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Systematic review with meta-analysis: effects of implementing a nutrition support team for in-hospital parenteral nutrition

Marcel Kjærsgaard Eriksen[1] | Benjamin Crooks[2] | Simon Mark Dahl Baunwall[1] | Charlotte Lock Rud[1] | Simon Lal[2] | Christian Lodberg Hvas[1]

[1]Department of Hepatology and Gastroenterology, Aarhus University Hospital, Aarhus, Denmark

[2]Intestinal Failure Unit, Salford Royal NHS Foundation Trust, Salford, UK

Correspondence
Dr Marcel Kjærsgaard Eriksen, Department of Hepatology and Gastroenterology, Aarhus University Hospital, Palle Juul-Jensens Boulevard 99, DK-8200, Aarhus N, Denmark.
Email: marcer@rm.dk

Summary

Background: Nutrition support teams (NST) may improve parenteral nutrition (PN) outcomes. No previous systematic review has provided conclusive data on catheter-related infection (CRI) occurrence after NST introduction, nor have previous studies performed meta-analysis or graded the evidence.

Aims: To systematically evaluate the effects of implementing an NST for hospitalised adults on PN and compare these with standard care.

Methods: This was a systematic review and meta-analysis, pre-registered in PROSPERO (CRD42020218094). On November 24, 2020, PubMed, Web of science, Scopus, Embase, Cochrane Library, and Clinical Key were searched. Clinical trials and observational studies with a standard care comparator were included. Primary outcome was relative reduction in CRI rate. A random-effects meta-analysis was used to estimate effects, and evidence was rated using Cochrane and GRADE methodologies.

Results: Twenty-seven studies with 8166 patients were included. Across 10 studies, NST introduction reduced the CRI rate (IRR = 0.32, 95% CI: 0.19-0.53) with −8 (95% CI: −12 to −5) episodes per 1000 catheter days compared with standard care. Hypophosphataemia occurred less frequently (IRD = −12%, 95% CI: −24% to −1%) and 30-day mortality decreased (IRD = −6%, 95% CI: −11% to −1%). Inappropriate PN use decreased, both judged by indication (IRD = −18%, 95% CI: −28% to −9%) and duration (IRD = −21%, 95% CI: −33% to −9%). Evidence was rated very low to moderate.

Conclusions: This study documents the clinical impact of introducing an NST, with moderate-grade evidence for the reduction of CRI occurrence compared with standard care. Further, NST introduction significantly reduced metabolic complications, mortality, and inappropriate PN use.

Christian Lodberg Hvas and Simon Lal should be considered joint senior authors.

The Handling Editor for this article was Dr Mike Burkitt, and this commissioned review was accepted for publication after full peer-review.

1 | INTRODUCTION

Nutrition support teams (NST) are specialised in effective and safe provision of parenteral nutrition (PN).[1] Despite being lifesaving, good practice PN care is delivered to no more than 19% of patients, according to the UK 2010 National Confidential Enquiry into Patient Outcome and Death (NCEPOD) report.[2] Also, PN delivery implies potentially life-threatening risks. Catheter-related infections (CRI) pose a particular challenge, independently accounting for increased lengths of stay (LOS), costs and mortality.[3-5]

A multidisciplinary team for PN provision, including consistent expert participation, may improve the quality of care and reduce the occurrence of adverse events related to this treatment. Although recommended in all acute hospitals,[1,2] NSTs are only present in about 60% of UK hospitals, while the presence of these teams in hospitals in many other countries is unknown.[6] Establishing the evidence for effects of introducing an NST is essential to justify the continued implementation and further development of NSTs.

Multiple observational studies investigated the clinical impact of introducing an NST. While the overall impression from these studies is that NSTs may improve patient nutritional status, PN appropriateness,[7-9] clinical outcomes,[10-12] and reduce PN-related costs,[13-16] the level of evidence for these effects has never been evaluated. Previous systematic reviews[17,18] have independently summarised each parameter, but none provided parallel analyses of all the parameters using comparable methodologies to evaluate the overall impact of establishing an NST.

The aims of the present systematic review and meta-analysis were to evaluate the effects of implementing an NST for in-hospital PN and to compare these with standard care.

2 | MATERIALS AND METHODS

This international systematic review and meta-analysis followed the preferred reporting items for systematic review and meta-analysis (PRISMA) guidelines and the policies described in the Cochrane Handbook.[19,20] The review protocol was pre-registered in the PROSPERO database and can be accessed at https://www.crd.york.ac.uk/PROSPERO (CRD42020218094).

To evaluate the clinical importance of implementing an NST compared with standard care, the review addressed the following principal study question: What are the effects of introducing an NST in hospitalised patients receiving PN?

2.1 | Data sources and searches

On November 24, 2020, the medical databases PubMed, Web of science, Scopus, Embase, Cochrane Library, and Clinical Key were searched for all available literature. The search string was constructed in collaboration with a trained librarian and included multiple terminological variations of an NST (Supplementary File S1). No time or language limits were applied.

2.2 | Study selection

Published randomised clinical trials (RCT) and observational cohort studies with study populations of 15 or more patients were included. Non-English studies were translated using an online translating software service. All studies evaluating the effects of introducing an NST for hospitalised adults (18+ years) on PN were eligible of inclusion. Conference abstracts and unpublished studies were excluded. In accordance with the National Institute for Health and Care Excellence (NICE), an NST was defined as a multidisciplinary team with dietetic, nursing, pharmacy, and medical expertise to provide safe nutrition support.[1] Studies without a standard care comparator and studies including ≥10% paediatric patients were excluded.

