Quantification of the analgesic effect of intranasal coadministration of ketamine and sufentanil in adults to support the development of a pain relief treatment (CT001) in children

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Treating acute and procedural pain in children using CT001

- Non-invasive and effective treatment:
  - Nasal administration (non-invasive, so no extra stress) of sufentanil and ketamine (effective)
  - Ketamine is added for its opioid-sparing effect
  - Initially prepared by hospital pharmacies at the Rigshospitalet and the Karolinska institute
- Drug development upside down:
  - No information in adults on efficacy after nasal administration
  - Dose determined off-label in clinical practice in children
  - Intranasal doses of approximately 0.5 mg/kg ketamine and 0.5 µg/kg sufentanil
  - Second dose after 15 min if necessary
- The combination appears effective and is well tolerated
- Formal registration is required for wide-spread use
- After EMA consultation:
  - Placebo-controlled pain studies in children pose unsurmountable ethical issues
  - Determine optimal dose combination in adults
  - Extrapolate concentrations and effects to children

Pain study in adults after impacted mandibular third molar extraction

- Four main treatment arms (n=40 each)
  - CT001: 27 µg sufentanil and 27 mg ketamine
  - Placebo
  - Sufentanil alone: 27 µg
  - Ketamine alone: 27 mg

- 12 additional cells with intermediate and higher doses (n=5 each) to describe the full response surface

		Sufentanil			
		0 µg	13 µg	27 µg	40 µg
Ketamine	0 mg	**40**	5	**40**	5
	13 mg	5	5	5	5
	27 mg	**40**	5	**40**	5
	40 mg	5	5	5	5

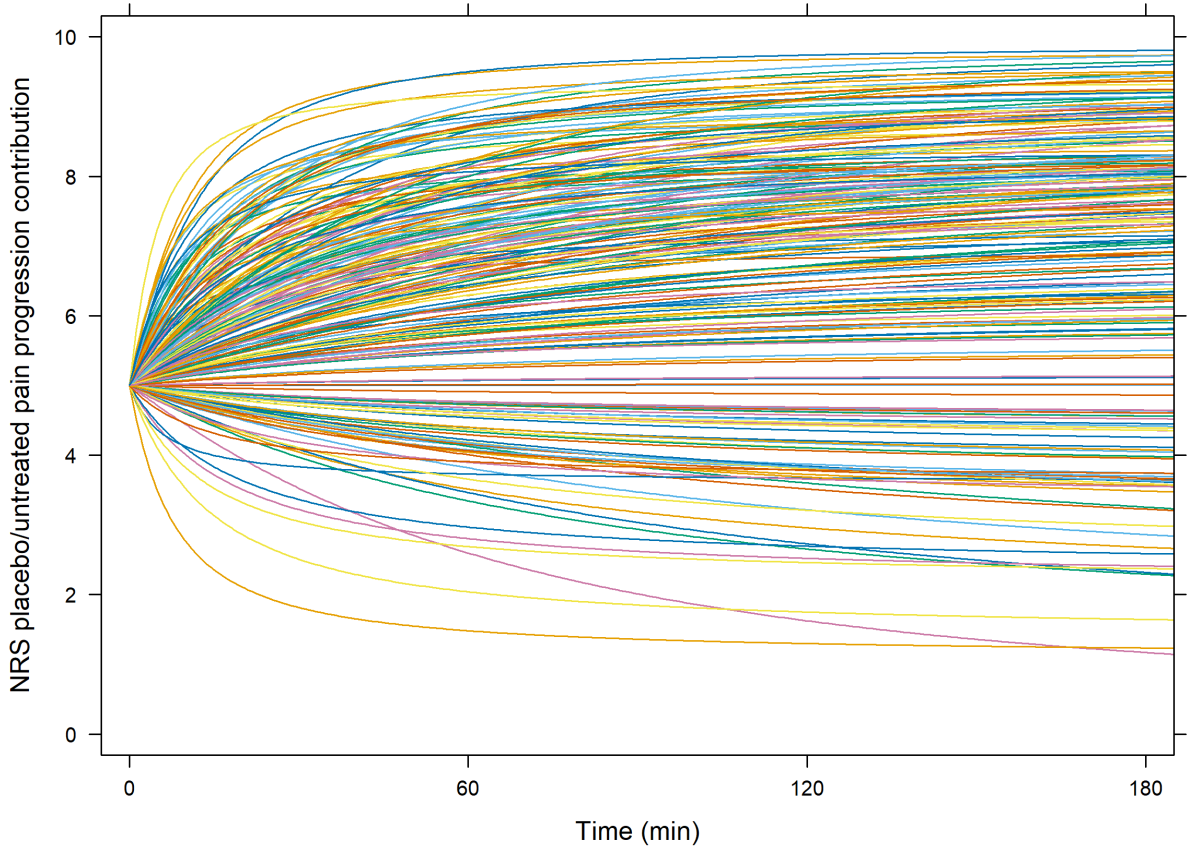
- Two doses –60 min apart– to increase information, and because a second dose is allowed in practice

PKPD model development

- Pain is measured using a verbal numerical rating scale (NRS) with discrete values from 0-10 (10=highest imaginable pain)
- NRS data are analysed after a logit transform to ensure values do not exceed the limits of the scale

PKPD model components: untreated pain progression

- Untreated pain progression is described using an E_{max} over time component
- Observed under placebo but present for all subjects



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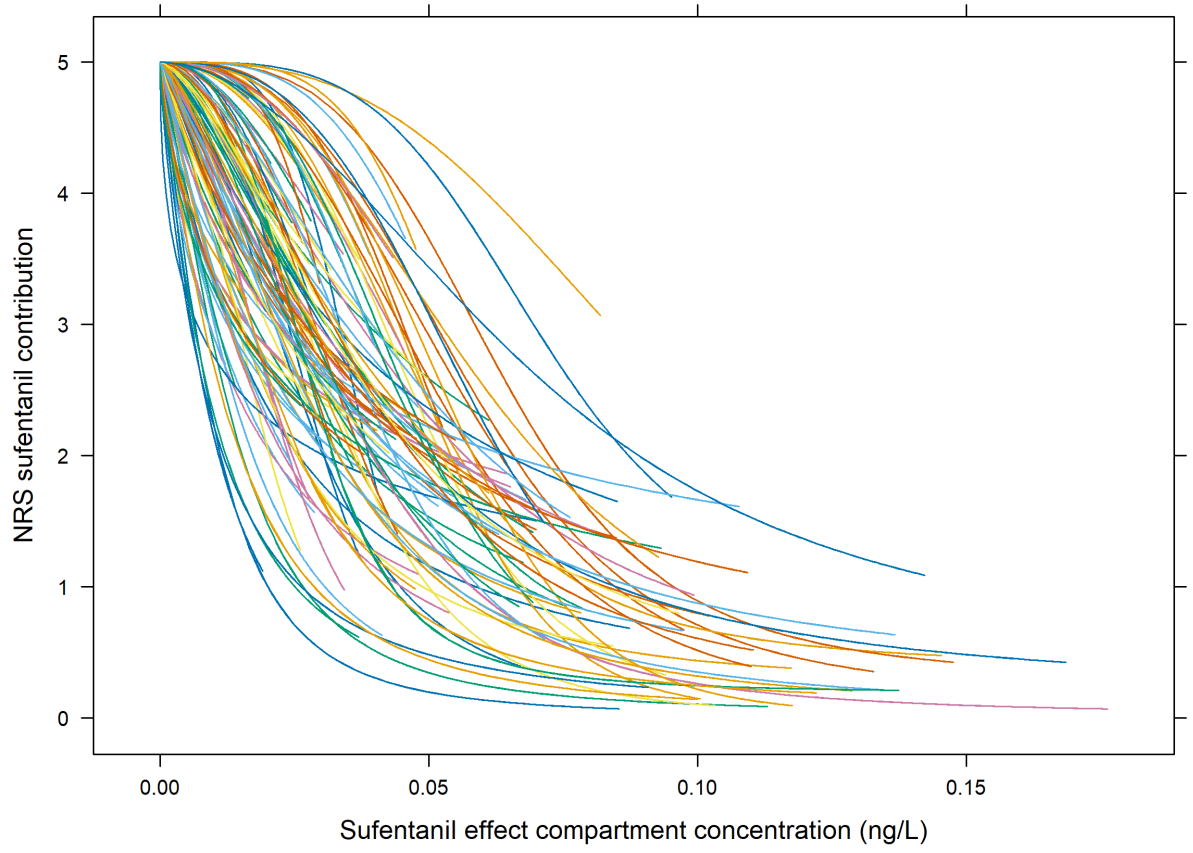
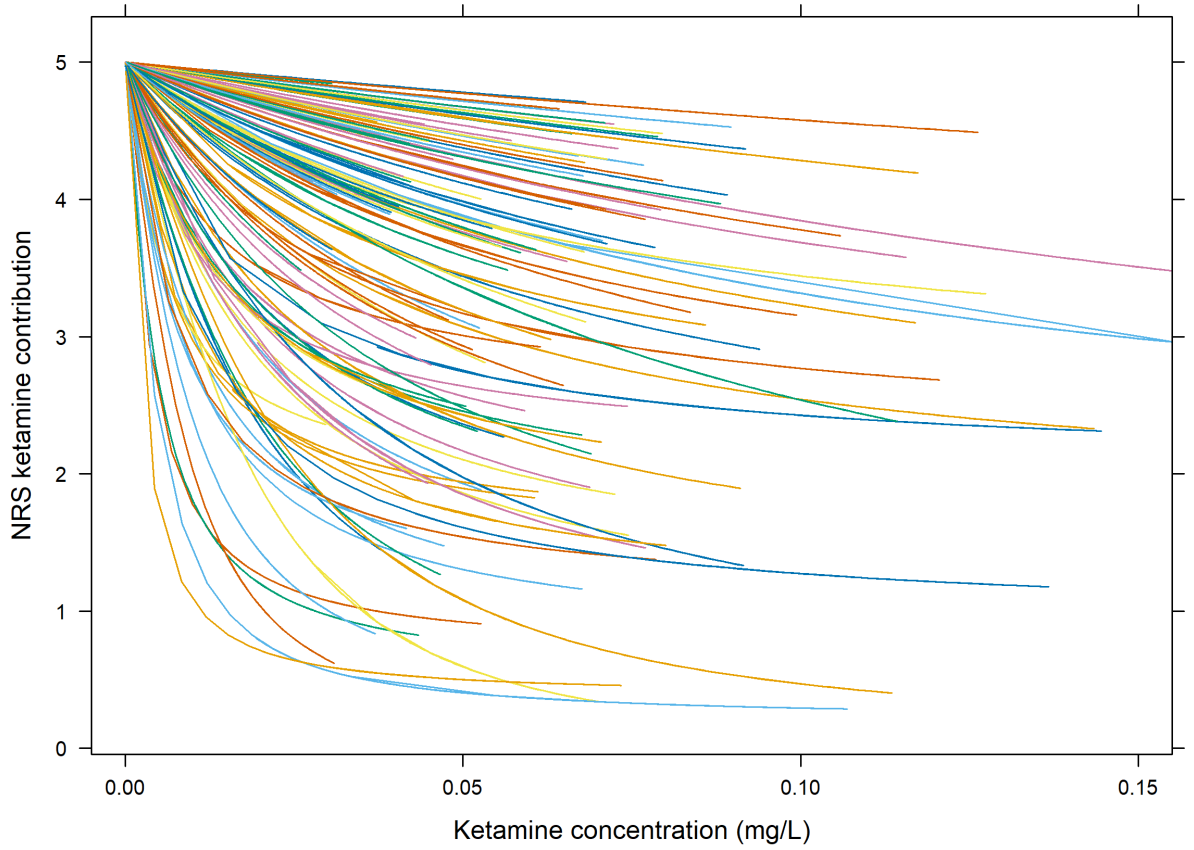
PKPD model components: sufentanil effect

- Sufentanil effect is implemented using a sigmoid E_{max} model and an effect compartment to capture delays between concentration and effect



