Cambridge hybrid closed-loop in very young children with type 1 diabetes:
a multi-national 4-month randomised trial (KidsAP02)

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Disclosures

Speaker honoraria: Ypsomed

# Artificial pancreas - automated insulin delivery
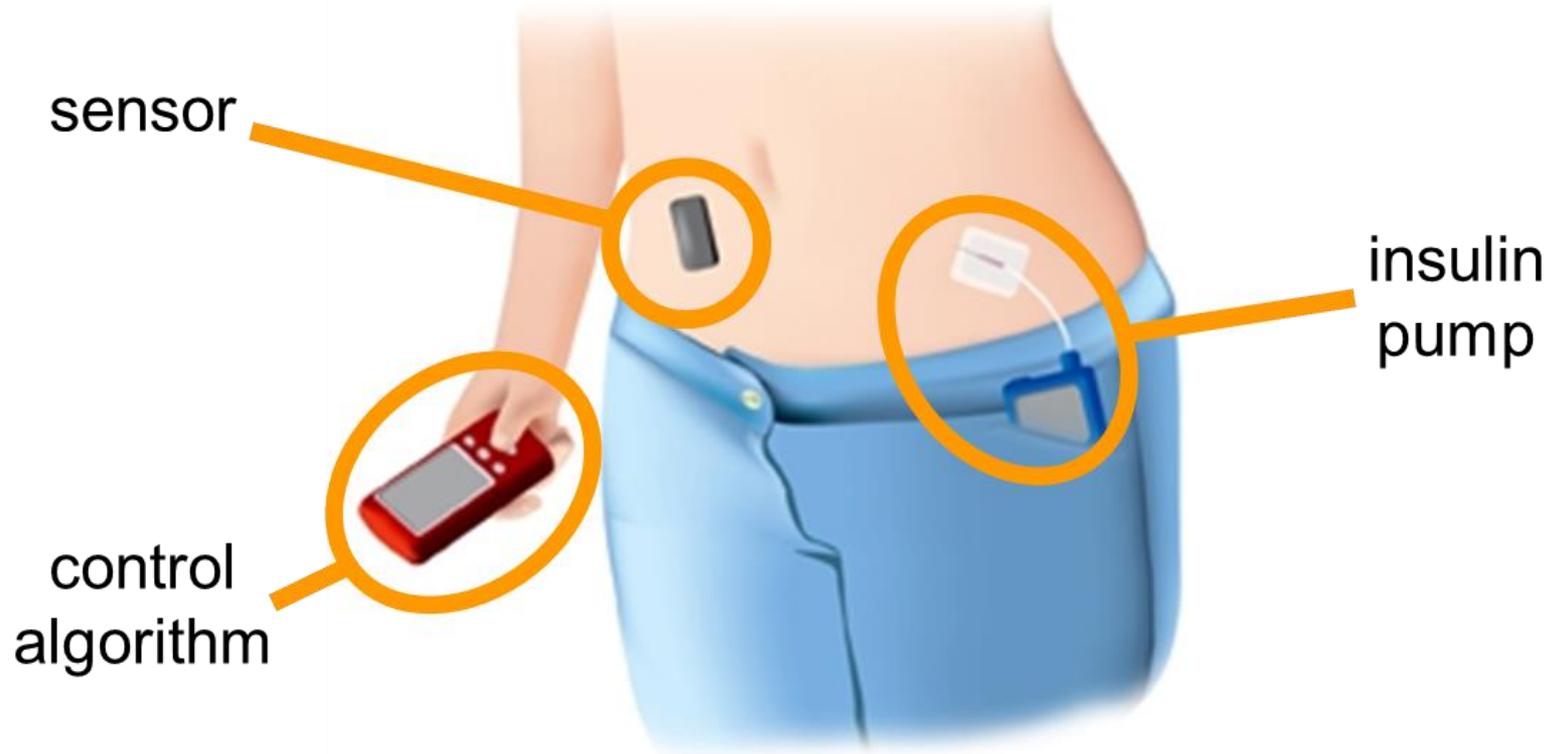
"Hybrid" closed-loop
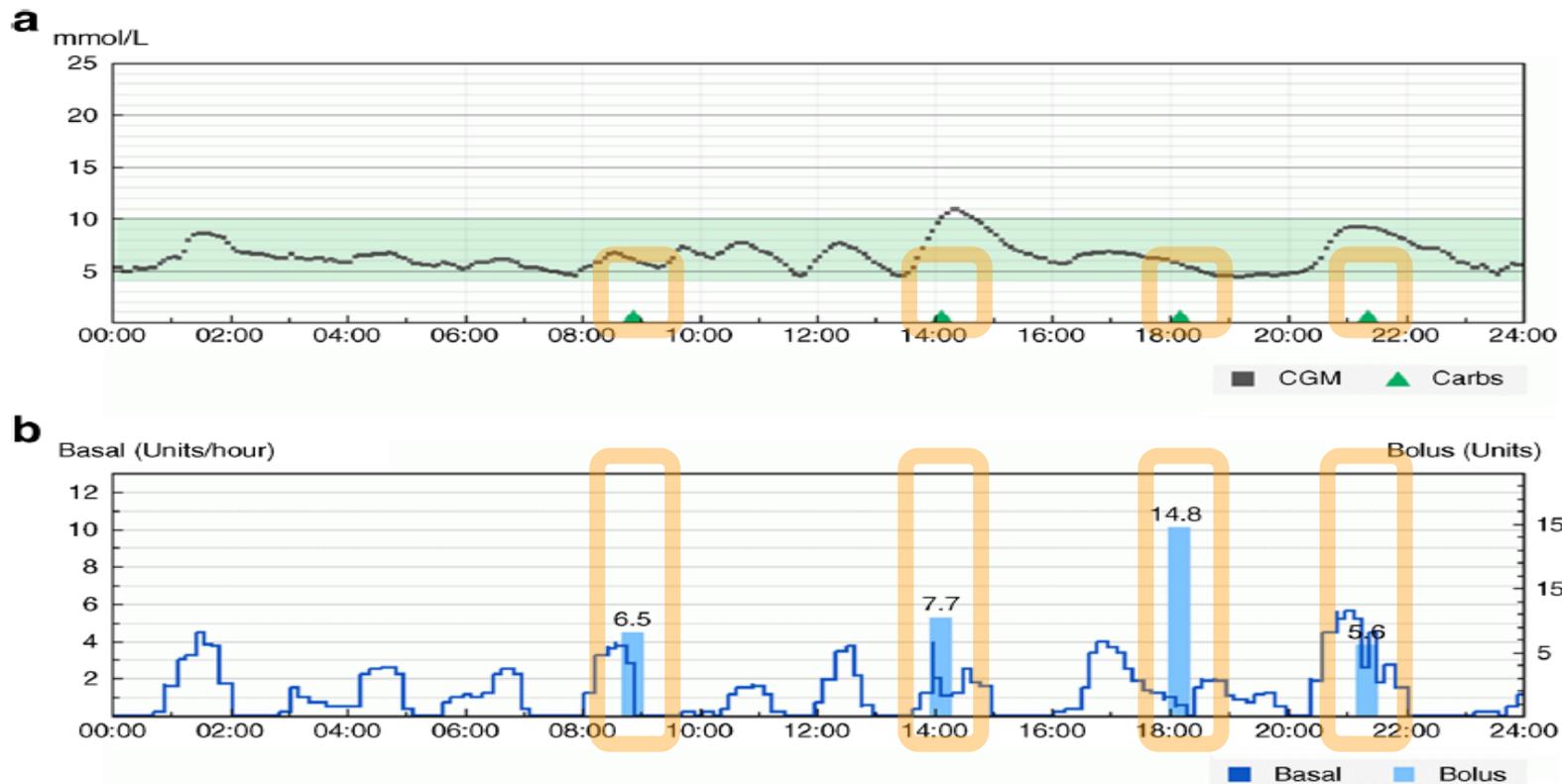
What makes "good closed loop"

