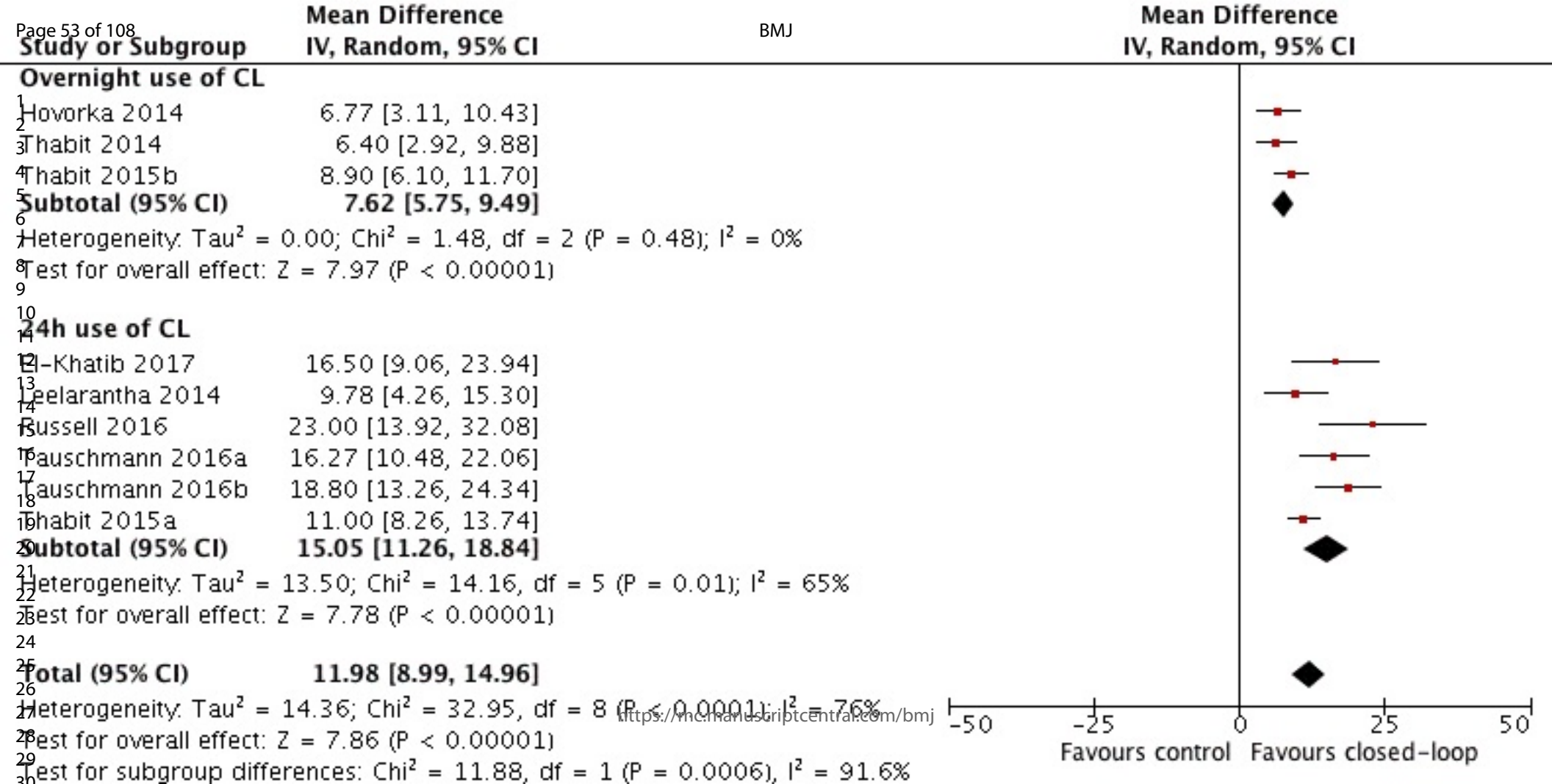

Study or Subgroup
Mean Difference
IV, Random, 95% CI
Mean Difference
IV, Random, 95% CI
Overnight use of CL
Hovorka 2014 -0.50 [-1.62, 0.62]
Kropff 2015 -0.17 [-0.33, -0.01]
Sharifi 2016 -0.13 [-0.52, 0.26]
Thabit 2014 -0.50 [-0.78, -0.22]
Thabit 2015b -0.50 [-0.87, -0.13]
Subtotal (95% CI) -0.31 [-0.49, -0.13]
Heterogeneity: Tau² = 0.01; Chi² = 6.25, df = 4 (P = 0.18); I² = 36%
Test for overall effect: Z = 3.34 (P = 0.0008)
24h use of CL
Biester 2016 -0.94 [-2.16, 0.28]
Blauw 2016 -0.70 [-1.33, -0.07]
Chernavvsky 2016 -2.16 [-3.52, -0.80]
De Bock 2015 -0.40 [-1.43, 0.63]
El-Khatib 2017 -1.20 [-1.74, -0.66]
Favero 2016 1.22 [0.57, 1.87]
Haidar 2017a 0.40 [-0.15, 0.95]
Haidar 2017b 0.47 [-0.18, 1.12]
Kovatchev 2014 0.51 [0.06, 0.96]
Leelarantha 2014 -0.70 [-1.27, -0.13]
Ly 2015a 0.55 [-0.20, 1.30]
Ly 2015b -0.46 [-1.03, 0.11]
Ly 2016a -0.72 [-1.16, -0.28]
Russell 2014a -1.44 [-2.17, -0.71]
Russell 2014b -0.89 [-1.45, -0.33]
Russell 2016 -1.70 [-2.46, -0.94]
Tauschmann 2016a -1.37 [-1.99, -0.75]
Tauschmann 2016b -1.80 [-2.54, -1.06]
Thabit 2015a -0.61 [-0.90, -0.32]
Subtotal (95% CI) -0.59 [-0.95, -0.22]
Heterogeneity: Tau² = 0.53; Chi² = 124.56, df = 18 (P < 0.00001); I² = 86%
Test for overall effect: Z = 3.15 (P = 0.002)
Total (95% CI) -0.51 [-0.76, -0.27]
Heterogeneity: Tau² = 0.28; Chi² = 137.68, df = 23 (P < 0.00001); I² = 83%
Test for overall effect: Z = 4.07 (P < 0.0001)
Test for subgroup differences: Chi² = 1.77, df = 1 (P = 0.18), I² = 43.4%
-4
-2
0
2
4
Favours closed-loop
Favours control

| Study or Subgroup | Mean Difference IV, Random, 95% CI |
|---|---|
| Kropff 2015 | -0.20 [-0.39, -0.01] |
| Thabit 2015a | -0.30 [-0.49, -0.11] |
| Thabit 2015b | -0.30 [-0.63, 0.03] |
| **Total (95% CI)** | **-0.26 [-0.38, -0.13]** |

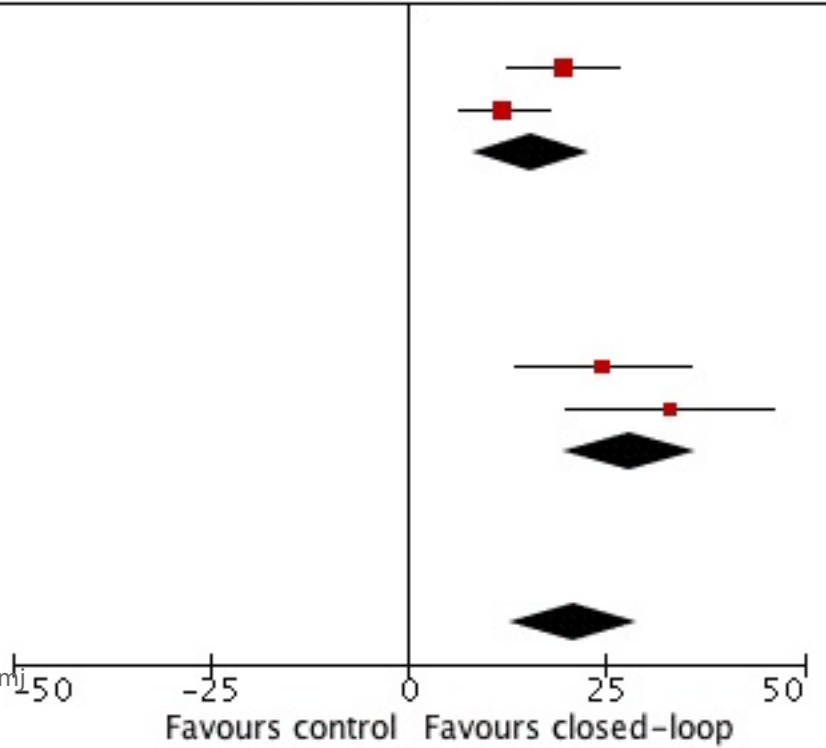
Heterogeneity: Tau² = 0.00; Chi² = 0.60, df = 2 (P = 0.74); I² = 0%

Test for overall effect: Z = 4.04 (P < 0.0001)





| Study or Subgroup | Mean Difference IV, Random, 95% CI |
|---|---|
| **Overnight use of CL** | |
| Hovorka 2014 | 19.58 [12.61, 26.55] |
| Thabit 2014 | 12.00 [6.32, 17.68] |
| **Subtotal (95% CI)** | **15.51 [8.10, 22.92]** |
| Heterogeneity: $Tau^2 = 18.21$; $Chi^2 = 2.73$, df = 1 (P = 0.10); $I^2 = 63\%$ | |
| Test for overall effect: Z = 4.10 (P < 0.0001) | |
| | |
| **24h use of CL** | |
| El-Khatib 2017 | 24.50 [13.45, 35.55] |
| Russell 2016 | 33.10 [20.03, 46.17] |
| **Subtotal (95% CI)** | **28.09 [19.65, 36.52]** |
| Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.97$, df = 1 (P = 0.32); $I^2 = 0\%$ | |
| Test for overall effect: Z = 6.52 (P < 0.00001) | |
| | |
| **Total (95% CI)** | **20.86 [12.69, 29.03]** |
| Heterogeneity: $Tau^2 = 48.04$; $Chi^2 = 10.93$, df = 3 (P = 0.01); $I^2 = 73\%$ | |
| Test for overall effect: Z = 5.00 (P < 0.00001) | |
| Test for subgroup differences: $Chi^2 = 4.82$, df = 1 (P = 0.03), $I^2 = 79.2\%$ | |



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

Eleni Bekiari, Konstantinos Kitsios, Hood Thabit, Martin Tauschmann, Eleni Athanasiadou, Thomas Karagiannis, Anna-Bettina Haidich, Roman Hovorka, Apostolos Tsapas

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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, incidence of severe hypoglycaemia, 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 with data for 37 comparisons) were included. Twenty-eight comparisons assessed a single-hormone closed-loop system, while a dual-hormone closed-loop system was assessed in nine comparisons. Only nine studies were at low risk of bias. 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. The main limitations of current research evidence on closed-loop systems are related to inconsistency in outcome reporting, small sample size and short follow-up duration of individual trials.

## 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. Currently, insulin treatment strategies in type 1 diabetes include either multiple daily insulin injections (MDIs) or continuous subcutaneous insulin infusion (CSII) with an insulin pump. In 2008, the National Institute for Health and Care Excellence (NICE) concluded that CSII therapy had a favourable effect on glycated haemoglobin ($HbA_{1c}$) and incidence of hypoglycaemia in patients with type 1 diabetes.[1] Until recently, CSII therapy was mostly guided by self-monitoring of capillary glucose testing.[2] However, in recent years, insulin pumps are also used in conjunction with real-time continuous glucose monitoring (CGM), hence allowing the patient to manually modify the insulin infusion rate according to CGM values (sensor augmented pump therapy, SAP).[2 3] Lately, introduction of a low glucose suspend (LGS) feature allows for automatic pump suspension when a pre-programmed CGM threshold value is reached.[4]

Closed-loop glucose control, also referred to as the artificial pancreas, is an emerging therapeutic option combining insulin pump and CGM with a control algorithm to deliver insulin in a glucose-responsive manner (single-hormone closed-loop system). 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. An early pooled analysis included only four studies in an inpatient setting,[5] while an overview published in 2015 summarised existing data from RCTs until September 2014.[6] Finally, a recent meta-analysis summarised evidence from published trials of closed loop systems in outpatients with type 1 diabetes.[7] Notably, the U.S. Food and Drug Administration (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.[8]

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 is reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement (**appendix 2**).[9]

### 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.[10 11] 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 MDIs, insulin pump therapy without CGM or with blinded CGM, and SAP with or without LGS.

**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, incidence of severe hypoglycaemia, mean sensor glucose level, total daily insulin needs and $HbA_{1c}$. We also used overnight low blood glucose index as an additional outcome for assessing hypoglycaemia. Low blood glucose index is a weighted average of the number of hypoglycaemic readings with progressively increasing weights as glucose levels decrease and is associated with risk for hypoglycaemia and prediction of severe hypoglycaemic episodes.[12]

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), applying an inverse-variance weighted random effects model using the DerSimonian and Laird estimation method.[13] We also calculated 95% prediction intervals to estimate a predicted range for the true treatment effect in any one individual study.[14] In addition, to account for uncertainty related to heterogeneity estimates, we calculated 95% confidence intervals applying the Hartung Knapp correction method.[15] 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.[16] 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.[17]

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 $Tau^2$ and $I^2$ statistics. 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 in individual studies**

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).[18] 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.