All references were imported to the screening and data extraction tool Covidence (Covidence systematic review software, Veritas Health Innovation). Two independent reviewers from different institutions (MKE and BC) screened and fully read potential articles for eligibility. Discrepancies were arbitrated by different reviewers (CLH and SL).

2.3 | Outcome assessment

CRIs and monitoring of catheter sepsis rates are key outcome and benchmarking variables of NST performance.[21] In this systematic review, the primary outcome was relative reduction in occurrence of CRI episodes per 1000 catheter days. Because the estimated rate depends on its definition and to allow for stratification, a CRI was classified as either a catheter-related bloodstream infection (CRBSI) or a central line-associated bloodstream infection (CLABSI).[21-23] CRBSI is defined by the verification of the catheter as the source of infection, using either quantitative or semi-quantitative catheter cultures, quantitative paired blood cultures, or differential time to positivity of paired blood cultures.[22] CLABSI requires no laboratory evidence of catheter contamination, but merely a central venous catheter in situ for ≥48 hours, laboratory confirmed bloodstream infection (BSI) on peripheral blood culture, an no evidence of another infectious site.[22] To obtain comparable rates, catheter days were calculated by multiplying the number of patients on PN with mean PN duration in studies only reporting CRI episodes. In studies distinguishing between "definite" or "probable" catheter sepsis, episodes were combined to provide the most conservative estimate.

Secondary outcomes included changes in 30-day mortality, catheter-related metabolic and thrombotic complications, LOS, readmissions, PN duration, appropriateness and PN-related costs. Outcomes were selected according to their clinical importance as recommended in the grading of recommendations assessment, development and evaluation (GRADE) Handbook.[24]

2.4 | Data extraction

One reviewer (MKE) extracted data from eligible articles to an Excel spreadsheet. In the final dataset, an independent reviewer (BC) validated all data. Organisation of care prior to and after NST formation was extracted to allow comparison of PN management within cohorts.

Patient data were extracted comprehensively and included age, sex, intensive care unit (ICU) stay, LOS and mortality. Comparable mortality rates were obtained by extrapolating to 30-days mortality if no other mortality timeframe was given. This was considered reasonable if the timeframe was comparable to mean in-hospital LOS.

PN-related outcomes included complications, PN duration, appropriateness and costs. The latter was extracted as PN cost per patient and appropriateness was measured according to indication. As a secondary measure, short term PN (<7 days) was used as a surrogate marker of inappropriateness.[25,26] In studies distinguishing between inappropriate and preventable PN, the latter was considered as inappropriate as well. CRIs were classified as either CRBSI or CLABSI. Besides catheter-related infectious complications, data included catheter-related thrombotic and metabolic events. Only few data on symptomatic refeeding syndrome were available and various biochemical definitions were used. To extract comparable data, metabolic outcomes were defined as laboratory levels above (hyperglycaemia) or below (hypophosphataemia) reference range, with or without associated symptoms.

2.5 | Risk of bias assessment and quality of evidence

The quality of each study was evaluated by one reviewer (MKE). RCTs were evaluated with the Cochrane Risk of Bias 2 (RoB2) tool and cohort studies with the Newcastle-Ottawa quality assessment Scale (NOS).[27,28] NOS scores ranged from 0 (lowest) to 9 (highest) and required the reviewer to incorporate pre-defined quality determinants for comparability. For NST performance, reporting a catheter sepsis definition was critical for comparability. Using the RoB2 tool, risk of bias was categorised as low, high or some concerns. To obtain comparable estimates, a NOS score of 8-9 was considered as low, 5-7 as moderate and ≤4 as high risk of bias.

The quality of evidence of primary and secondary outcomes was determined using the GRADE methodology.[24] The GRADEpro® was used to derive a summary of findings tables.

2.6 | Data analysis

Statistical analyses were conducted in R version 3.6.1 with the "meta", "metafor" and "dmetar" extension packages.[29,30] For all meta-analyses, a random effects model with a DerSimonian-Laird τ^2-estimator and Z-based statistics were applied. When applicable, forest plots were used to summarise results. *P*-values < 0.05 were considered statistically significant, and all data were presented as incidence rate differences (IRD) and incidence rate ratios (IRR) with 95% confidence intervals (CI) where appropriate.

