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FLUIDS EXCLUSIVELY ENTERAL FROM DAY 1

Fluids exclusively enteral from day one (FEED1) versus gradual feeding in preterm infants: a randomised, open-lbel, superiority trial

Authors: Shalini Ojha, Eleanor J Mitchell, Mark J Johnson, Chris Gale, William McGuire, Sam Oddie, Sophie Hall, Garry Meakin, Josie Anderson, Christopher Partlet, Yuanfei Su, Samanthan Johnson, Kate Walker, Reuben Ogollah, Hema Mistry, Seyran Naghdi, Alan Montgomery, Jon Dorling

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Fluids exclusively enteral from day one (FEED1) versus gradual feeding in preterm infants: a randomised, open-label, superiority trial

To access full publication: DOI: 10.1016/S2352-4642(25)00271-8
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For more information about the trial: www.feed1.ac.uk

Contact: shalini.ojha@Nottingham.ac.uk
feed1@Nottingham.ac.uk

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Background

Infants born preterm or low birth weight are typically initially given intravenous fluids or parenteral nutrition.

Milk feeds started at small volumes and gradually increased.

- perception that feeding too soon or too fast could increase the risk of necrotising enterocolitis (NEC)

Feeding milk faster does not increase the risk of adverse outcome.

Incidence of NEC reduces with increasing gestational age

- <1% of infants born ≥30 week develop severe NEC.

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Background

In infants born at 1,000 to 1,500 g weight, **early full milk feeding** could improve growth and reduce the length of hospital stay compared with delayed or gradual incremental feeds without increasing the risk of complication.

- 4 studies,
- 436 infants,
- Length of hospital stay
  - median difference (95% CI) -3·07 (-4·13 to -2·02) days
- No difference in
  - NEC
  - Hypoglycaemia
  - Death

Reference: Walsh et al., *Cochrane Database Syst Rev*; **2020**. DOI:10.1002/14651858.CD013542.pub2.

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Background

In infants born at 1,000 to 1,500 g weight, **early full milk feeding** could improve growth and reduce the length of hospital stay compared with delayed or gradual incremental feeds without increasing the risk of complication.

- Uncertain evidence: small number of infants included
- All single centre studies conducted in India
  - unclear if the results would be generalisable to high resource settings

Reference: Walsh et al., *Cochrane Database Syst Rev*; **2020**. DOI:10.1002/14651858.CD013542.pub2.

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Aim

to determine, whether, in infants

- born at 30 weeks and 0 days to 32 weeks and 6 days
- full milk feeds from day 1 (within three hours of birth)
- reduces the length of hospital stay
- compared to gradual milk feeding with supplemental intravenous fluids or parenteral nutrition.

Reference: Ojha et al., *Lancet Child and Adolescent Health 2025*. DOI: 10.1016/S2352-4642(25)00271-8

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Methods: trial design

prospective, open-label, parallel-group, multicentre, randomised, superiority trial

46 neonatal units
in England, Scotland and Wales

Reference: Ojha et al., *Lancet Child and Adolescent Health 2025*. DOI: 10.1016/S2352-4642(25)00271-8

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Methods: inclusion criteria

- born at 30 weeks and 0 days to 32 weeks and 6 days, inclusive
- Infants <3hours (180 minutes) since recorded time of birth

Infants requiring respiratory support (such as via continuous positive airway pressure) or other supportive treatments were included if the attending clinician was in equipoise about the infant being randomised to either the “full milk” or the “gradual milk” arm.

Reference: Ojha et al., *Lancet Child and Adolescent Health 2025*. DOI: 10.1016/S2352-4642(25)00271-8

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Methods: exclusion criteria

- Infant with known congenital abnormalities of the gastrointestinal tract or other congenital conditions that make enteral feeding unsafe
- Infant who are small for gestational age (birth weight <10th centile) AND evidence of reversed end-diastolic flow on antenatal umbilical artery Doppler ultrasound*
- Mother has participated in the trial during a previous pregnancy

*Small for gestational age infants with antenatal Doppler ultrasound scan showing absent umbilical artery flow or whose mothers did not have antenatal umbilical Doppler ultrasound were eligible for the trial if they meet the other inclusion criteria.

Reference: Ojha et al., *Lancet Child and Adolescent Health 2025*. DOI: 10.1016/S2352-4642(25)00271-8

Methods: outcomes

Primary outcome

- Length of hospital stay
    - in days
    - defined as the total duration in any neonatal unit measured from day of birth to the day of discharge home, from neonatal care

Reference: Ojha et al., *Lancet Child and Adolescent Health 2025*. DOI: 10.1016/S2352-4642(25)00271-8

Methods: outcomes

Primary outcome

- Length of hospital stay
    - in days
    - defined as the total duration in any neonatal unit measured from day of birth to the day of discharge home, from neonatal care

Secondary outcome

- Time until objective discharge criteria were met
    - current weight at least 1700g
    - ability to take at least one suck feed assessed as adequate
    - not receiving additional temperature support for at least 24 h

Reference: Ojha et al., *Lancet Child and Adolescent Health 2025*. DOI: 10.1016/S2352-4642(25)00271-8