**Assessment of risk of bias across studies**

We explored risk of bias across studies, both visually using a contour enhanced funnel plot, and formally utilising Egger's statistical test.[19 20] In case of evidence of small study effects, we used the trim and fill method as a sensitivity analysis, to provide an adjusted estimate of the meta-analysis.[21]

**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, 32 publications describing 34 trials (792 participants with data for 37 comparisons) were used to inform our systematic review.[22-53] One trial did not report data for outcomes assessed and was not included in the meta-analysis.[47]

Study and participants' baseline characteristics are shown in **Table 1**. The vast majority of included trials utilised a crossover design,[22-37 40 42-53] whereas only three trials were of parallel design.[38 39 41] In twenty-eight trials duration was less than four weeks,[22-32 34 36-41 43-51] whereas in the remaining six trials it ranged from eight to thirty weeks.[33 35 42 52 53] Thirteen trials recruited children or adolescents,[26 29 30 33 40 41 44-47 50 51 53] eleven trials recruited adults,[23-25 28 32 34-36 45 52 53] while ten trials recruited a mixed population.[22 27 31 37-39 42 43 48 49] In sixteen trials closed-loop was used overnight,[24 25 30 31 33 35 37 40 42-44 47-49 52 53] while in the remaining eighteen trials closed-loop was used throughout 24

hours.[22 23 26-29 32 34 36 38 39 41 45 46 50 51 53] Twenty-five trials compared a single-hormone closed-loop system (mostly with unblinded SAP therapy),[22 24 25 27 29 33-39 41 40 42-44 47-53] while six trials assessed dual-hormone closed-loop systems in comparison mainly to insulin pump therapy (consisting of CSII combined with a blinded CGM system).[23 26 28 45 46] Additionally, three studies evaluated both a single-hormone and a dual-hormone system against control treatment (three-way cross-over trials).[30-32] Of note, in four studies assessing SAP therapy, the control comprised a SAP combined with an LGS feature.[27 39 48 49] Among trials evaluating single hormone closed-loop systems, nine trials used the DiAs platform,[24-26 29 34 35 37 38 41] eight trials used the Florence algorithm,[33 36 47 50-53] four trials used the MD-Logic algorithm,[22 42-44] and five trials used the Medtronic closed-loop.[27 39 40 48 49] Most of the trials used a model predictive control algorithm,[28-36 45-47 50-53] six trials used a proportional integral derivative algorithm,[23 27 39 40 48 49] four trials used a fuzzy logic algorithm,[22 42-44] while the rest of the trials used other algorithms or did not provide relevant details.[24-26 37 38 41] Seventeen closed-loop comparisons utilised the Dexcom G4® CGM sensor,[24-26 28-30 32 34 35 37 38 45 46 54] while an Enlite™ Sensor, a FreeStyle Navigator® or a Medtronic 4s sensor were used in the closed-loop systems in nine,[23 27 31 40 42-44 49] eight,[33 36 47 50-53] and one comparisons,[39] respectively. Type of CGM sensor wan not reported in two trials.[22 48] Of note, in 30 comparisons, type of CGM sensor was identical between closed-loop and control arms, one trial used a different sensor in the control arm,[39] and six trials did not report information for type of sensor used in the control arm.[22 25 26 38 41 48]

Finally, eleven trials were held in a diabetes camp or a guesthouse,[29 30 34 37-41 44-46] while in twenty-three trials subjects were at home.[22-28 31-33 35 36 42 43 45 47-53] Only in a small subset of trials were subjects using closed-loop unsupervised under free-living conditions,[22 33 36 50-53] 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**. Only nine studies were at low risk of bias. Most studies were deemed at high risk for bias, 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 small study effects for percentage of overall time near normoglycaemia (P=0.247). However, there was evidence of small study effects (P=0.010) for percentage of overnight time spent in near normoglycaemia, and visual inspection of the contour-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 closed-loop therapy (weighted mean difference 12.52%, 95% confidence interval 8.90 to 16.13, P<0.001).

**Primary outcome**

All meta-analysis results are presented as summary effect estimates for closed-loop versus control.

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) (overall effect estimate 9.54%, 95% confidence interval 6.99 to 12.09, $I^2$ 81%, $Tau^2$ 30.47, 25 studies). This effect was consistent both for trials using closed-loop overnight (7.80%, 6.06 to 9.54, 24%, 1.11, six studies), or throughout 24h (10.46%, 6.58 to 14.34, 85%, 58.04, 19 studies) (**Figure 2**). 95% confidence intervals for the overall effect estimate after applying the Hartung Knapp correction were 6.84 to 12.24, while 95% prediction intervals were -2.19 to 21.27. Of note, 95% prediction intervals were statistically

significant when closed-loop was used overnight (3.97 to 11.62) suggesting that closed-loop will be beneficial in at least 95% of the individual study settings when applied overnight, but not when applied throughout 24h (-6.14 to 27.06).

The favourable effect of closed-loop over control was more evident on the percentage of time spent in near normoglycaemia overnight (16.44%, 12.85 to 20.02, 76%, 54.78, 24 studies), and was consistent both when closed-loop was used either only overnight (17.15%, 13.26 to 21.04, 60%, 24.3, 12 studies) or throughout 24h (15.67%, 9.19 to 22.16, 83%, 105.48, 12 studies) (**Figure 3**), even when the Hartung Knapp correction was applied (**appendix 13**). Respective 95% prediction intervals calculated suggest that effect on time spent in near normoglycaemia overnight (95% prediction intervals 0.63 to 32.25) will be beneficial in at least 95% of the individual study settings when applied overnight (5.30 to 28.99), but not when applied throughout 24h (-8.37 to 39.71).

**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, 84%, 36.43, 17 studies) compared to control, both in trials where closed-loop was used only overnight (−6.51%, −9.42 to −3.60, 0%, 0.0, two studies), and in trials using closed-loop throughout 24h (−8.62%, −12.41 to −4.84, 86%, 45.87, 15 studies) (**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, 80%, 49.68, 19 studies), both in trials that used closed-loop either only overnight (−10.85%, −14.61 to −7.09, 70%, 21.96, 10 studies), or throughout the day (24h) (−15.44%, −23.12 to −7.76, 86%, 114.43, nine studies) (**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, 67%, 0,71, 23 studies) (**Figure 5**). Results were consistent for overnight time spent at concentrations lower than 3.9 mmol/L (−2.54%, −3.13 to −1.94, 54%, 1.06, 27 studies) (**appendix 10**). Data on incidence of severe hypoglycaemia (hypoglycaemia requiring third-party assistance) were available in 22 studies (559 patients). Overall, incidence of severe hypoglycaemia was low both in closed-loop (six episodes) and comparator (three episodes) arms. Use of closed-loop was also associated with a decrease in overnight low glucose blood index (−0.42, −0.56 to −0.27, 26%, 0.01, eight studies).

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, 83%, 0.28, 24 studies) (**Figure 6**). Results were more favourable for overnight mean sensor blood glucose levels (−0.84 mmol/L, −1.10 to −0.58, 79%, 0.39, 32 studies) (**appendix 11**). These findings were consistent with the effect of closed-loop on $HbA_{1c}$ (−0.26%, −0.38 to −0.13, 0%, 0.0, 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, 79%, 6.56, 12 studies) (**appendix 12**). 95% Hartung Knapp confidence intervals and prediction intervals for all outcomes are presented in **appendix 13**.

**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, nine studies) and for overnight (20.86%, 12.69 to 29.03, four studies) (**Figures 8 and 9**). 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, for all outcomes, results were consistent with those of the main analysis in a pre-specified subgroup analysis based on type of closed-loop utilised (single- versus dual-hormone closed-loop) (**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 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.[35 53 55] In total, our results reflect the progress made over the last decades of extensive research and development in this field.

### Strengths and limitations

Despite heterogeneity in interventions and comparators utilised, our systematic review provides the most valid and up-to-date overview on the field of artificial pancreas. An early pooled analysis of randomised controlled trials with closed-loop systems, published in 2011, included only four studies in an inpatient setting.[5] The effect of artificial pancreas in the outpatient setting was examined in a recent systematic review and meta-analysis.[7] However, validity and clinical interpretation potential of results were undermined by methodological decisions met regarding definition of outcomes, handling of median values, and exclusion of evidence from grey literature sources leading to missing a significant amount of the body of evidence (10 of 34 eligible studies).[56] Instead, the present meta-analysis incorporated a larger pool of eligible studies and assessed a broader variety of outcomes, focusing on outcome definitions that are considered most important in trials evaluating closed-loop systems.[54 57 58]

Composition of the review team ensured appropriate methodological and subject expertise, but also access to additional study data from individual studies.[33 36 50-53] To ensure internal validity of our conclusions we implemented current guidelines for the conduct and reporting of systematic reviews,[9] 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.

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.[59] 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,[38 39 41] 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.[54] 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.[60] 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. This could explain wide prediction intervals which included zero values for most outcomes in trials using CL for 24h, thus related findings should be interpreted with caution. On the contrary, there is strong evidence that overnight use of CL is beneficial for outcomes regarding time spent in near normoglycaemia or hypoglycaemia (95% prediction intervals excluding zero values) suggesting that this treatment effect can be expected in future patients.

**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.[61] It is important for research groups to report a minimum set of agreed outcome measures and respective metrics.[54 57 58] 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.[62 63] 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,[64] 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,[65] who may benefit from it. Moreover, the impact of artificial pancreas on quality of life and its effect on reducing patient burden should be

further explored,[66] considering that patients with type 1 diabetes and their carers have demonstrated a positive attitude towards closed-loop systems.[67-69] 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**

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**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.

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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.

Findings of previous meta-analyses on closed-loop systems are limited mainly due to low number of studies incorporated and heterogeneous definitions of outcomes.

**What this study adds**

The totality of available evidence from randomised controlled trials 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.

The main limitations of current research evidence on closed-loop systems are related to inconsistency in outcome reporting, small sample size and short follow-up duration of individual trials.

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67 Barnard KD, Pinsker JE, Oliver N, et al. Future artificial pancreas technology for type 1 diabetes: what do users want? *Diabetes Technol Ther* 2015;17(5):311-5. doi: 10.1089/dia.2014.0316

68 Elleri D, Acerini CL, Allen JM, et al. Parental attitudes towards overnight closed-loop glucose control in children with type 1 diabetes. *Diabetes Technol Ther* 2010;12(1):35-9. doi: 10.1089/dia.2009.0084

69 van Bon AC, Brouwer TB, von Basum G, et al. Future acceptance of an artificial pancreas in adults with type 1 diabetes. *Diabetes Technol Ther* 2011;13(7):731-6. doi: 10.1089/dia.2011.0013