- Glucose outcomes
  - ≥70% Time in Range between 3.9 to 10 mmol/l
  - Low hypoglycaemia exposure
    - ≤4% below 3.9 mmol/l

- Low diabetes burden
  - User interaction 10 to 20 min a day
  - Low alarm burden
  - Low device burden
  - Low rate of technical issues

Battelino et al. Diabetes Care 2019;42(8):1593-1603

Why is there a need for closed-loop therapy?
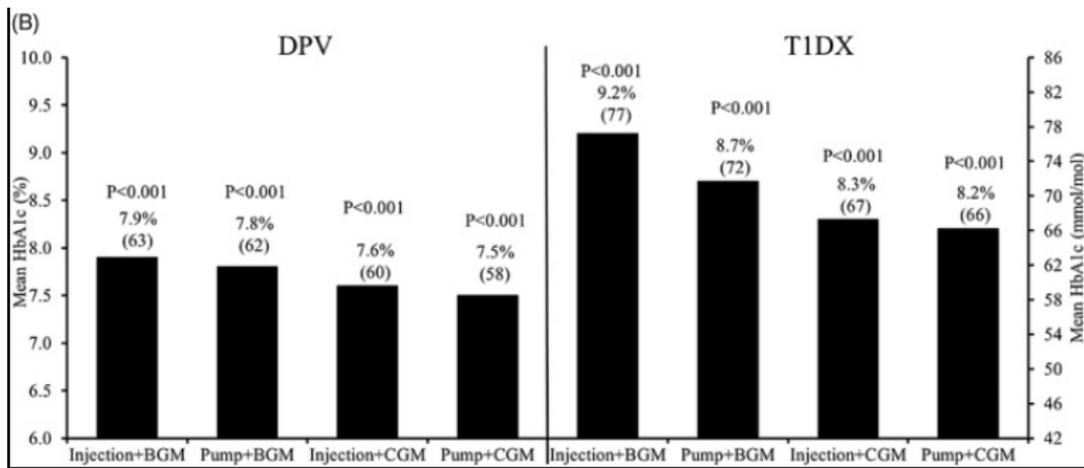
DeSalvo DJ et al. Pediatr Diabetes 2018;19:1271-5.