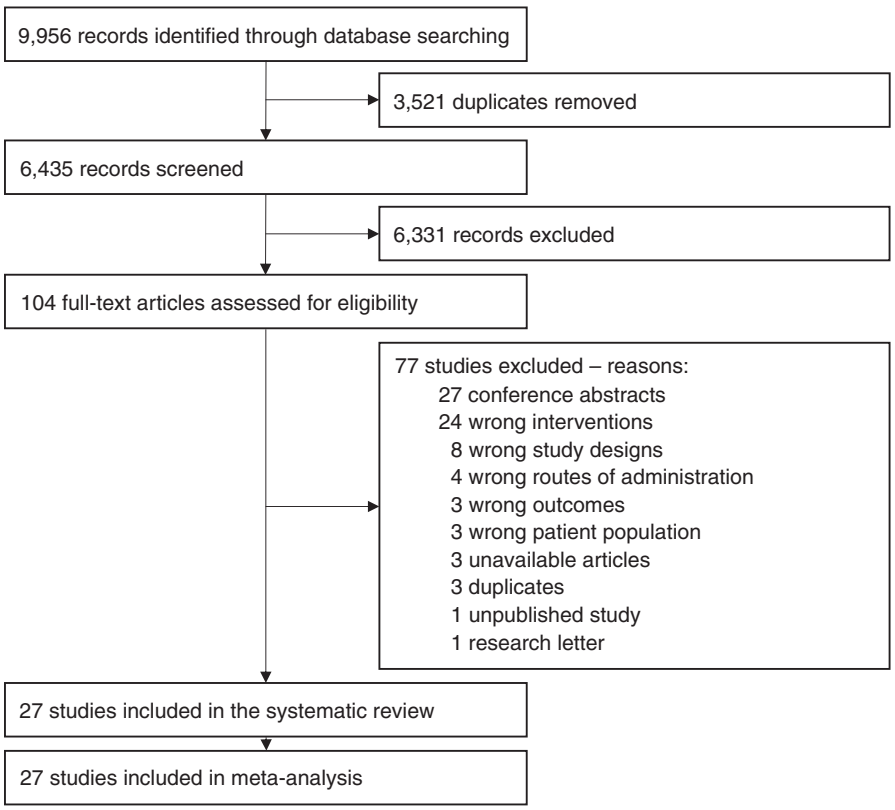

FIGURE 1 PRISMA flow diagram

TABLE 1 Study characteristics of all included adult inpatients on PN

Author	Country	Study type	Patients (N)		Females (%)		Age (mean)		ICU (%)		Care organisation								Quality assessment (NOS)
											Physician		Dietitian		Nutrition nurse		Pharmacist		
Standard care (⊟) vs NST (⊞)			⊟	⊞	⊟	⊞	⊟	⊞	⊟	⊞	⊟	⊞	⊟	⊞	⊟	⊞	⊟	⊞	
Hickey,[32] 1979	USA	Cohort	41	9	2.4	11.1	57.4	52.3	..	..	+	+	−	+	−	+	−	+	Low risk
Nehme,[33] 1980	USA	Cohort	164	211	..	..	..	..	0.0	0.0	+	+	−	+	−	+	−	+	Low risk
Jacobs,[34] 1984	USA	Cohort	21	57	..	..	61.0	56.6	..	..	+	+	−	..	−	+	+	+	Low risk
Traeger,[35] 1986	USA	Cohort	45	24	53.3	50.0	64.0	62.0			+	+	−	+	−	+	−	+	Low risk
Faubion,[36] 1986	USA	Cohort	162	377	..	..	..	..	..	..	..	+	..	..	..	+	..	..	Low risk
Oakes,[12] 1991	UK	Cohort	46	205	39.2	37.1	52.2	55.1	47.8	47.3		+	..	..	..	+	..	+	Moderate risk
Gales,[37] 1994	USA	Cohort	17	11	58.8	54.5	64.0	48.0	..	..	+	−	−	+	−	+	−	+	Moderate risk
Fisher,[38] 1996	USA	Cohort	77	122	..	..	..	..	..	..	−	+	−	+	+	+	−	+	Low risk
ChrisAnderson,[39] 1996	USA	Cohort	29	128	66.0	64.0	52.0	52.0	..	..	+	+	−	+	+	+	−	+	Moderate risk
Png,[40] 1997	Singapore	Cohort	37	36	48.6	47.2	60.0	63.0	0.0	0.0	+	+	−	+	−	+	−	+	Low risk
Trujillo,[41] 1999	USA	Cohort	160	49	..	..	..	..	33.0	33.0	+	+	−	+	−	+	−	−	Moderate risk
Fettes,[42] 2000	UK	Cohort	28	19	32.1	52.6	69.0	66.0	..	..	+	+	−	+	−	+	+	+	Moderate risk
Saalwachter,[43] 2004	USA	Cohort	194	383	..	..	..	..	..	..	+	+	−	+	−	−	−	−	Moderate risk
Kennedy,[44] 2005	UK	Cohort	54	75	24.1	37.3	61.0	58.0	..	..	+	+	+	+	−	+	+	+	Moderate risk
Hearnshaw,[45] 2007	UK	Cohort	132	61	40.9	54.1	67.0	67.0	48.5	49.2	..	..	..	..	..	..	..	..	Moderate risk
Walshe,[46] 2010	Ireland	Cohort	305	1087	42.0	42.0	58.0	58.0	..	..	..	+	..	+	+	+	..	−	Low risk
Sriram,[47] 2010	USA	Cohort	303	271	41.5	39.6	51.9	52.0	0.0	0.0	+	+	+	+	+	+	−	−	Moderate risk
Boitano,[48] 2010	USA	Cohort	30	30	..	..	..	..	..	..	+	+	−	+	−	−	+	+	Moderate risk
Martin,[49] 2011	USA	Cohort	111	167	49.0	49.0	..	..	..	..	..	..	+	+	..	..	..	..	Moderate risk
López-Martín,[50] 2012	Spain	Cohort	24	38	42.0	58.0	62.0	58.0	0.0	0.0	..	+	..	+	..	−	..	+	Moderate risk
Chong,[51] 2013	Malaysia	Cohort	106	106	29.0	27.0	48.0	50.0	72.0	64.0	+	+	−	+	−	+	−	+	Low risk
Hvas,[7] 2014	UK	Cohort	180	303	..	..	60.0	64.0	0.0	0.0	−	+	−	+	−	+	−	+	Low risk
Parent,[52] 2015	USA	Cohort	372	422	31.1	34.1	53.0	53.7	59.4	55.8	..	+	..	+	..	−	..	+	Moderate risk
Prado,[53] 2016	Spain	Cohort	29	29	24.1	55.2	59.9	62.0	0.0	0.0	..	+	..	−	..	−	..	−	Moderate risk
Braun,[54] 2016	USA	Cohort	378	357	..	..	65.7	64.9	..	..	..	+	..	+	..	+	..	+	Moderate risk
Lee,[55] 2018	South Korea	Cohort	62	62	50.7	44.0	64.2	65.9	100.0	100.0	+	+	−	+	−	+	−	+	Moderate risk
Meyer,[56] 2019	USA	Cohort	202	218	53.0	49.5	58.7	58.8	..	..	−	+	(+)[a]	+	−	−	(+)[a]	+	Moderate risk