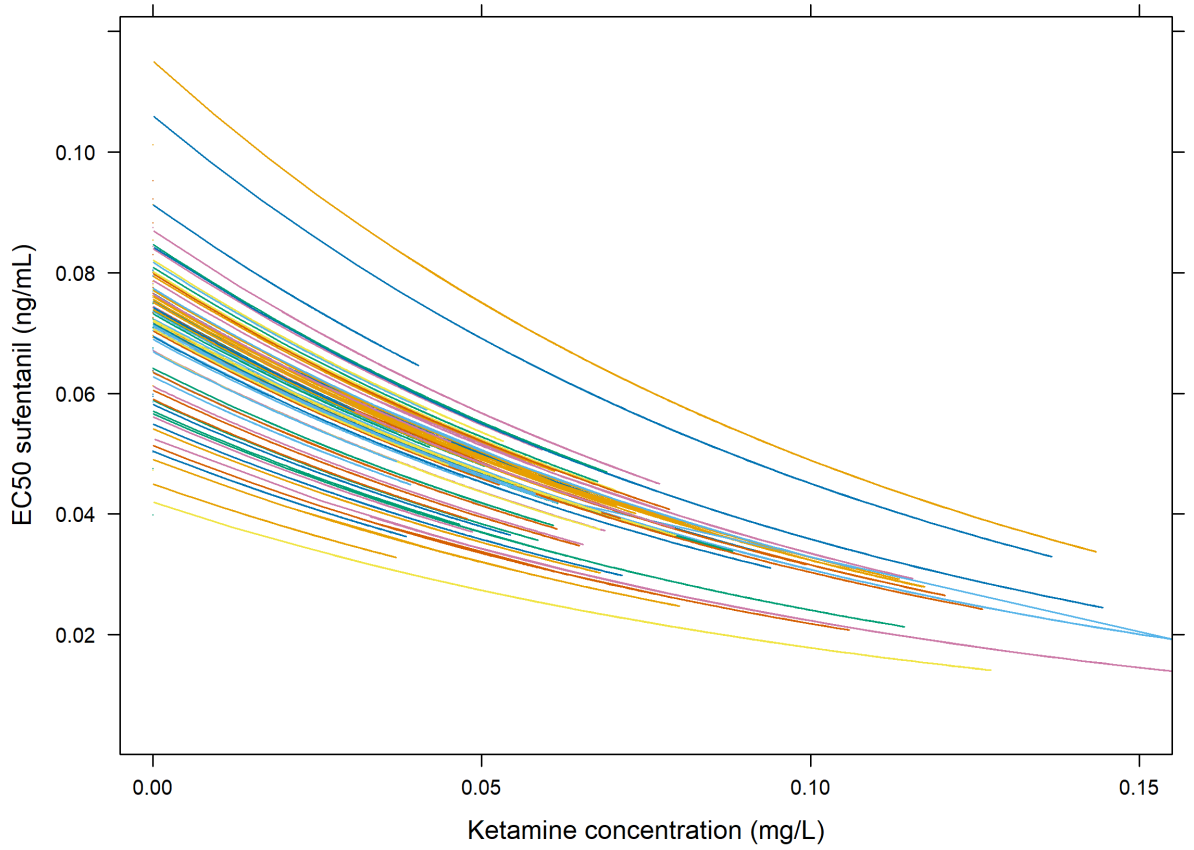
PKPD model components: ketamine effect

- Ketamine effect is implemented using a direct E_{max} model

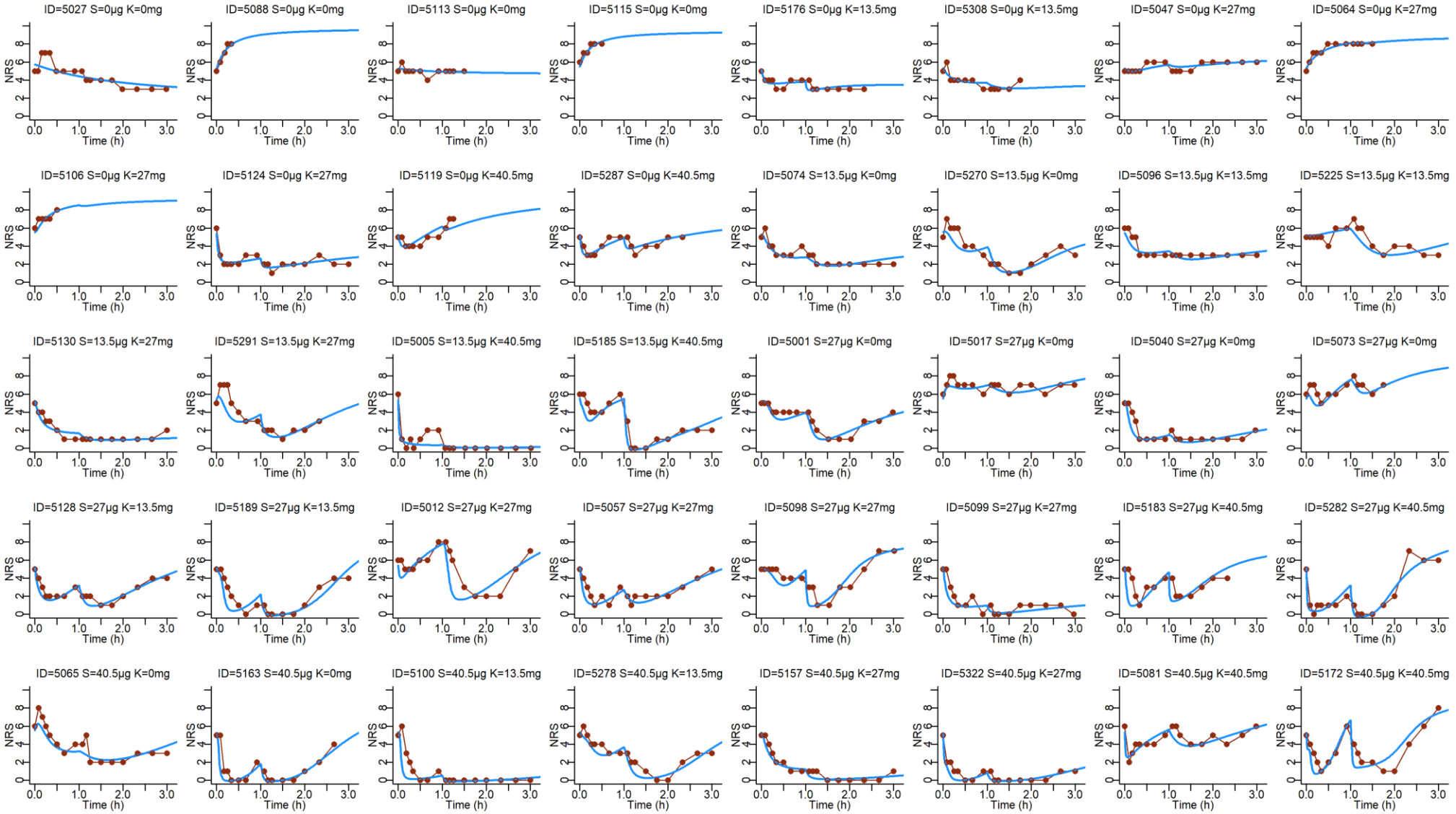


PKPD model components: ketamine effect on sufentanil efficacy

- Interaction between ketamine and sufentanil (i.e. the opioid sparing effect) is implemented using a log-linear relationship between ketamine concentration and sufentanil EC_{50}



Examples of NRS observations (red) and estimated profiles (blue)



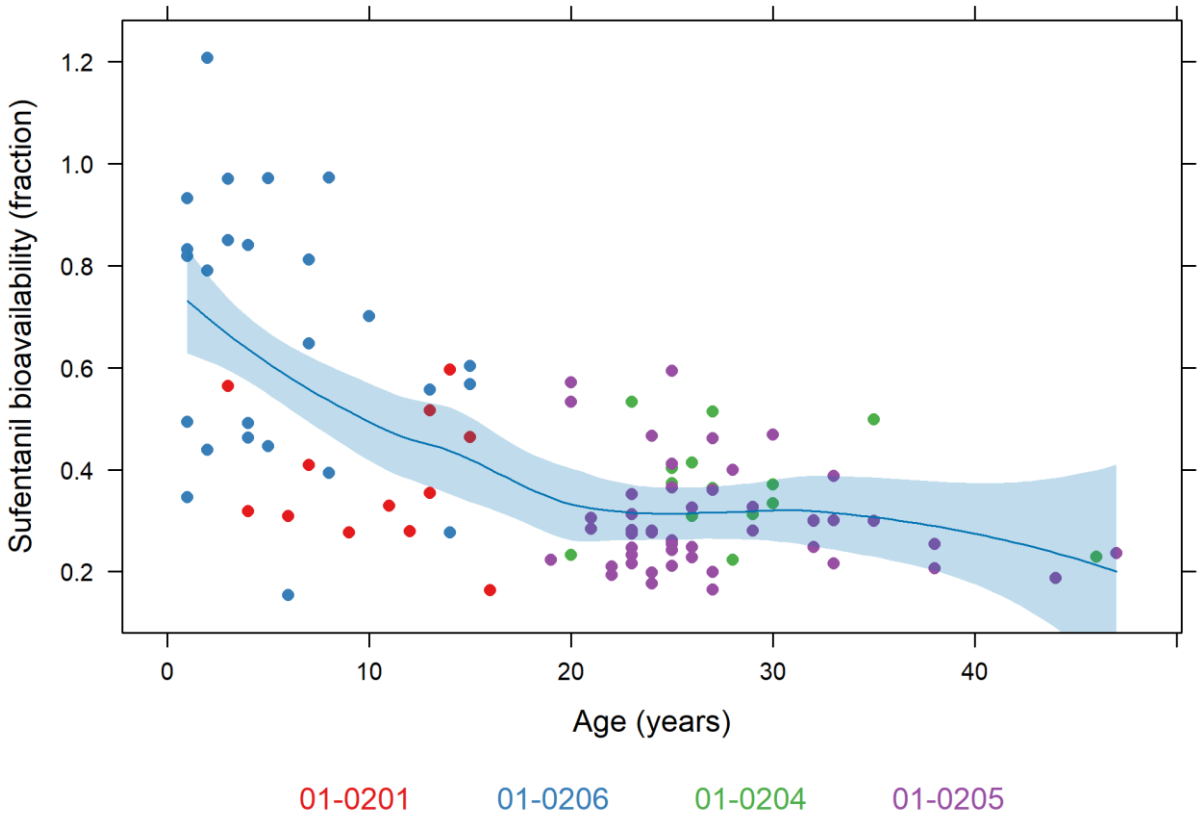
Ketamine and sufentanil PK scaled between adults and children

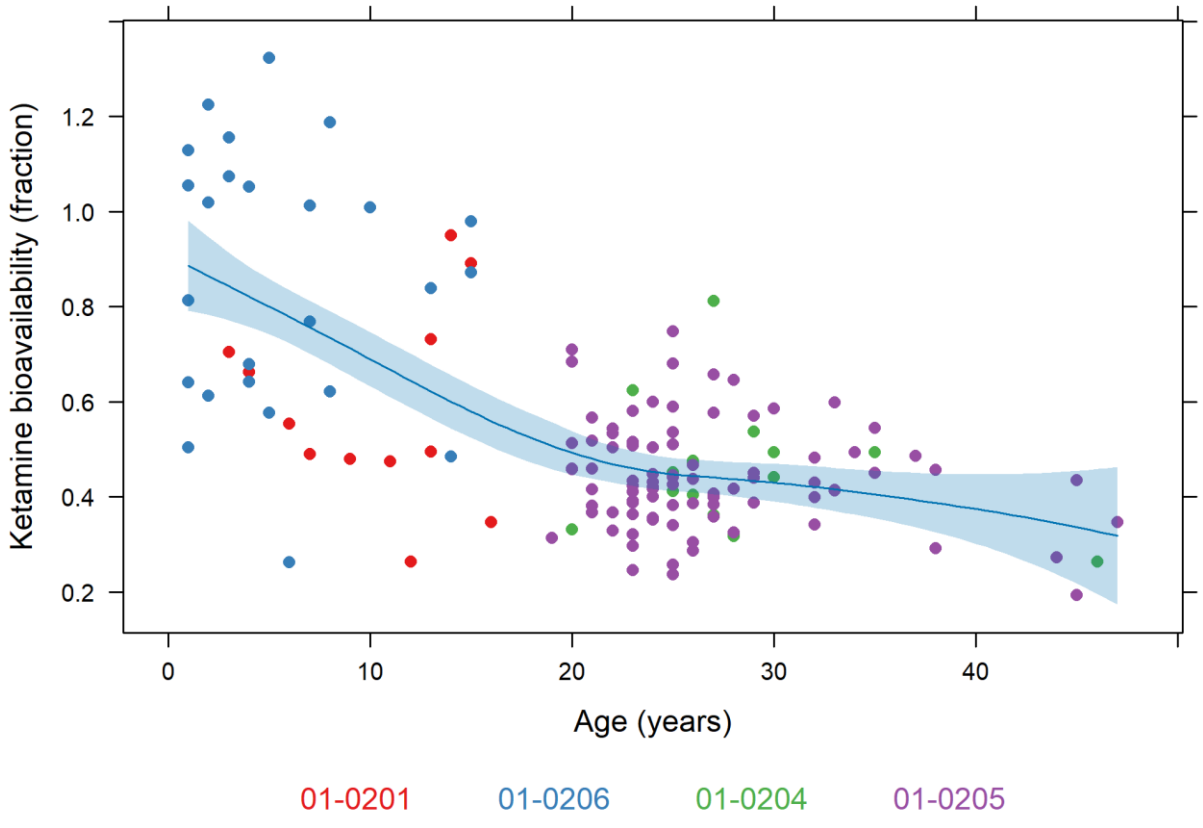
- Data from two paediatric studies (n=37 in total), one adult bioavailability study (n=14), and the factorial adult efficacy study after impacted mandibular third molar extraction (n=220)
- Both ketamine and sufentanil PK can be described using a two-compartment model with data restricted to four hours
- Combined adult/paediatric model allows estimating absolute bioavailability
- PK parameters are scaled on weight using allometric principles with fixed theoretical coefficients

- Are children well described?