ADA HbA1c goal is <6.5% (<48mmol/mol)
BGM – blood glucose monitoring
CGM – continuous or flash glucose monitoring
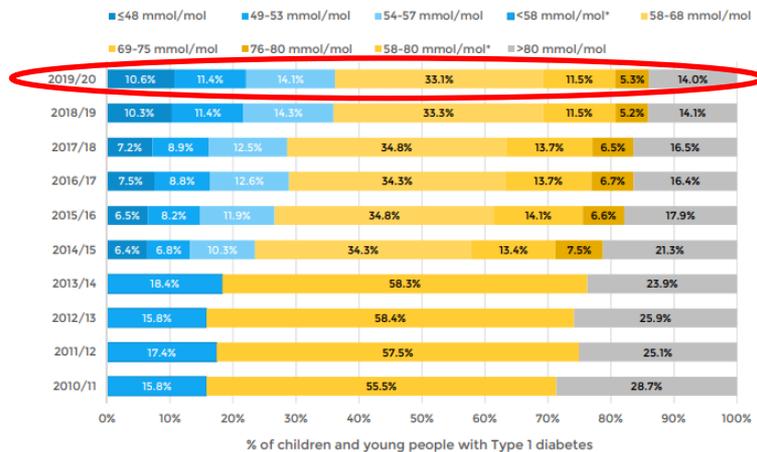
National Paediatric Diabetes Audit, RCPCH, 2019-2020.

- HbA1c & glycaemic targets are not being achieved
- Management burden is high
- Negative impact on quality of life

Why very young children?

Dovc et al. Diabetes Care 2019.
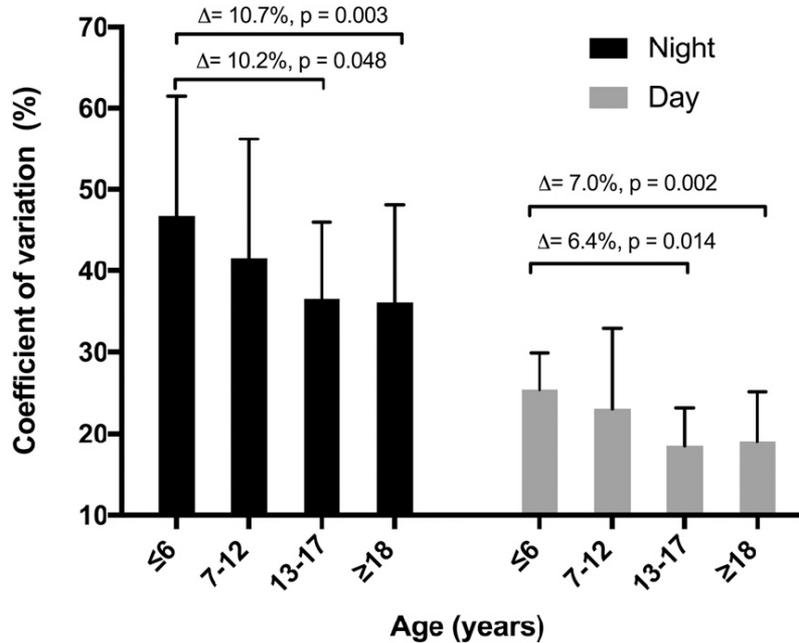
Aim

To compare safety and efficacy of the Cambridge hybrid closed-loop algorithm with sensor-augmented pump therapy over 16 weeks in very young children with type 1 diabetes

Study centres
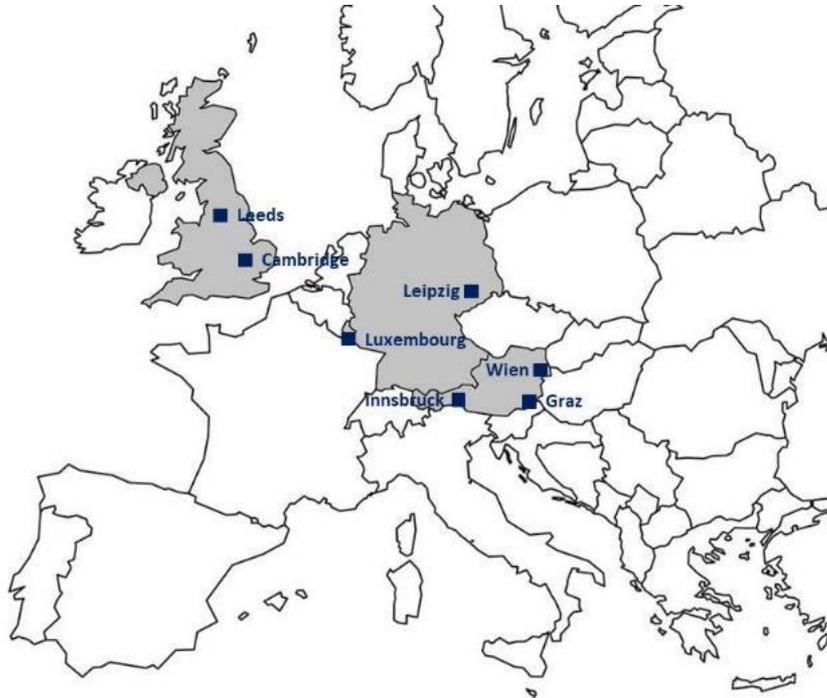
Multi-centre, multi-national, randomised, crossover design