| Identifier | Trial registration details | Setting | Population | CL | Comparator | Intervention duration | Length of follow-up* | Patients (n) |
|---|---|---|---|---|---|---|---|---|
| **Biester 2016**[22] | NCT02636491 | Home | Adults & adolescents | MD-Logic | SAP | 24h | 2 days | 10 |
| **Blauw 2016**[23] | NCT02160275 | Home | Adults | Inreda Dual-hormone | Insulin pump therapy | 24h | 4 days | 10 |
| **Brown 2015a**[24] | NCT01939834 NCT02008188 | House/Hotel | Adults | DiAs USS | SAP | Overnight | 5 days | 10 |
| **Brown 2015b**[25] | R01DK085623 | Home | NR | DiAs | SAP | Overnight | 5 days | 5 |
| **Chernavvsky 2016**[26] | NCT01890954 | Research house | Adolescents | DiAs USS | Insulin pump therapy | 24h | 1 day | 16 |
| **De Bock 2015**[27] | ACTRN12614001005640 | Home | Adults & adolescents | Medtronic PID IFB | SAP + LGS | 24h | 5 days | 8 |
| **El-Khatib 2016**[28] | NCT02092220 | Home | Adults | Dual-hormone CL | Insulin pump therapy or SAP | 24h | 11 days | 39 |
| **Favero 2016**[29] | NCT0260878 | Diabetes camp | Children | DiAs | SAP | 24h | 3 days | 30 |
| **Haidar 2015a**[30] | NCT02189694 | Diabetes camp | Adolescents | Single-hormone CL | Insulin pump therapy | Overnight | 3 days | 33 |
| **Haidar 2015b**[30] | NCT02189694 | Diabetes camp | Adolescents | Dual-hormone CL | Insulin pump therapy | Overnight | 3 days | 33 |
| **Haidar 2016a**[31] | NCT01905020 | Home | Adults & adolescents | Single-hormone CL | Insulin pump therapy | Overnight | 2 days | 28 |
| **Haidar 2016b**[31] | NCT01905020 | Home | Adults & adolescents | Dual-hormone CL | Insulin pump therapy | Overnight | 2 days | 28 |
| **Haidar 2017a**[32] | NCT01966393 | Home | Adults | Single-hormone CL | SAP | 24h | 60 hours | 23 |
| **Haidar 2017b**[32] | NCT01966393 | Home | Adults | Dual-hormone CL | SAP | 24h | 60 hours | 23 |
| **Hovorka 2014**[33] | NCT01221467 | Home | Adolescents | Florence | SAP | Overnight | 3 weeks | 16 |
| **Kovatchev 2014**[34] | NCT01714505 NCT01727817 NCT01742741 | Hotel/Guesthouse | Adults | DiAs SSM | SAP | 24h | 40 hours | 20 |
| **Kropf 2015**[35] | NCT02153190 | Home | Adults | DiAs SSM | SAP | Evening and night | 8 weeks | 32 |
| **Leelarantha 2014**[36] | NCT01666028 | Home | Adults | Florence | SAP | 24h | 8 days | 17 |
| **Ly 2014**[37] | NCT01973413 | Diabetes camp | Adults & adolescents | DiAs USS | SAP | Overnight | 5-6 days | 20 |
| **Ly 2015a**[39] | NCT02366767 | Diabetes camp | Adults & adolescents | Medtronic PID IFB | SAP + LGS | 24h | 6 days | 21 |
| **Ly 2015b**[38] | NR | Diabetes camp | Adults & adolescents | DiAs | SAP | 24h | 5 days | 16 |
| **Ly 2016a**[41] | NCT02147860 | Diabetes camp | Adolescents | DiAs USS | SAP | 24h | 5 days | 33 |
| **Ly 2016b**[40] | NR | Diabetes camp | Children & adolescents | Medtronic PID IFB | SAP | Overnight | 1 day | 21 |
| **Nimri 2014**[42] | NCT01238406 | Home | Adults & adolescents | MD-Logic | SAP | Overnight | 6 weeks | 24 |
| **Nimri 2016**[43] | NCT01726829 | Home | Children, adolescents & adults | MD-Logic | SAP | Overnight | 4 days | 75 |
| **Phillip 2013**[44] | NCT01238406 | Diabetes camp | Adolescents | MD-Logic | SAP | Overnight | 1 day | 54 |
| **Russell 2014a**[45] | NCT01762059 | Home & Hotel | Adults | Dual-hormone CL | Insulin pump therapy or SAP | 24h | 5 days | 20 |
| **Russell 2014b**[45] | NCT01833988 | Diabetes camp | Adolescents | Dual-hormone CL | Insulin pump therapy or SAP | 24h | 5 days | 32 |
| **Russell 2016**[46] | NCT02105324 | Diabetes camp | Preadolescents | Dual-hormone CL | Insulin pump therapy or SAP | 24h | 5 days | 19 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Schierloh 2015**[47 †] | NR | Home | Children | Florence | SAP | Overnight | 4 days | 15 |
| **Sharifi 2015**[48] | NR | Home | Adults & adolescents | CL PID IFB | SAP + LGS | Overnight | 5 days | 11 |
| **Sharifi 2016**[49] | NR | Home | Adults & adolescents | Medtronic PID IFB | SAP + LGS | Overnight | 4 days | 28 |
| **Tauschmann 2016a**[51] | NCT01873066 | Home | Adolescents | Florence | SAP | 24h | 7 days | 12 |
| **Tauschmann 2016b**[50] | NCT01873066 | Home | Adolescents | Florence | SAP | 24h | 3 weeks | 12 |
| **Thabit 2014**[52] | NCT01440140 | Home | Adults | Florence | SAP | Overnight | 4 weeks | 24 |
| **Thabit 2015a**[53] | NCT01961622 | Home | Adults | Florence | SAP | 24h | 12 weeks | 33 |
| **Thabit 2015b**[53] | NCT01778348 | Home | Children & adolescents | Florence | SAP | Overnight | 12 weeks | 25 |

**Table 1. Baseline characteristics of comparisons 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. *For cross-over trials, length of follow-up refers to the duration of each period, excluding wash-out period.

| Outcome | Number of studies (single/dual hormone) | Single hormone CL | Dual-hormone CL |
|---|---|---|---|
| % of overall time between 3.9 – 10.0 mmol/L | 19/6 | 8.02 (5.25 to 10.80), 83%, 28.26 | 15.16 (10.68 to 19.63), 43%, 13.08 |
| % of overnight time between 3.9 – 10.0 mmol/L | 16/8 | 13.88 (9.94 to 17.81), 75%, 43.86 | 22.84 (15.08 to 30.60), 74%, 88.82 |
| % of overall time > 10.0 mmol/L | 11/6 | −6.82 (−10.58 to −3.06), 86%, 33.29 | −11.58 (−18.17 to −4.99), 81%, 36.43 |
| % of overnight time > 10.0 mmol/L | 11/8 | −10.50 (−14.39 to −6.60), 73%, 27.68 | −17.21 (−25.58 to −8.85), 87%, 121.35 |
| % of overall time < 3.9 mmol/L | 18/5 | −1.39 (−1.84 to −0.93), 65%, 0.53 | −2.95 (−4.03 to −1.87), 30%, 0.45 |
| % of overnight time < 3.9 mmol/L | 20/7 | −2.15 (−2.74 to −1.57), 47%, 0.68 | −4.04 (−5.59 to −2.48), 47%, 1.93 |
| Overnight LBGI | 8/0 | −0.42 (−0.56 to −0.27), 26%, 0.01 | NE |
| Overall mean sensor glucose value (mmol/L) | 18/6 | −0.38 (−0.65 to −0.12), 82%, 0.23 | −0.90 (−1.48 to −0.32), 80%, 0.42 |
| Overnight mean sensor glucose value (mmol/L) | 24/8 | −0.67 (−0.94 to −0.39), 78%, 0.32 | −1.47 (−2.14 to −0.79), 80%, 0.72 |
| Overall daily insulin needs (IU) | 11/1 | −0.64 (−2.40 to 1.13), 77%, 5.58 | NE |

**Table 2**. Summary of subgroup meta-analyses results based on type of closed-loop utilised (single-hormone closed-loop studies mainly used sensor-augmented pump therapy as comparator; dual-hormone closed-loop studies mainly used insulin pump therapy as comparator). Values presented are weighted mean differences (95% confidence intervals), $I^2$, $Tau^2$ between closed-loop and comparator. CL: closed-loop. LBGI: low blood glucose index. NE: Not estimable.

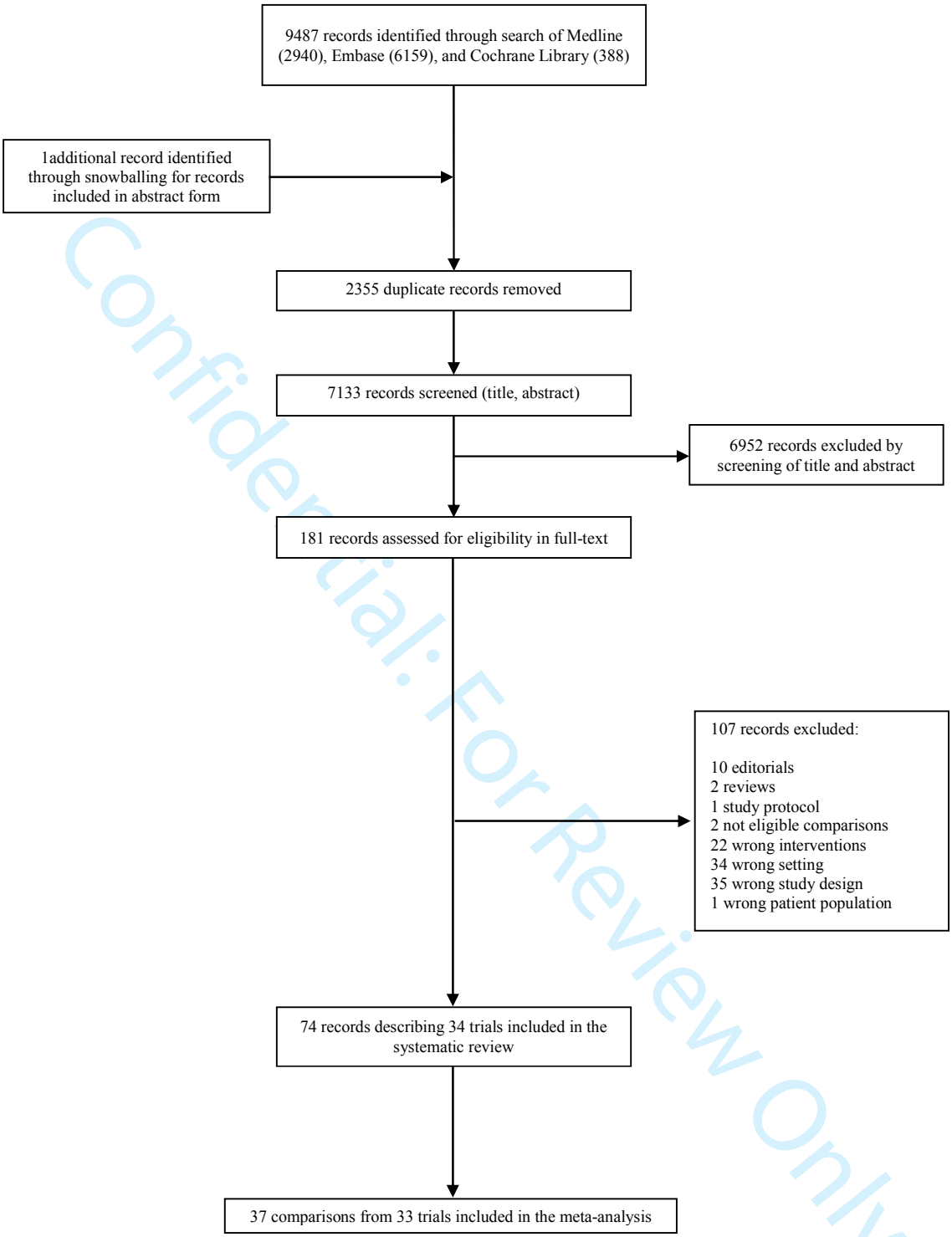



**Figure 1.** Flow diagram of study selection process.

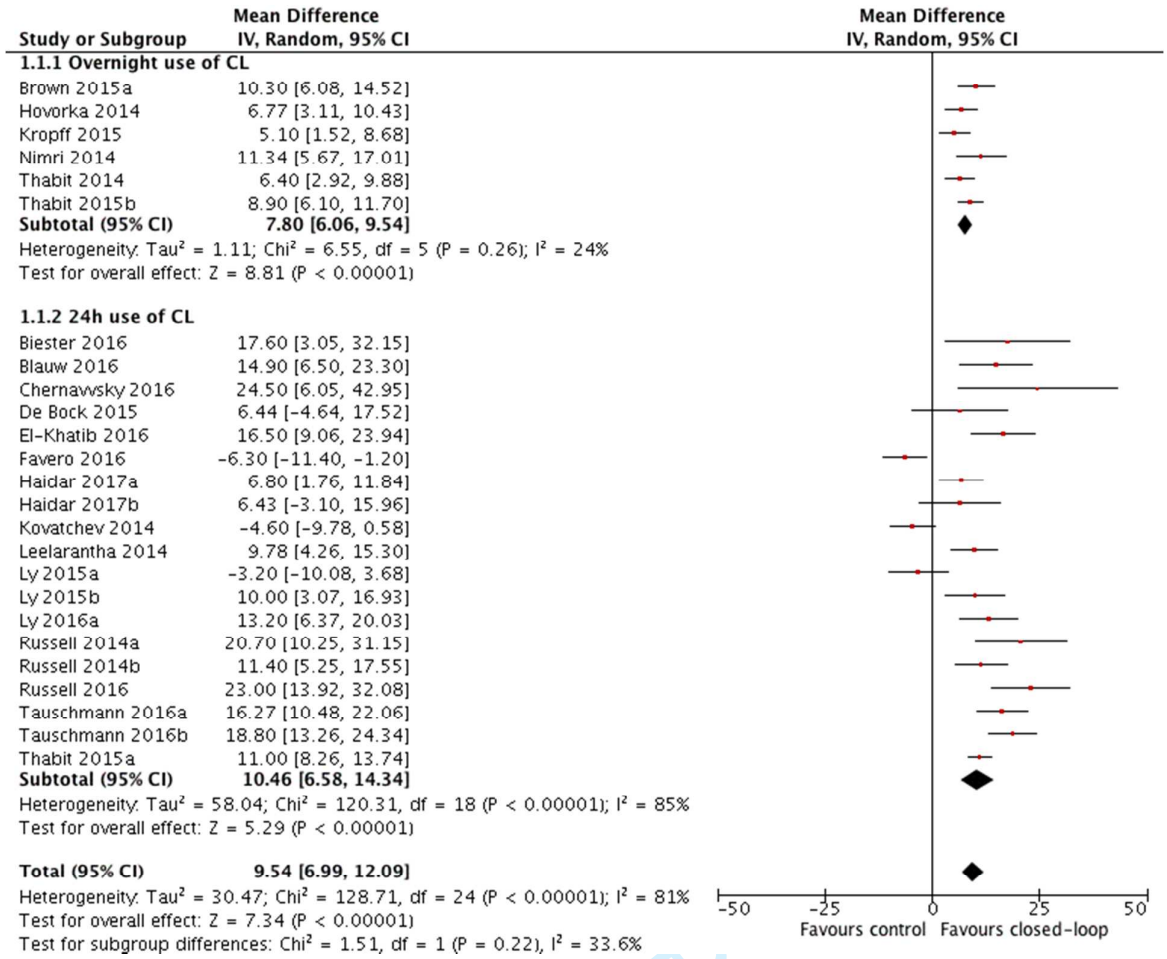



**Figure 2**. Weighted mean difference in % of overall time in near normoglycaemic range (3.9 – 10.0 mmol/L). Closed loop versus control treatment.