Relative exposure is much higher for young children: bioavailability appears to decrease significantly with increasing age

Markers are individual estimates, and line is a loess smooth through the data with 95% confidence interval.





Babies heads are relatively twice as large as adults: does that apply to the nasal surface area as well?

C.H. Stratz. Lebensalter und Geschlechter. Ferdinand Enke in Stuttgart (1926), p24.

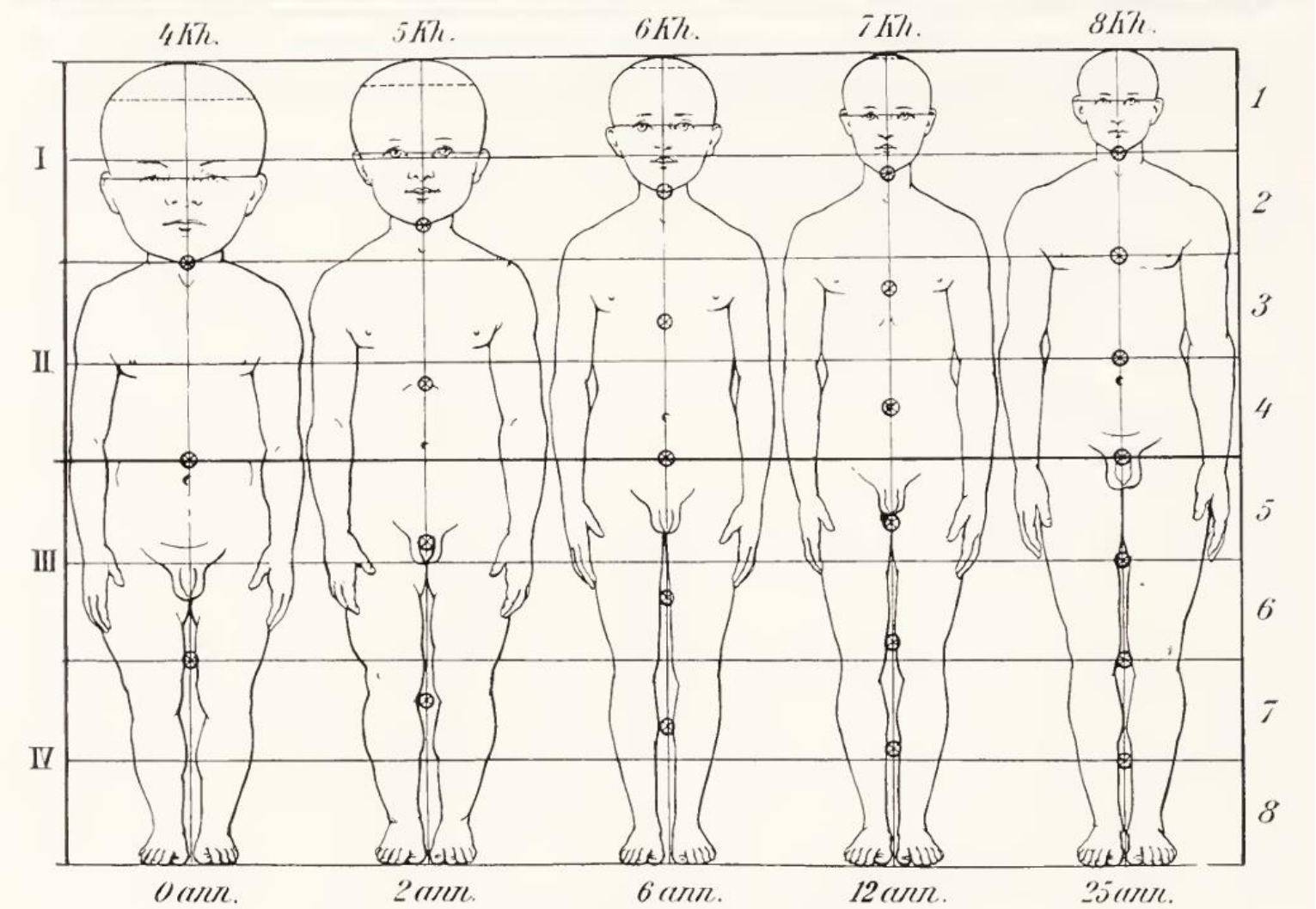


Fig. 7. Wachstumsproportionen

Amazing publication estimating volume of the nasal cavity in 342 children from 0-18 years using MRI

VIA MEDICA

ORIGINAL ARTICLE

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Age-related changes of nasal cavity and conchae volumes and volume fractions in children: a stereological study

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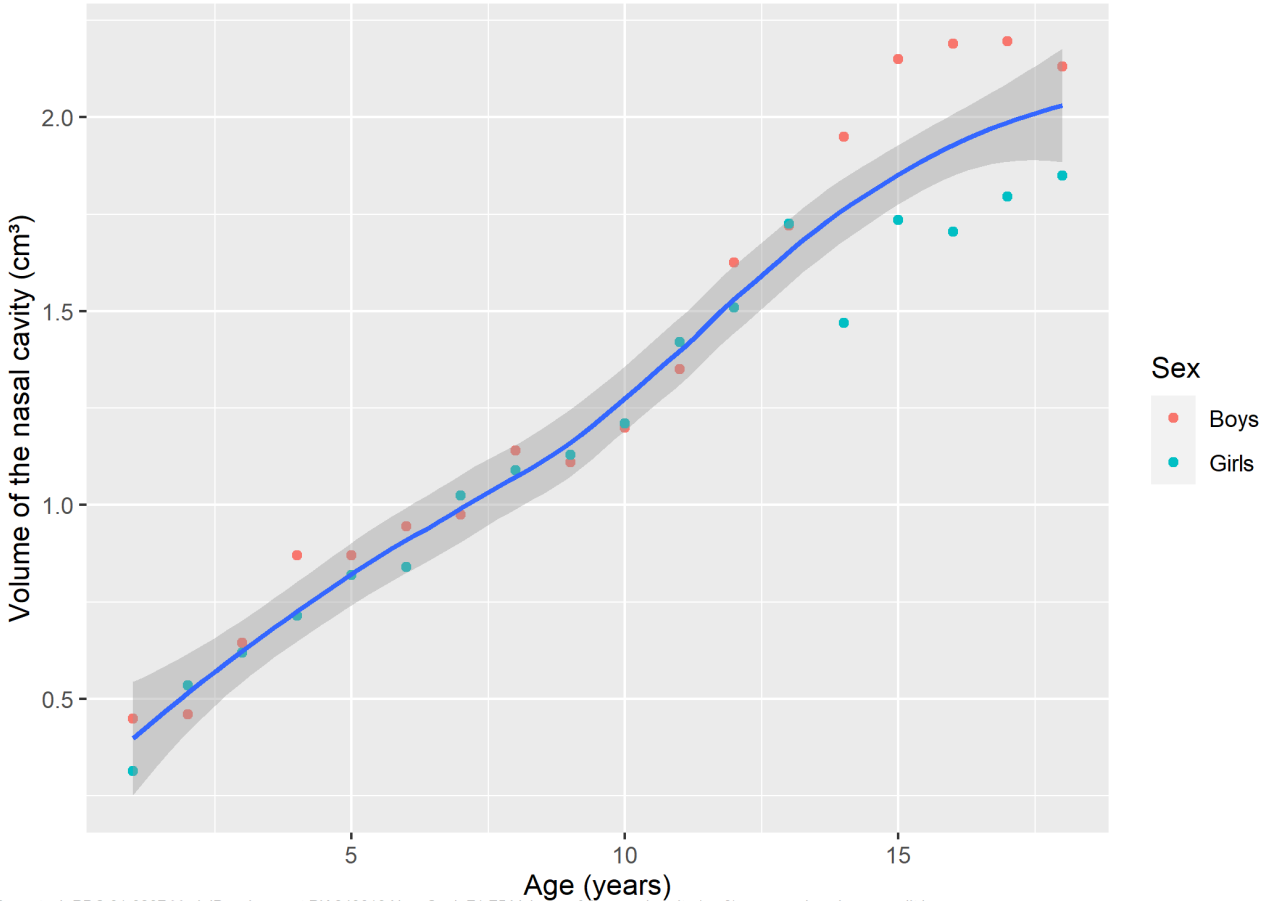
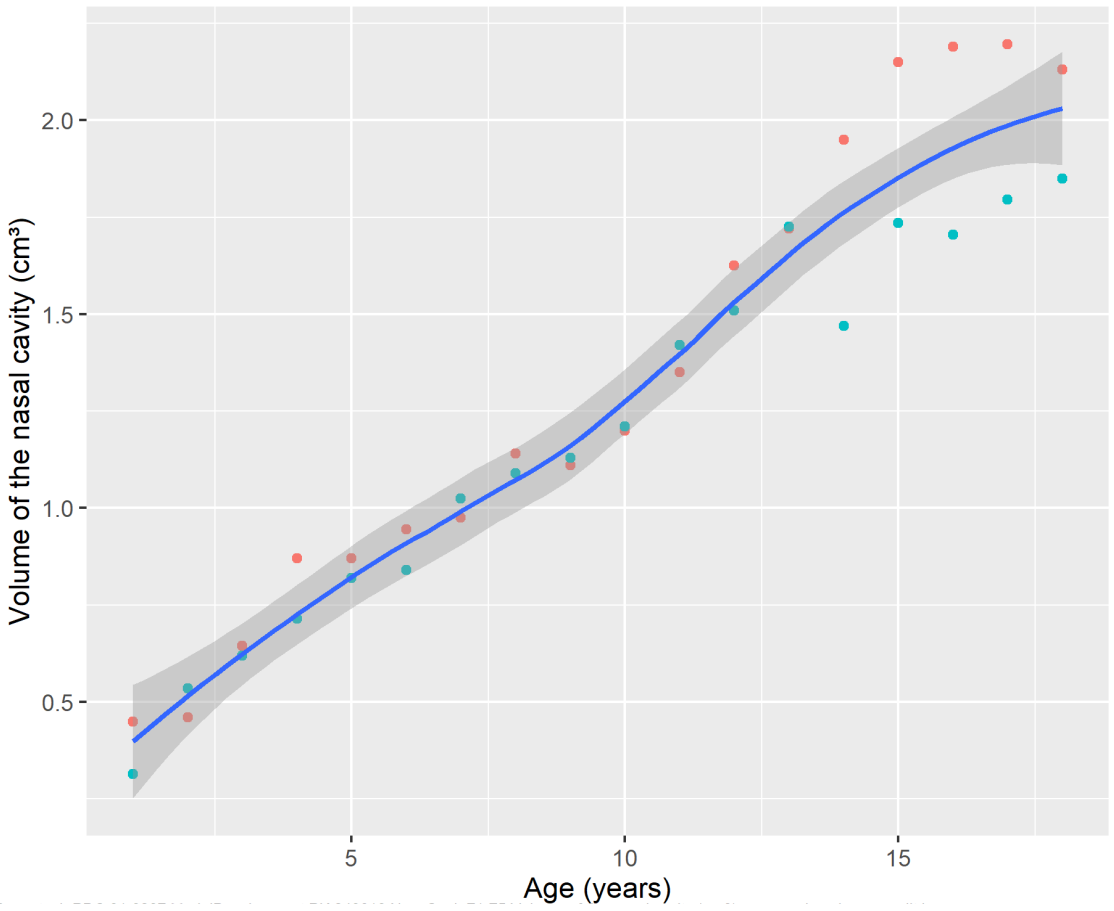
The paper provides volumes of the nasal cavity…