Methods: outcomes

Key secondary outcomes

- Survival to discharge
- Necrotising enterocolitis* (Bells stage 2 or 3)
- Incidence of late onset sepsis – microbiologically confirmed or clinically suspected
- Hypoglycaemia*
- Breastfeeding own mother's milk at discharge

*pre-designated safety outcomes

Reference: Ojha et al., *Lancet Child and Adolescent Health 2025*. DOI: 10.1016/S2352-4642(25)00271-8

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Methods: outcomes

Secondary outcomes

- Time taken to maintain full enteral feeding (defined as at least 140 ml/kg/day for three consecutive days)
- Time to regain birth weight
- Growth (z scores for gestational age at hospital discharge (as per UK-NICM growth charts))
  - weight
  - length
  - head circumference
- Number of days of
  - peripheral cannula
  - parenteral nutrition
  - central lines
- Number of
  - intravenous cannula inserted
  - central venous lines
- Retinopathy of prematurity until discharge
- Chronic lung disease until discharge
- Brain injury on imaging until discharge (Grade 1-4 intraventricular haemorrhage)

Reference: Ojha et al., *Lancet Child and Adolescent Health 2025*. DOI: 10.1016/S2352-4642(25)00271-8

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Methods: outcomes

Secondary outcomes – follow up

6 weeks of age, corrected for preterm birth	2 years of age, corrected for preterm birth
- Survival - Breast-feeding - Mother's breast milk feeding - Parental satisfaction and wellbeing	- Survival without moderate to severe neurodevelopmental impairment

Health economics analysis – reported separately

Reference: Ojha et al., *Lancet Child and Adolescent Health 2025*. DOI: 10.1016/S2352-4642(25)00271-8

Methods: trial procedures

Antenatal or postnatal verbal assent or written consent
Randomised within 3 hours of birth
Unit of **randomisation**: mother

- 1:1 ratio via a secure web-based system
- Minimisation for
  - site
  - single or multiple birth
  - gestation (in weeks) at birth
  - small for gestational age
  - whether intravenous fluids were started prior to randomisation

Blinding: investigators and data analysts

Reference: Ojha et al., *Lancet Child and Adolescent Health 2025*. DOI: 10.1016/S2352-4642(25)00271-8

Methods: trial procedures

Full milk group

- milk feeds within three hours of birth at 60 to 80 ml/kg/day via a gastric tube and continued milk feeds without intravenous fluids or parenteral nutrition

Gradual feeding group

- intravenous fluids or parenteral nutrition and small volumes of milk feeds (maximum of 30 ml/kg/day on day 1) according to local standard practice

All other care was according to local practice.

Reference: Ojha et al., *Lancet Child and Adolescent Health 2025*. DOI: 10.1016/S2352-4642(25)00271-8

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Methods: compliance

Full milk group

- ≤24 hours of intravenous fluids or parenteral nutrition from birth until reaching full enteral feeds

Gradual feeding group

- >24 hours of intravenous fluids or parenteral nutrition from birth to achieving full enteral feeds

We permitted change from the allocated treatment if the infant was unable to tolerate the allocated feeding regimen in the opinion of the attending clinician and recorded this reasoning.

Reference: Ojha et al., *Lancet Child and Adolescent Health 2025*. DOI: 10.1016/S2352-4642(25)00271-8

Methods: data collection

Primary and key secondary outcomes
- Up to hospital discharge

Feeding logs until the infant reached **full enteral feeds** (at least 140 ml/kg/day sustained for three consecutive days)
- intravenous fluid or parenteral nutrition and milk feed volumes
- type of milk (own mother's milk, donor human milk, or formula)
- any measured blood glucose values

At 6 weeks of age corrected for preterm birth

At 2 years of age corrected for preterm birth

Methods: sample size estimation

2,088 infants

length of hospital stay: 20 to 40 days (SD, 9 to16).

- 1778 infants would detect a **between group difference in means of 2 days** with 90% power, 1:1 allocation, and 5% two-sided significance level.
- 15% inflation for multiple birth
- 2% inflation for non-collection of primary outcome data

Reference: Ojha et al., *Lancet Child and Adolescent Health 2025*. DOI: 10.1016/S2352-4642(25)00271-8

Methods: statistical analysis

Baseline demographic and clinical characteristics, summarised with

- counts and percentages for categorical variables
- means and SDs or IQR for continuous variables.

Intention-to-treat analysis

Infants who died prior to discharge were not included in the analysis of the primary outcome but were included in other outcome analyses.

