Research Paper

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Pain in very preterm infants—prevalence, causes, assessment, and treatment. A nationwide cohort study

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Background

- Survival of very preterm (<32 weeks GA) & extremely preterm (<28 weeks GA) has increased.

- While beneficial, infants experience painful conditions, procedures, and interventions.

Backgroun

- Pain is difficu
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- Neonatal pai
  - → Neurologic
    developed
- Growing con
  prevention a

velopment

n are not fully

increase

Infants' Sense of Pain Is Recognized, Finally

But why did it take decades for the reality to dawn?

By PHILIP M. BOFFEY

Special to The New York Times

WASHINGTON, Nov. 23 — Newborns do feel pain. Parents don't have to be told that, and many pediatricians don't either. But the contrary belief — that the smallest babies are such primitive organisms that they are oblivious to pain — has persisted for decades among many physicians who have routinely operated on these children with little or no anesthesia.

They did so for the purest of reasons, fearing that potent anesthetics might kill these seriously ill infants.

But now, medical evidence demonstrating the newborn's capacity for pain is building. Anesthesia has become safer, too. And in recent months, various groups have issued policy statements urging painkillers for these infants.

lieved to give anesthesia for major surgery. But some anesthesiologists are said to persist in the old ways, and many hospitals still decline to give even a local anesthetic for minor procedures such as circumcision.

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The failure to relieve pain was a "barbarous" and "nasty business", according of Dr. John W. Scanlon, director of neonatology at the Columbia Hospital for Women in Washington.

Few other experts would put it so harshly. But a joint policy statement issued by the American Academy of Pediatrics in September and approved by the American Society of Anesthesiologists the following month cited "an increasing body of evidence" that newborns, including those born prematurely, show physiologic responses to surgery that can be relieved by anesthetics. An editorial in The New England Journal of Medicine last week called the evidence "so overwhelming that physicians can no longer act as if all infants were indifferent to pain."

Better pain relief for tiny infants has clearly been possible for a long time. For almost 20 years, doctors at some academic medical centers have been safely giving anesthetics to premature babies. And over the past

Current studies and limitations

- Utilize painful procedures as a proxy for pain
- Limited study sizes, center-based studies (no population-based data)
- Lacking information on
  - → the most vulnerable (extremely preterm)
  - → the timing
  - → the duration of pain

Study Aims

1. Explore the epidemiology of painful conditions and procedures, as well as pain, in very preterm infants

2.
   - Validity of pain assessment
   - Evaluate pain treatment

Data and Methods

- Database: Swedish Neonatal Quality Register (SNQ)
- Study Population:
  - → 22-31 weeks GA
  - → Neonatal units reporting daily (34/37)
  - → Discharged 01/01/2020 – 31/03/2023
  - → PNA day 0 – 36 weeks PMA

Outcomes

- Painful conditions (ICD10-codes)
- Daily web-reporting by RN:
  - → Painful procedures

Pain — Documented pain in last 24 h?
- Yes or No

Scale — Assessed via pain scale?
- Yes or No
- Select which pain scale

Treatment — Pharmacologically treated?
- Yes or No
- How administered (and drug)

Results

- 3686 infants included (mean birthweight: 1176g, GA 28.2 weeks, 45.3% girls)
  - → 84% reported to have experienced pain
  - → Pain reported in 28,137 of 185,008 (15%) days of neonatal care
  - → In 22-23 wk infants, the median (IQR) number of days with pain was 8 (3-24)
  - → In infants born at 30-31 wks, the median (IQR) number of days with pain in was 4 (2-7)

Painful conditions.

Table 2

Prevalence of painful or potentially painful neonatal conditions and of conditions associated with frequent use of intensive care procedures in very preterm infants, stratified by gestational age.

Condition	Gestational age strata in weeks					
	22-23 wk	24-25 wk	26-27 wk	28-29 wk	30-31 wk	22-31 wk
	No (%)	No (%)	No (%)	No (%)	No (%)	No (%)
	N = 224 (6.1)	N = 487 (13.2)	N = 693 (18.8)	N = 942 (25.6)	N = 1340 (36.4)	N = 3686
Painful conditions						
Birth trauma	1 (0.5)	3 (0.6)	8 (1.2)	3 (0.3)	6 (0.5)	21 (0.6)
Intestinal obstruction	6 (2.7)	11 (2.3)	12 (1.7)	9 (1.0)	12 (0.9)	50 (1.4)
Necrotizing enterocolitis	49 (21.9)	83 (17.0)	62 (9.0)	28 (3.0)	23 (1.7)	245 (6.7)
Gut perforation, peritonitis	19 (8.5)	29 (6.0)	20 (2.9)	8 (0.9)	10 (0.8)	86 (2.3)
Skin abscess, pressure ulcer	9 (4.0)	26 (5.3)	23 (3.3)	17 (1.8)	6 (0.5)	81 (2.2)
Arterial embolus/thrombosis	2 (0.9)	7 (1.4)	2 (0.3)	1 (0.1)	3 (0.2)	15 (0.4)
Otitis, meningitis	2 (0.9)	1 (0.2)	7 (1.0)	5 (0.5)	11 (0.8)	26 (0.7)
Any painful condition	67 (29.9)	125 (25.7)	112 (16.2)	63 (6.7)	61 (4.6)	428 (11.6)
Rate ratio (95% CI)*	6.6 (4.8-9.0)	5.6 (4.2-7.5)	3.6 (2.6-4.8)	1.5 (1.0-2.2)	Reference	—

Painful conditions.