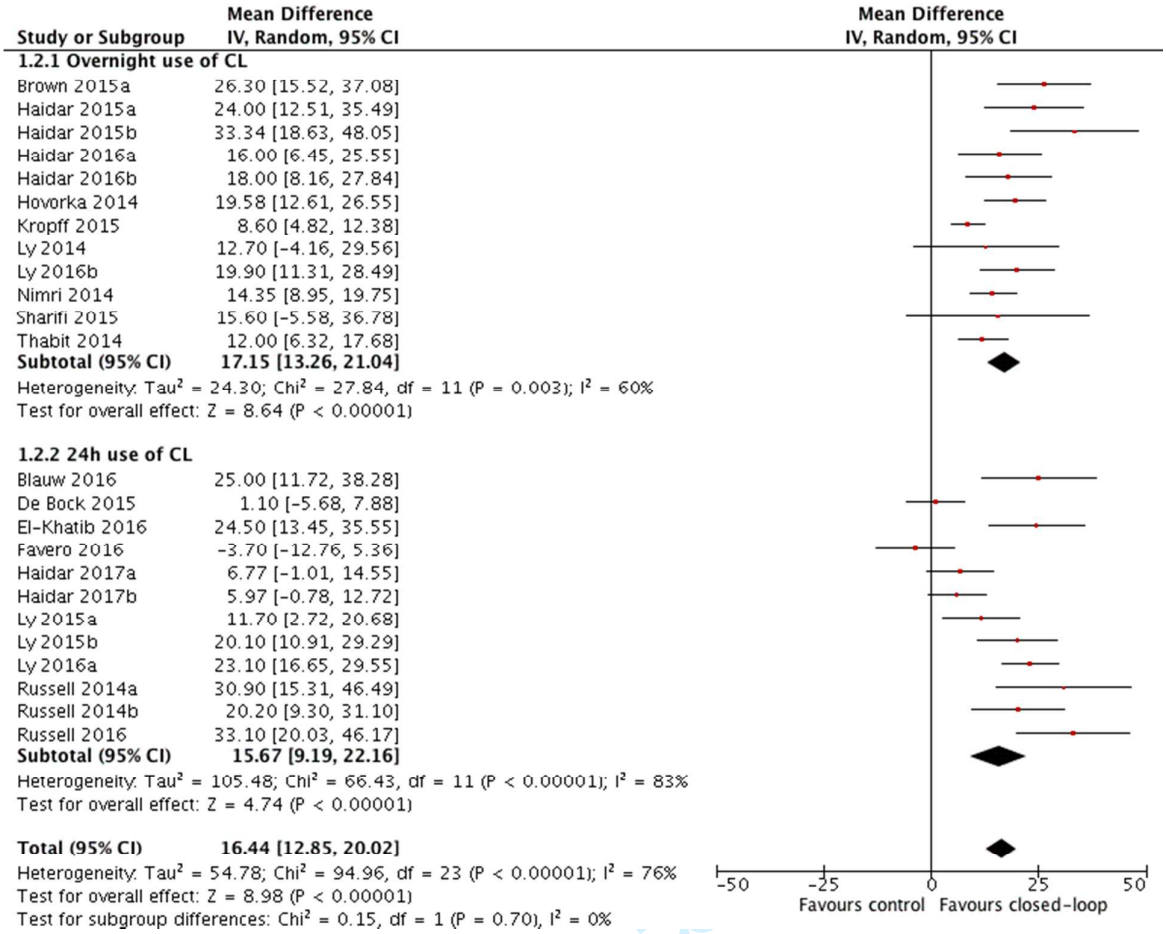



**Figure 3**. Weighted mean difference in % of overnight time in near normoglycaemic range (3.9 – 10.0 mmol/L). Closed-loop versus control treatment.

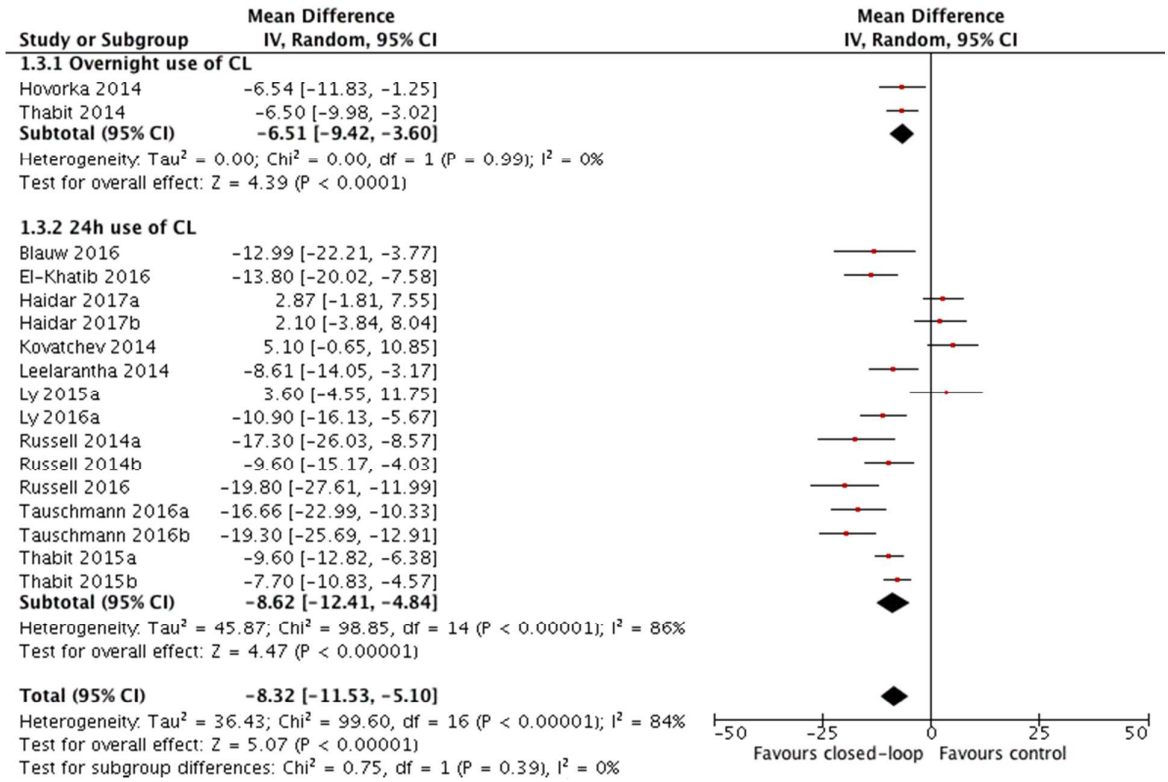



**Figure 4**. Weighted mean difference in % of overall time glucose was > 10.0 mmol/L. Closed-loop versus control treatment.

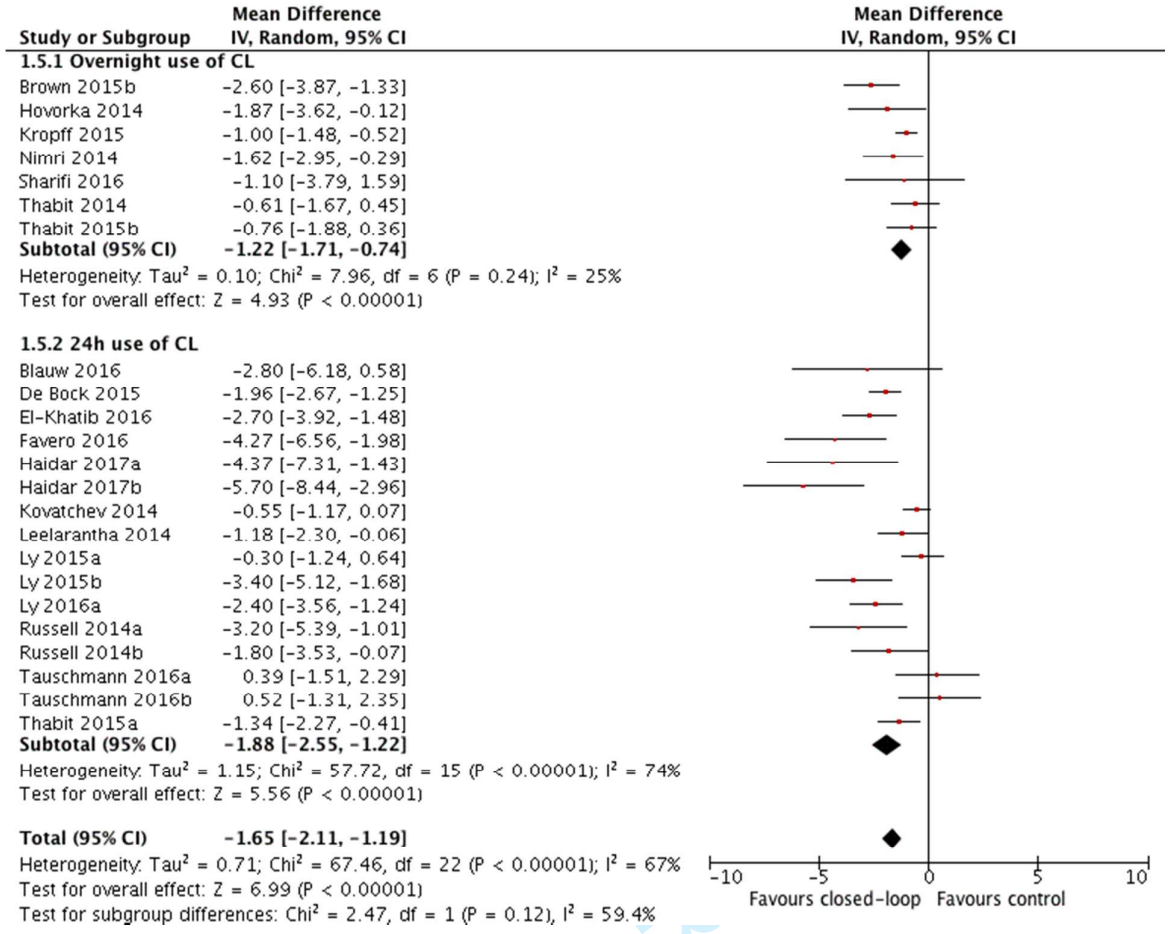



**Figure 5**. Weighted mean difference in % of overall time glucose was < 3.9 mmol/L. Closed-loop versus control treatment.