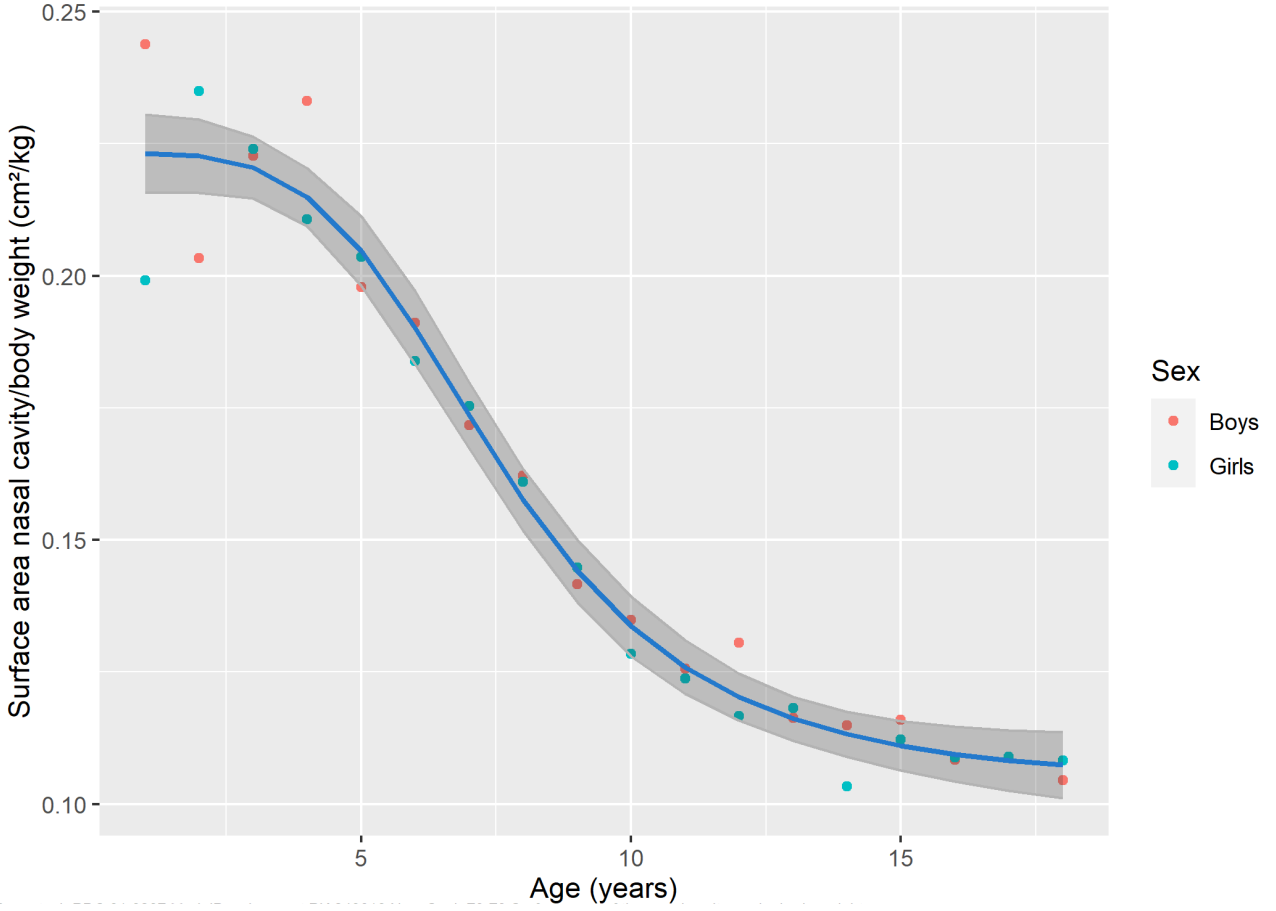
Dots are means of 8-11 boys or girls for each age. Line is a loess smooth through the data with 95% confidence interval.



…that can be translated to intranasal surface area divided by body weight

Assuming the volume can be approximated by a sphere, and using average weights for age from the Nhanes database. Line is a loess smooth through the data with 95% confidence interval.





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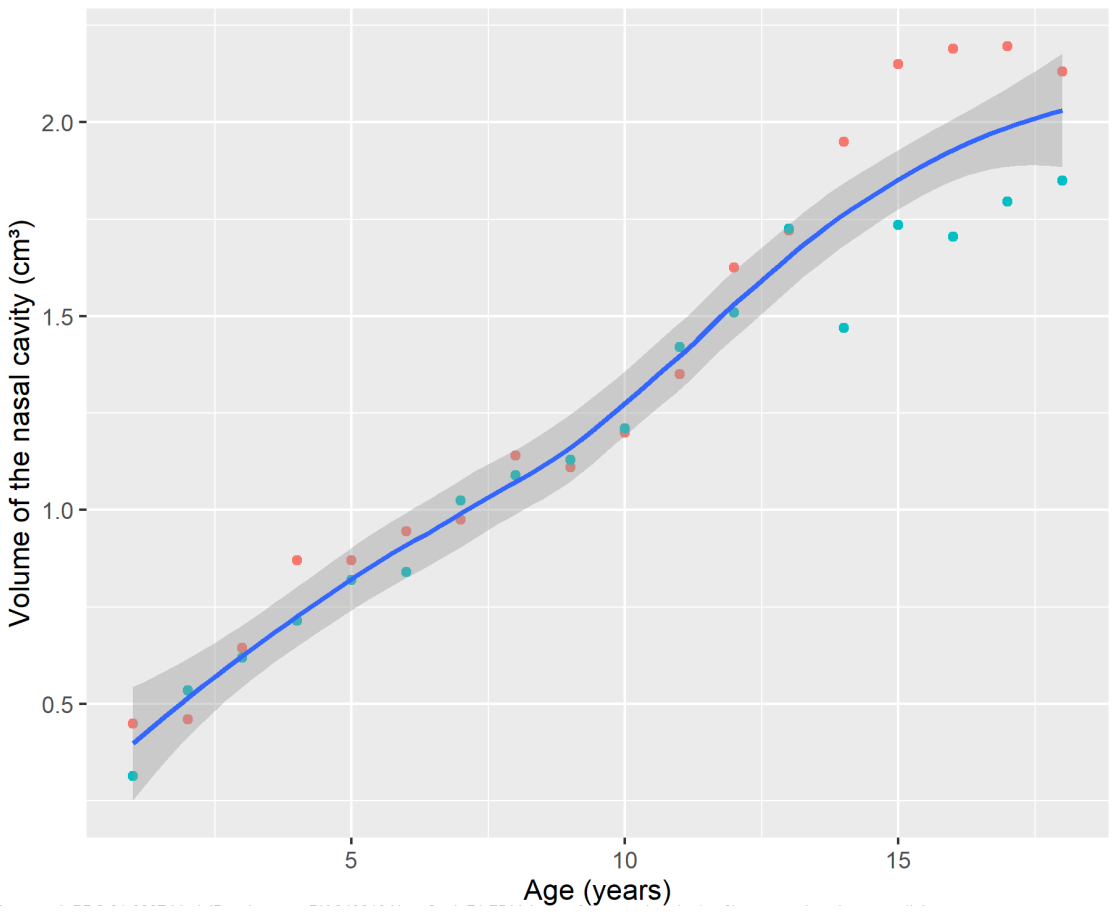
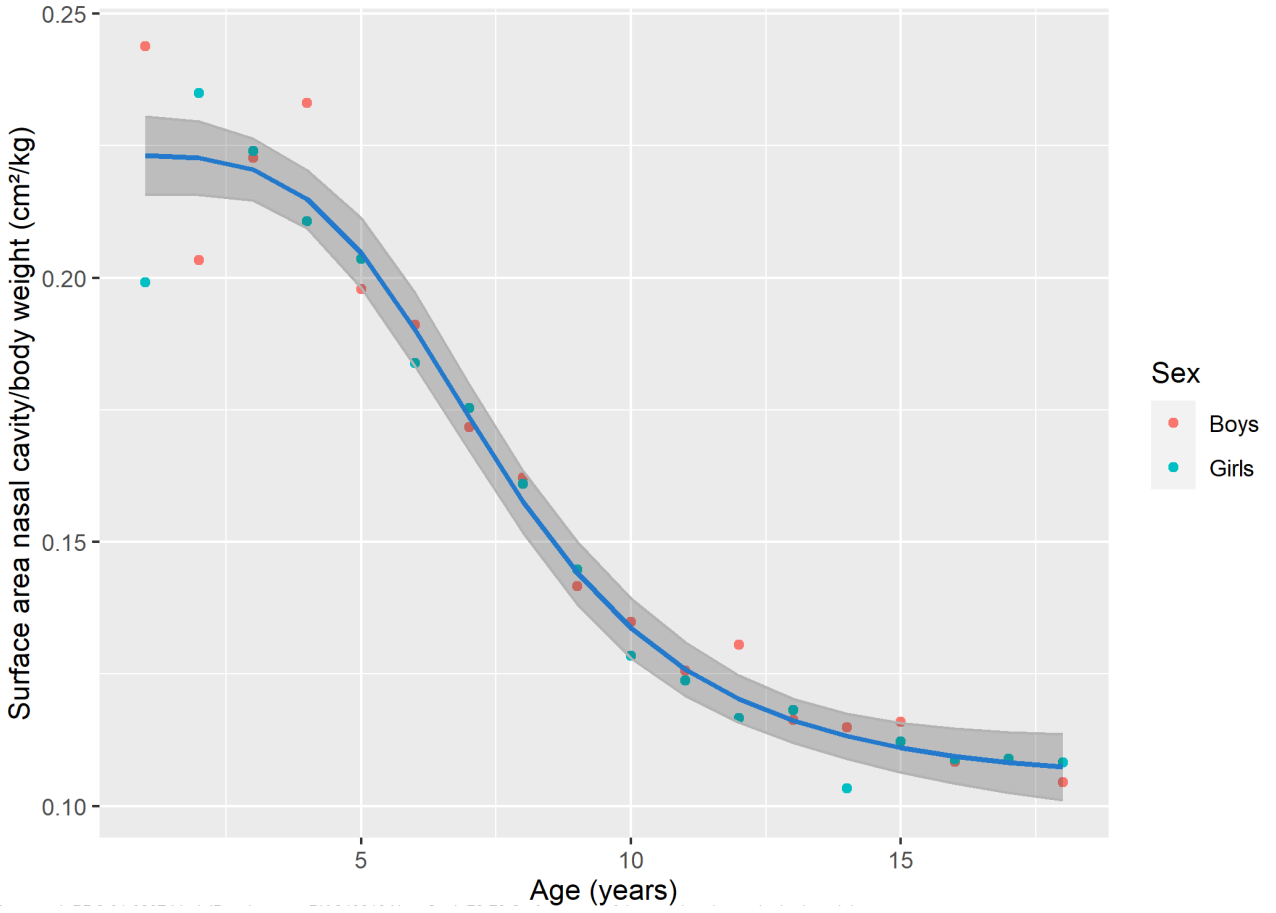
Infants have almost twice the relative nasal surface area compared to adults!





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- Combined adult/paediatric model allows estimating absolute bioavailability
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- Estimated sigmoid E_{max} relationship between bioavailability and age

- PK for sufentanil and ketamine is now well described

Proposed posology

Weight (kg)	Approx. age (years)	Sufentanil 60 µg/ml + ketamine 60 mg/ml, 50 µl/spray	Sufentanil 90 µg/ml + ketamine 90 mg/ml, 100 µl/spray	Dose: sufentanil µg/ ketamine mg	Dose range: sufentanil µg/kg, ketamine mg/kg
10 - <15	1 - 3	2 sprays		6 µg/6 mg	0.40-0.60 µg/kg, 0.40-0.60 mg/kg
15 - <20	3 – 5	3 sprays		9 µg/9 mg	0.45-0.60 µg/kg, 0.45-0.60 mg/kg
20 - <30	5 – 9	4 sprays		12 µg/12 mg	0.40-0.60 µg/kg, 0.40-0.60 mg/kg
30 -<45	9 – 13		2 sprays	18 µg/18 mg	0.40-0.60 µg/kg, 0.40-0.60 mg/kg
≥45	>13		3 sprays	27 µg/27 mg	0.45-0.60 µg/kg, 0.45-0.60 mg/kg

- Nose spray device in two strengths
- Number of sprays determined by body weight: similar dose per kg across weight bands
- Additional dose at 15 min if efficacy is insufficient

