Laleh et al. BMC Pediatrics (2025) 25:145
https://doi.org/10.1186/s12887-025-05504-z

BMC Pediatrics

RESEARCH

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The effect of breast milk odor on infant pain and stress levels: a systematic review and meta-analysis

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Abstract

Background Effective management of neonatal pain and stress is crucial, with non-pharmacological approaches like maternal odor showing promise. However, mixed evidence exists on its efficacy. This study aims to comprehensively assess the effects of breast milk odor on pain and stress (primary outcomes) and on oxygen saturation (SpO2) and heart rate (secondary outcomes) in neonates.

Methods A thorough search was conducted on PubMed, Cochrane, SID, Embase, and Google Scholar until January 14, 2025, without time restrictions. A meta-analysis was performed to compare outcomes between intervention and control groups, assessing heterogeneity using the I^2 statistic and chi-squared test. A random effects model was applied for high heterogeneity ($I^2 \geq 30\%$, $p < 0.05$), analyzing continuous outcomes with mean difference (MD) and standardized mean difference (SMD) at a 95% confidence interval (CI). Subgroup analyses were conducted based on newborn procedures and term status, along with meta-regression and sensitivity analyses. Trial Sequential Analysis (TSA) was employed to ensure reliable conclusions about the intervention effects, and the certainty of evidence was evaluated using GRADE.

Results The systematic review included seven studies (RCT and quasi-experimental) revealing that breast milk odor significantly reduces pain responses in neonates (SMD: -1.60, 95% CI: -2.48, -0.72; $I^2 = 94\%$; 7 trials; 478 neonates; low-certainty evidence). It also improved key physiological parameters, such as oxygen saturation (MD: 1.64, 95% CI: 0.49, 2.80; $I^2 = 57\%$; 5 trials; 288 neonates; very low-certainty evidence) and heart rate (MD: -6.73, 95% CI: -12.33, -1.13; $I^2 = 78\%$; 5 trials; 288 neonates; very low-certainty evidence). Although a reduction in stress levels was noted, it did not reach statistical significance (MD: -0.64, 95% CI: -1.87, 0.59; $I^2 = 89\%$; 2 trials; 128 neonates; very low-certainty evidence). Meta-regression indicated a significant correlation between cesarean delivery rates and neonatal pain response ($p = 0.010$). TSA results confirmed the analysis was adequately powered for pain outcome.

Conclusion The review underscores the potential of breast milk odor as a non-pharmacological intervention for managing pain in neonates. However, the low to very low certainty of evidence calls for further research to validate these findings and improve neonatal care protocols.

Keywords Olfactory Stimulation, Maternal Behavior, Newborn, Non-pharmacological, Pain, Stress

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Background

Olfaction is a vital sensory modality that facilitates the connection between infants and their mothers, aiding infants in locating the breast. This sensory ability begins developing in utero, with olfactory cells fully formed by the 11th week of pregnancy, indicating the olfactory system's functionality during the first trimester [1, 2]. The olfactory sense continues to develop between the 26th and 28th weeks of pregnancy, contributing to both motor and emotional responses [3].

The fetus, surrounded by amniotic fluid, experiences this fluid's odor as a familiar and comforting scent, which it retains after birth [4]. Both full-term and preterm infants, with their heightened olfactory sensitivity, can distinguish their mother's scent from others [5]. This olfactory recognition helps infants identify their mother and surroundings, which is crucial for breastfeeding and establishing a sense of safety [6]. Research indicates that infants possess a keen sense of smell, which significantly influences their early social development [7].

Healthy, full-term infants are innately capable of adapting to diverse environmental conditions [8]. A mature olfactory system supports the immature visual system by providing stability amidst visual changes [9]. Infants exhibit physiological and behavioral reactions to odors; pleasant and familiar scents elicit positive responses, while unpleasant odors can have adverse effects [10]. Notably, familiar odors can facilitate psycho-physiological adjustments, especially in premature infants, enhancing their emotional well-being [3].