81 participants enrolled at 7 centres in
- Austria
- Germany
- Luxembourg
- United Kingdom

Coordinating centre
- Jaeb Center, Tampa, FL, USA

Study design
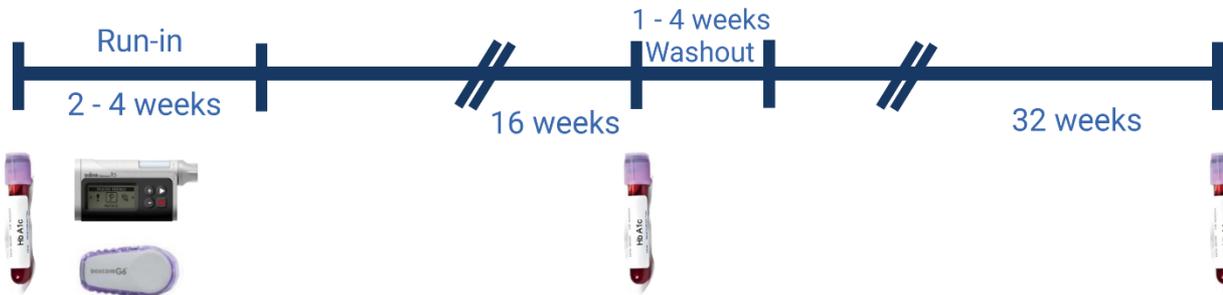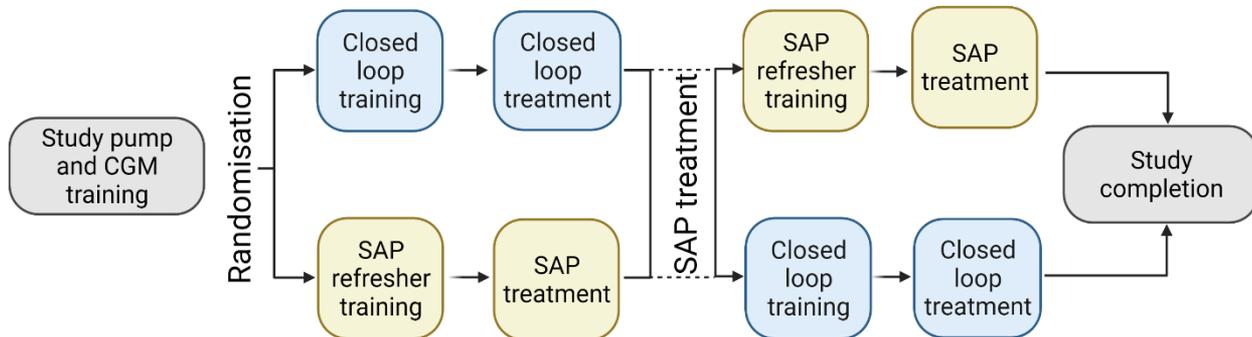
Inclusion
- Age 1 – 7 years
- T1D ≥ 6 months
- Pump therapy ≥ 3 months
- HbA1c < 11% (97 mmol/mol)

Exclusion
- Use of CL system in last 2 months
- Physical or psychological condition likely to interfere with the normal conduct of the study

Closed-loop system

Dexcom G6 sensor

Unlocked Android smartphone
with Cambridge control algorithm

Dana Diabecare RS

- CamAPS FX app incorporates Cambridge model predictive control algorithm and is used to stop/start Auto mode, deliver boluses and view data

- Pump, app & sensor communicate directly via Bluetooth

- App provides Dexcom alerts and real-time SMS alerts for caregivers

- Automatic upload to Diasend enabling remote data sharing

Study endpoints

Primary endpoint: between-treatment difference in time in range 3.9 to 10.0mmol/L over 16 weeks

Key secondary endpoints:

- Time >10.0mmol/L
- HbA1c
- Mean glucose
- Time <3.9mmol/L

Safety: severe hypoglycaemia, DKA, and other adverse events

Utility: Closed-loop usage

Study Flow
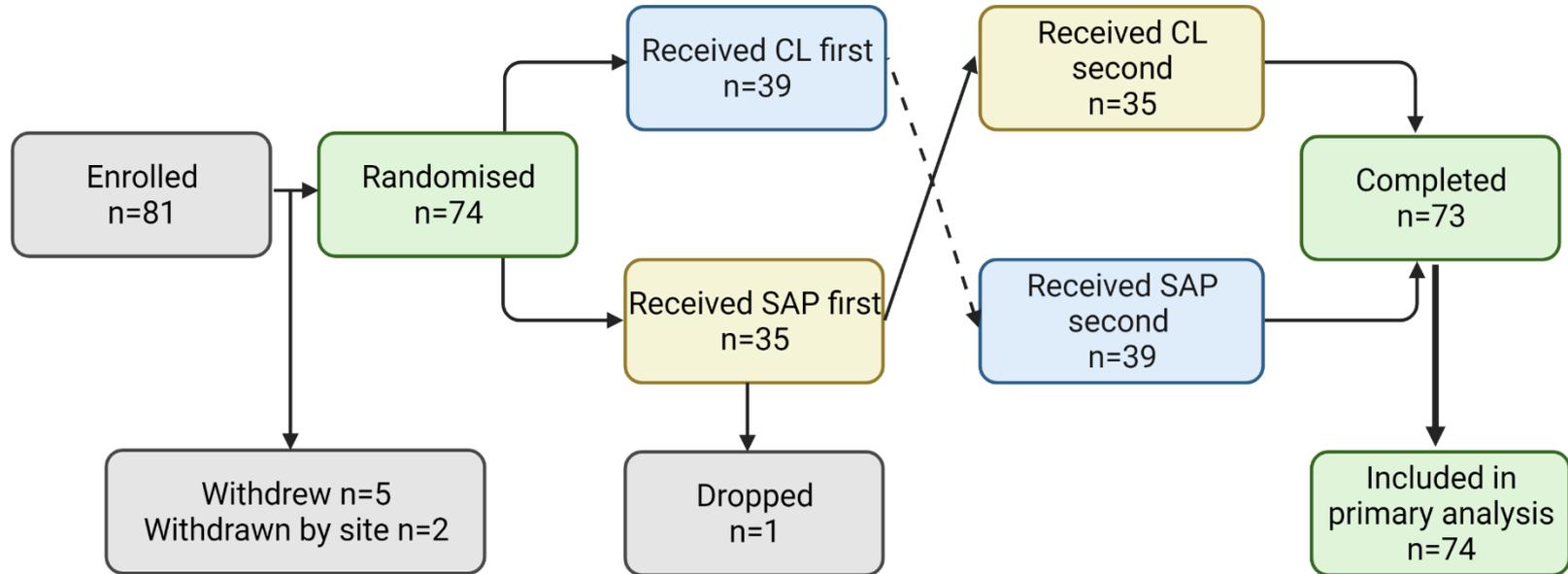
Demographics

|	Overall (n=74)	Closed-loop first (n=39)	Sensor-augmented pump first (n=35)
Age (years), mean ± SD	5.6 ± 1.6	5.5 ± 1.5	5.6 ± 1.7
Sex – Male, n (%)	43 (58)	18 (46)	25 (71)
Ethnicity n (%)			
White	66 (89)	34 (87)	32 (91)
Black African/American	2 (3)	2 (5)	0 (0)
Asian	2 (3)	1 (3)	1 (3)
More than one race	4 (5)	2 (5)	2 (6)
Duration of diabetes (years), mean ± SD	2.6 ± 1.8	2.5 ± 1.7	2.7 ± 1.9
Baseline HbA1c in mmol/mol [%], mean ± SD	57 ± 7 [7.3 ± 0.7]	56 ± 7 [7.3 ± 0.7]	57 ± 7 [7.4 ± 0.6]
Use of continuous glucose monitor, n (%)			
Current	67 (91)	35 (90)	32 (91)
In past, but not current	1 (1)	0 (0)	1 (3)
Never	6 (8)	4 (10)	2 (6)

36% aged 2-4 yrs

Key results

Hierarchical Endpoints	Closed-loop (n=73)	Sensor-augmented pump (n=74)	Mean adjusted difference (95% CI)	P value
Time in range 3.9 to 10.0mmol/L (%)	72 ± 6	63 ± 9	8.7 (7.4, 9.9)	<0.001
Time glucose >10.0mmol/L (%)*	23 (19, 27)	32 (23, 40)	-8.5 (-9.9, -7.1)	<0.001
HbA1c (mmol/mol)*	49 ± 6	53 ± 7	-3.9 (-4.9, -2.9)	<0.001
[HbA1c %]	[6.6 ± 0.5]	[7.0 ± 0.7]	[-0.4 (-0.5, -0.3)]	
Mean glucose (mmol/L)	8.1 ± 0.7	8.8 ± 1.0	-0.7 (-0.8, -0.5)	<0.001
Time glucose <3.9mmol/L (%)*	4.3 (3.3, 6.7)	4.5 (2.9, 7.3)	0.1 (-0.4, 0.5)	0.74

Data are mean ± SD or median (IQR). *Tested in hierarchy as listed to control the type 1 error using the fixed-sequence method.