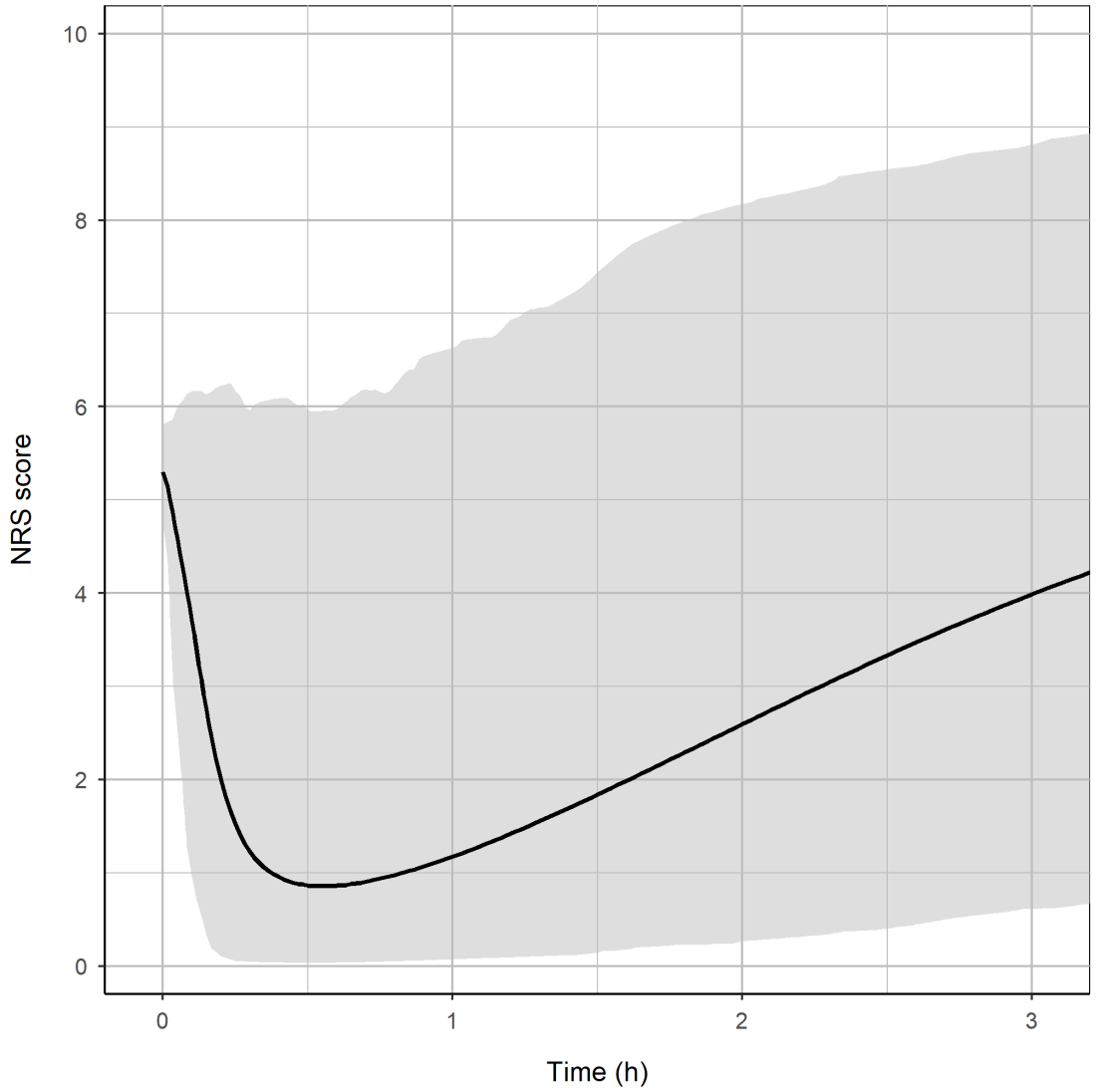
Answers to four questions

- Individuals are simulated (using rxode2) to obtain concentration and pain profiles

- Simulation can provide answers to the following questions:
  - Do we have the right dose combination?
  - Is it effective?
  - How much opioid do we spare by adding ketamine?
  - Do we need a second dose?

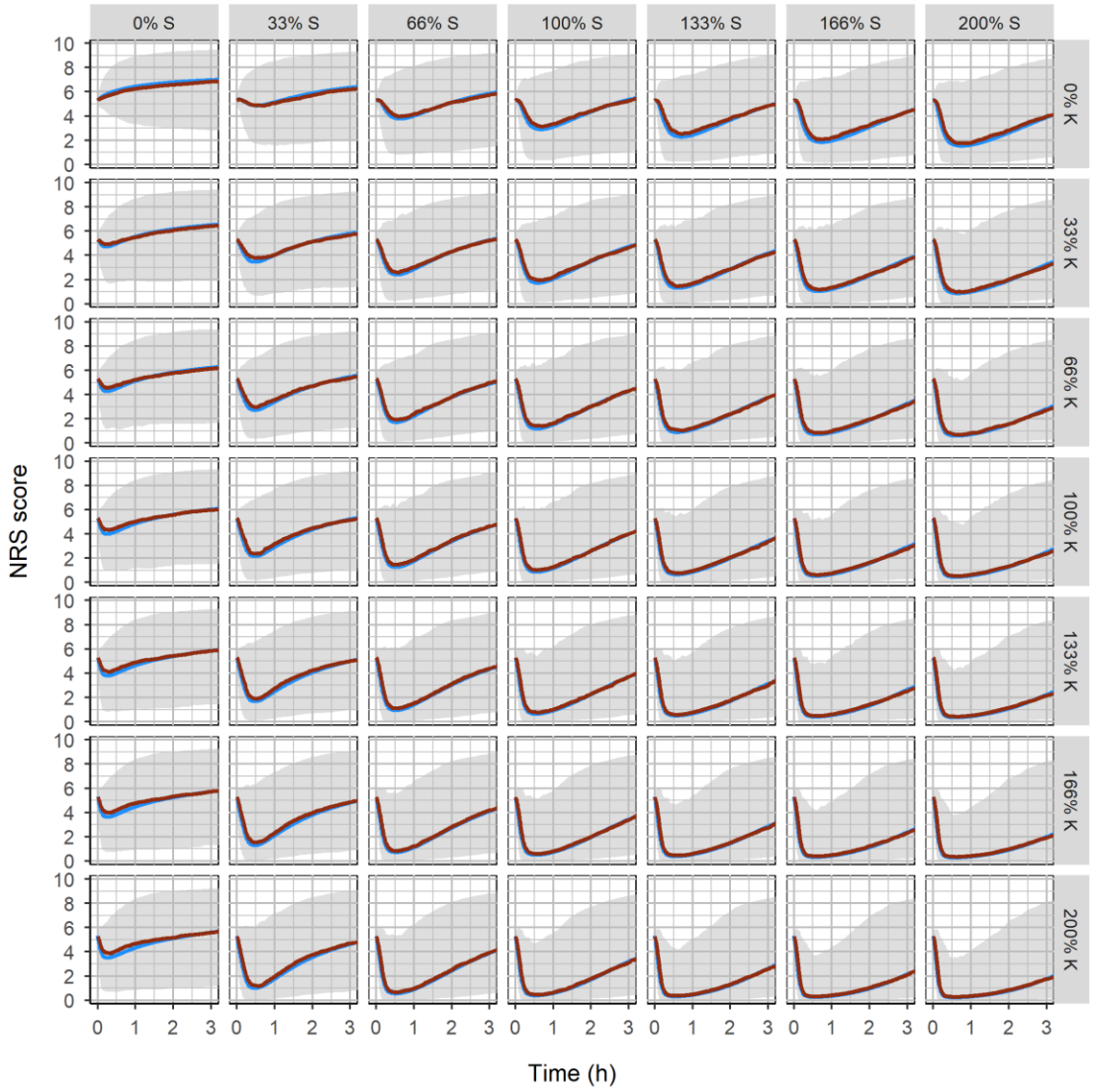
Do we have the right dose combination and is it effective?
Simulated NRS scores using the proposed posology

Single CT001 dose in children. Mean (line) and 90% (area) of simulated NRS scores. The mean is calculated on the logit scale and back-transformed to regular NRS scores.



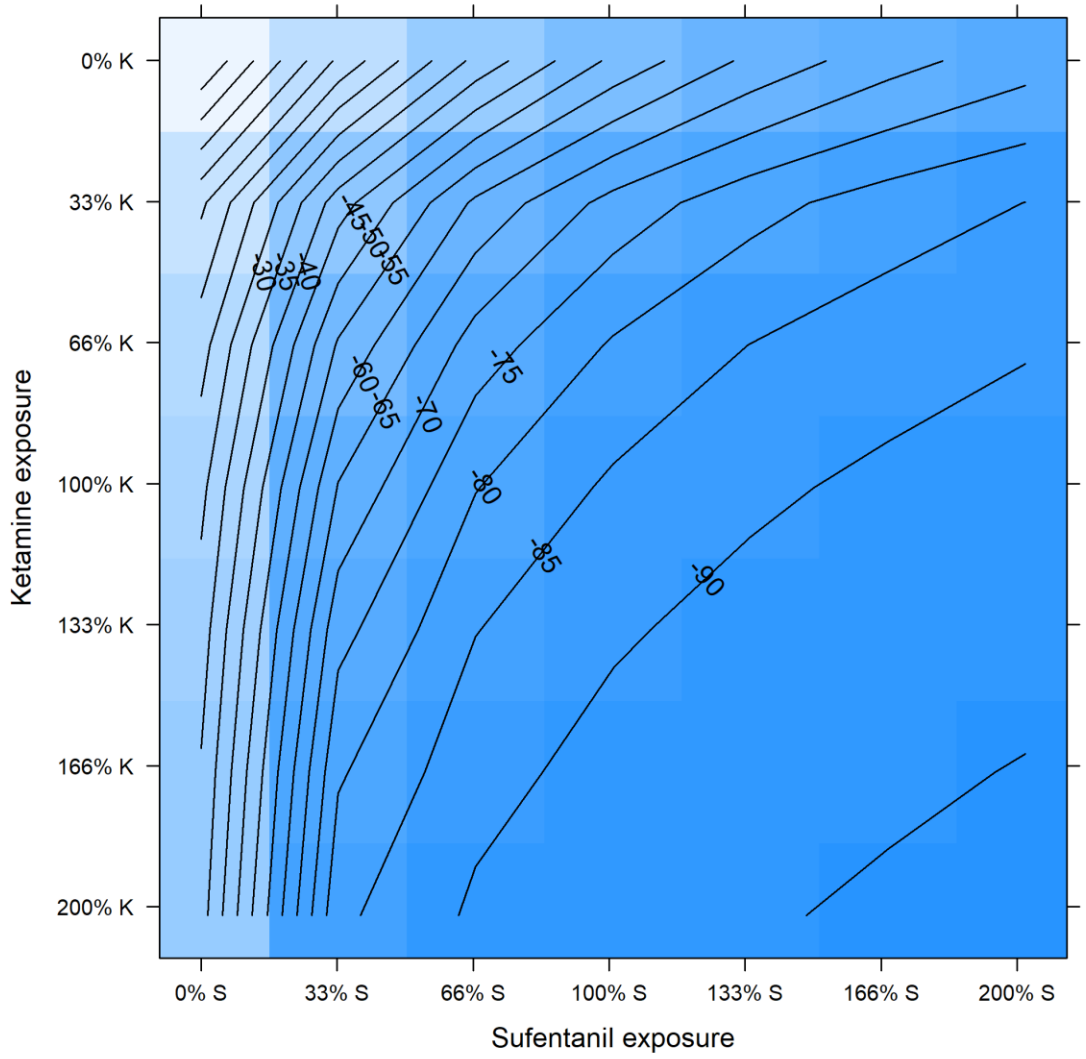
Change sufentanil and ketamine exposure and derive efficacy metrics

Simulated NRS scores for a single dose in children, by sufentanil adjusted exposure percentage (columns) and ketamine adjusted exposure percentage (rows). Median (red line), mean (blue line) and 90% of simulated NRS scores. 100% S and 100% K is the CT001 dose applied using the proposed posology. Zero exposure of sufentanil or ketamine is provided by the 0% panels, and doubling of exposure by the 200% panels. The mean is calculated on the logit scale and back-transformed to regular NRS scores.



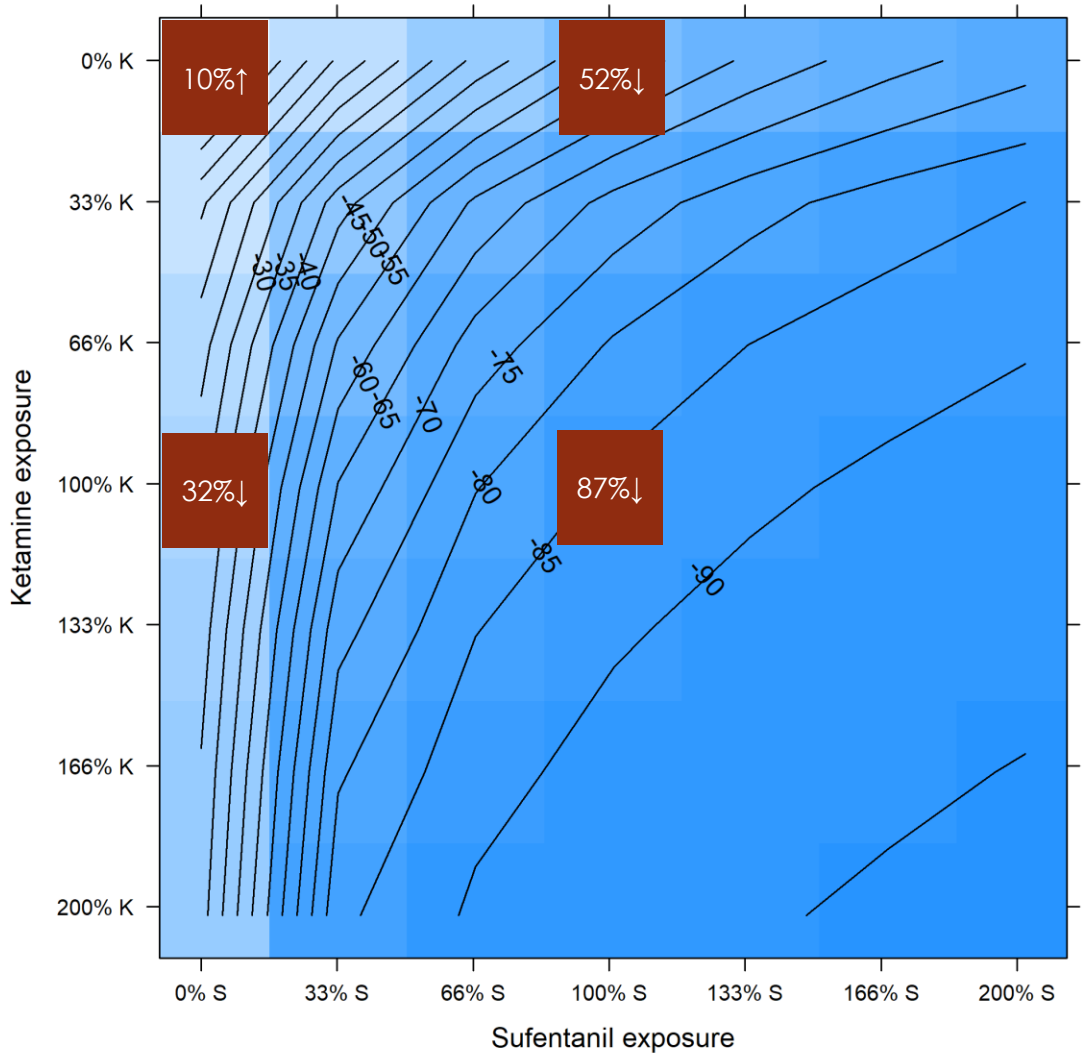
Predicted NRS change at 30 min for the different exposure modifications

Mean percentage change in NRS scores at 30 min after a single dose in children by sufentanil adjusted exposure percentage (x-axis) and ketamine adjusted exposure percentage (y-axis)
100% S and 100% K is the CT001 dose applied using the proposed posology. Zero exposure of sufentanil or ketamine is provided by the 0% cells, and doubling of exposure by the 200% cells.
Mean percentage is calculated by back-transforming the difference of log-transformed values at baseline and 30 min.