Abbreviations: ICU, intensive care unit; NOS, Newcastle-Ottawa quality assessment Scale; NST, nutrition support team.

[a]Reports that two of five hospitals used pharmacists. Dietitians were used in four of five hospitals.

TABLE 2 Outcome overview of all included adult inpatients on PN

Author	Patients (N)		CVC (N)		Catheter days (N)		Infective complications (N)				
							CRI definition	CRIs		CRIs per 1000 catheter days	
Standard care (⊟) vs NST (⊞)	⊟	⊞	⊟	⊞	⊟	⊞	⊟/⊞	⊟	⊞	⊟	⊞
Hickey,[32] 1979	41	9	..	..	885.6	98.1	CLABSI	10	1	11.3	10.2
Nehme,[33] 1980	164	211	389	284	3384.3	5282.4	CRBSI	43	5	12.7	0.9
Jacobs,[34] 1984	21	57	..	..	546.0	1219.0	CLABSI	5	1	9.2	0.8
Traeger,[35] 1986	45	24	74	33			CRBSI	5	1		
Faubion,[36] 1986	162	377	179	622	3953.3	9200.0	CLABSI	39	22	9.8	2.4
Oakes,[12] 1991	46	205	48	225	650.0	3648.0	[c]	5	10	7.7	2.7
Gales,[37] 1994	17	11	..	..	123.0	79.0	..	..	..	..	..
Fisher,[38] 1996	77	122	77	122	..	..	CRBSI	8	7		
ChrisAnderson,[39] 1996	29	128	..	..	..	..	..	..	..	..	..
Png,[40] 1997	37	36			259.0	396.0	CLABSI	13	6	50.2	15.2
Trujillo,[41] 1999	160	49	..	..	..	..	..	..	..	..	..
Fettes,[42] 2000	28	19	23	15	234.6	138.8	[c]	5	5	21.3	36.0
Saalwachter,[43] 2004	194	383	..	..	..	..	..	..	..	..	..
Kennedy,[44] 2005	54	75	68	78	665.0	752.0	[c]	47	23	70.7	30.6
Hearnshaw,[45] 2007	132	61	..	..	..	..	[c]	[c]	[c]	..	..
Walshe,[46] 2010	305	1087	651	1914	3666.0	11 731.0	CRBSI	75	144	20.5	12.3
Sriram,[47] 2010	303	271	..	..	..	..	..	..	..	..	..
Boitano,[48] 2010	30	30									
Martin,[49] 2011	111	167	..	..	..	..	..	..	..	..	..
López-Martín,[50] 2012	24	38									
Chong,[51] 2013	106	106	84	76	..	..	..	..	..	..	..
Hvas,[7] 2014	180	303	178	303	1911.8	4285.7	CRBSI	13	3	6.8	0.7
Parent,[52] 2015	372	422	..	..	..	..	..	..	..	..	..
Prado,[53] 2016	29	29	..	..							
Braun,[54] 2016	378	357	..	..	..	..	..	..	..	..	..
Lee,[55] 2018	62	62	62	62	..	..	..				
Meyer,[56] 2019	202	218	..	..	..	..	..	..	..	..	..

Abbreviations: CLABSI, central line-associated bloodstream infection; CRBSI, catheter-related BSI; CRI, catheter-related infection; CVC, central venous catheter; ICU, intensive care unit; LOS, length of stay; NST, nutrition support team.

[a]Defined as laboratory levels above (hyperglycaemia) or below (hypophosphataemia) reference range with or without associated symptoms.

[b]Extrapolated to 30-day mortality. Two studies (Traeger and Kennedy) did not report mortality unit or LOS data.

[c]Studies did not provide a clear definition of catheter-related sepsis.

Heterogeneity was quantified with I^2 statistics and examined for significance using a chi-squared test. *P*-values < 0.10 were considered significant heterogeneity. In accordance with the Cochrane Handbook, I^2-values between 0% and 40% were considered as low, 30%-60% as moderate, 50%-90% as substantial and 75%-100% as considerable heterogeneity.[20] To detect if extreme study outliers influenced the estimates too heavily, extreme outlier analyses were performed for all compiled meta-analyses. Extreme outliers were pre-specified as studies whose CIs did not overlap with the pooled estimate's CI.