Infants frequently undergo painful medical procedures, such as heel blood collection and intubation, which can lead to immediate physiological changes, including alterations in heart rate and oxygen saturation [11, 12]. Contrary to earlier beliefs that infants lacked pain perception due to underdeveloped nociceptors, research has shown that they can detect and respond to pain, often exhibiting more sensitivity than adults [13]. Pain in infants can lead to significant physiological and behavioral changes, complicating pain assessment due to their inability to articulate pain verbally [14–16].

Stress, a state of physical and mental tension, is closely linked to pain and can arise from various factors, including separation from mothers [8, 17]. Frequent painful procedures can exacerbate stress, negatively impacting an infant's clinical state [10]. Infants develop early social bonds through recognition of their mother's face and voice, but olfactory cues, particularly maternal scents like breast milk and amniotic fluid, are also crucial for early affection and socialization [7, 18]. Infants demonstrate a marked preference for their mother's unclean breast over cleansed ones, indicating that maternal odor significantly influences breastfeeding behavior and attachment [7, 19]. The scent of breast milk not only aids breastfeeding but also has calming effects, potentially reducing pain during procedures [20].

The first 28 days of life are critical for infant survival. Global infant mortality rates have decreased, yet in 2021, approximately 6,400 infants died daily, totaling 2.3 million deaths [21–24]. Monitoring infant mortality is essential for assessing a country's health status. Implementing effective treatment and care strategies is crucial to mitigate health issues in infants. Both pharmacological and non-pharmacological approaches are employed to alleviate pain and reduce stress, with maternal odor being a notable non-pharmacological method. Research suggests that maternal scents, particularly breast milk, can diminish stress responses in newborns [25, 26]. Studies have shown that maternal voice and breast milk odor can lower discomfort during painful procedures [27]. However, some findings indicate that maternal odor may not consistently predict pain relief, and its effects can be comparable to those of other scents, such as roses [28]. Given the mixed findings regarding the effectiveness of maternal odor in pain alleviation, there is a pressing need for systematic investigation. Therefore, this study aims to comprehensively assess the effects of breast milk odor on pain, stress, oxygen saturation (SpO2), and heart rate in neonates.

Methods

We employed the Cochrane Manual for Systematic Reviews of Interventions [29] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [30]. We also registered the study in the International Prospective Register of Systematic Reviews (PROSPERO) (PROSPERO ID: CRD42024546862).

The search strategy

The study data were obtained through a comprehensive search across multiple databases, including the Cochrane Library, PubMed, SID (Scientific Information Database), Embase and Google Scholar. The search utilized Boolean operators (OR and AND) to refine the results, and the search terms were tailored to meet the specific requirements of each database.

A systematic search was conducted using standard keywords derived from the MeSH Browser, focusing on terms such as olfactory stimulation, non-pharmacological measures, pain, and stress. The search strategy included: ((newborn) OR (neonate) OR (infant) [MeSH] OR Baby) AND (olfactory OR maternal odor OR breast milk odor OR mother scent OR nonpharmacological OR sense of smell) AND ("pain" OR venipuncture OR discomfort OR stress OR "heart rate" OR "pulse" OR oxygen saturation OR physiological parameters) AND ("randomized-controlled trial" OR "controlled clinical trial" OR randomized OR randomly OR trial OR quasi-experimental OR RCT).

The search was performed across PubMed, Embase, Cochrane Library, SID (Persian database), and Google Scholar (search engine) until January 14, 2025. Articles published in languages other than Persian, Turkish, and English were excluded based on the established inclusion criteria. Additionally, a thorough manual search of citations from relevant journals was performed to ensure comprehensive coverage of the topic. Articles published in conferences, seminars, and other types of studies, excluding RCT articles and quasi-experimental articles, were excluded from the present study. The search strategy for each database is provided in theadditional file.