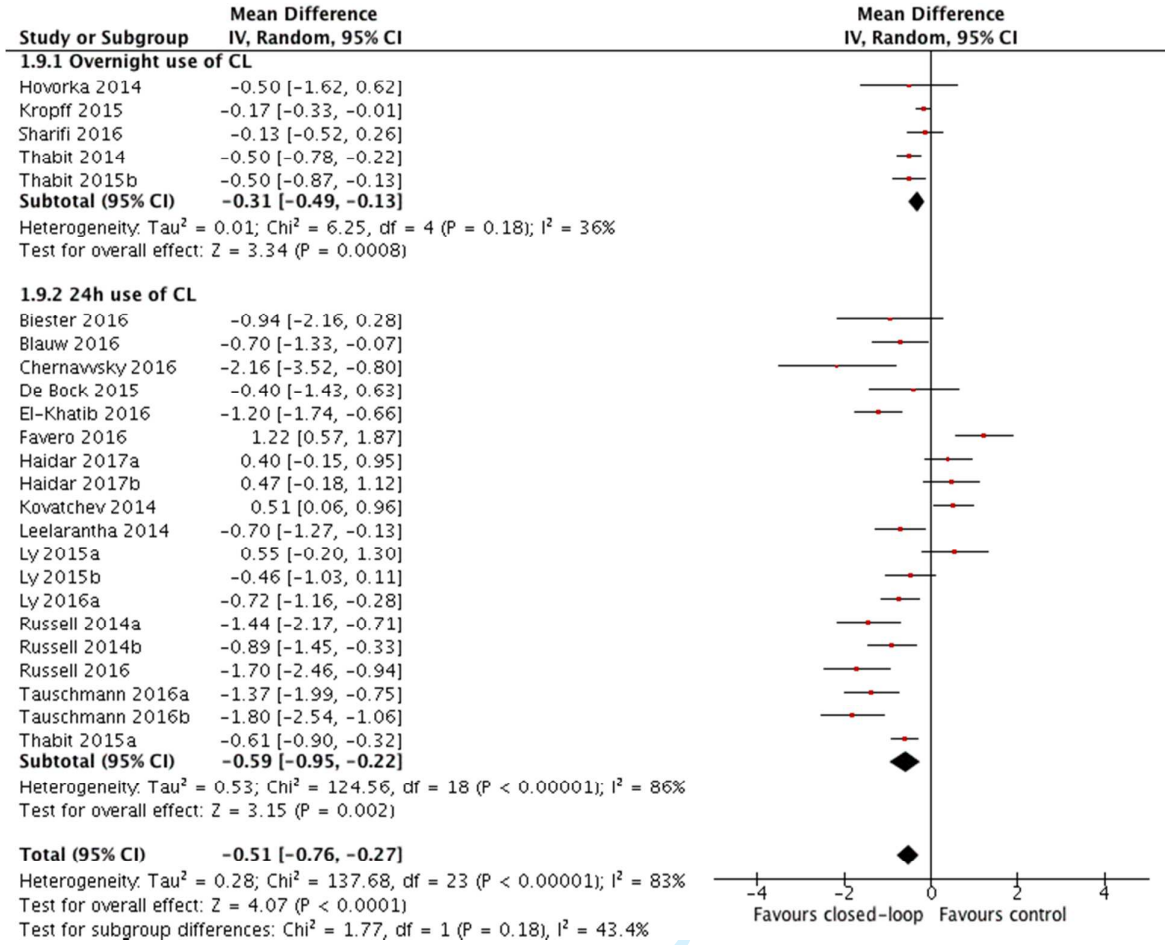



**Figure 6**. Weighted mean difference in overall mean sensor blood glucose (mmol/L). Closed-loop versus control treatment.

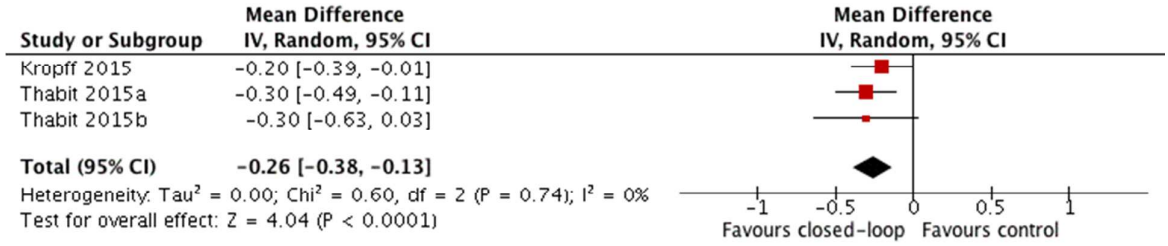



**Figure 7**. Weighted mean difference in change in $HbA_{1c}$ (%). Closed-loop versus control treatment.

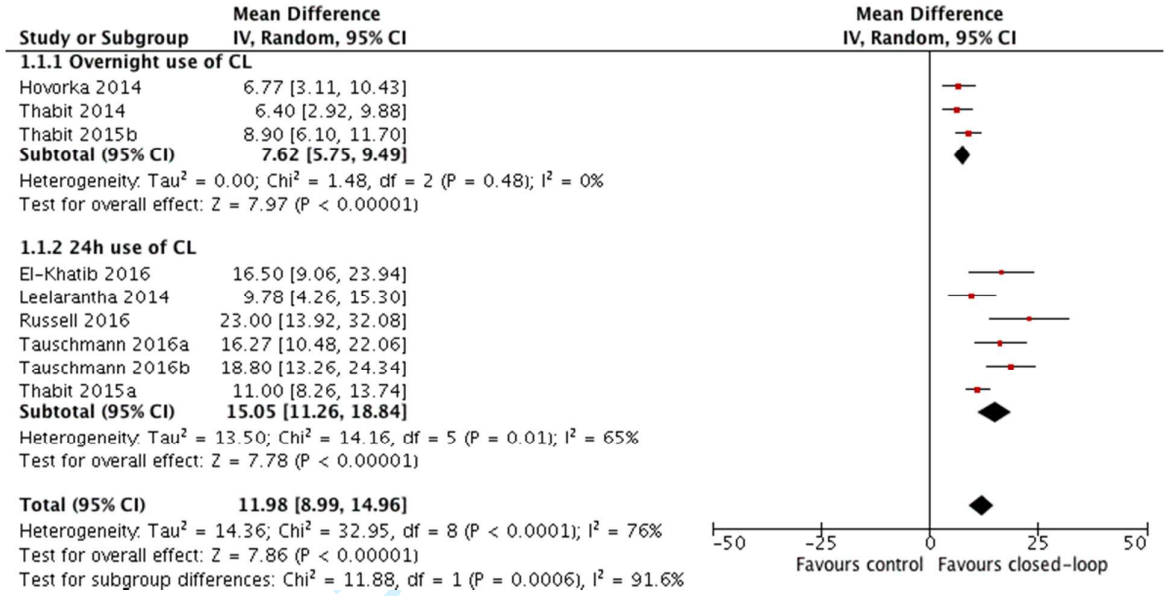



**Figure 8**. Weighted mean difference in % of overall time in near normoglycaemic range (3.9 – 10.0 mmol/L). Closed-loop versus control treatment. Sensitivity analysis including only trials at low risk of bias.

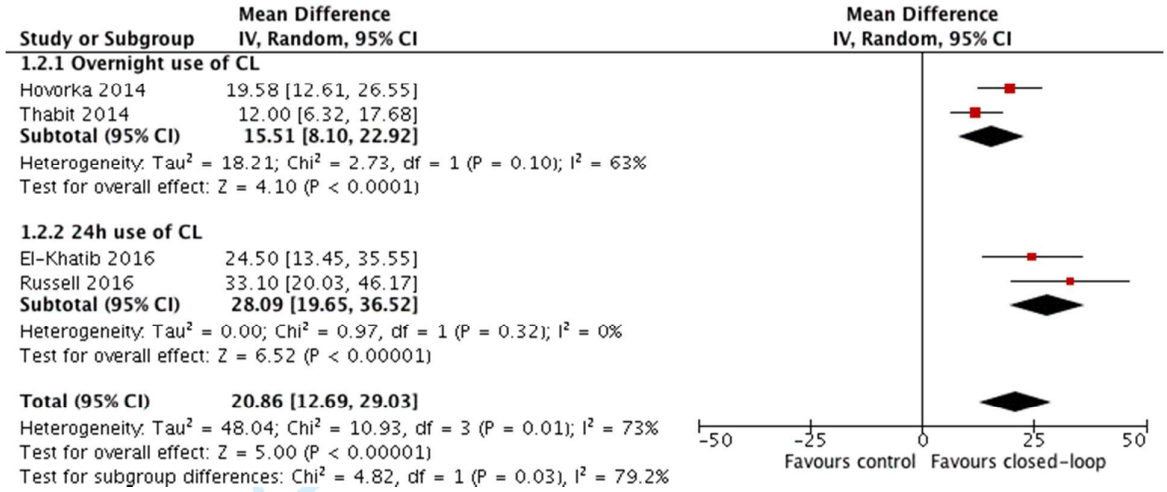



**Figure 9**. Weighted mean difference in % of overnight time in near normoglycaemic range (3.9 – 10.0 mmol/L). Closed-loop versus control treatment. Sensitivity analysis including only trials at low risk of bias.

**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, 4 |
| 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. | 5, 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, 5 |

| 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. | 4-5 |
| **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). | 6, 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. | 6-7, Figures 2-9, appendices 9-13 |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | 6, Figures 2-8, appendices 9-13 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | 6, appendix 8 |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | 7, Table 2, appendices 14-19 |
| **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). | 8 |
| 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). | 8-9 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 9 |
| **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. | 10 |

**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**

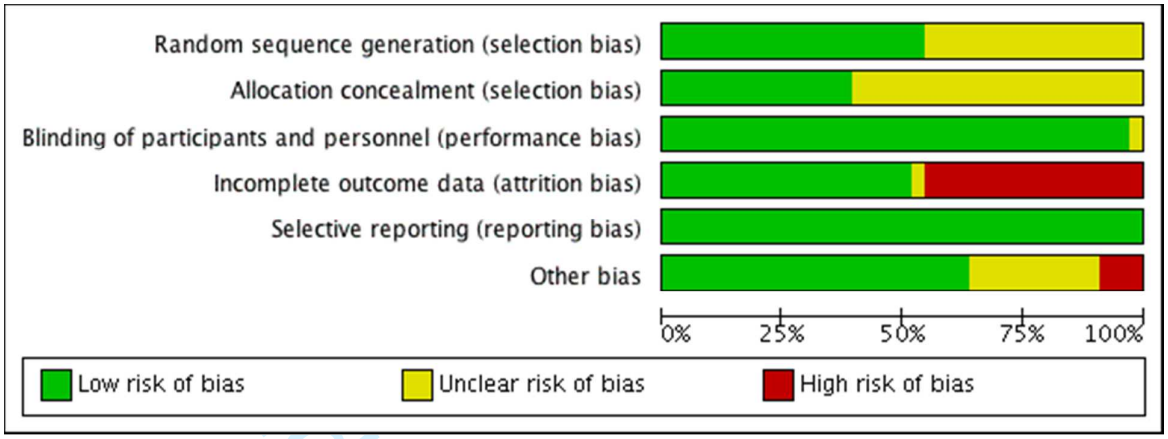
**Overall risk of bias assessment**

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

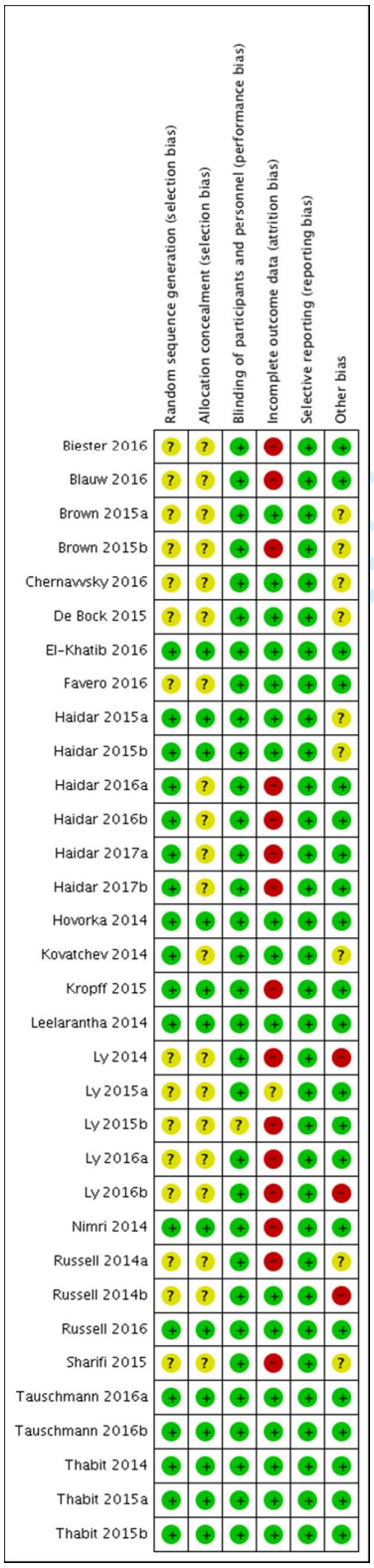
- Sequence generation (or randomised treatment order for cross-over studies)
- Allocation concealment
- Blinding
- Selective reporting
- Incomplete outcome data
- Other bias
  - Appropriateness of cross-over design (only for cross-over studies)
  - Carry-over effects (only for cross-over studies)
  -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