Publication bias was evaluated by visual inspections of funnel plots and tested for asymmetry with Egger's test when appropriate. Duval and Tweedie's trim-and-fill procedure was applied to objectively determine the direction of potential publication bias.[31]

3 | RESULTS

During initial title and abstract screening, 6435 unique studies were identified. Of these, 104 articles were fully read, and 27 cohort studies were included.[7,12,32-56] No RCTs were eligible for inclusion. All studies contributed data for meta-analysis. Figure 1 displays the PRISMA search strategy diagram, and Supplementary File S2 lists exclusion reasons for the excluded studies. Risk of bias

Mortality (%)[b]		Metabolic complications (%)[a]								Inappropriateness (%)			
		Hyper-glycaemia		Hypo-phosphataemia		LOS (days)		PN duration (N)		Indication		Short term PN (<7 days)	
⊟	⊞	⊟	⊞	⊟	⊞	⊟	⊞	⊟	⊞	⊟	⊞	⊟	⊞
29.0	33.0	63.4	66.7	..	..	45.6	29.7	21.6	10.9	..	..	..	..
		6.7	0.0	36.0	2.8			16.0	28.0	..	..	..	..
..	..	47.6	63.2	..	..	..	..	26.0	21.4	..	..	..	..
27.0	38.0	11.1	12.5	..	..	..	..	18.0	22.0	..	..	..	..
..	..	..	..	..	..	..	..		14.5	..	..	..	..
..	..	..	..	..	..	..	..	13.2	13.6	..	..	..	..
..	..	..	..	..	..	..	..	7.2	7.1	..	..	..	..
..	..	..	..	..	..	..	..	..	..	24.7	0.8	..	..
..	..	41.0	38.0	21.0	24.0			13.7	12.9	3.5	3.9	..	..
..	..	..	..	..	..	..	..	7.0	11.0	..	..	51.4	19.4
..	..	..	..	..	..	..	..	11.0	17.0	44.0	18.0	40.6	16.3
..	..	16.0	3.0	33.0	21.0	..	..	8.4	7.3				
..	..	..	..	..	..	..	..	..	..	32.0	10.2	..	..
42.6	24.0	..	..	..	..	..	..	8.0	10.0	..	..	..	..
22.0	16.0	..	..	..	..	..	..	5.0	5.0	18.2	18.0	33.0	20.0
..	..	..	..	..	..	..	..	..	..	..	..	..	..
..	..	..	..	..	..	..	..	7.1	6.9	28.7	16.6	..	..
..	..	36.7		17.0	13.0	..	..	9.0	8.7	40.0	3.0	47.0	17.0
..	..	..	..	..	..	..	..	..	..	34.2	26.2		
..	..	..	34.0	..	0.0	..	..	..	..	..	..	67.0	22.0
37.0	25.0	..	..	11.3	0.0	18.0	17.0	9.0	8.0	..	..	26.4	26.4
15.6	12.2	..	..	..	..	..	..	..	..	..	..	..	..
20.8	19.1	..	..	..	..	22.5	23.3	10.5	10.4	..	..	..	..
..	..	3.4	17.2	..	44.8	..	..	6.0	8.0	41.4	17.2	41.4	20.7
12.7	10.6	..	..	64.0	53.0	38.0	49.8	9.7	9.4	..	..	..	..
19.2	10.7	..	..	..	..	46.5	44.9	..	..	..	..	..	..
..	..	..	..	..	..	..	..	6.0	7.0	41.1	2.8	..	..

assessments of included studies are available from Supplementary File S3.

Study characteristics and outcomes of all included adult inpatients on PN are available from Tables 1 and 2. The summary of findings and corresponding GRADE quality of evidence levels are presented in Table 3 and elaborated in Supplementary File S4. Included studies evaluated 8166 patients, including 3309 (40.5%) under standard care and 4857 (59.5%) under NST care. The mean patient age was 58.9 years (SD ±5.7 years, range 48-69) and 42.6% were female. Patients under standard care were admitted for mean 34.1 days (95% CI: 17.8-50.5 days) and received PN for mean 11.2 days (95% CI: 8.4-13.9 days). Patients under NST care had a LOS of mean 32.9 days (95% CI: 15.5-50.3 days) and a mean PN duration of 11.9 days (95% CI: 9.1-14.8 days). In 11 (41%) studies reporting data on study setting, 30.9% patients were admitted to an ICU.

3.1 | CRIs without and with an NST

Ten (37%) studies reported CRI rates or calculable rates per 1000 catheter days,[7,12,32-34,36,40,42,44,46] including 1038 patients under standard care and 2379 patients under NST care. Supplementary File S5 illustrates the significantly different pooled risk difference in CRI rate per 1000 catheter days in patients under standard care

vs NST care ($P < 0.01$). Across all eligible studies, NST introduction reduced the CRI rate threefold (IRR = 0.32, 95% CI: 0.19-0.53; Table 3) with −8 (95% CI: −12 to −5, $P < 0.01$, $I^2 = 53$) episodes per 1000 catheter days (Figure 2) compared with standard care. The standard care subpopulations contributed with cumulated 16 279 catheter days and 268 CRI episodes, while 36 830 catheter days in the NST subpopulations gave rise to 228 CRIs. A CRI definition, but not necessarily concomitant rates, was available in 13 studies, including four studies adhering to the CLABSI definition[32,34,36,40] and five to the CRBSI definition.[7,33,35,38,46] Four studies did not report a clear definition,[12,42,44,45] one of which did not stratify by NST presence.[45]

Sensitivity analysis identified one extreme outlier study in which the CRI rate dropped from 71 to 31 episodes per 1000 catheter days after NST introduction.[44] Excluding this study explained most heterogeneity between studies while the effect rate remained unchanged (IRD = −8, 95% CI: −10 to −6, $I^2 = 25\%$). No indication of publication bias regarding CRI rate was identified (Supplementary File S6.1).