Subgroup analyses

- completed weeks of gestation at birth
- small for gestational age

Reference: https://www.feed1.ac.uk/documents/newsletters/feed1-statistical-analysis-plan-final-v2.0-03feb2025.pdf

Methods: regulations

Funder: NIHR (HTA17/94/31)

Sponsor: University Hospitals of Derby and Burton NHS Foundation Trust

Approval: East Midlands Derby Research Ethics Committee (19/EM/0258)

Registration

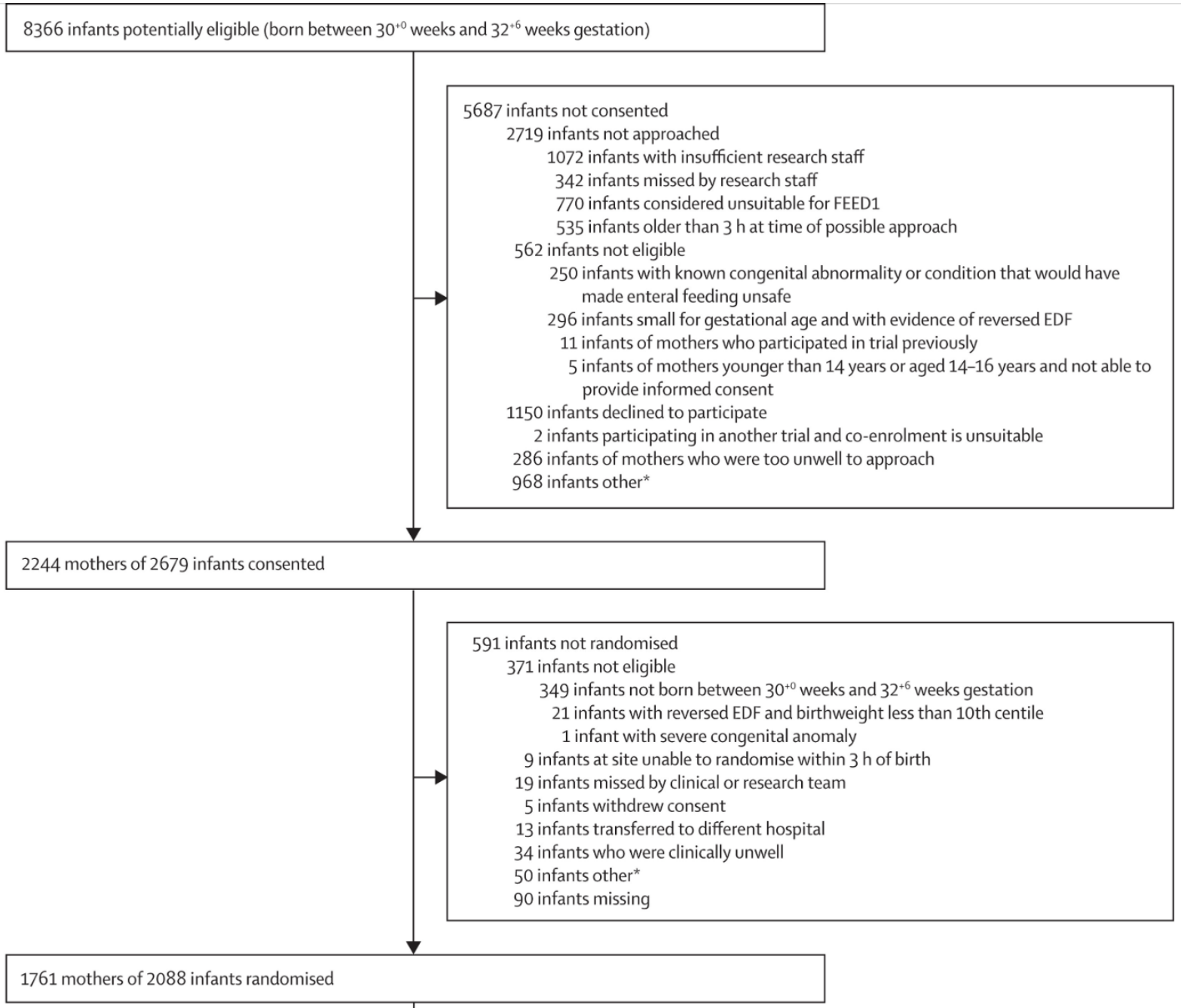
- prospectively registered ISRCTN89654042
- protocol published
- statistical analysis plan is available online.

Independent Data Monitoring Committee

Independent Trial Steering Committee

Reference: Mitchell et al., 2022; doi: 10.1186/s13063-021-05994-z

https://www.feed1.ac.uk/documents/newsletters/feed1-statistical-analysis-plan-final-v2.0-03feb2025.pdf