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	N = 224 (6.1)	N = 487 (13.2)	N = 693 (18.8)	N = 942 (25.6)	N = 1340 (36.4)	N = 3686
Potentially painful conditions						
Neonatal sepsis	114 (50.9)	247 (50.7)	194 (28.0)	131 (13.9)	93 (6.9)	779 (21.1)
Expansive cerebral bleedings	57 (25.5)	74 (15.2)	61 (8.8)	24 (2.6)	25 (1.9)	241 (6.5)
Drug abstinence	2 (0.9)	4 (0.8)	6 (0.9)	6 (0.6)	11 (0.8)	29 (0.8)
Any potentially painful condition	147 (65.6)	287 (58.9)	239 (34.5)	153 (16.2)	126 (9.4)	952 (25.8)
Rate ratio (95% CI)†	7.0 (5.8-8.5)	6.3 (5.2-7.5)	3.7 (3.0-4.5)	1.7 (1.4-2.3)	Reference	—

Painful conditions.

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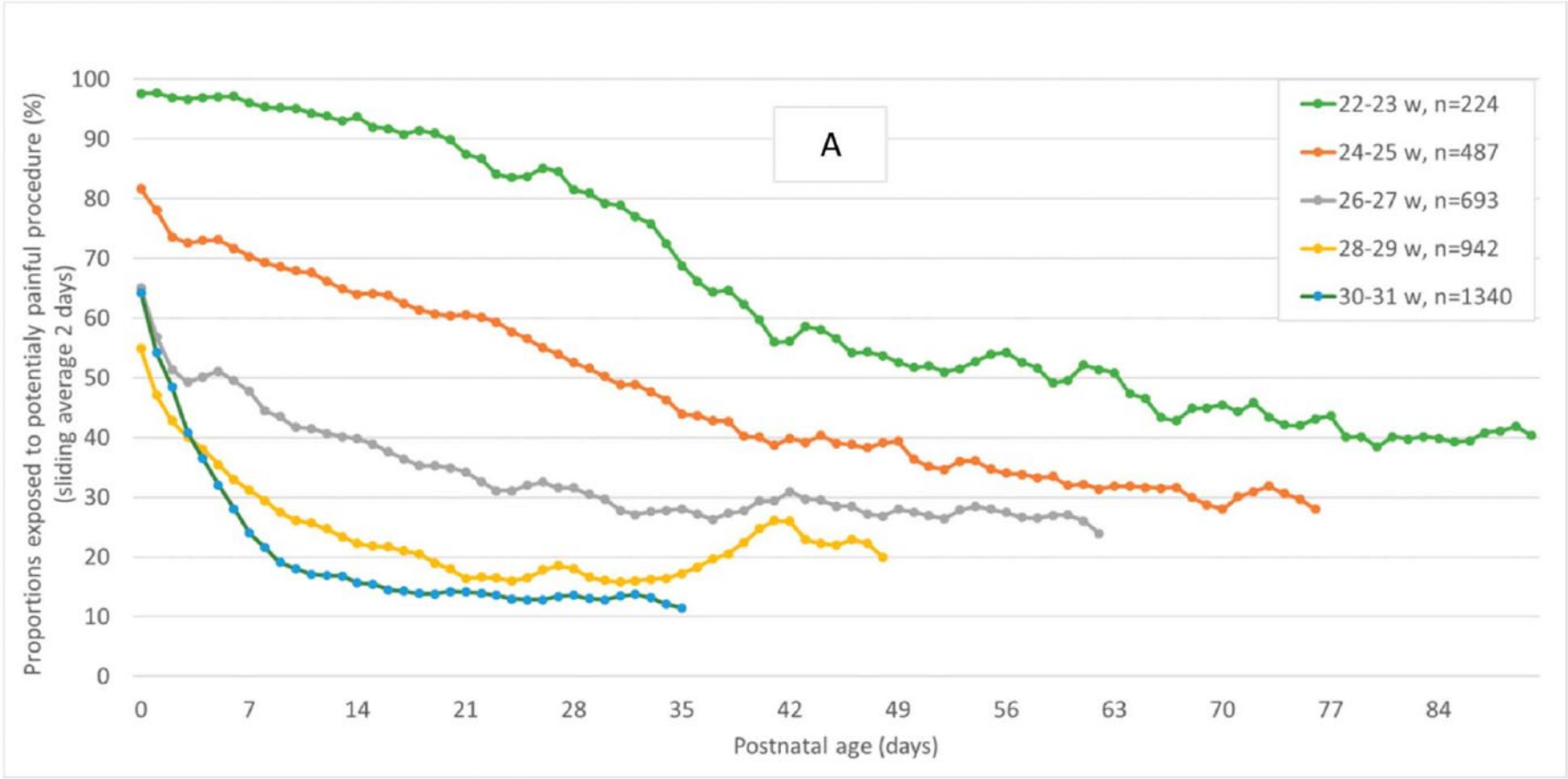
Conditions (other than above) associated with frequent use of invasive procedures						
Apgar score <4, asphyxia	112 (50.0)	169 (34.7)	186 (26.8)	191 (20.3)	171 (12.8)	829 (22.5)
Respiratory distress	213 (95.1)	462 (94.9)	659 (95.1)	874 (92.8)	1157 (86.3)	3365 (91.3)
Heart failure	8 (3.6)	12 (2.5)	14 (2.0)	13 (1.4)	8 (0.6)	55 (1.5)
Convulsions	5 (2.2)	10 (2.1)	10 (1.4)	5 (0.5)	8 (0.6)	38 (1.0)
Major malformation	58 (25.9)	141 (29.0)	157 (22.7)	158 (16.8)	186 (13.9)	700 (19.0)
Any condition associated with frequent use of invasive procedures	222 (99.1)	477 (98.0)	674 (97.3)	891 (94.6)	1204 (89.9)	3468 (94.1)
Rate ratio (95% CI)‡	1.1 (1.1-1.1)	1.1 (1.1-1-1)	1.1 (1.1-1.1)	1.1 (1.0-1.1)	Reference	—