3.2 | Secondary outcomes

Patient mortalities were compared in nine studies.[7,32,35,44,45,51,52,54,55] Across these studies, a total of 280 (20%) and 220 (16%) patients died under standard care and NST care, respectively. The pooled 30-days mortality rate was lower (IRD = −6%, 95% CI: −11% to −1%, $P = 0.02$, $I^2 = 54$) in patients under NST care compared with standard care (Supplementary File S5.1 and Table 3). Again, one study was an extreme outlier, accounting for all study heterogeneity.[44] Exclusion of this study decreased the effect of NST introduction (IRD = −3%, 95% CI: −6% to −0.2%, $I^2 = 0\%$; Supplementary File S6.2).

Among non-infectious catheter-related complications, thrombotic and metabolic events were evaluated before and after the introduction of an NST. Venous thromboembolisms were reported in just two studies,[32,33] and a meta-analysis was therefore omitted. PN-related hypophosphataemia was evaluated in five studies.[33,39,48,51,54] Under NST care, risk of hypophosphataemia seemed to decrease (IRD = −12%, 95% CI: −24% to −1%, $P = 0.03$, $I^2 = 87\%$) compared with standard care (Supplementary File S5.2). One study was an extreme outlier explaining the study heterogeneity.[33] When omitted, the effect decreased (IRD = −9%, 95% CI: −14% to −5%, $I^2 = 11\%$) while still being statistically significant (Supplementary File S6.3). PN-related hyperglycaemia was evaluated in 329 patients under standard care and 65 under NST care across six studies.[32-35,39,53] Analysis showed no statistically significant effect of an NST on hyperglycaemia ($P = 0.66$; Supplementary File S5.3). No extreme outliers were identified, but one study explained all heterogeneity.[33] After omission, the effect remained unchanged (95% CI: −2% to 15%, $I^2 = 0\%$; Supplementary File S6.4).

Five studies[32,51,52,54,55] reported LOS outcomes and 20 studies[12,32-37,39-42,44,45,47,48,51-54,56] reported data for PN duration. All studies reported comparable means but failed to report corresponding standard deviations and meta-analyses could not be performed in accordance with the Cochrane handbook.[20] No studies evaluated the occurrence of re-admissions.

Three of the included studies included cost calculations; two US studies[39,41] reporting PN-related charges and one UK study[44] including derived hospital costs. In the US studies, PN charges per patient changed from €2486 to €2105 in one study and from €2801 to €4342 in the other, following NST introduction. In the UK study, PN costs decreased from €826 to €673 after NST introduction, while most cost changes were related to avoided inappropriate PN episodes (55 episodes, €42 741) or CRI episodes (39 episodes, €7974). Data were insufficient for a reliable meta-analysis.

Across 10 studies[38,39,41,43,45,47-49,53,56] that compared PN appropriateness in 1267 patients under standard care and 1458 under NST care, inappropriate PN was less frequently prescribed (IRD = −18%, 95% CI: −28% to −9%, $P < 0.01$, $I^2 = 89\%$) under NST care compared with standard care (Supplementary File S5.4). Sensitivity analyses did not explain heterogeneity, but two studies were extreme outliers.[48,56] Visual inspection of the funnel plot indicated no publication bias (Eggert $P = 0.86$; Supplementary File S6.5). Seven studies[40,41,45,48,50,51,53] reported short term PN outcomes, which may be a surrogate marker of inappropriateness. Judged by PN duration, the pooled risk estimate was lower (IRD = −21%, 95% CI: −33% to −9%, $P < 0.01$, $I^2 = 70$) under NST care compared with standard care (Supplementary File S5.5). No extreme outliers were identified. Omission of one study[51] explained some heterogeneity and increased the effect of NST introduction (IRD = −25%, 95% CI: −35 to −15, $I^2 = 46\%$). Funnel plot inspection revealed evidence of negative publication bias, indicating that studies with higher effect were more likely to be published, but this did not reach statistical significance (Eggert $P = 0.057$; Supplementary File S6.6).

4 | DISCUSSION

This is the first systematic review and meta-analysis to establish the clinical evidence and provide conclusive data for reduction of CRI occurrence following the introduction of an NST. Furthermore, the meta-analysis also demonstrated very low to moderate quality of evidence for implementing an NST for other benchmarking outcome variables including mortality and inappropriate PN use in adult hospitalised patients on PN. While NSTs have been developed in many hospitals, deficits worldwide warrant a data synthesis applicable to international health care providers to facilitate decision making around nutrition service developments. The superiority of NST care regarding key clinical quality indicators should justify the continued implementation of NSTs globally.