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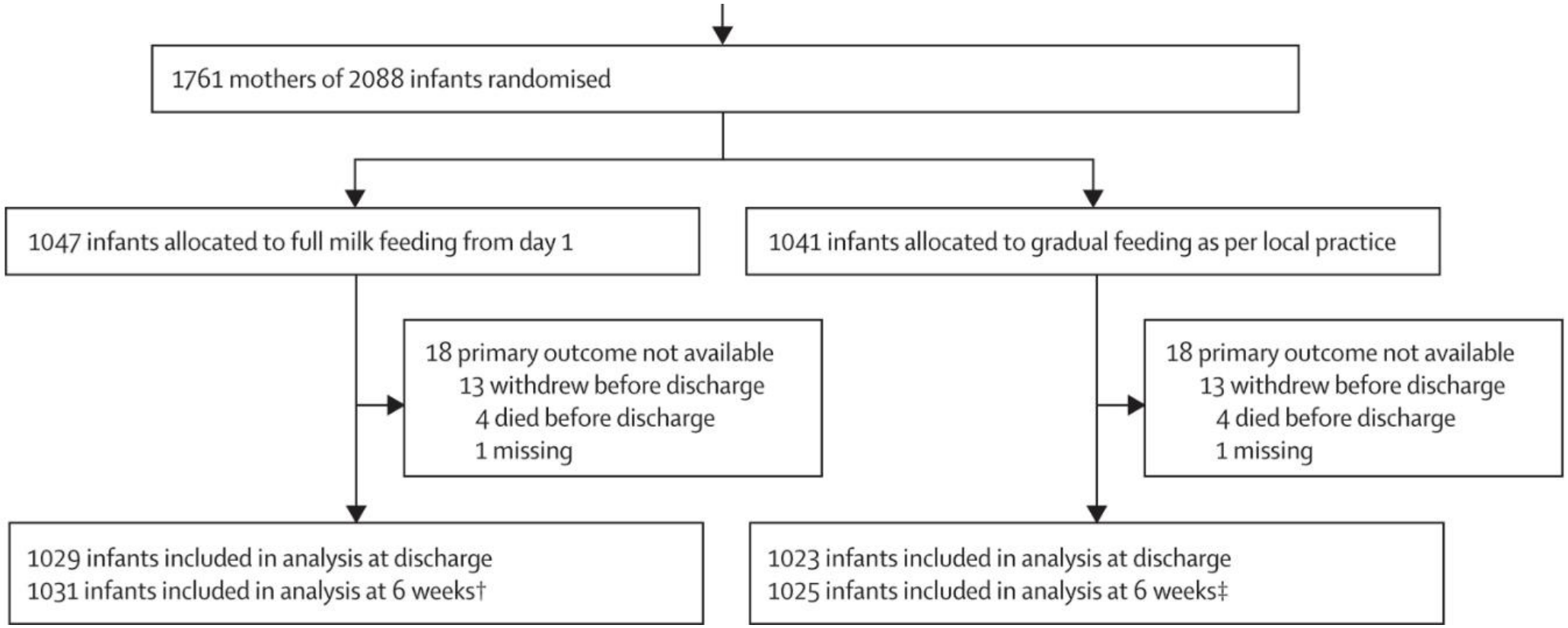

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Results: baseline characteristics

	Full milk (n = 1,047)	Gradual feeding (n = 1,041)
Sex, females	494 (47·2%)	500 (48%)
Age at randomisation (hours), Mean [SD]	1·7 [·8]	1·7 [·8]
Gestational age at birth (weeks), Mean [SD]	31·7 [·8]	31·7 [·8]
30+0 to 30+6	229 (21·9%)	233 (22·4%)
31+0 to 31+6	348 (33·2%)	345 (33·1%)
32+0 to 32+6	470 (44·9%)	463 (44·5%)
Birthweight (grams), Mean [SD]	1626 [301·8]	1617·1 [295·2]
Birthweight less than 10th centile for gestational age	126 (12%)	116 (11·1%)

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Results: baseline characteristics

	Full milk (n = 1,047)	Gradual feeding (n = 1,041)
IV fluids started prior to randomisation	531 (50·7%)	534 (51·3%)
Heart rate >100bpm at 5 mins	983 (95·3%)	981 (95·4%)
Temperature on admission (°C) mean [SD]	36·9 [·5]	36·9 [·4]
Worst base excess within first 24 hours of birth, Mean [SD]	-3·7 [4]	-3·5 [3·7]
Receiving respiratory support at time of randomisation*	831 (80·4%)	821 (79·6%)
Mechanical ventilation	50 (6%)	62 (7·6%)
Continuous positive airway pressure	598 (72%)	594 (72·4%)
High flow oxygen	169 (20·3%)	154 (18·8%)
Any other supplemental oxygen	45 (5·4%)	42 (5·1%)

Reference: Ojha et al., *Lancet Child and Adolescent Health 2025*. DOI: 10.1016/S2352-4642(25)00271-8

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Results: compliance

Full milk group

644 (61·5%) infants received no or ≤24 hours of intravenous fluids or parenteral nutrition

- 214 (20·4%) were fully milk fed from birth and did not receive any intravenous fluid or parenteral nutrition.

Reason for non-adherence

- 130 (12·4%), did not tolerate milk feeds
- 27 (2.6%), abdominal concerns including suspected NEC
- 68 (6.5%), hypoglycaemia
- 5 (0·5 %), changed due to parental choice
- 74 (7·1%), feeds interrupted due to escalation of respiratory support
- 83 (7·9%) had other reasons

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Results: compliance

Gradual feeding group
947 (91%) received >24 hours of intravenous fluids or parenteral nutrition

Reason for non-adherence
- Unable to get intravenous access, 3 (0.3%)
- Clinical reasons, 44 (4.2%)
- No specific reason given

Reference: Ojha et al., *Lancet Child and Adolescent Health 2025*. DOI: 10.1016/S2352-4642(25)00271-8