CT001: 87%↓ ; sufentanil alone: 52%↓ ; ketamine alone: 32%↓ ; placebo: 10%↑

The simulated pain reduction in NRS in children using the proposed posology was 87% (76%/92%) with a 95% CI for n=37. Corresponding values with only sufentanil exposure were 52% (34%/65%) and only ketamine exposure were 32% (12%/47%), with a 10% (1%/20%) increase for placebo



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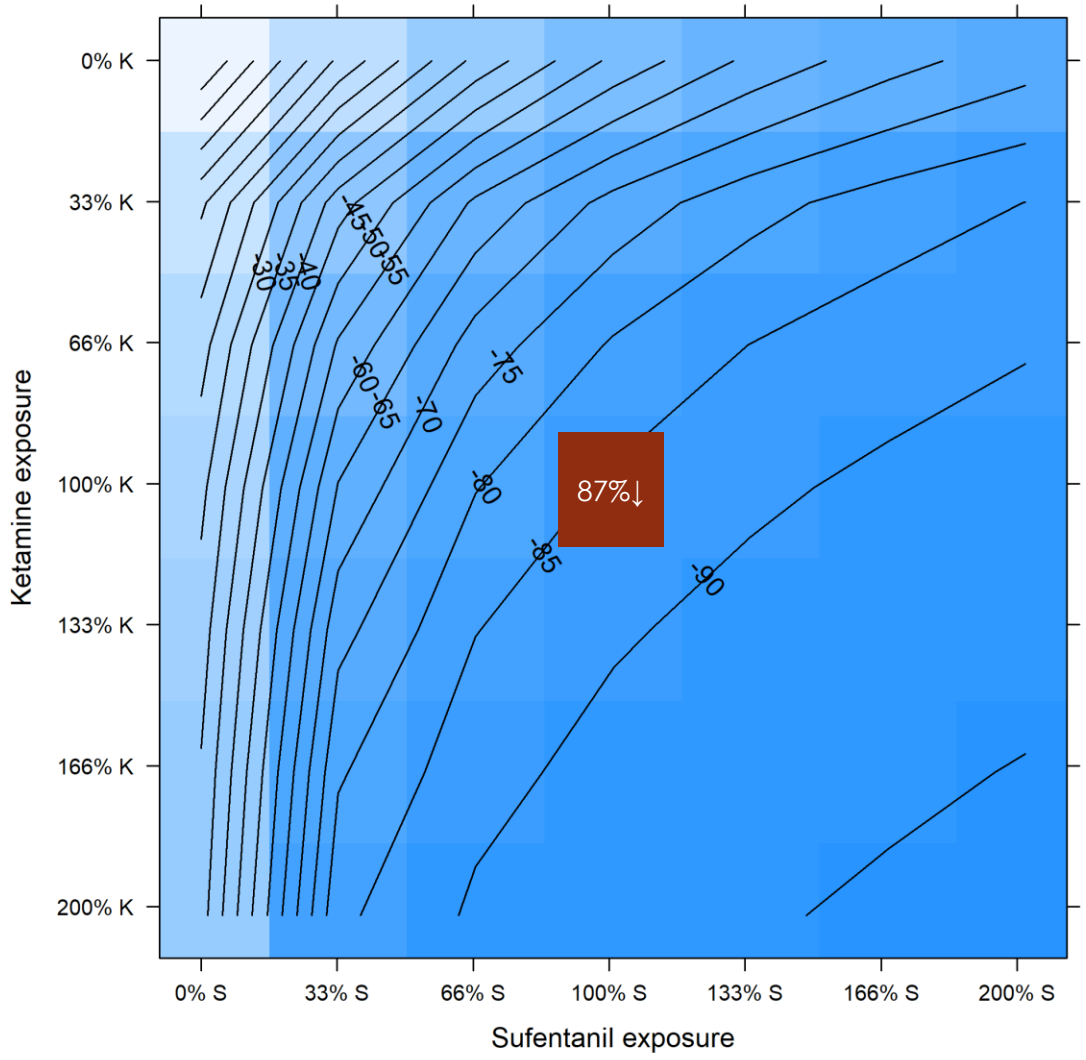
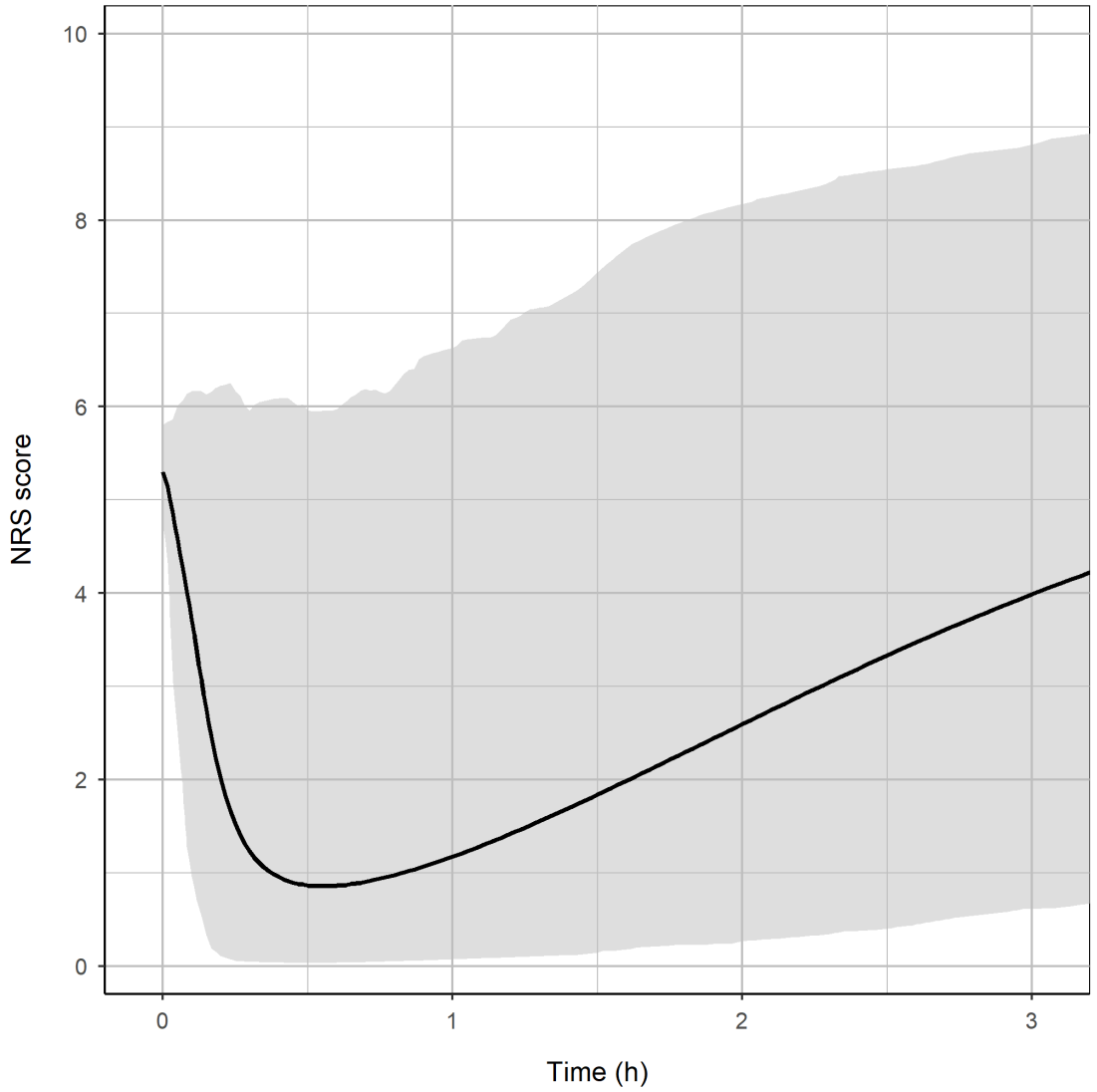
- Increasing sufentanil or ketamine exposure in children would lead to only small increases in pain reduction
- Decreasing exposure would quickly result in insufficient effects

- The proposed posology sits at a good location on the response surface, and is effective



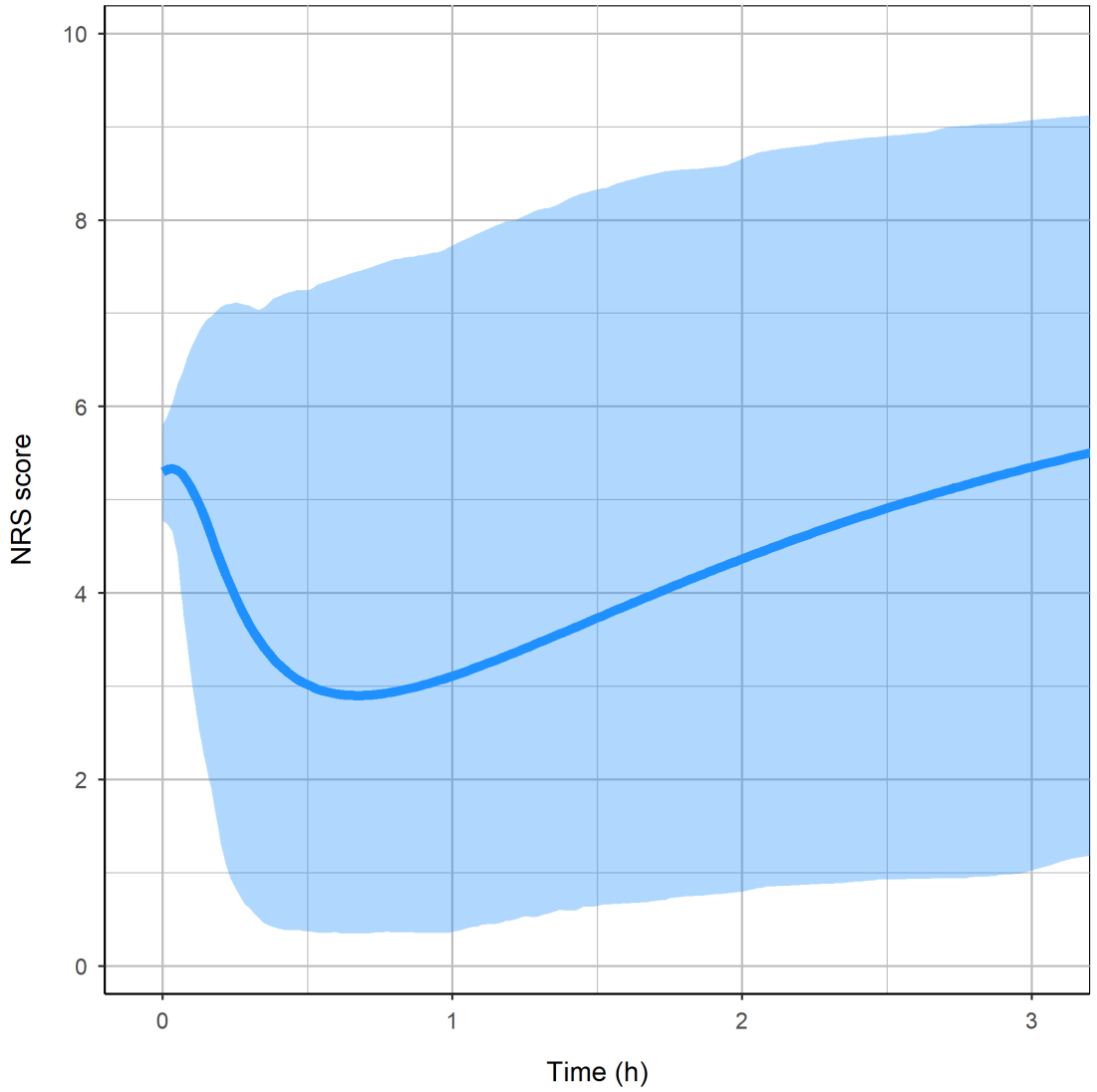
How much opioid do we spare by adding ketamine?
Simulated NRS scores with the proposed posology

Single CT001 dose in children. Mean (line) and 90% (area) of simulated NRS scores. The mean is calculated on the logit scale and back-transformed to regular NRS scores.