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

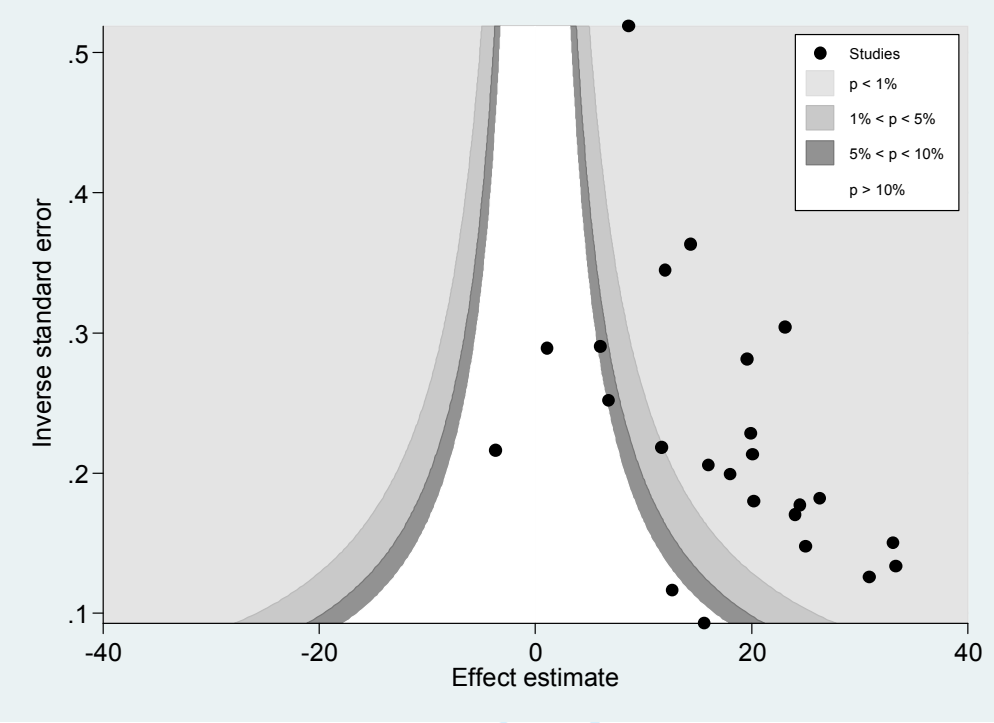
- If a study was considered at high risk of bias for any of the aforementioned domains, the study was characterised as "high risk study"
- If a study was considered at low risk of bias for all aforementioned domains, the study was characterised as "low risk study"
- In any other case the study was considered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



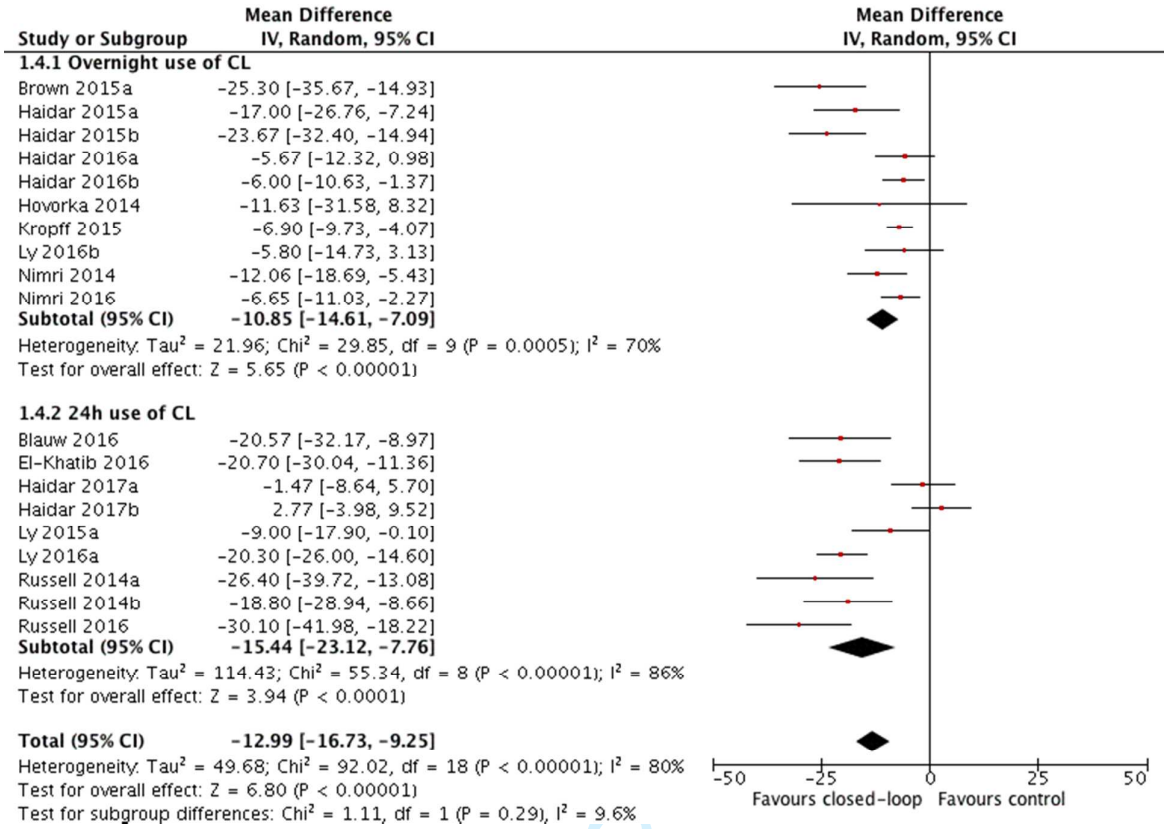

**Appendix 6**. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies



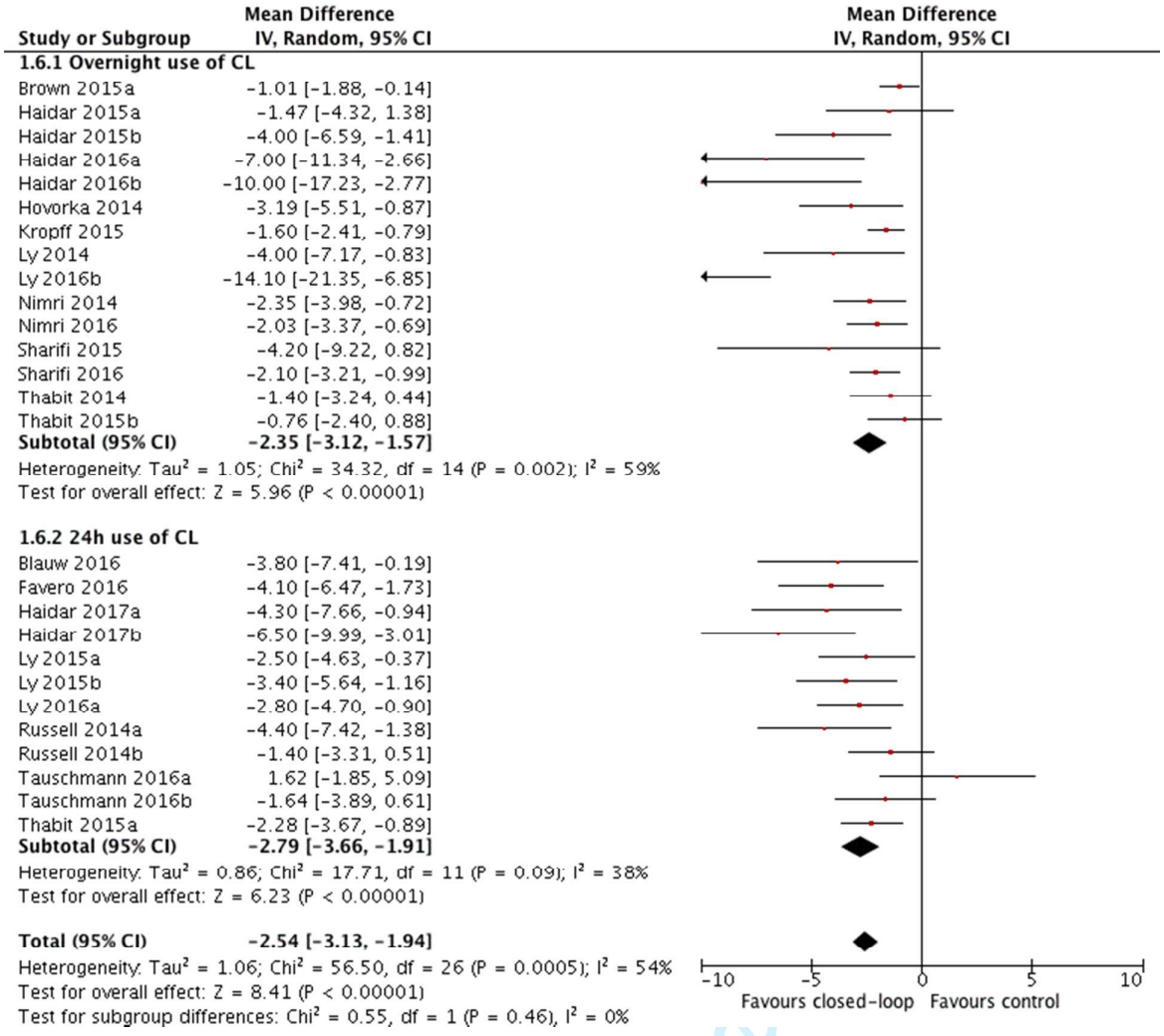

**Appendix 7**. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



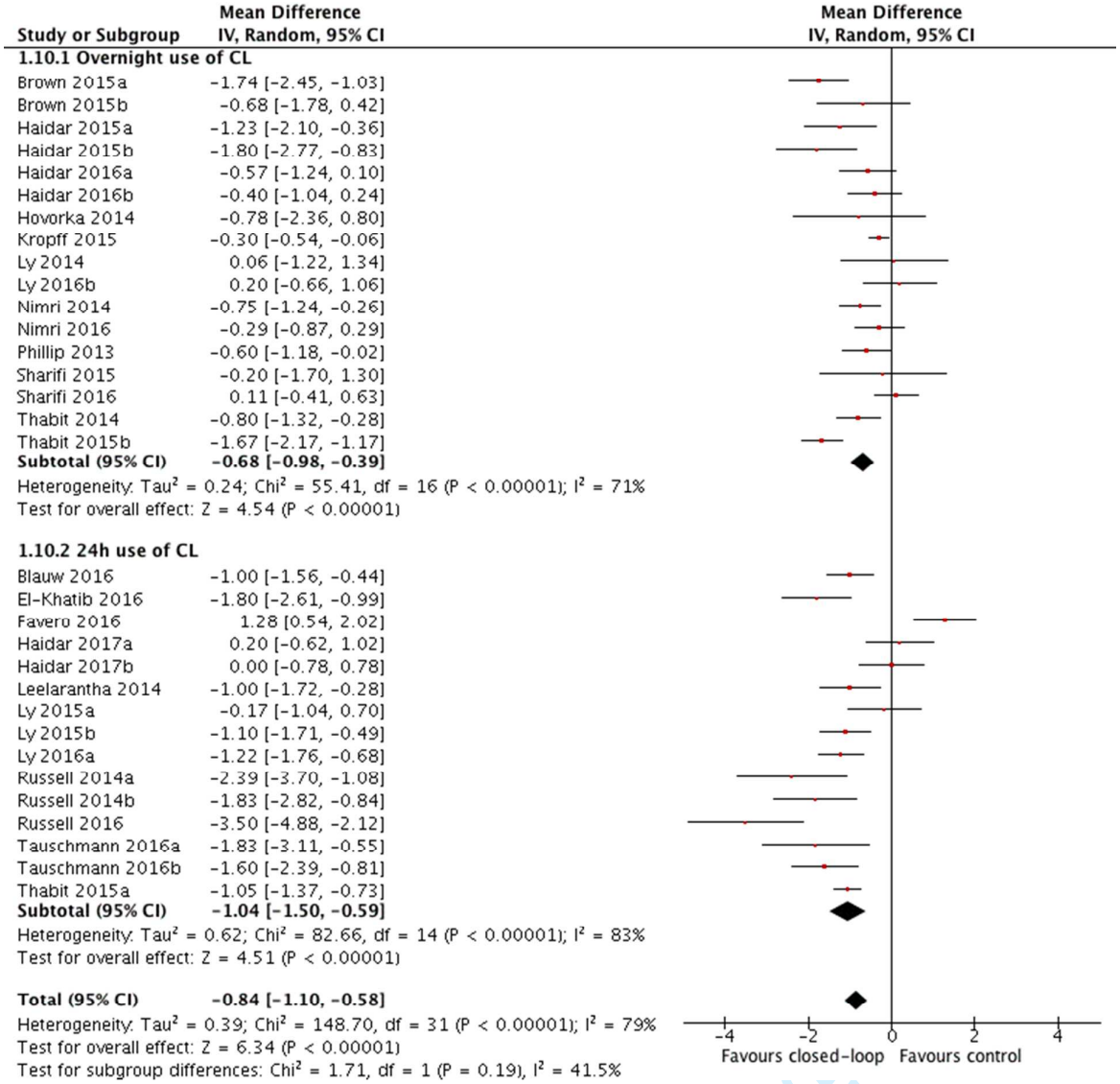

**Appendix 8**. Counter-enhanced funnel plot for studies assessing overnight time spent in near normoglycaemia.



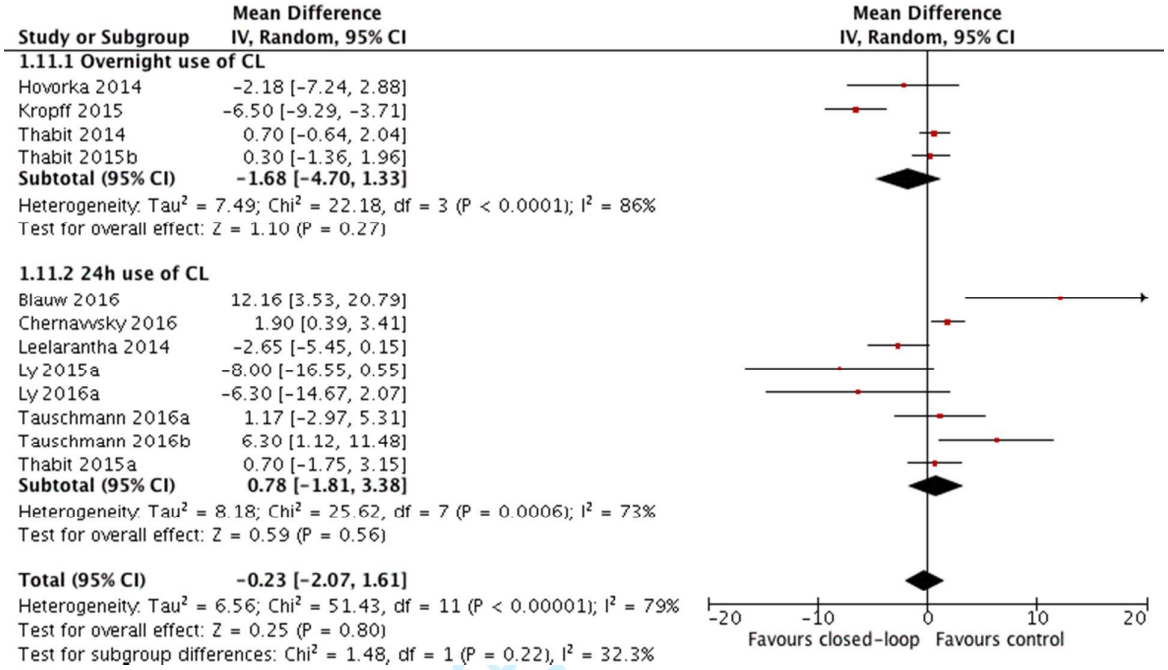

**Appendix 9**. Weighted mean difference in % of overnight time glucose was > 10.0 mmol/L. Closed-loop versus control treatment.