Inclusion criteria

Data were collected using standardized extraction forms based on the PICOS framework, which included the following elements: participants, intervention, comparison, outcomes, and study design. In this review, the participants (P) were newborn infants. The intervention (I) involved exposure to breast milk odor. The control or comparison group (C) consisted of infants receiving only routine treatments. The outcomes of interest (O) were pain and stress, SPO2 and heart rate (secondary outcomes) (S). The study designs were either randomized controlled trials (RCTs) or quasi-experimental studies.

The exclusion criteria encompassed the absence of a control or comparison group, the lack of complete article content, and papers written in languages other than Farsi, Turkish, and English.

Study selection process

The research was organized using Endnote (version 21), a program for information resource management. The study selection approach involved initially searching databases and other sources. All identified articles and sources were inputted into the Endnote program, where duplicate articles were eliminated. The titles and abstracts of the remaining articles were scrutinized, followed by the removal of non-relevant items. The complete texts of pertinent articles were then examined based on predefined inclusion and exclusion criteria.

To enhance credibility, the article searches and selection procedures were conducted by two autonomous researchers (S.SL and M. Ma). In cases of disagreement, the third and fourth researchers (M. Mi and S.I) were involved to finalize the selection of articles. This dual workflow ensured that the process was blinded and rigorous, integrating the Endnote management with a thorough human review.

Data extraction

Two researchers (S.SL and M. Ma) independently extracted data using a checklist made by the researcher. The checklist comprises details on the author's name, publication year, country of origin, study design, sample size, intervention and control groups, duration of follow-up, blinding method, outcome and results.

Risk of bias assessment

Two researchers (S.SL and M. Ma) independently assessed the article's quality. In instances of dispute, a third researcher (M. Mi) was involved to facilitate a consensus. The risk of bias in the included studies was assessed using the Cochrane Risk of Bias 2.0 (RoB 2.0) tool, which evaluates five domains along with an overall assessment. The results were classified as "low risk of bias," "some concerns," or "high risk of bias" [31]. The risk of bias in the quasi-experimental publication was assessed using the ROBINS-1 tool [32].

Data analysis

A meta-analysis was performed using Review Manager 5.3 to evaluate the outcomes of interest between the intervention and control groups. The heterogeneity among studies was assessed using the I^2 statistic and the p-value from the chi-squared test. A high level of heterogeneity was defined as an I^2 statistic of 30% or greater, with a corresponding p-value of less than 0.05, in which case a random effects model was utilized [33]. For continuous variables, we use mean difference (MD) and standardized mean difference (SMD) with a 95% confidence interval (CI). A p-value of less than 0.05 was considered statistically significant for all analyses.

Subgroup analyses were conducted based on the types of procedures performed on newborns (including Hepatitis B vaccination, venipuncture, endotracheal suction, and peripheral cannulation) and the term status (term or preterm) of the infants for all outcomes.

Meta-regression analyses were executed using Stata 18 (College Station, TX: StataCorp LLC), focusing on the percentage of male infants and the percentage of cesarean deliveries. Additionally, sensitivity analyses were performed using a leave-one-out meta-analysis approach, applying the DerSimonian and Laird method for the primary outcome of pain.

Trial Sequential Analysis (TSA) was conducted using the TSA software package version 0.9.5.10 Beta, with an alpha level set at 1% and a beta level at 90%. The MD and variance were assessed empirically, and the I^2 was derived from model-based variance to determine the

Required Information Size (RIS) and the alpha spending boundaries.

We planned to assess publication bias for the outcome with more than 10 included studies. The certainty of evidence was assessed using the grading system of recommendations, assessment development, and evaluation (GRADE) in five dimensions Risk of bias, Inconsistency, Indirectness, Imprecision and Publication bias [34].