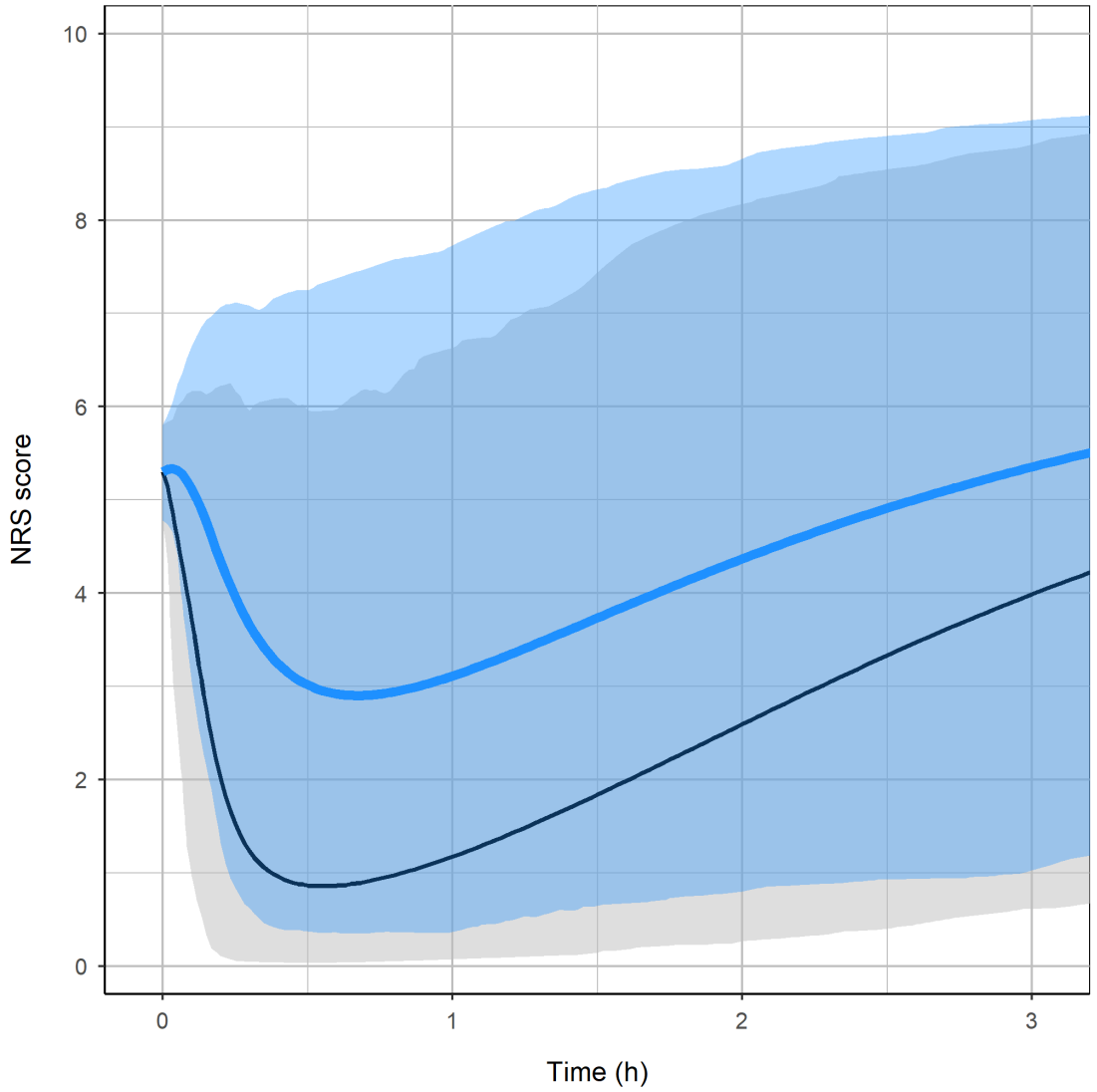
Simulated NRS scores after taking out the ketamine

Mean (line) and 90% (area) of simulated NRS scores. The mean is calculated on the logit scale and back-transformed to regular NRS scores.



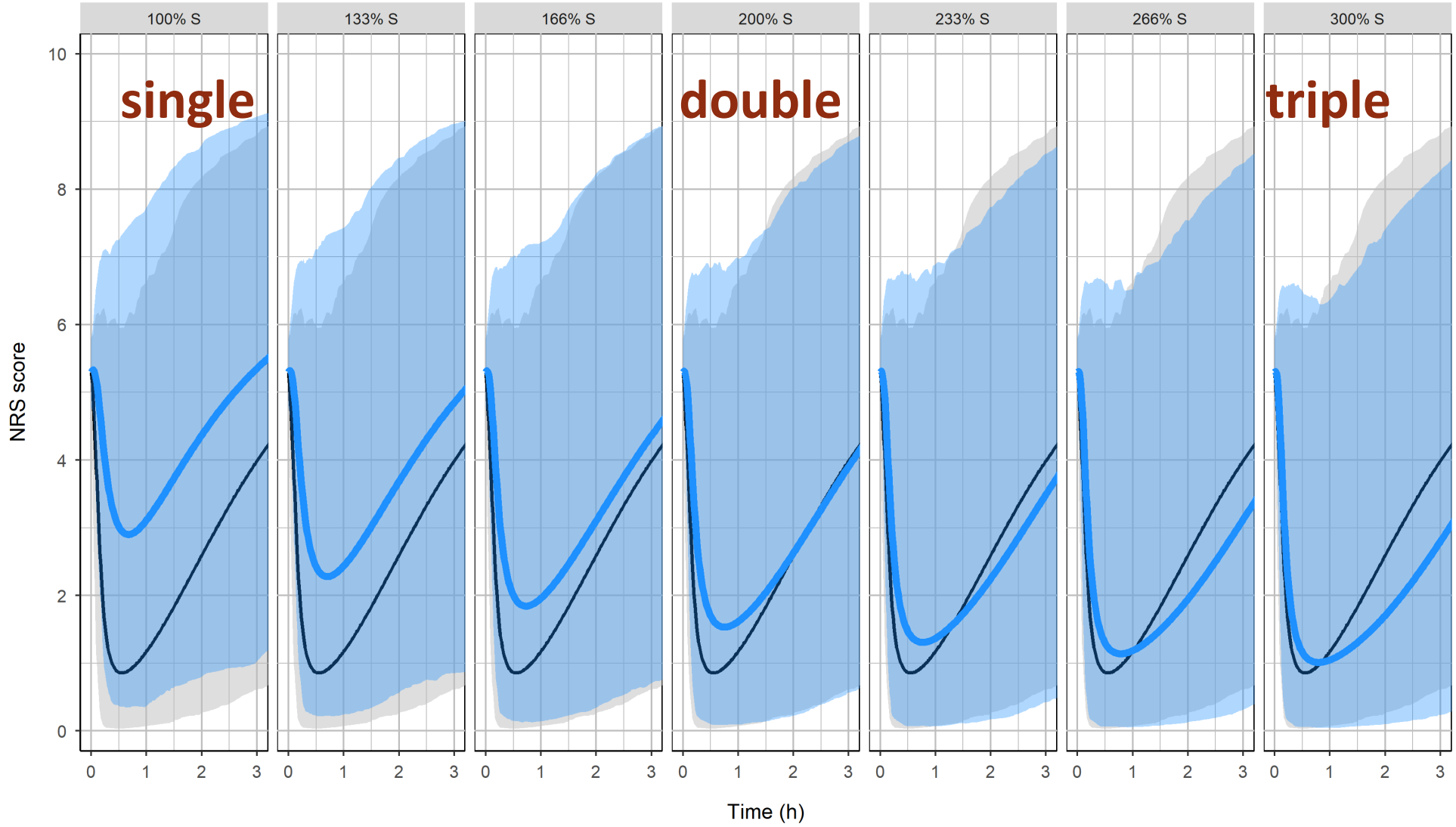
With the CT001 profile in the back as target: how much more sufentanil would we need to give if we left out ketamine?

Mean (lines) and 90% (areas) of simulated NRS scores. The mean is calculated on the logit scale and back-transformed to regular NRS scores.



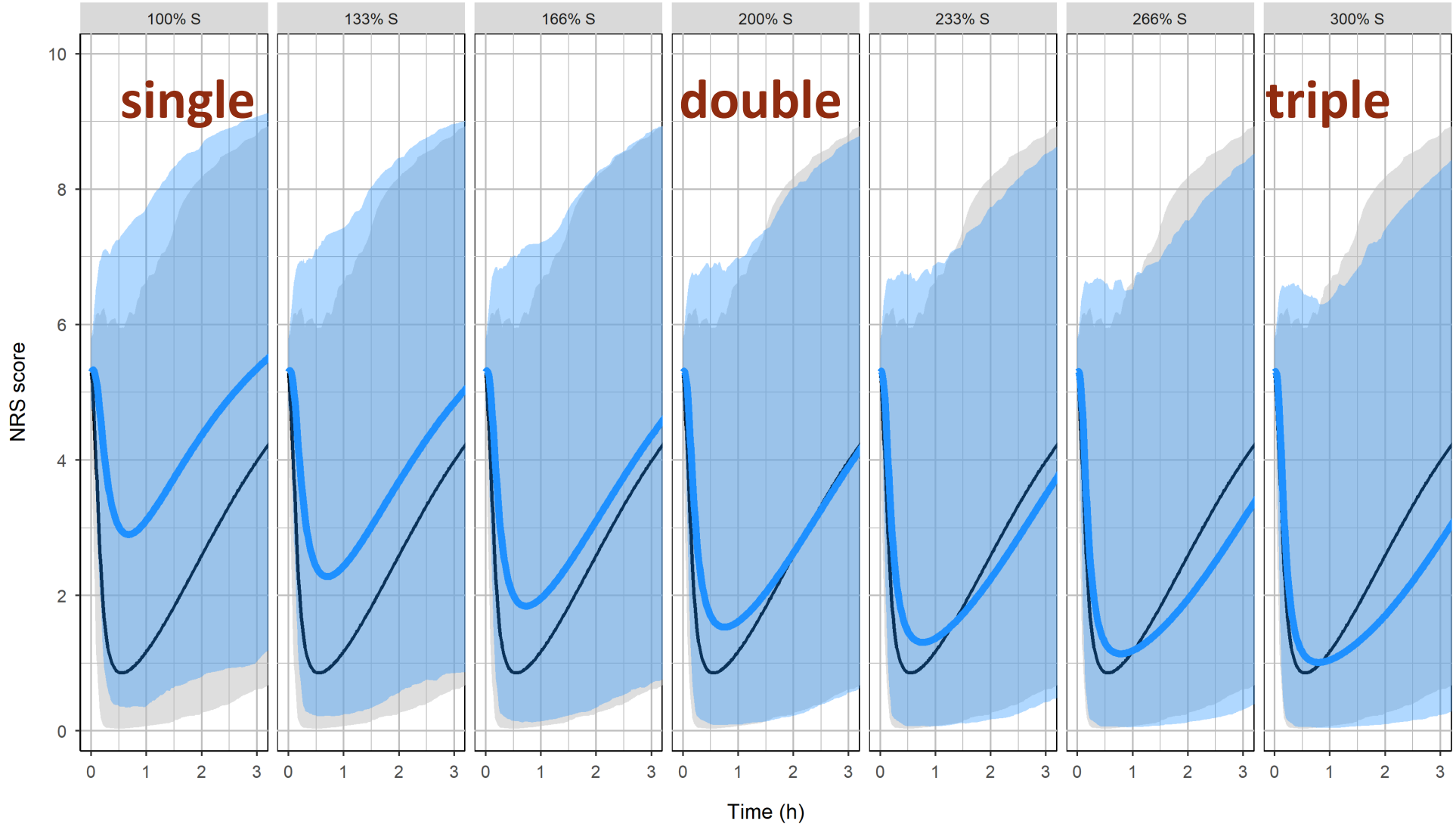
Increasing sufentanil exposure without ketamine in 33% steps

Mean (lines) and 90% (areas) of simulated NRS scores. 100% S is the sufentanil dose applied using the current dosing schedule, 200% and 300% are a doubling and tripling of sufentanil exposure. The black lines and grey areas are the values for CT001, provided as reference for the panels (same line and area for all panels)