Previous systematic reviews primarily evaluated PN appropriateness and the enteral nutrition (EN) to PN trend.[17,18] These literature reviews found a decrease in inappropriate PN use and an increase in the EN to PN use ratio after NST introduction.[17,18] Both reviews restricted eligible studies to those published after 2000 and neither

TABLE 3 Summary of findings of effects following the introduction of a nutrition support team for PN compared with standard care

Nutrition support team compared with standard care in adult inpatients receiving PN **Patient or population: Adult inpatients receiving PN** **Setting: Hospital** **Intervention: Nutrition support team (NST)** **Comparison: Standard care**				
	Relative effect, IRD (95% CI)	**Relative effect, IRR (95% CI)**	**Participants (studies)**	**Quality of the evidence (GRADE)**
Primary outcome				
CRIs per 1000 catheter days	−8.48 (−11.72 to −5.24)	0.32 (0.19-0.53)	3422 (10)	⊕⊕✶○○[a] MODERATE
Secondary outcomes				
Mortality (combined)	−0.06 (−0.11 to −0.01)	0.76 (0.60-0.97)	2795 (9)	⊕○○○ LOW
Metabolic catheter complications (pooled)	−0.05 (−0.27 to 0.16)	0.87 (0.41-1.85)	663 (3)	○○○○[b,c,d] VERY LOW
Thrombotic catheter complications	−1.71 (−6.60 to 3.17)	0.71 (0.02-21.80)	425 (2)	○○○○[c,d] VERY LOW
Length of stay	N/A	N/A	N/A	N/A
PN duration	N/A	N/A	N/A	N/A
Appropriateness: inappropriate indication	−0.18 (−0.28 to −0.09)	0.36 (0.22-0.60)	2725 (10)	○○○○[a,b,e] VERY LOW
Appropriateness: duration <1 wk	−0.21 (−0.33 to −0.09)	0.52 (0.36-0.75)	867 (7)	○○○○[b,c,e] VERY LOW
PN cost per patient	N/A	N/A	N/A	N/A

Abbreviations: CI, confidence interval; CRI, catheter-related infection; IRD, incidence rate difference; IRR, incidence rate ratio; LOS, length of stay; N/A, not available/not possible to calculate; NST, nutrition support team; PN, parenteral nutrition.

[a]Rated 1 up for large magnitude of effect.

[b]Rated 1 down for inconsistency of results.

[c]Rated 1 down for indirectness of evidence.

[d]Rated 1 down for imprecision.

[e]Rated 1 down for publication bias.

performed meta-analyses nor graded the evidence. One previous systematic review attempted to evaluate infectious and metabolic catheter-related complications after NST introduction, but failed to provide conclusive data.[14]

This review suggests a relative reduction in CRI rate of 68% equivalent to an absolute reduction of eight CRI episodes per 1000 catheter days after NST introduction compared with standard care. One outlier explained most study heterogeneity, and sensitivity analyses documented overall robust effect estimates. In this systematic review, all but one study evaluating CRI occurrence demonstrated a reduced CRI rate after NST introduction. The deviating study lacked a consistent method of diagnosing CRI.[42] Multiple CRI definitions were used across all included studies, and some studies failed to provide a clear definition. This is a common challenge throughout the literature.[57] It is apparent that CRI rates may differ depending on the definition, as CLABSI is thought to overestimate and CRBSI underestimate the true CRI rate.[58] Consequently, precautions should be taken when interpreting and comparing CRI rates because definition differences may result in discrepancies and comparability difficulties.[21,58] While dedicated intestinal failure units may achieve extremely low CRI rates, the corresponding rates in general wards may be higher.[59] Under NST supervision, quality improvement initiatives aimed to unify insertion and catheter care may significantly reduce CRI rates in these wards.[7,59,60] It has been proposed that NSTs may aim for an in-patient CRI target of <1 episode per 1000 catheter days both in dedicated units and general wards.[59,61]

Among the secondary outcomes in the present study, NST introduction statistically significantly reduced 30-day mortality and inappropriate PN use compared with standard care. While the reduction in mortality may reflect differences in-patient selection and the multidisciplinary nature of NST care, it may also result from the reduction in CRI occurrence, because CRIs independently increase LOS, hospital costs, and mortality.[3-5] In evaluating the mortality, study heterogeneity was entirely explained by one study[44] which obtained pre-NST data during retrospective analysis, increasing the risk of selection bias.

In studies evaluating catheter-related metabolic complications, the study from 1980 by Nehme et al accounted for all heterogeneity.[33] This may be explained by the study being one of the first to compare an NST with what was then standard care and to