Results

The search results

The results of the search strategy are summarized in the PRISMA diagram (Fig. 1). A total of 429 studies were identified, of which 85 were removed due to duplicate records. From the remaining studies, 12 were assessed for eligibility, and 5 were excluded: four lacked control groups [28, 35–37], and one was a duplicate publication [38]. Ultimately, seven papers that met the study criteria were thoroughly reviewed and included in the meta-analysis [17, 26, 39–43].

Characteristics of included studies

The study characteristics table summarizes Table 1 the characteristics of the trials included in this systematic review. This systematic review comprised six RCTs and one semi-experimental study [17, 26, 39–43]. Involving a total of 478 term and preterm infants from Iran [26, 40, 42, 43], Turkey [17, 39], and Egypt [41]. Three studies [26, 41, 43] focused on preterm neonates, while the others included term infants. The publication dates of these papers range from 2015 to 2024. Two articles [38, 43] were written in Farsi, while the remaining studies were published in English. In all trials, the control group received only routine care treatments, whereas the intervention group was provided with olfactory stimulation approaches using maternal odor alongside routine

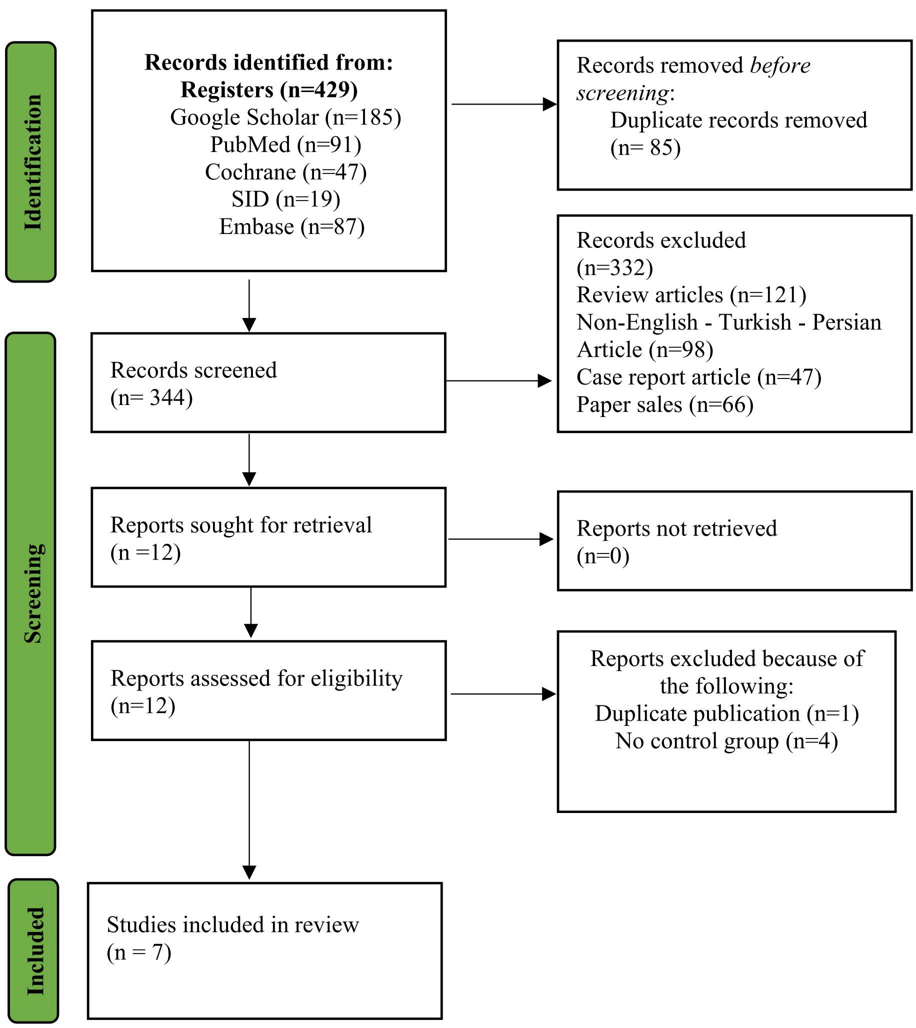

Fig. 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram

Table 1 Characteristics of included studies

Author (s) Location/ (year)/ Country	Study design	Overall risk of bias	Study groups	Type of intervention/s	Type of blinding	Follow-up period	Number of participants in each group	Main outcome/s	Results
Deniz & Sarıalioğlu / 2024, Türkiye [39]	RCT	Low risk	Group 1: Smelling mother's milk smell Group 2: Control group	Infants in the intervention group were exposed to 1 ml of breast milk placed on a sterile sponge, held 10 cm from their nose, before and after endotracheal suction. The control group received no intervention	Unclear	Time 1: Before procedure Time 2: During procedure Time 3: After procedure	Intervention group: 44 Control group: 44	Pain, stress, SpO2, and heart rate	Breast milk odor showed no significant difference in mean pain, stress, SpO2, and heart rate compared to the control group
Asadian et al. / 2023, Iran [40]	RCT	Some concerns	Group 1: Smelling mother's milk smell Group 2: Control group	The intervention group smelled breast milk placed 3 cm from their nose for 3 min before and during venipuncture, while the control group received no intervention	Two-blind	Time 1: Before the procedure Time 2: Immediately after the procedure	Intervention group: 20 Control group: 20	Pain, SpO2, and heart rate	Breast milk odor showed no significant difference in mean SpO2 and heart rate compared to the control group. Mean pain scores significantly decreased in the breast milk odor group compared to the control group