**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.

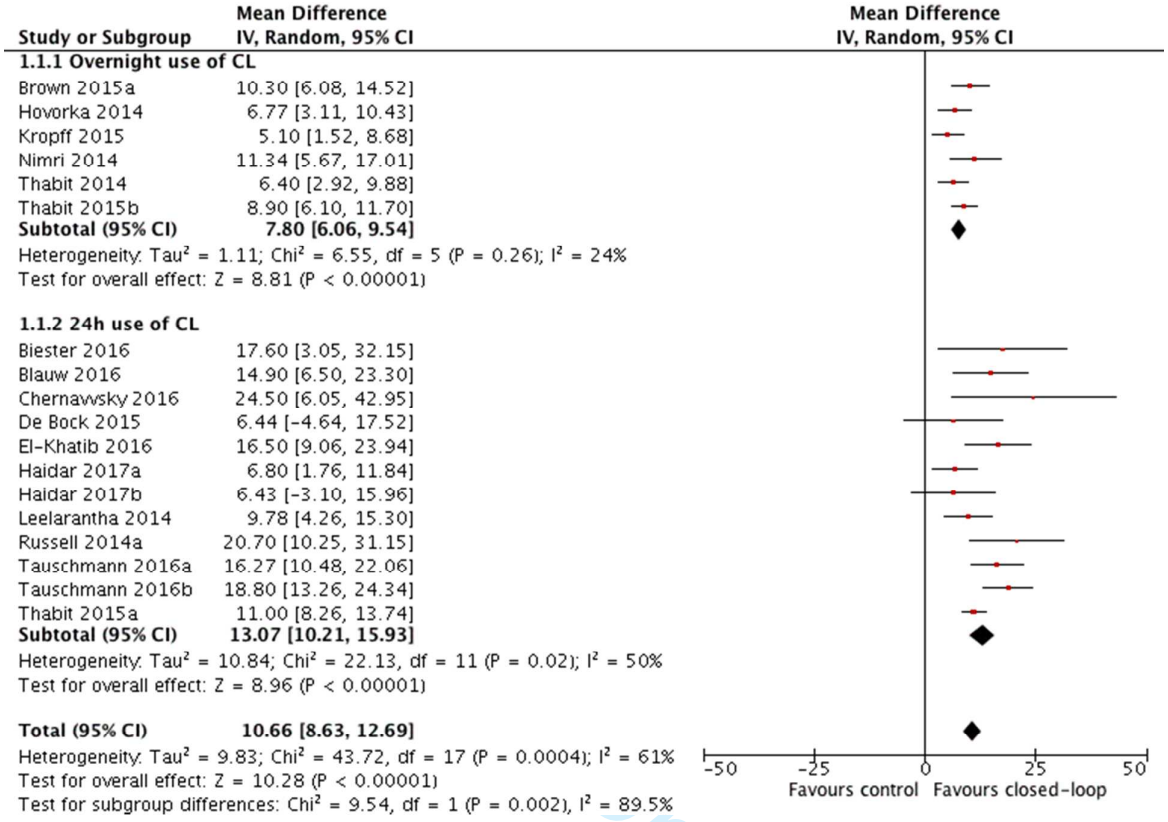



**Appendix 12**. Weighted mean difference in overall daily insulin needs (IU). Closed-loop versus control treatment.

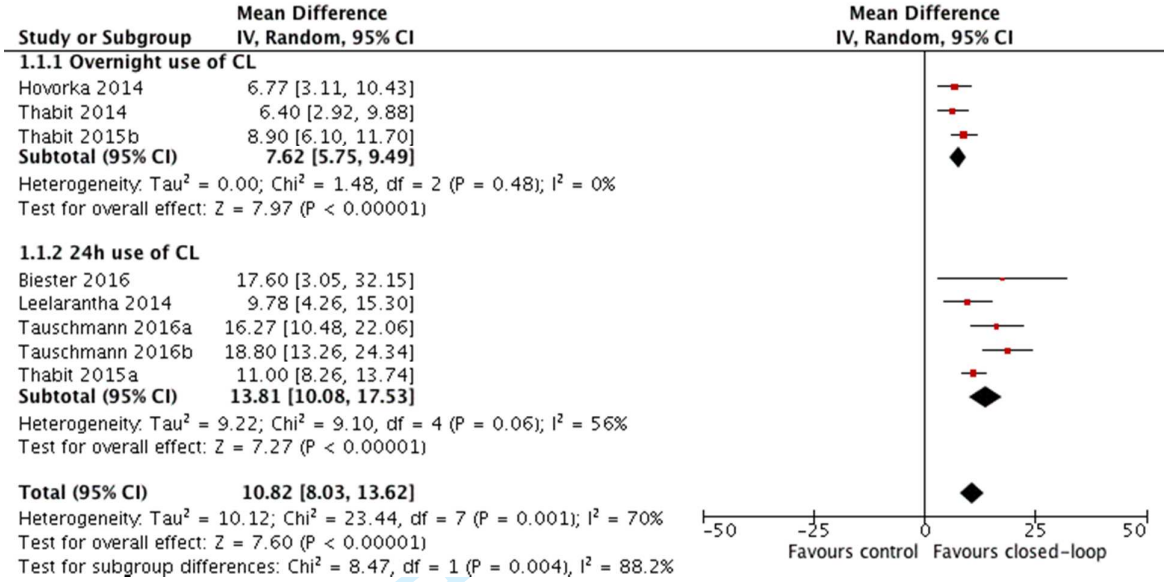
**Appendix 13.** Summary of findings of main analysis for all outcomes. Both overall effect estimates and subgroup effect estimates (based on overnight or 24h use of closed-loop system) between closed-loop and comparator are presented. BG: blood glucose. CIs: confidence intervals. CL: closed-loop. LGBI: low glucose blood index. NE: not estimable.

| Outcome | Number of studies | Effect estimate | Der Simmonian Laird 95% CIs | 95% Hartung-Knapp CIs | 95% Prediction intervals | $I^2$ (%) | $Tau^2$ |
|---|---|---|---|---|---|---|---|
| % of overall time between 3.9 – 10.0 mmol/L, Overall effect estimate | 25 | 9.54 | 6.99 to 12.09 | 6.84 to 12.24 | -2.19 to 21.27 | 81 | 30.47 |
| % of overall time between 3.9 – 10.0 mmol/L, Overnight use of CL | 6 | 7.8 | 6.06 to 9.54 | 5.26 to 10.34 | 3.97 to 11.62 | 24 | 1.11 |
| % of overall time between 3.9 – 10.0 mmol/L, 24h use of CL | 19 | 10.46 | 6.58 to 14.34 | 3.44 to 12.16 | -6.14 to 27.06 | 85 | 58.04 |
| % of overnight time between 3.9 – 10.0 mmol/L, Overall effect estimate | 24 | 16.44 | 12.85 to 20.02 | 12.91 to 19.97 | 0.63 to 32.25 | 76 | 54.78 |
| % of overnight time between 3.9 – 10.0 mmol/L, Overnight use of CL | 12 | 17.15 | 13.26 to 21.04 | 12.92 to 21.38 | 5.30 to 28.99 | 60 | 24.3 |
| % of overnight time between 3.9 – 10.0 mmol/L, 24h use of CL | 12 | 15.67 | 9.19 to 22.16 | 8.22 to 23.12 | -8.37 to 39.71 | 83 | 105.48 |
| % of overall time above 10.0 mmol/L, Overall effect estimate | 17 | -8.32 | -11.53 to -5.1 | -12.34 to -4.3 | -21.65 to 5.01 | 84 | 36.43 |
| % of overall time above 10.0 mmol/L, Overnight use of CL | 2 | -6.51 | -9.42 to -3.6 | -6.79 to -6.23 | NE | 0 | 0 |
| % of overall time above 10.0 mmol/L, 24h use of CL | 15 | -8.62 | -12.41 to -4.84 | -13.26 to -3.98 | -23.83 to 6.59 | 86 | 45.87 |
| % of overnight time above 10.0 mmol/L, Overall effect estimate | 19 | -12.99 | -16.73 to -9.25 | -17.46 to -8.52 | -28.39 to 2.41 | 80 | 49.68 |
| % of overnight time above 10.0 mmol/L, Overnight use of CL | 10 | -10.85 | -14.61 to -7.09 | -16.16 to -5.54 | -22.52 to 0.82 | 70 | 21.96 |
| % of overnight time above 10.0 mmol/L, 24h use of CL | 9 | -15.44 | -23.12 to -7.76 | -24.11 to -6.77 | -42.37 to 11.49 | 86 | 114.43 |
| % of overall time below 3.9 mmol/L, Overall effect estimate | 23 | -1.65 | -2.11 to -1.19 | -2.16 to -1.14 | -3.46 to 0.16 | 67 | 0.71 |
| % of overall time below 3.9 mmol/L, Overnight use of CL | 7 | -1.22 | -1.71 to -0.74 | -1.89 to -0.55 | -2.24 to -0.19 | 25 | 0.1 |
| % of overall time below 3.9 mmol/L, 24h use of CL | 16 | -1.88 | -2.55 to -1.22 | -2.1 to -0.34 | -4.29 to 0.53 | 74 | 1.15 |
| % of overnight time below 3.9 mmol/L, Overall effect estimate | 27 | -2.54 | -3.13 to -1.94 | -3.2 to -1.88 | -4.75 to -0.32 | 54 | 1.06 |