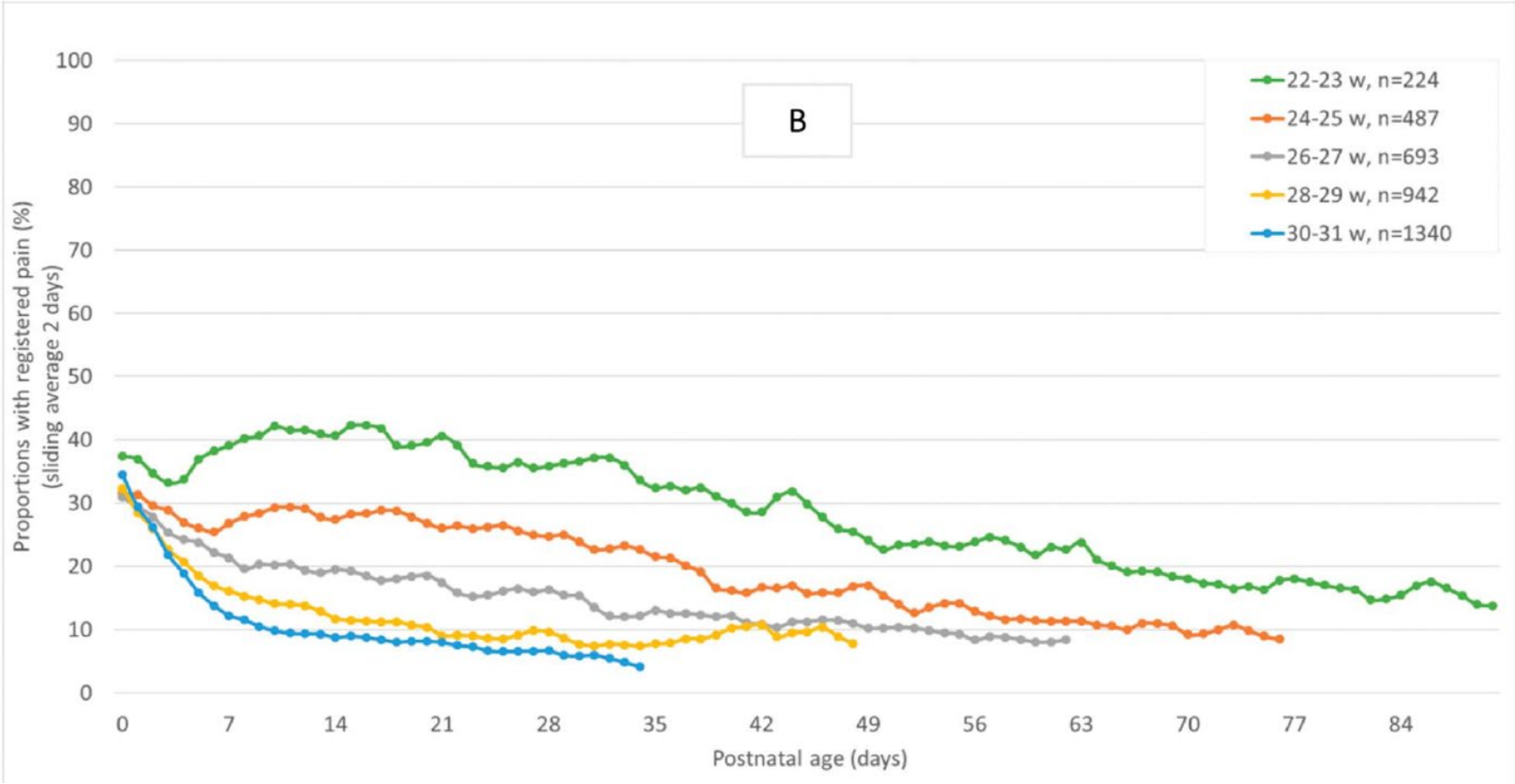
Painful procedures

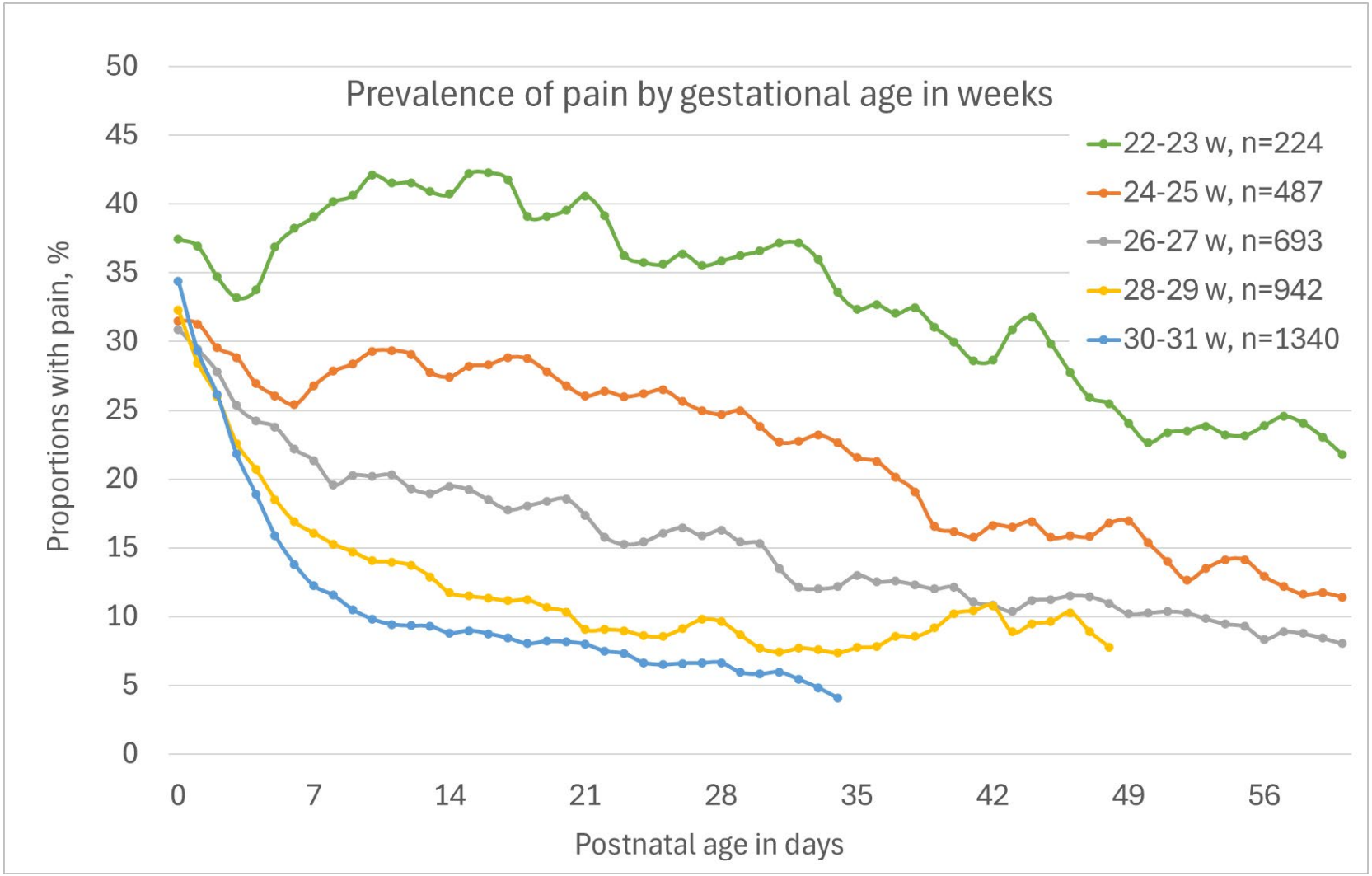
- Daily use of potentially painful procedures, any of the following:
  - → respiratory support delivered through a tracheal tube (including day with intubation, extubation, tracheal suctioning)
  - → chest tube drainage
  - → surgery (including surgery of the skull, thorax and abdominal cavity, inguinal hernia repair, placement of gastric or enteral stoma)
  - → any procedural skin puncture (for sampling of body fluids or vascular access)
  - → screening examinations for retinopathy of prematurity.

Proportions (%) exposed to a potentially painful procedure by postnatal day and stratified by gestational age in weeks (22–31, 2-week groupings) up to a postmenstrual age of 36 weeks (N = 3,686).



Proportions (%) of very preterm infants with reported pain per postnatal day and stratified by gestational age in weeks (22–31, 2-week groupings) up to a postmenstrual age of 36 weeks (N = 3,686)




Prevalence of pain by gestational age in weeks
Proportions with pain, %
Postnatal age in days
0
5
10
15
20
25
30
35
40
45
50
0
7
14
21
28
35
42
49
56
22-23 w, n=224
24-25 w, n=487
26-27 w, n=693
28-29 w, n=942
30-31 w, n=1340

Pain scale use

Pain Assessment Scale*	**Total ($\%_{col}$)**
ALPS (ALPS1 & ALPSn)[a]	2843 (67.4)
Échelle de Douleur et d'Inconfort du Nouveau-né (EDIN)	354 (9.6)
Face, Legs, Activity, Cry, Consolability (FLACC)	18 (0.5)
Other	684 (18.6)
Any Pain Assessment Scale	**Total ($\%_{col}$)**
Pain Scale Utilized	2763 (75.0)
No scale utilized	923 (25.0)