Özdemir et al. / 2022, Türkiye [17]	RCT	Low risk	Group 1: Smelling mother's milk smell Group 2: Control group	Participants in the intervention groups smelled breast milk, were placed in a prone position, or used a pacifier during blood sampling, while the control group received standard care	Single-blind	Time 1: Before the procedure Time 2: During the procedure Time 3: After the procedure	Intervention group 1: 20 Intervention group 2: 20 Intervention group 3: 20 Control group: 20	Pain, stress, SpO2, and heart rate	Breast milk odor showed no significant difference in mean heart rate compared to the control group. Mean pain and stress scores significantly decreased, and SpO2 significantly increased in the breast milk odor group compared to the control group

Table 1 (continued)

Author (s) Location/ (year)/ Country	Study design	Overall risk of bias	Study groups	Type of intervention/s	Type of blinding	Follow-up period	Number of participants in each group	Main outcome/s	Results
Ali et al. / 2022, Egypt [41]	Quasi-experimental research design	Some concerns	Group 1: Smelling mother's milk smell Group 32: Control group	Infants in the intervention group smelled breast milk for 15 min prior to and during the procedure, while another group listened to their mother's voice, and the control group received standard care		Time 1: Before procedure Time 2: During procedure Time 3: Immediately after procedure Time 4: 5 min after cannulation	Intervention group 1: 50 Intervention group 2: 50 Control group: 50	Pain	Breast milk odor resulted in significantly decreased mean pain scores compared to the control group
Akbarian Rad et al. / 2021, Iran [26]	RCT	Some concerns	Group 1: Breast milk odor Group 2: Control group (receiver of the odor of distilled water)	Infants were exposed to their own mother's milk odor, another mother's milk odor, or distilled water odor for 3 min before receiving a hepatitis B vaccine	Single-blind	Time 1: Before intervention Time 2: After intervention	Intervention group 1: 30 Intervention group 2: 30 Control group: 30	Pain, SpO2, and heart rate	Breast milk odor showed no significant difference in mean SpO2 compared to the control group. Mean pain and heart rate scores significantly decreased in the breast milk odor group compared to the control group
Amiri Shadmehri et al. / 2020, Iran [42]	RCT	Some concerns	Group 1: Smelling mother's milk odor Group 3: Control group	The intervention group smelled breast milk for 3 min before vaccination, while another group used a pacifier, and the control group received no intervention	Unclear	Time 1: Before intervention Time 2: After intervention	Intervention group 1: 30 Intervention group 2: 30 Control group: 30	Pain, SpO2, and heart rate	Mean pain and heart rate scores significantly decreased, and SpO2 significantly increased in the breast milk odor group compared to the control group