Ware J et al. N Engl J Med 2022; 386:209-219

Time in range over 4 months

Boxplot shows median as horizontal line, mean as + symbol, IQR as box and range as whiskers.

Ware J et al. N Engl J Med 2022; 386:209-219

Sensor glucose levels

Data shown as median (line) and IQR (shaded area) with n=73 (closed-loop) and n-74 (sensor-augmented pump)

Ware J et al. N Engl J Med 2022; 386:209-219
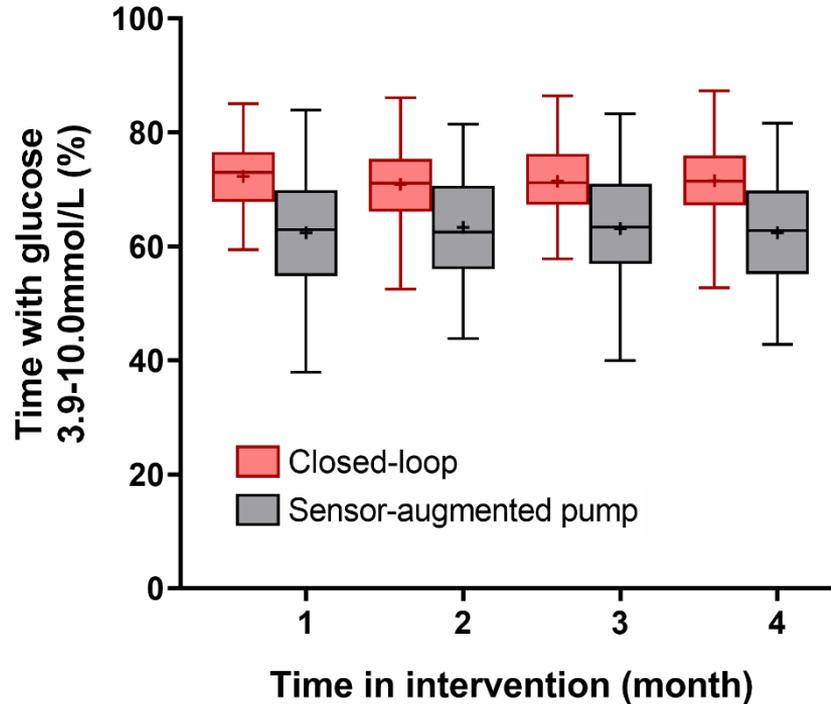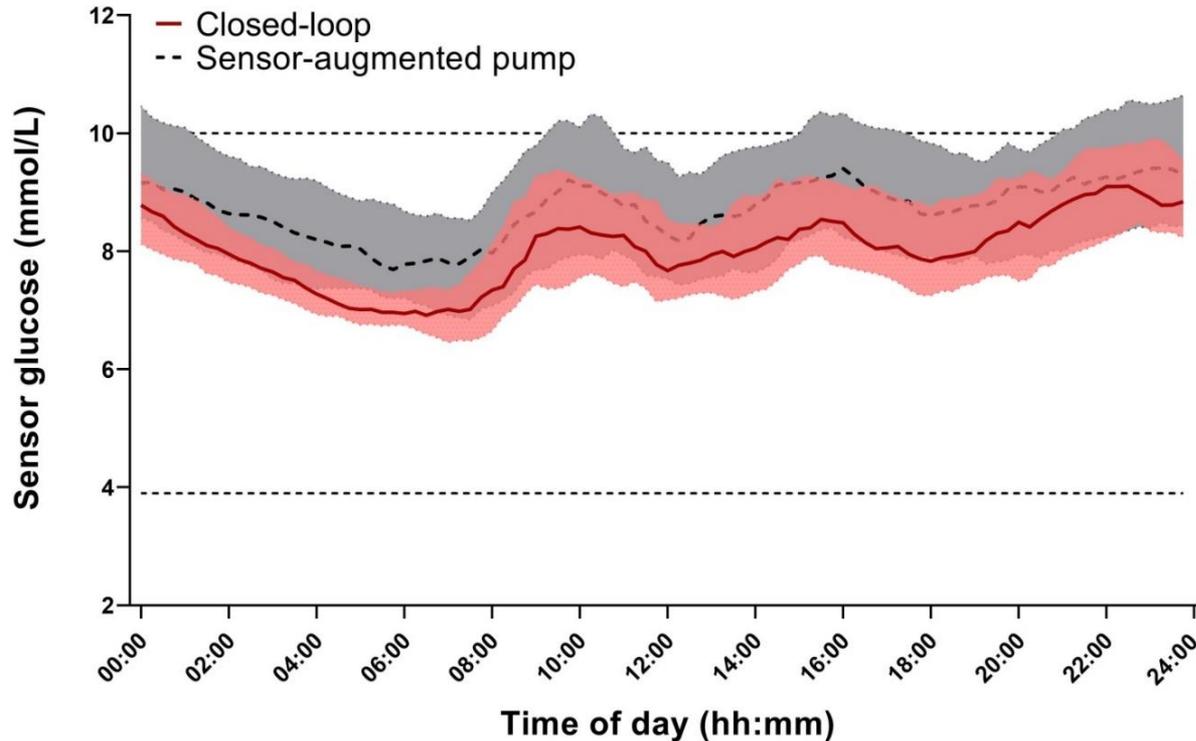
Secondary endpoints