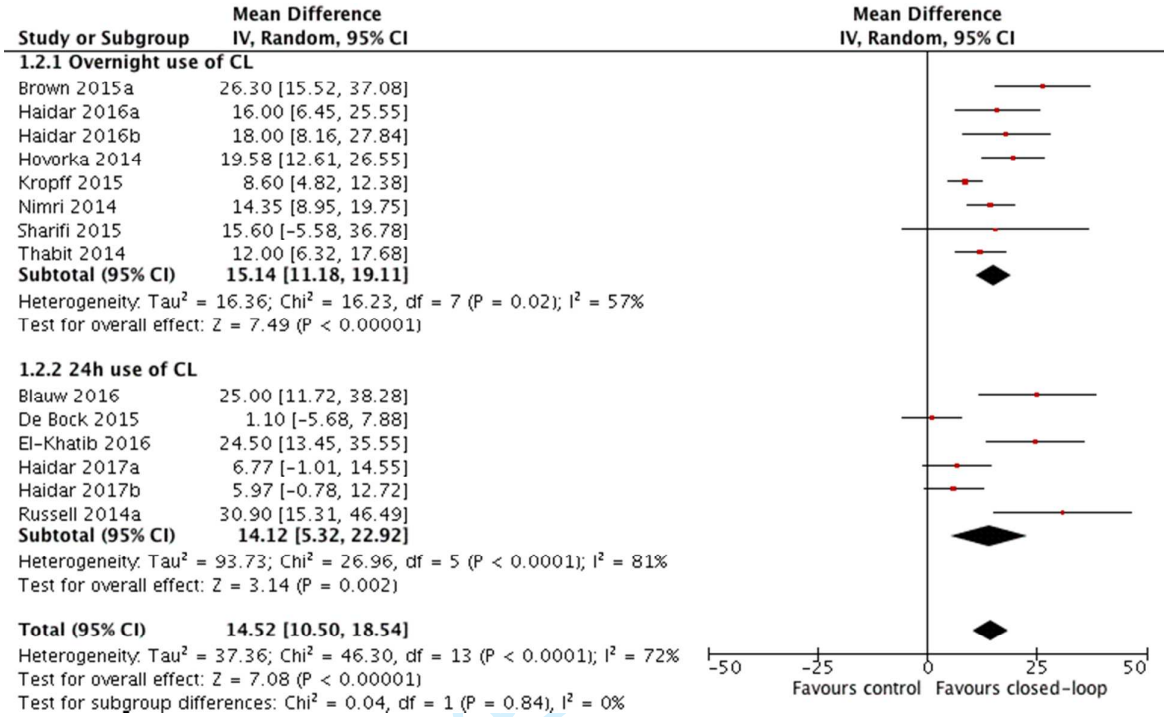
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| % of overnight time below 3.9 mmol/L, Overnight use of CL | 15 | -2.35 | -3.12 to -1.57 | -3.44 to -1.26 | -4.72 to 0.02 | 59 | 1.05 |
| % of overnight time below 3.9 mmol/L, 24h use of CL | 12 | -2.79 | -3.66 to -1.91 | -3.87 to -1.71 | -5.08 to -0.49 | 38 | 0.86 |
| Overnight LGBI, Overall effect estimate | 8 | -0.42 | -0.56 to -0.27 | -0.6 to -0.24 | -0.72 to -0.11 | 26 | 0.01 |
| Overnight LGBI, Overnight use of CL | 7 | -0.35 | -0.46 to -0.24 | -0.48 to -0.22 | -0.49 to -0.20 | 0 | 0 |
| Overnight LGBI, 24h use of CL | 1 | -1.07 | -1.64 to -0.5 | NE | NE | NE | NE |
| 24h Mean BG (mmol/L), Overall effect estimate | 24 | -0.51 | -0.76 to -0.27 | -0.79 to -0.23 | -1.63 to 0.61 | 83 | 0.28 |
| 24h Mean BG (mmol/L), Overnight use of CL | 5 | -0.31 | -0.49 to -0.13 | -0.56 to -0.06 | -0.74 to 0.12 | 36 | 0.01 |
| 24h Mean BG (mmol/L), 24h use of CL | 19 | -0.59 | -0.95 to -0.22 | -1.02 to -0.16 | -2.17 to 0.99 | 86 | 0.53 |
| Overnight Mean BG (mmol/L), Overall effect estimate | 32 | -0.84 | -1.1 to -0.58 | -1.07 to -0.61 | -2.14 to 0.46 | 79 | 0.39 |
| Overnight Mean BG (mmol/L), Overnight use of CL | 17 | -0.68 | -0.98 to -0.39 | -1 to -0.36 | -1.77 to 0.41 | 71 | 0.24 |
| Overnight Mean BG (mmol/L), 24h use of CL | 15 | -1.04 | -1.5 to -0.59 | -1.64 to -0.44 | -2.81 to 0.73 | 83 | 0.62 |
| 24h Total insulin delivered (IU), Overall effect estimate | 12 | -0.23 | -2.07 to 1.61 | -2.98 to 2.52 | -6.30 to 5.84 | 79 | 6.56 |
| 24h Total insulin delivered (IU), Overnight use of CL | 4 | -1.68 | -4.7 to 1.33 | -7.08 to 3.72 | -15.18 to 11.82 | 86 | 7.49 |
| 24h Total insulin delivered (IU), 24h use of CL | 8 | 0.78 | -1.81 to 3.38 | -3.3 to 4.86 | -6.93 to 8.49 | 73 | 8.18 |
| $HbA_{1c}$ | 3 | -0.26 | -0.38 to -0.13 | -0.41 to -0.11 | -1.10 to 0.58 | 0 | 0 |



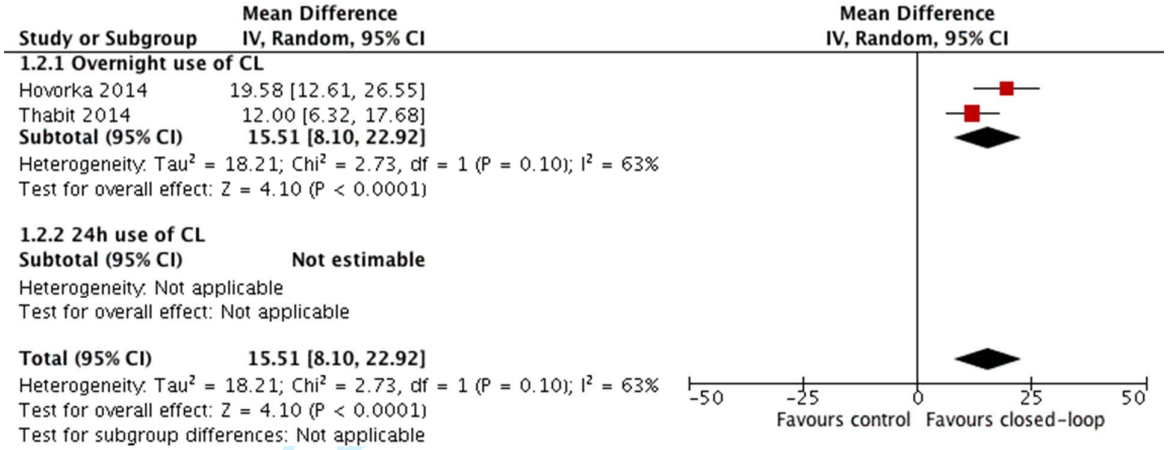

**Appendix 14**. Weighted mean difference in % of overall time in near normoglycaemic range (3.9 – 10.0 mmol/L). Closed-loop versus control treatment. Sensitivity analysis excluding trials recruiting patients in camps.



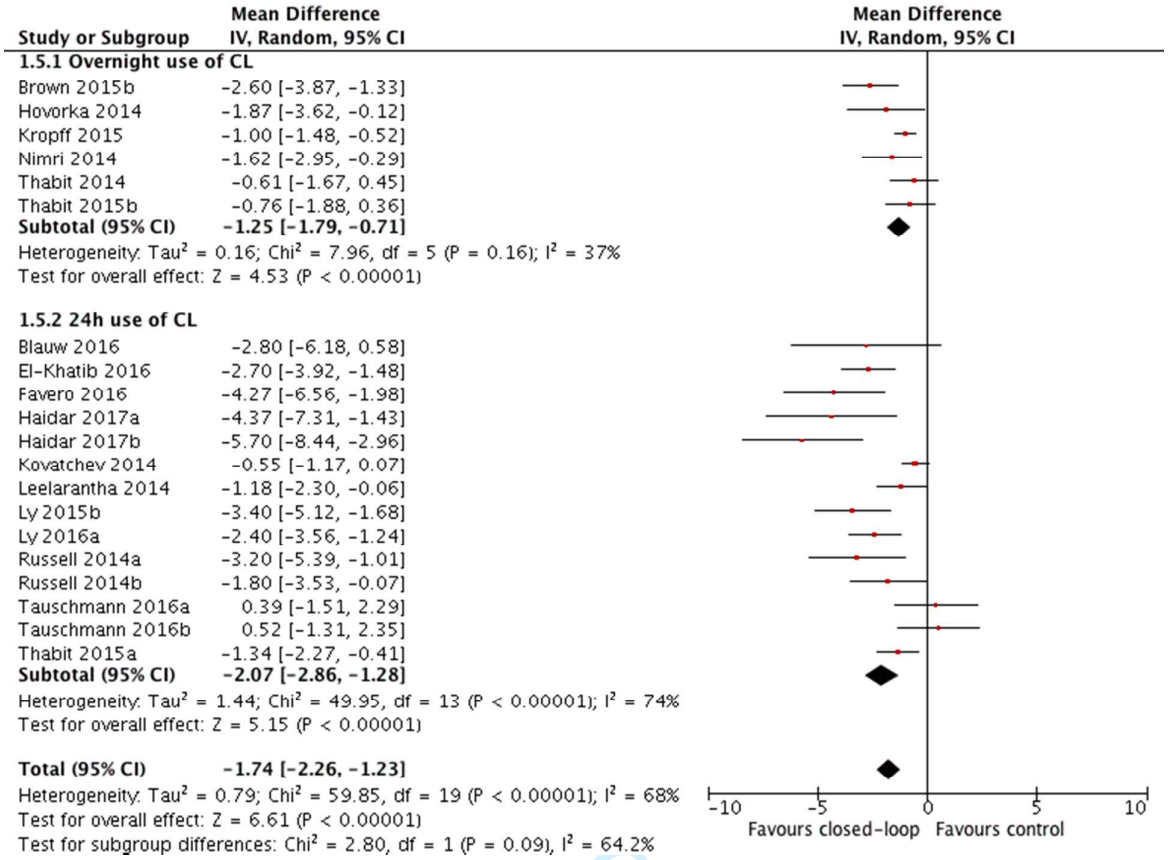

**Appendix 15**. Weighted mean difference in % of overall time in near normoglycaemic range (3.9 – 10.0 mmol/L). Closed-loop versus control treatment. Sensitivity analysis including only trials recruiting unsupervised patients in free-living conditions.



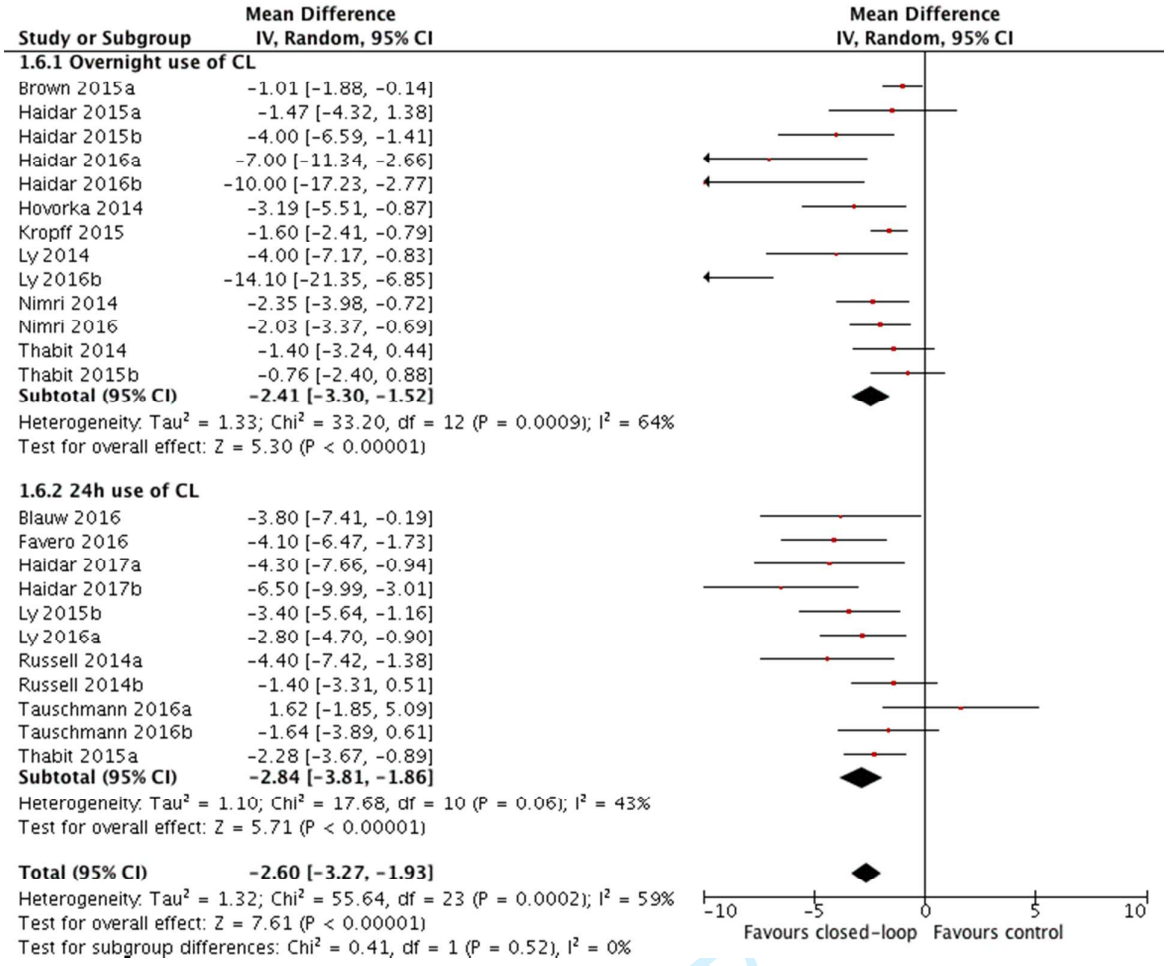

**Appendix 16**. Weighted mean difference in % of overnight time in near normoglycaemic range (3.9 – 10.0 mmol/L). Closed-loop versus control treatment. Sensitivity analysis excluding trials recruiting patients in camps.




**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.