Table 1 (continued)

Author (s) Location/ (year)/ Country	Study design	Overall risk of bias	Study groups	Type of intervention/s	Type of blinding	Follow-up period	Number of participants in each group	Main outcome/s	Results
Jebreili et al. / 2015, Iran [43]	RCT	Some concerns	Group 1: Smelling mother's milk smell Group 2: Control group (receiver of the smell of distilled water)	Infants in the intervention group smelled breast milk from a cotton ball positioned near their nose during blood sampling, while the control group smelled distilled water	In the study, two research assistants were unaware of the random assignment of each sample to the groups	Time 1: Before the procedure Time 2: During the procedure Time 3: After the procedure	Intervention group: 45 Control group: 45	Pain	Breast milk odor showed no significant difference in mean pain scores compared to the control group

SpO2 Oxygen Saturation, *RCT* Randomized Controlled Trial

treatments. The studies involved infants aged between 28 and 42 weeks.

In the studies included in the meta-analysis, the Newborn Pain and Stress Assessment Scale (ALPS-Neo) and The Neonatal Stress Scale were used to measure stress. Newborn Pain and Stress Assessment Scale (ALPS-Neo) as the primary tool to measure stress levels in infants. ALPS-Neo is a 3-point Likert scale consisting of 5 items. As a result of the assessment, 3-5 points indicate the presence of mild pain and stress, and more than 5 points indicate the presence of serious pain and stress [39]. The Neonatal Stress Scale, developed by Ceylan and Bolışık, is designed to assess stress in infants in NICUs. It consists of 24 items divided into eight subgroups, evaluating behaviors such as facial expression, body color, and activity level using a Likert-type response scale. Each subgroup is scored from 0 to 2 points, with a total possible score of 0 to 16. The scale is based on observation, allowing caregivers to tailor interventions and improve care for stressed infants [17].

Risk of bias in included studies

Out of the included studies, 2 RCTs (33.3%) were rated as having a low risk of bias, while 4 studies (66.7%) were assessed as presenting some concerns regarding bias. Additionally, the risk of bias for one quasi-experimental study, evaluated using the ROBINS-1 tool, was rated as low risk of bias (Table S1 and Figures 2).

Publication bias

Due to the limited number of studies (fewer than 10) for the outcomes analyzed, a formal assessment of publication bias was not conducted.

Meta-analysis results

Primary Outcomes

Pain

The use of breast milk odor may reduce pain in neonates compared to the control group (SMD: -1.60, 95% CI: -2.48, -0.72; I^2 = 94%; 7 trials; 478 neonates; low-certainty evidence, Fig. 3A). The TSA results indicated that the Z-curve reached the Required Information Size (RIS) of 454 neonates, suggesting that the analysis was sufficiently powered to draw definitive conclusions regarding the effect of breast milk odor on neonatal pain (Fig. 3B).

Subgroup analysis based on the procedures performed (Hepatitis B vaccination, venipuncture, endotracheal suction, and peripheral cannulation) revealed significant differences among them. The results of the test for subgroup differences were as follows: Chi^2 = 32.32, degrees of freedom (df) = 3 (p < 0.0001), and I^2 = 90.7%. Pain was significantly reduced by breast milk odor in all procedures except for endotracheal suction (Fig. 3A).

Another subgroup analysis based on the categorization of neonates (term vs. preterm) did not reveal significant differences. The results of the test for subgroup differences were as follows: Chi^2 = 0.09, df = 1 (p = 0.76), and I^2 = 0%. These findings suggest that the treatment effect is consistent for both term and preterm neonates (Fig S1).