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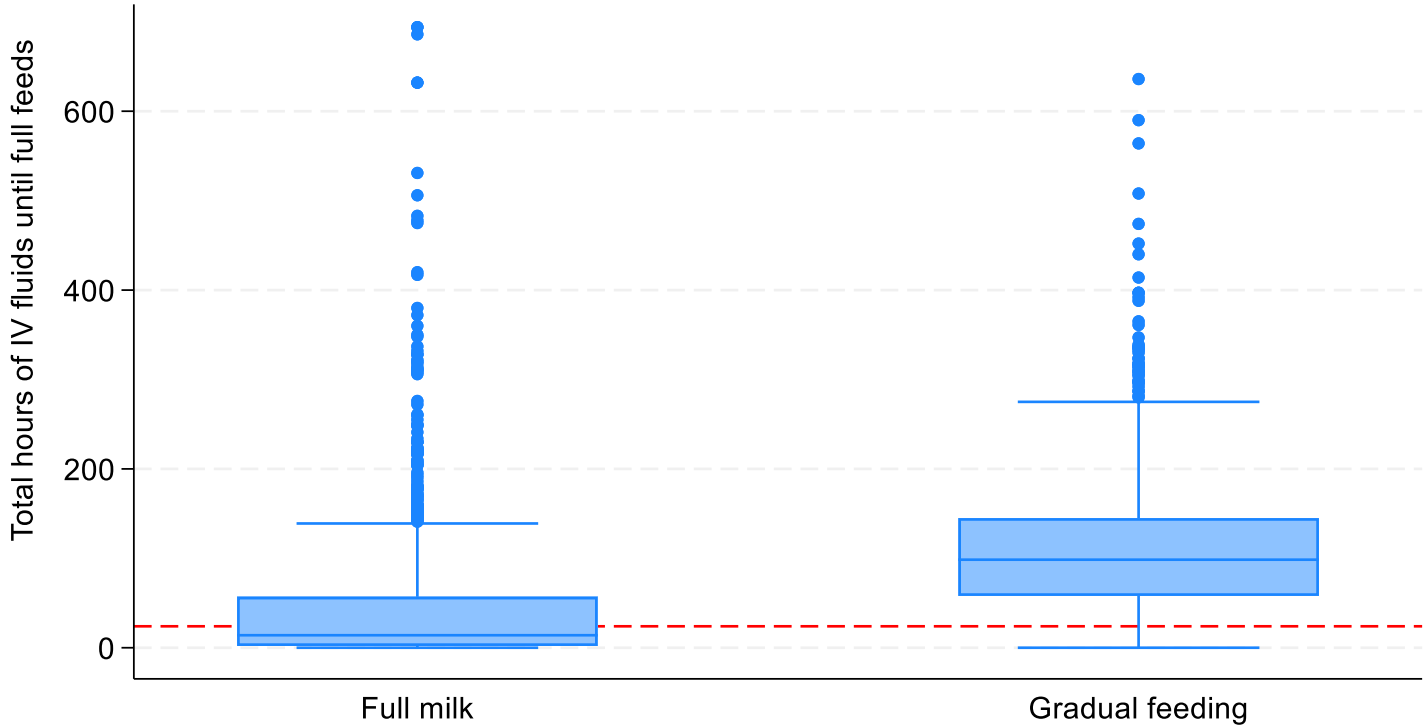
Results: duration of IV nutrition

Duration of intravenous fluids or parenteral nutrition, median (IQR)

- Full milk group, 14 hours (IQR, 55)
- Gradual feeding group, 99 hours (IQR, 87)



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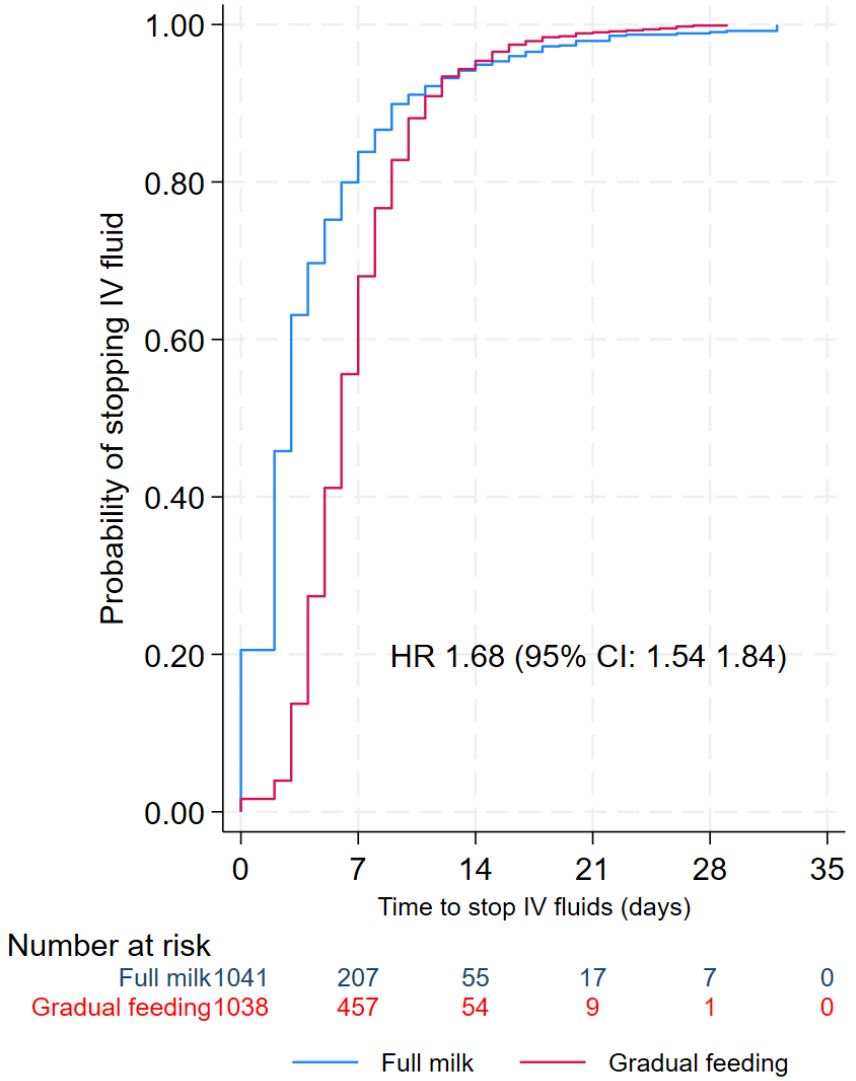
Results: time of full milk feeds