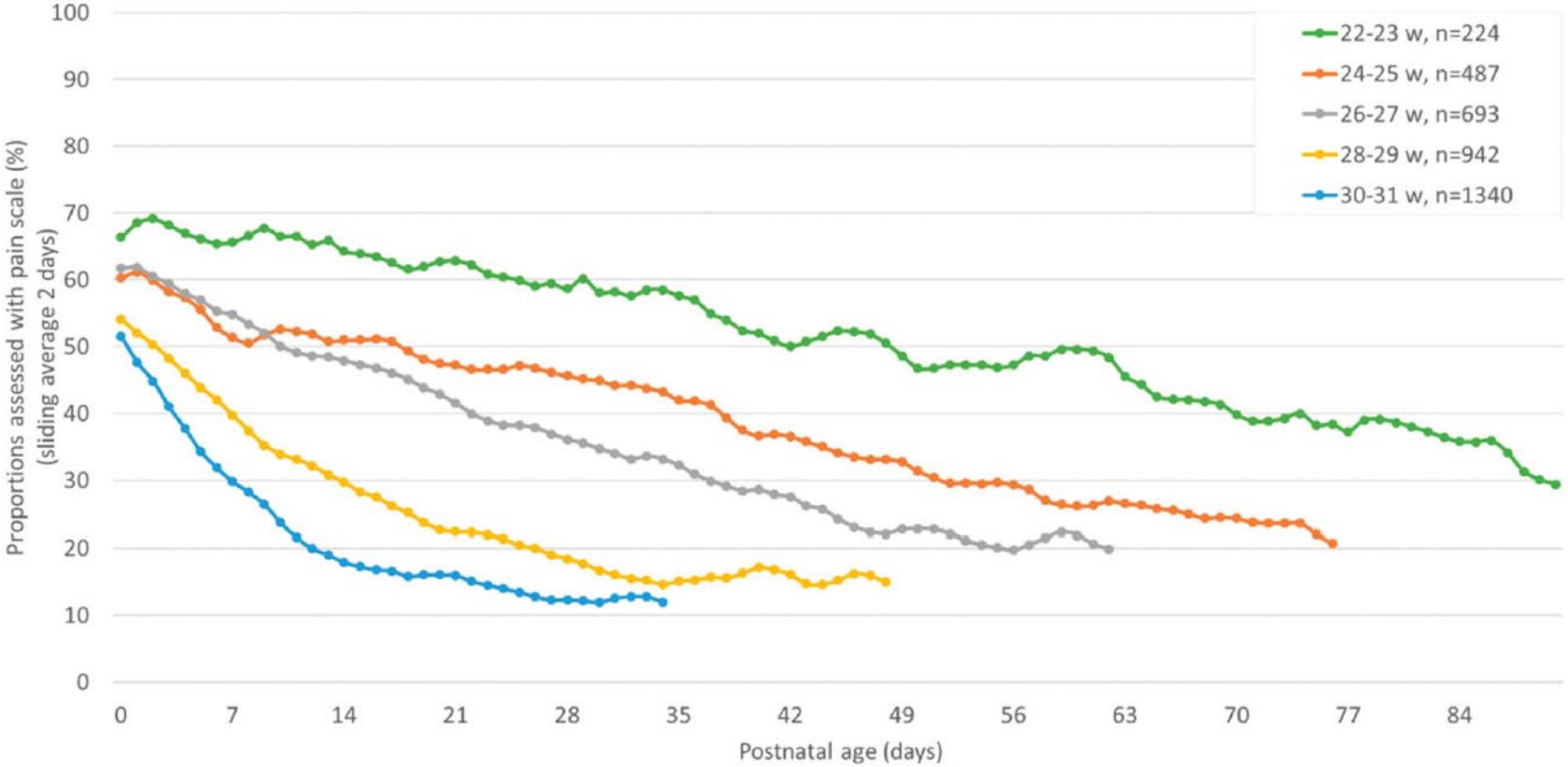


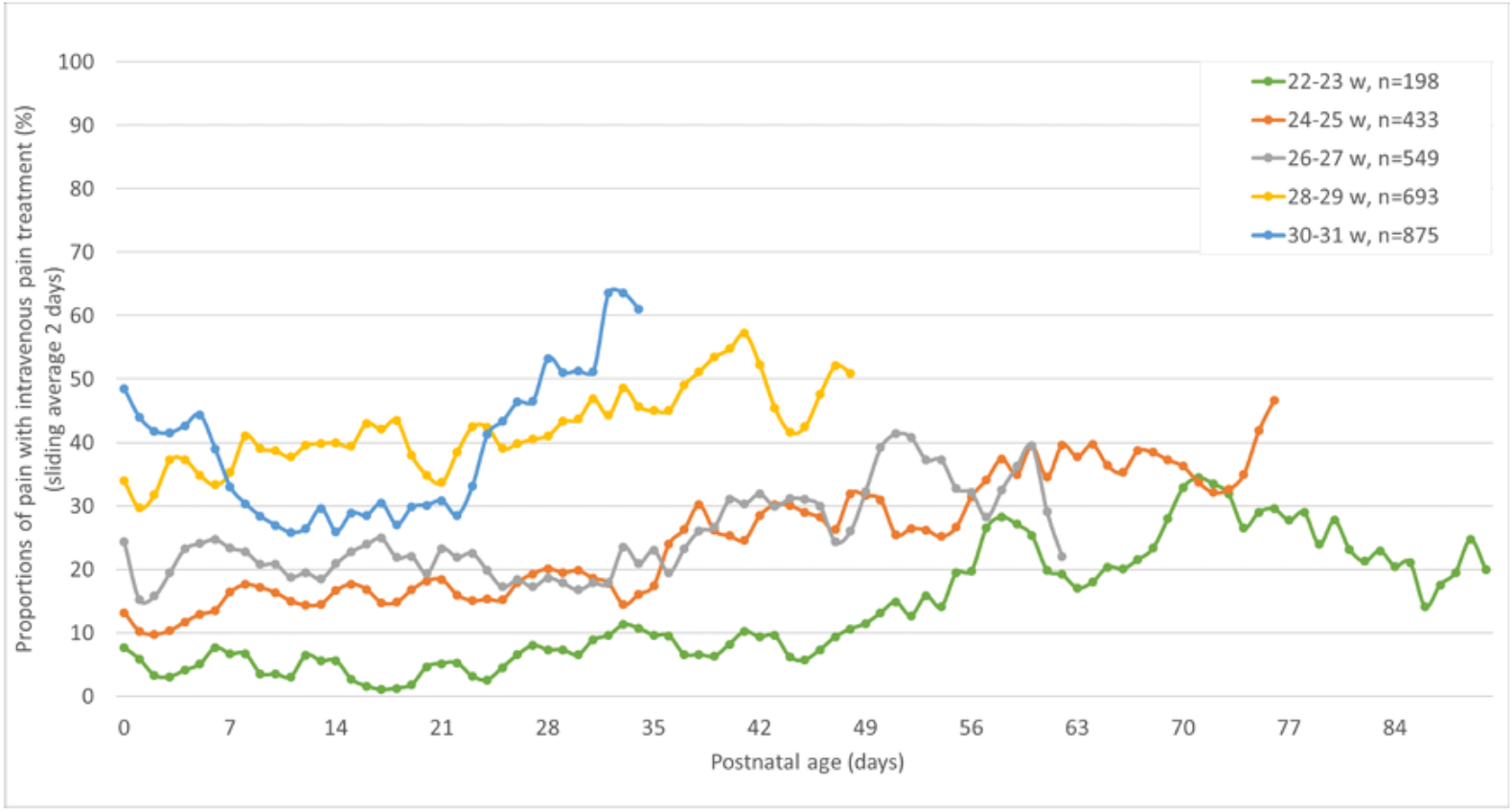
Figure 3. Proportions (%) of very preterm infants evaluated with a pain scale per postnatal day and stratified by gestational age in weeks (22-31, 2-week groupings) up to a postmenstrual age of 36 weeks (N = 3686).

Pharmacological Treatments of Pain in Very Preterm Infants (N=3,087)

Pharmacological Treatment, Mode of Administration	**Total (%total)***
Dermal / Topical	1870 (60.6)
Oral	405 (13.2)
Intramuscular	407 (13.2)
Intravenous	719 (23.3)
No treatment utilized	1635 (53)
Any Pharmacological Treatment	**Total (%col)**
Yes	2647 (85.7)
No pharmacological treatment utilized	440 (14.3)

*Infants could receive more than one pain treatment delivery method during their admission, percent's next to each total reflect out of the total study population n = 3087, not columnar.

eFigure 2: Proportions (%) of very preterm infants with reported pain who received intravenous pain treatment per postnatal day and stratified by gestational age in weeks (22-31, 2-week groupings) up to a postmenstrual age of 36 weeks (N=2,748).



Conclusions

- Painful conditions and potentially painful procedures common in VPT and EXPT infants.

- In contrast, proportions with registered pain were approx. half of those exposed to painful procedures. Suggested & potential explanations:
  - → successful analgesia/anaesthesia/non-pharmacologic mitigation strategies.
  - → some procedures (like MV) may not always be painful.
  - → underreporting? Are some forms of pain "normalized" in the NICU and poorly documented?
  - → masked by sedatives (rarely used)? Muscle relaxants not used.
  - → pain assessments in the smallest babies insufficient/invalid?

- Lower GA and earlier PNA correlated with higher proportions of pain and more frequent use of the pain assessment scales which contrasted to i.v. pain treatment (greater proportions among higher GAs and later PNA).

- Remaining problem: VPT in neonatal intensive care still experience pain. EXPT infants seemingly exposed to pain for long periods or repeated pain exposures.
- Next step: to evaluate associations between neonatal pain and later neurodevelopmental outcome.

Thank you!

Questions?