| Secondary endpoints	Closed-loop (n=73)	Sensor-augmented pump (n=74)	Mean adjusted difference (95% CI)	P value
Time glucose <3.0mmol/L (%)	1.0 (0.6, 1.4)	0.9 (0.4, 1.6)	0.02 (-0.1, 0.1)	0.63
Time glucose >16.7mmol/L (%)	2.0 (1.2, 3.1)	3.1 (1.3, 5.7)	-1.0 (-1.6, -0.6)	<0.001
Glucose SD (mmol/L)	3.3 (3.0, 3.6)	3.6 (3.2, 4.0)	-0.3 (-0.4, -0.3)	<0.001
Glucose CV (%)	41 (39, 43)	41 (38, 44)	-0.7 (-1.5, 0.05)	0.07

System remained in Auto Mode for median 95% (IQR 92, 97) during closed-loop treatment

Glycaemic outcomes by time of day

	Daytime (08:00 to 23:59)		Nighttime (00:00 to 07:59)	
	Closed-loop (n=73)	Sensor-augmented pump (n=74)	Closed-loop (n=73)	Sensor-augmented pump (n=74)
Time spent at glucose level (%)				
3.9 – 10.0mmol/L	66 ± 7	61 ± 9	82 ± 6	66 ± 11
<3.9mmol/L	6 (4, 8)	4 (3, 7)	3 (2, 4)	5 (3, 7)
Mean glucose (mmol/L)	8.4 ± 0.8	9.0 ± 1.1	7.6 ± 0.5	8.4 ± 1.0
Glucose SD (mmol/L)	3.5 (3.2, 3.8)	3.7 (3.3, 4.1)	2.6 (2.3, 3.0)	3.3 (2.9, 3.7)

24-hour insulin profiles

Average insulin delivered during each hour of the day.
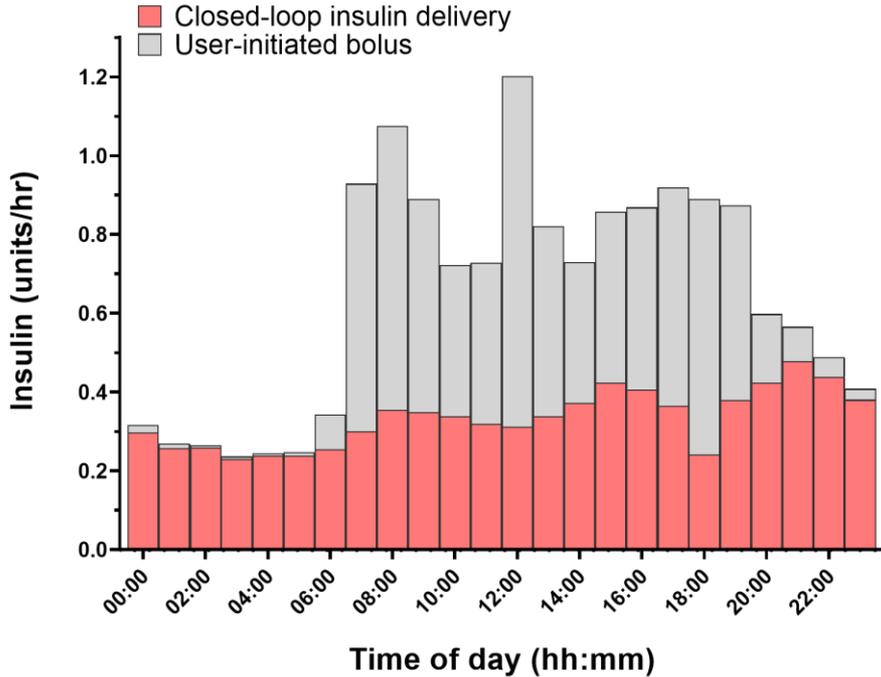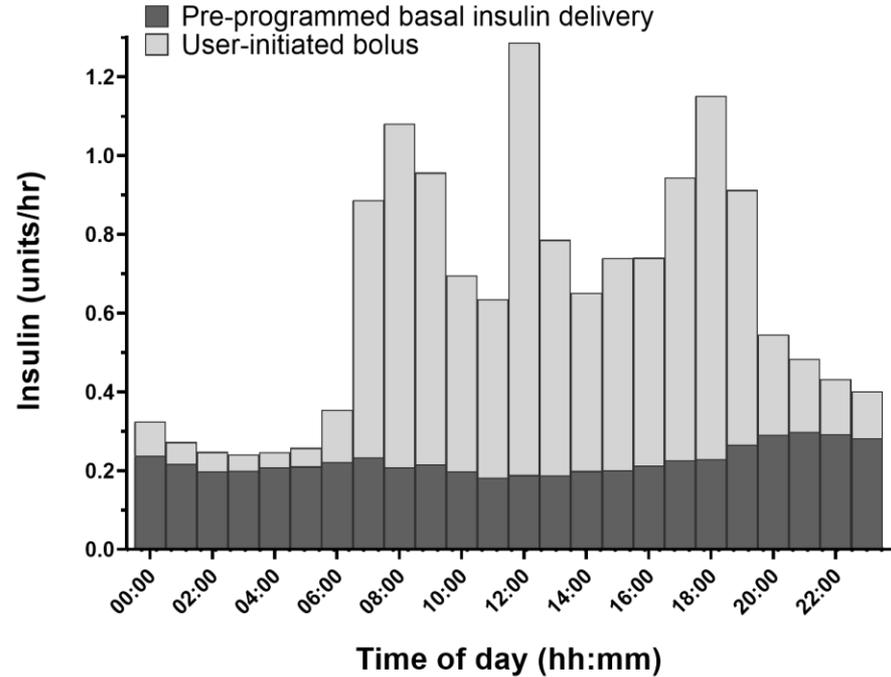
Safety outcomes