Time to full milk feeds without any intravenous fluids or parenteral nutrition, median (IQR)

Adjusted hazard ratio (95% CI):
1.68 (1.54 to 1.84) days



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Results: time of full enteral feeds

Time to reach full enteral feeds of 140ml/kg/day, in days, mean (SD)

- Full milk group, 7 (3.5)
- Gradual feeding group, 7.9 (3.9)

Adjusted hazard ratio (95% CI)
2.35 (1.91 to 2.89) days

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Results: primary outcome

Length of hospital stay, in days, mean (SD)

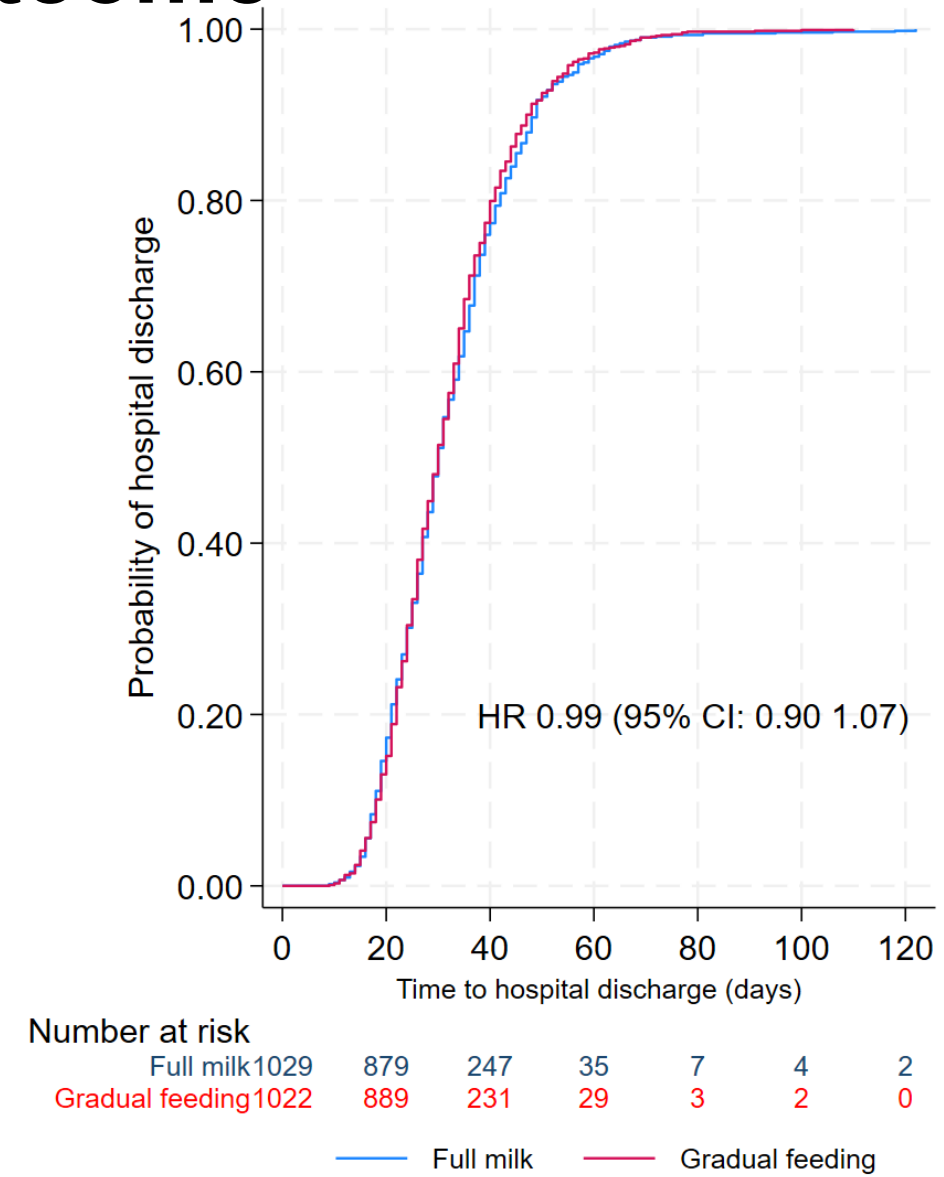
- Full milk group, 32.4 (13.3)
- Gradual feeding group, 32.1 (13.5)