We need more than double the sufentanil exposure for the same overall effect

Mean (lines) and 90% (areas) of simulated NRS scores. 100% S is the sufentanil dose applied using the current dosing schedule, 200% and 300% are a doubling and tripling of sufentanil exposure. The black lines and grey areas are the values for CT001, provided as reference for the panels (same line and area for all panels)



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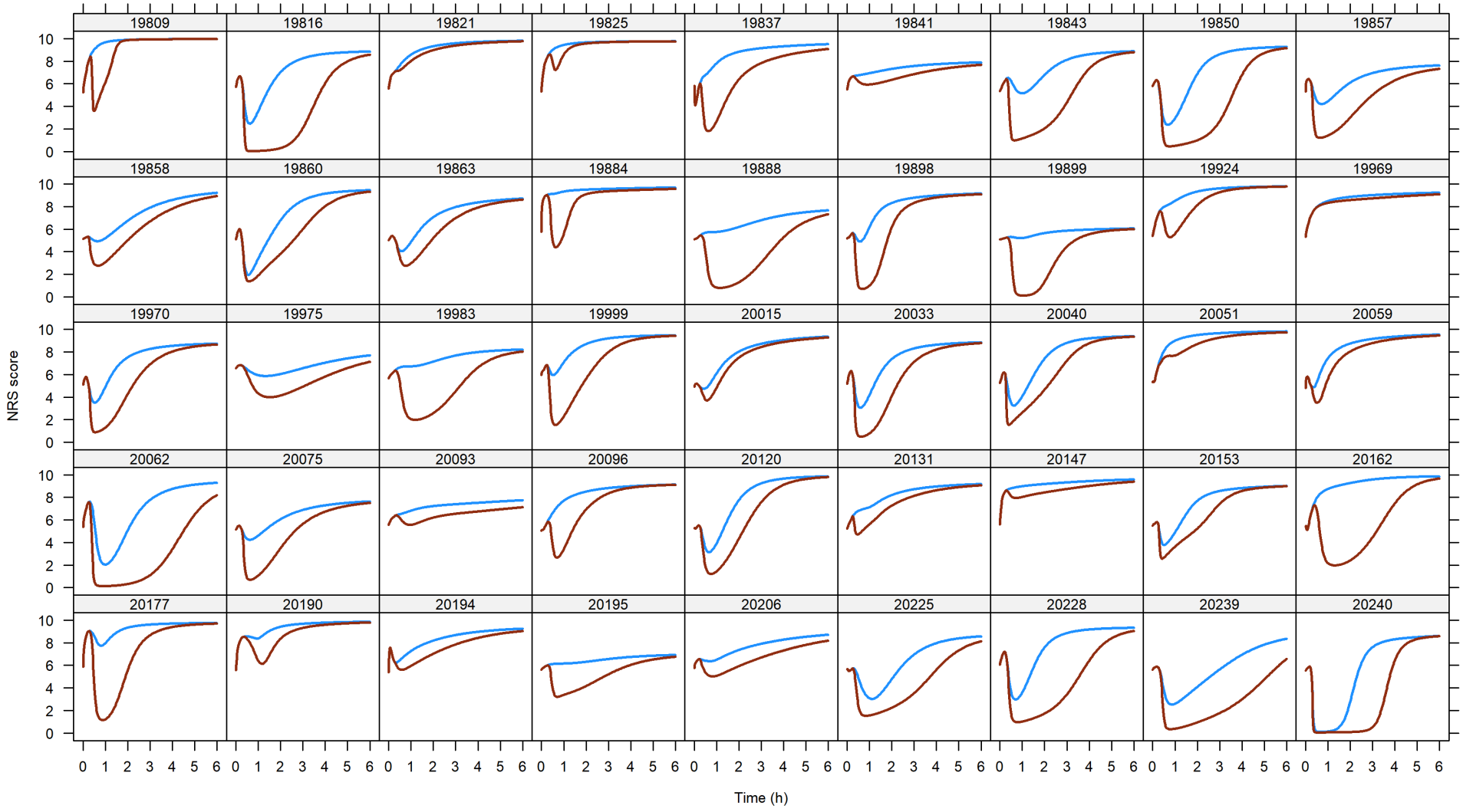
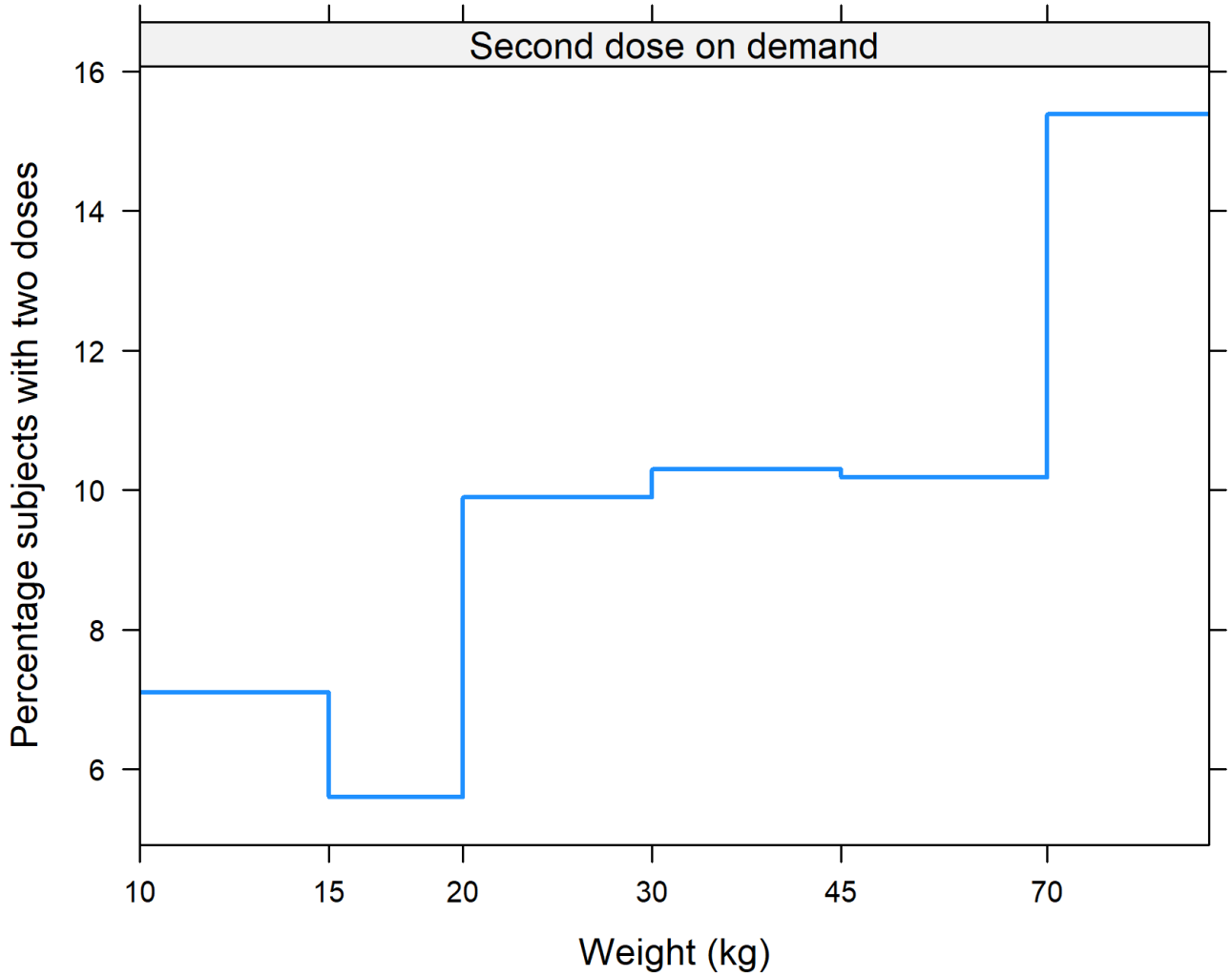
Do we need a second dose?

Example simulated NRS profiles in children where a second dose was given (red line) when no decrease in NRS was observed after 15 min for a single dose (blue line)



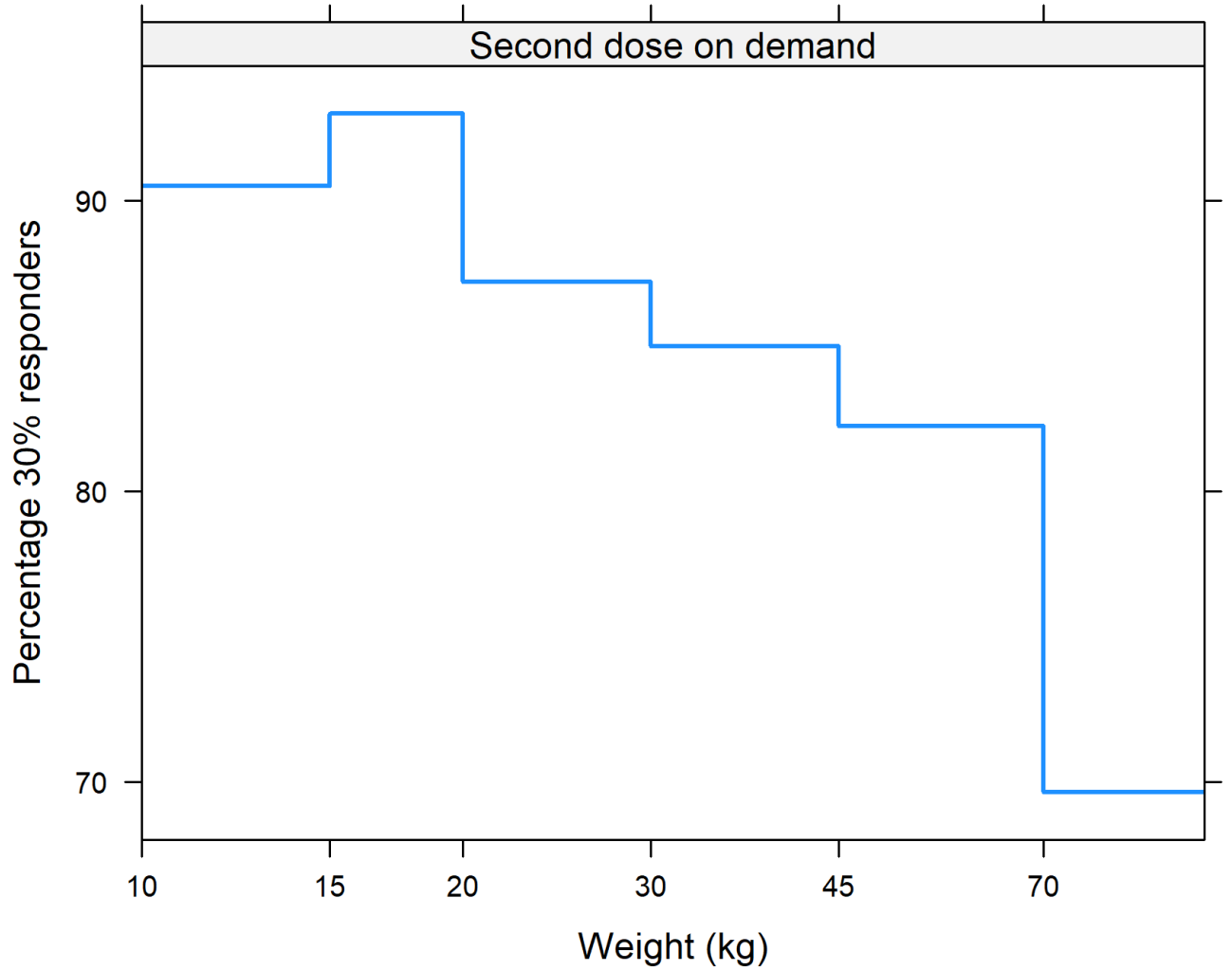
On average only 9% of children are predicted to need a second dose

Percentage of subjects with two doses for the proposed posology with a second dose at 15 min if change in NRS at 15 min is ≥0.



Predicted percentage responders is high: 80-90% for 10-70kg

Percentage of 30% responders for the proposed posology with a single dose and with a second dose on demand by body weight. 30 % responders are identified as subjects with predicted change in NRS >30% or an NRS score ≤3 at 30 min. Single dose: single dose at time zero, Second dose on demand: second dose at 15 min if change in NRS at 15 min is ≥0. The % predicted responders (with a second dose if necessary) was 90% for <15kg, 93% for 15-<20kg, 87% for 20-<30kg, 85% for 30-<45kg, and 79% for ≥45kg.



Conclusions

- Addition of ketamine increases efficacy and spares opioids
- The proposed posology of CT001 in children is expected to provide adequate pain relief
- Dose-changes of either ketamine or sufentanil are not suggested to lead to an improved efficacy profile

- The registration of CT001 as a safe and efficacious non-invasive treatment will likely improve the clinical management of pain in children