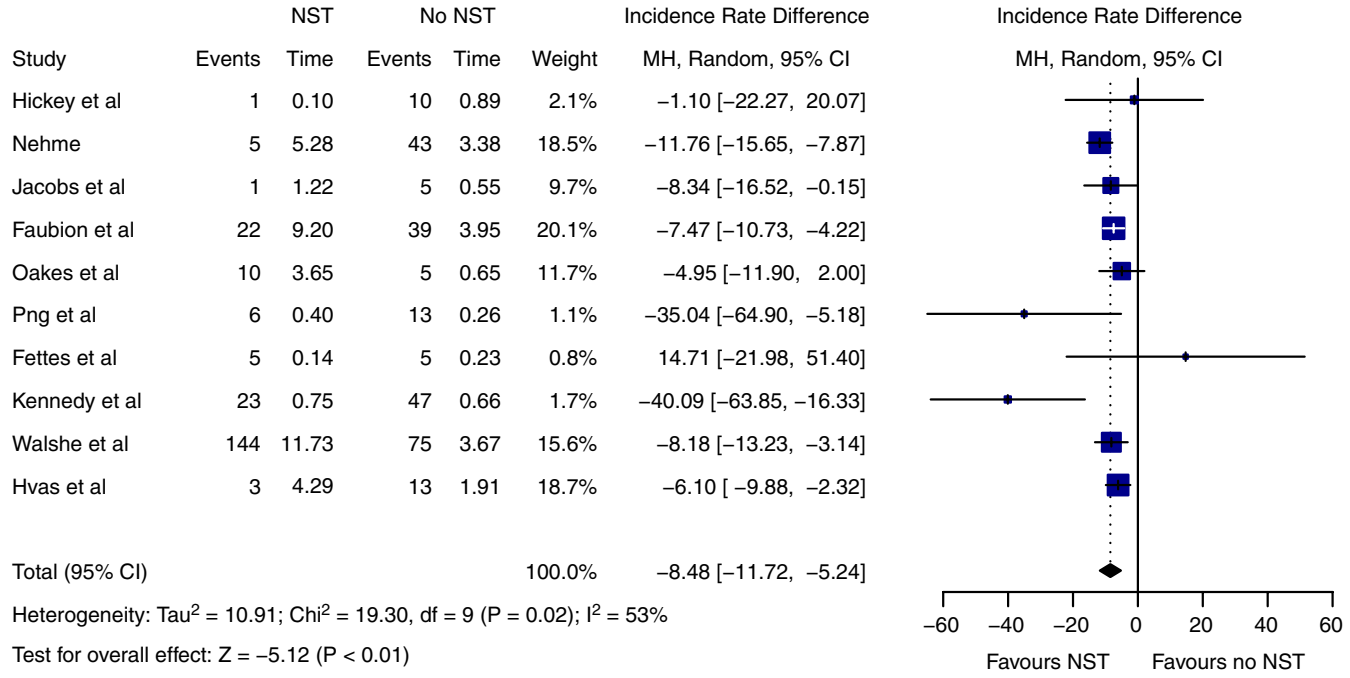

FIGURE 2 Forest plot of the differential effect of a nutrition support team on CRI rate compared with standard care

demonstrate the significant impact of introducing multidisciplinary care. This may have led to improvements of standard care in the later studies, thereby limiting the effect size of later introductions of NSTs because some practices may have been adapted to the standard care.

In this systematic review, short term PN use was used as surrogate marker of inappropriateness. This was considered reasonable for comparison because alternatives such as EN have shown to decrease infective complications and to be more cost-effective than PN.[62] The European Society for Clinical Nutrition and Metabolism[25] agrees with the American Society for Parenteral and Enteral Nutrition (PEN)[26] on PN being indicated only if the duration is anticipated to be above 7 days. In contrast, NICE[1] states there is no minimum length of time for this duration, and the use of short duration as a proxy for inappropriateness may therefore be contentious.

Important limitations apply to this systematic review. PN-related cost is an important outcome measure when implementing a new service, but cost data in the included studies were sporadic and did not allow meta-analysis. Future studies should include modern cost-effectiveness analysis methods. Results from observational studies with historical controls may be influenced by concomitant improvements in practice, equipment, and new PN solutions, leading to an overestimation of the true benefits of introducing an NST. Also, establishing quality of evidence for NSTs is challenged by inconsistent use of terminology, especially regarding CRIs and NSTs. Most frequently, nutrition support teams are referred to as NSTs, but several terminological variations exist. Additional literature searches identified terms such as nutrition support service, metabolic support service, nutrition advisory team, total parenteral nutrition team, or PEN team. These variations along with inconsistencies in team composition challenges comparability and may lead to exclusion of studies otherwise eligible of inclusion. This is further challenged by the lack of an "NST" MeSH term in literature databases. Another limitation to the present study is the mere reporting of NST presence without consideration of the organisation of care. Only one previous study examined the impact of different NST setups.[63] Future studies should determine the impact of an advisory/consultative team vs a bedside prescribing team. Furthermore, the creation of a "NST" MeSH term could harmonise future literature searches and potentially find more eligible studies. Future studies including proper cost-effectiveness analyses may contribute to the beneficial effects of introducing NSTs. This is important as NSTs still only has limited availability worldwide and needs continued evaluation of the evidence to help justify their existence and continued implementation.

In conclusion, this systematic review and meta-analysis provided moderate quality of evidence for the primary outcome effect of an NST and very low to low quality of evidence for secondary outcome effects. Compared with standard care, NST introduction reduced CRI occurrence, mortality, and inappropriate PN use. The study was limited by inconsistencies in CRI and NST terminologies. Future studies should investigate the impact of differences in organisation of care within NSTs.

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AUTHORSHIP

Author contributions: M. K. Eriksen is the corresponding author and the guarantor of the article. M. K. Eriksen, B. Crooks, S. M. D. Baunwall, C. L. Rud, S. Lal, C. L. Hvas equally contributed to the

conception and design of the study. M. K. Eriksen extracted the data and B. Crooks validated them. M. K. Eriksen and S. M. D. Baunwall equally contributed to the analysis of the data. All authors contributed to the interpretation of the data, and M. K. Eriksen drafted the manuscript. All authors critically revised the manuscript and read and approved the final manuscript.

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DATA AVAILABILITY STATEMENT

Study protocol is available from https://www.crd.york.ac.uk/PROSPERO (CRD42020218094). The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Marcel Kjærsgaard Eriksen https://orcid.org/0000-0001-7563-8154
Simon Mark Dahl Baunwall https://orcid.org/0000-0002-5135-7435
Simon Lal https://orcid.org/0000-0002-6245-8864

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SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

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