Adjusted difference in means (95% CI)

-0·02 days; (-1·07 to 1·03)
P=0·97

Adjusted hazard ratio (95% CI)

0.99 (0.90 to 1.07)



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Results: key secondary outcomes

	Full milk (n = 1,047)	Gradual feeding (n = 1,041)	
			Risk difference (95% CI)
Survived to discharge	1030 (99·6%)	1027 (99·6%)	-0·004 (-0·54 to 0·53)
Microbiologically-confirmed or clinically suspected late-onset sepsis	32 (3·1%)	25 (2·4%)	0·66 (-0·75 to 2·07)
Necrotising enterocolitis	4 (·4%)	6 (·6%)	-0·19 (-0·80 to 0·41)
Any breastfeeding at discharge	447 (43·6%)	434 (42·5%)	1·51 (-2·47 to 5·49)
			Hazard ratio (95% CI)
Time to objective discharge criteria met (days) mean (SD)	23·2 [10·7]	23 [10·7]	1·07 (·89 to 1·29)
Number of glucose tests <2·2 mmol/L until full feeds, mean (SD)	0.6 (1)	0.5 (0.7)	

Reference: Ojha et al., *Lancet Child and Adolescent Health 2025*. DOI: 10.1016/S2352-4642(25)00271-8

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Results: key secondary outcomes

	Full milk (n = 1,047)	Gradual feeding (n = 1,041)	
	Mean (SD)	**Mean (SD)**	**Difference (95% CI)**
Days parenteral nutrition	1·1 [3·4]	2·7 [7·2]	-1·52 (-1·98 to -1·06)
Number of central venous lines inserted	·2 [·8]	·4 [1]	-0·16 (-0·23 to -0·08)
Days with central line	1 [3·4]	2·1 [7]	-0·87 (-1·31 to -0·42)
Days peripheral cannula	4·3 [3]	5·3 [2·9]	-1·4 (-1·29 to -0·78)
Number of intravenous cannulae inserted	1·6 [1·4]	2·1 [1·8]	-0·52 (-0·66 to -0·38)
Days peripheral cannula	4·3 [3]	5·3 [2·9]	-1·4 (-1·29 to -0·78)
Number of intravenous cannulae inserted	1·6 [1·4]	2·1 [1·8]	-0·52 (-0·66 to -0·38)
Length of stay in intensive care (days)	1 [2·5]	1·8 [3·2]	-0·56 (-0·8 to -0·32)
Length of stay in high dependency care (days)	5·1 [7]	5 [7·3]	0·42 (-0·16 to 1·01)
Length of stay in special care (days)	25·9 [11·3]	24·7 [10]	1·04 (0·2 to 1·88)

Reference: Ojha et al., *Lancet Child and Adolescent Health 2025*. DOI: 10.1016/S2352-4642(25)00271-8

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Results: Outcomes at 6 weeks

	Full milk (n = 1,047)	Gradual feeding (n = 1,041)	
	n (%)	n (%)	Difference (95% CI)
Survival	1031 (99·7%)	1027 (99·6%)	0·09 (-0·41 to 0·60)
Missing	13	10	
Breastfeeding	301 (43·2%)	276 (42%)	
Missing	350	384	
Mother's breast milk fed	370 (53·4%)	314 (48·9%)	
Missing	354	399	

Reference: Ojha et al., *Lancet Child and Adolescent Health 2025*. DOI: 10.1016/S2352-4642(25)00271-8

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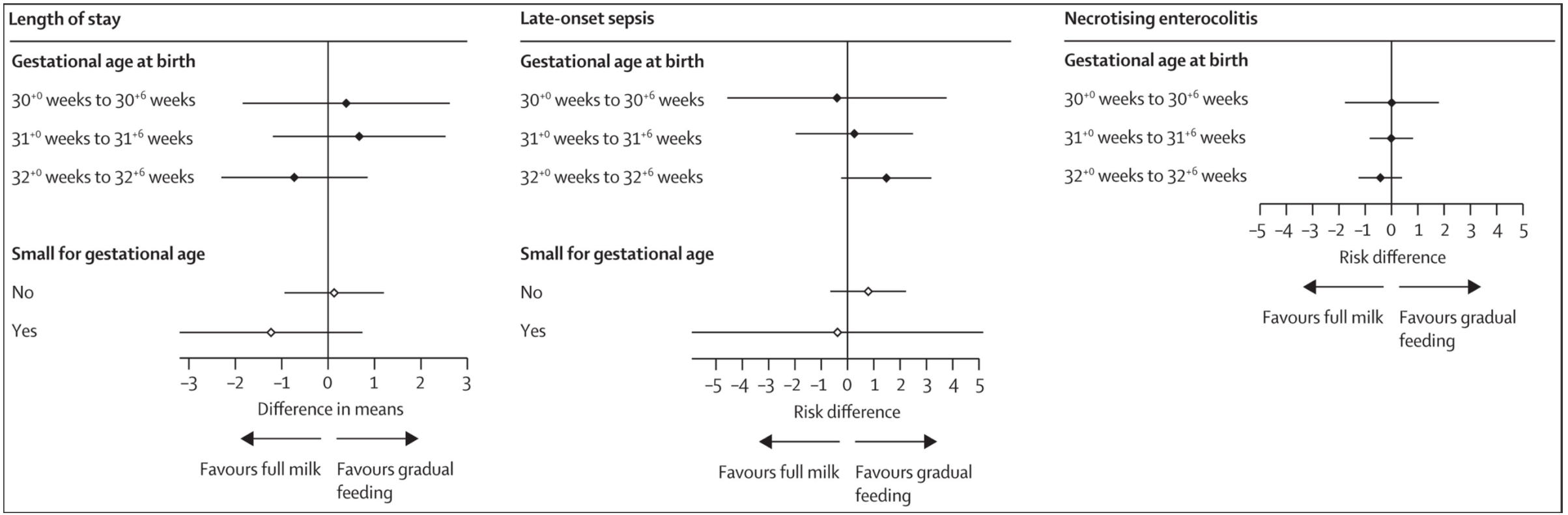
Results: Subgroup analyses