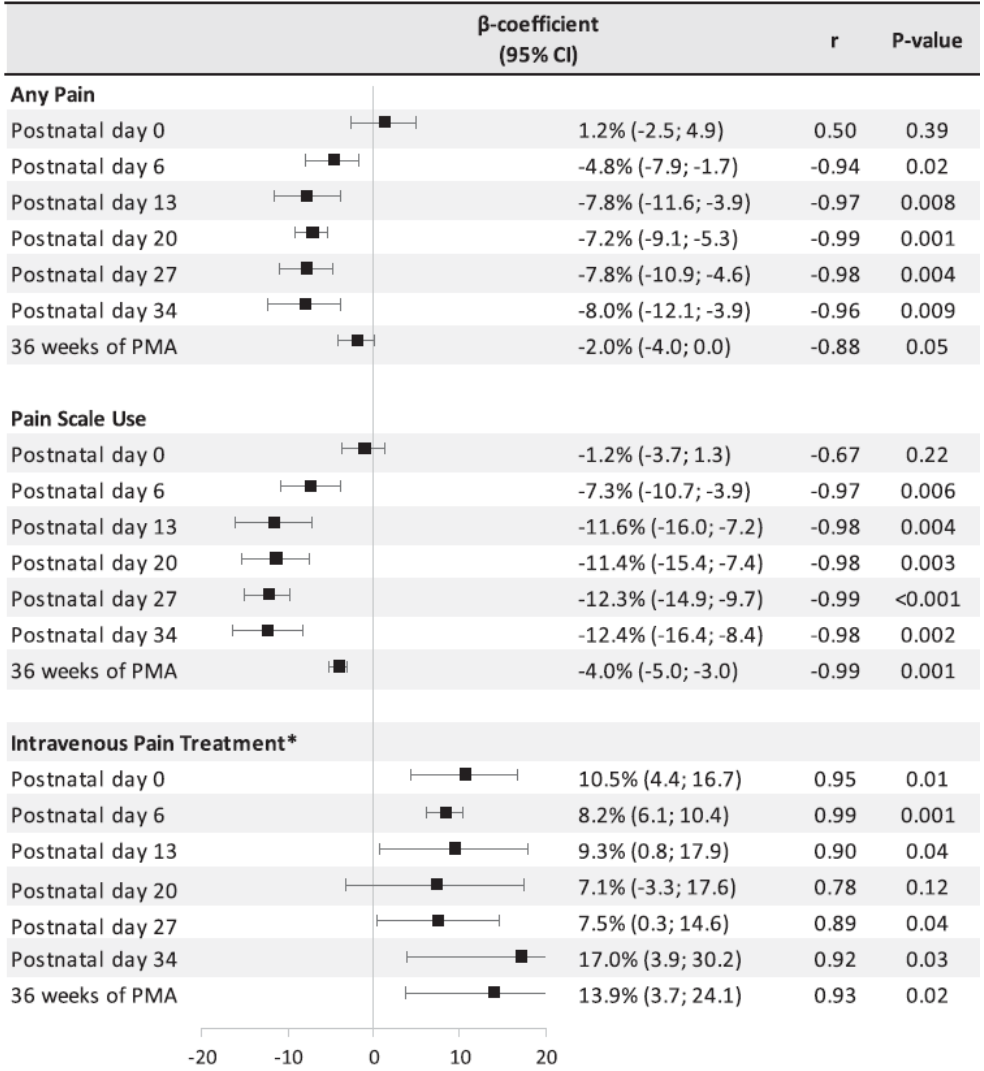
Figure 4: Forrest plot of linear regression β coefficients for associations between:

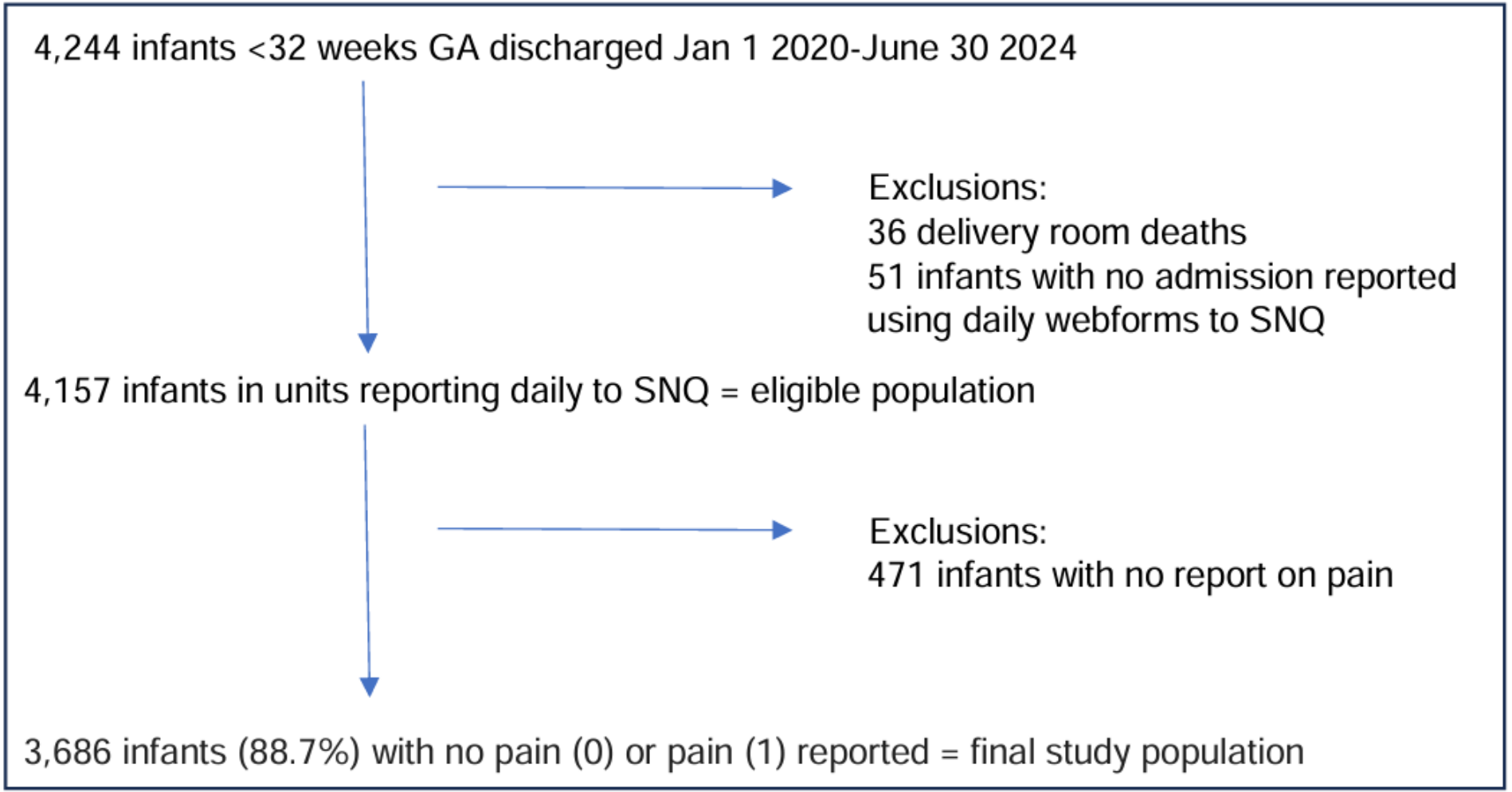
gestational age and pain (Panel A, denominator all admissions);