	Closed-loop (n=73)	Sensor-augmented pump (n=74)
Any reportable adverse event		
Participants with zero adverse events, n (%)	53 (73)	56 (76)
Participants with 1 adverse event, n (%)	15 (21)	12 (16)
Participants with ≥2 events, n (%)	5 (7)	6 (8)
Number of events per participant	0.4 ± 0.7	0.4 ± 0.8
Specific events (number of events)		
Severe hypoglycaemia (SH) events	1	0
Incidence rate per 100 person years	4.5	0.0
Diabetic Ketoacidosis events	0	0
Other serious adverse events*	0	1

*One participant was admitted to hospital due to gastroenteritis.

Qualitative sub-study of parents' experience

- 33 parents of 30 children

- Interviewed at 2 timepoints:

  - End of closed-loop period

  - End of SAP period

- Data analysed thematically

Life on standard therapy

- family life being dominated by conversations about, and the need to focus on, glucose management tasks

- poor sleep, due to the need for constant vigilance

- anxiety and worry when their child was being cared for by others

- their child missing out on normal childhood activities (e.g. sleepovers, parties) due to others' reluctance to oversee their care

- siblings missing out on parents' time and attention.

Consequences of using closed-loop

- Better sleep

- Worrying less about their child's safety

- Better able to get on with their own lives

- More time for siblings

- Leaving child with other caregivers

> *"I'd say night-time is probably the most dramatic difference, because…we probably are only woken by alarms now, like, twice a week. And we never set an alarm to test (child) now. And we trust it. Like, honestly, the line is deadly straight overnight."*
> *(002)*

Kimbell B et al. Diabetes Res Clin Prac 2022; 187:109877

Remote data viewing

- Being able to check near real-time glucose and insulin data on their own phones made parents feel:
  - More in control
  - More confident

'I don't need to sit and worry…I just log on and see, "Okay, fine, everything is cool, they (school) have got it under control – I can see when she got insulin," (and) I feel cool.' (017)

- Enabled the child to attend parties/sleepovers/playdates without direct parental supervision

Remote bolusing

- Less stress

- More dignity for their child

- Ability to administer insulin surreptitiously

'She can be playing in the garden outside and I can just kind of hang out of the window and give her [insulin]…I don't have to get her to stop what she's doing.' (018)

Kimbell B et al. Diabetes Res Clin Prac 2022; 187:109877

Suggestions for improvement

- Smartphone too big and heavy to stow easily on child
- Difficulties stepping back from correcting glucose
  - Incorporate into training / expectation setting
  - Transition period required

Kimbell B et al. Diabetes Res Clin Prac 2022; 187:109877

Conclusions

- Hybrid closed-loop is safe and significantly improves glycaemic control in very young children

- Children spent an extra 2.1 hours per day with glucose in target range, without an increase in hypoglycaemia

- HbA1c reduction of 3.9mmol/mol (0.4%) in cohort with tight glycaemic control at baseline

- Closed-loop was reliable and remained in Auto mode 95% of the time over 4 months

- Hybrid closed-loop therapy brings substantial benefits for the whole family: improved sleep, reduced anxiety and burden for parents and carers, more time for siblings and family activities, and a more 'normal' childhood experience.

Funders and supporters

- Our study participants and families

- KidsAP Consortium

More info

- Main study results:
    - https://www.nejm.org/doi/full/10.1056/NEJMoa2111673
- Qualitative study results:

    https://www.sciencedirect.com/science/article/pii/S0168822722006908?via%3Dihub
- KidsAP project website:
    - http://kidsap.mrl.ims.cam.ac.uk/