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Discussion

In infants born at 30 weeks and 0 days to 32 weeks and 6 days,
full milk feeds from day 1
did not reduce the length of hospital stay
compared to
intravenous fluids or parenteral nutrition with gradual feeding.

Reference: Ojha et al., *Lancet Child and Adolescent Health 2025*. DOI: 10.1016/S2352-4642(25)00271-8

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Discussion

- Almost 2/3rds were full milk fed on day 1
  - 1 in 5 received no IV fluids or parenteral nutrition
- Infants in the full milk group
  - fed more milk in the first 4 days
  - reached full enteral feeds sooner
  - had fewer intravenous cannulations, central lines, and days of intravenous fluids or parenteral nutrition
  - moved out of intensive care sooner.

without any increased risk of necrotising enterocolitis or other adverse outcomes.

Reference: Ojha et al., *Lancet Child and Adolescent Health 2025*. DOI: 10.1016/S2352-4642(25)00271-8

Discussion

Evidence contrary to findings of previous studies, in different setting

Recent studies from high-income settings: Alsheikh et al.,

- 70 infants born
- 30^{+0} to 33^{+6} weeks gestation
- full feeds within **48 hours** vs. gradual feeding
- length of stay, mean (SD)
  - full milk group: 31.5 (12.9) days
  - gradual feeding group: 39.5 (16.4) days
  - mean difference (IQR), -6·6 days (-12·9 to -0·2)

- Longer stay in gradual feeding group

Reference: Ojha et al., *Lancet Child and Adolescent Health 2025*. DOI: 10.1016/S2352-4642(25)00271-8
Alsheikh et al., J Matern Fetal Neonatal Med 2021. DOI: 10.1080/14767058.2019.1637848

Discussion: other studies

Evidence contrary to findings of previous studies, in different setting

Recent studies from high-income settings: Razzaghy et al.,

- 97 infants
- 28^{+0} to 32^{+6} weeks gestation
- full milk within **72 hours** of birth vs. gradual feeding
- mean length of stay, mean (SD)
  - full milk group: 40 days (SD, 18)
  - gradual feeding group: 47 (SD, 21)

- Larger and more mature infants in the full milk group
- No difference in length of stay after adjusting for these differences

Reference: Ojha et al., *Lancet Child and Adolescent Health 2025*. DOI: 10.1016/S2352-4642(25)00271-8
Razzaghy et al., Arch Dis Child Fetal Neonatal Ed. 2024; DOI: 10.1136/archdischild-2023-325969

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Discussion: strengths

- Recruitment and randomisation within 3 hours (mean 1.7 hours)
- Successful implementation of oral assent pathway
- 26 (1.3%) withdrawal after assent
- >98% follow up to discharge
- Follow up after discharge home

Reference: Ojha et al., *Lancet Child and Adolescent Health 2025*. DOI: 10.1016/S2352-4642(25)00271-8

Discussion: limitations

- Variation in feeding practices between sites
  - Feeding protocols not mandated
  - Feed interruptions allowed as per local protocols and clinical judgement
  - Pragmatic trial – results easily translatable to clinical practice

- Variations in discharge criteria between sites
  - Minimisation by site
  - Adjusted analyses
  - Measure objective readiness for discharge

Reference: Ojha et al., *Lancet Child and Adolescent Health 2025*. DOI: 10.1016/S2352-4642(25)00271-8

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Key take home points

1. Full or exclusive milk feeds from day 1 does not reduce length of hospital stay in all care settings.
2. Infants born at or later than 30 weeks gestation, can be full or exclusively milk fed from birth without adverse effect on outcomes up to 6 weeks of age corrected for preterm birth
3. Full or exclusive milk feeds from day 1 reduces the need for invasive clinical interventions such and need for intensive care.

Reference: Ojha et al., *Lancet Child and Adolescent Health 2025*. DOI: 10.1016/S2352-4642(25)00271-8

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