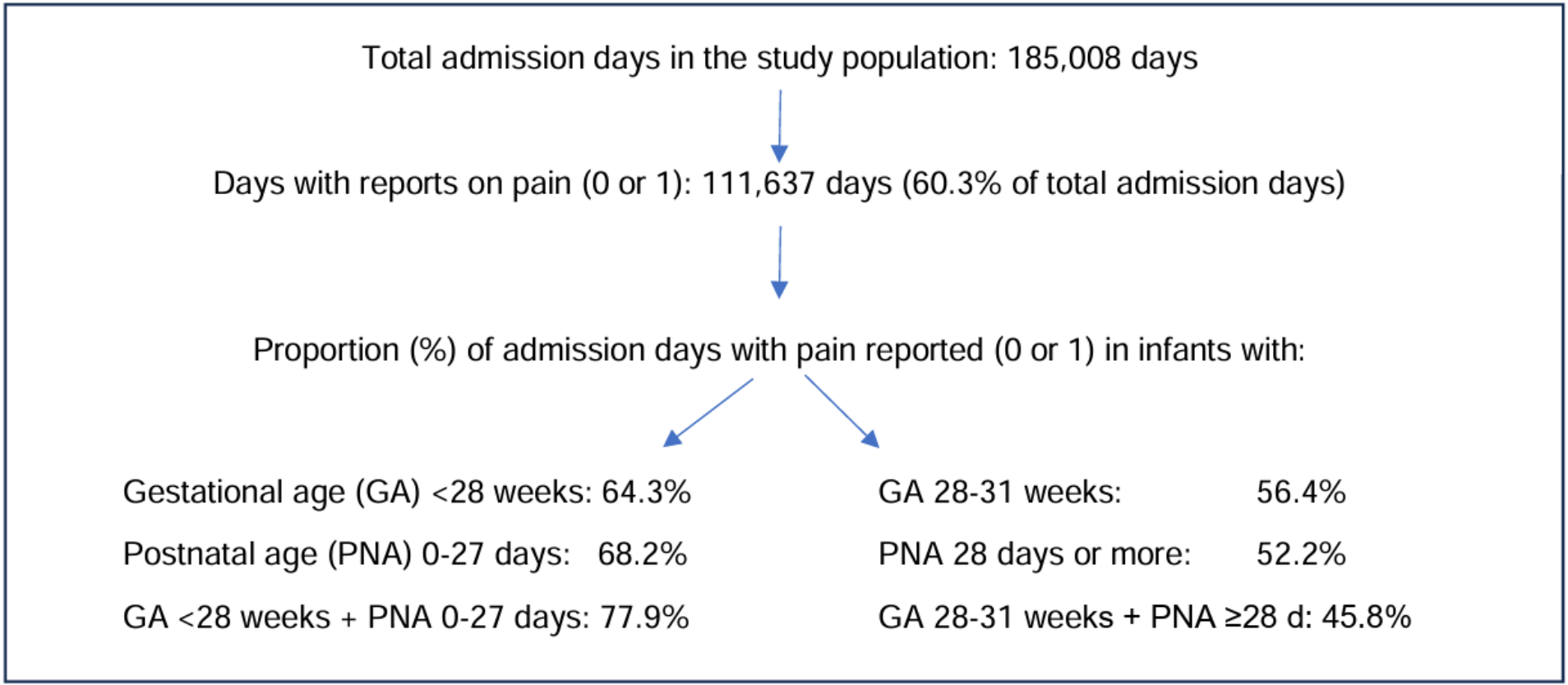
utilization of pain scales (Panel B, denominator all admissions);

intravenous treatment (Panel C,* denominator infants with recorded pain),

by postnatal age in days. The β coefficients indicate change in proportion (%) of infants by 2 weeks increase in gestational age.




4,244 infants <32 weeks GA discharged Jan 1 2020-June 30 2024
Exclusions:
36 delivery room deaths
51 infants with no admission reported using daily webforms to SNQ
4,157 infants in units reporting daily to SNQ = eligible population
Exclusions:
471 infants with no report on pain
3,686 infants (88.7%) with no pain (0) or pain (1) reported = final study population



SNQ: Swedish Neonatal Quality Register.