The meta-regression analyses demonstrated no significant correlation between pain scores and the percentage of male neonates (p = 0.613). In contrast, a significant correlation was observed between the percentage of cesarean deliveries and the effect size of neonatal pain, indicating that higher percentages of cesarean deliveries were associated with increased levels of neonatal pain (p = 0.010, Table 2).

Stress

The effect of breast milk odor on neonatal stress, compared to the control group, remains uncertain (MD: -0.64, 95% CI: -1.87, 0.59; I^2 = 89%; 2 trials; 128 neonates; very low-certainty evidence) (Fig. 4A). The TSA results indicated that the Z-curve did not reach the RIS of 1986 neonates, suggesting that additional trials are necessary to draw definitive conclusions regarding the effect of breast milk odor on neonatal stress (Fig. 4B).

Secondary outcomes

Oxygen saturation (SPO_2)

The use of breast milk odor may improve SPO_2 in neonates compared to the control group, but the evidence remains uncertain (MD: 1.64, 95% CI: 0.49, 2.80; I^2 = 57%; 5 trials; 288 neonates; very low-certainty evidence) (Fig. 5A). The TSA results indicated that the Z-curve did not reach the RIS of 556 neonates, suggesting that additional trials are necessary to draw definitive conclusions regarding the effect of breast milk odor on neonatal stress (Fig. 5B).

Subgroup analysis based on the procedures performed (Hepatitis B vaccination, venipuncture, and endotracheal suction) revealed significant differences among them. The results of the test for subgroup differences were as follows: Chi^2 = 9.02, df = 2 (p = 0.01), and I^2 = 77.8%. SPO2 was significantly improved by breast milk odor in all procedures except for endotracheal suction (Fig. 5A).

Another subgroup analysis based on the categorization of neonates (term vs. preterm) did not reveal significant differences. The results of the test for subgroup differences were as follows: Chi^2 = 1.48, df = 1 (p = 0.22), and I^2 = 32.6%. These findings suggest that the treatment effect is consistent for both term and preterm neonates (Fig S2).

The meta-regression analyses demonstrated no significant correlation between SPO_2 and the percentage

Fig. 2 Summary of Risk of Bias Assessments: Authors' Judgments for Each Study (**A**) and Item Percentages Across Studies (Risk of bias summary, **B**)

of male neonates (p = 0.298) or percentage of cesarean deliveries (p = 0.394, Table 2).

Heart rate

The use of breast milk odor may improve heart rate in neonates compared to the control group, but the evidence remains uncertain (MD: -6.73, 95% CI: -12.33, -1.13; I^2 = 78%; 5 trials; 288 neonates; very low-certainty evidence) (Fig. 6A). The TSA results indicated that the Z-curve did not reach the RIS of 788 neonates, suggesting that additional trials are necessary to draw definitive conclusions regarding the effect of breast milk odor on neonatal heart rate (Fig. 6B).

Subgroup analysis based on the procedures performed (Hepatitis B vaccination, venipuncture, and endotracheal suction) did not revealed significant differences among them. The results of the test for subgroup differences were as follows: Chi^2 = 5.18, df = 2 (p = 0.07), and I^2 = 61.4%. These findings suggest that the treatment effect is consistent for these three procedures (Fig. 6A).

Another subgroup analysis based on the categorization of neonates (term vs. preterm) did not reveal significant differences. The results of the test for subgroup differences were as follows: Chi^2 = 0.26, df = 1 (p = 0.61), and I^2 = 0%. These findings suggest that the treatment effect is consistent for both term and preterm neonates (Fig S3).

The meta-regression analyses demonstrated no significant correlation between heart rate and the percentage of male neonates (0.568) or percentage of cesarean deliveries (p = 0.463, Table 2).

Sensitivity analysis

Excluding individual studies did not alter the statistically significant effect size or direction of the overall impact of neonatal pain, demonstrating the robustness of the findings (Fig. 7).

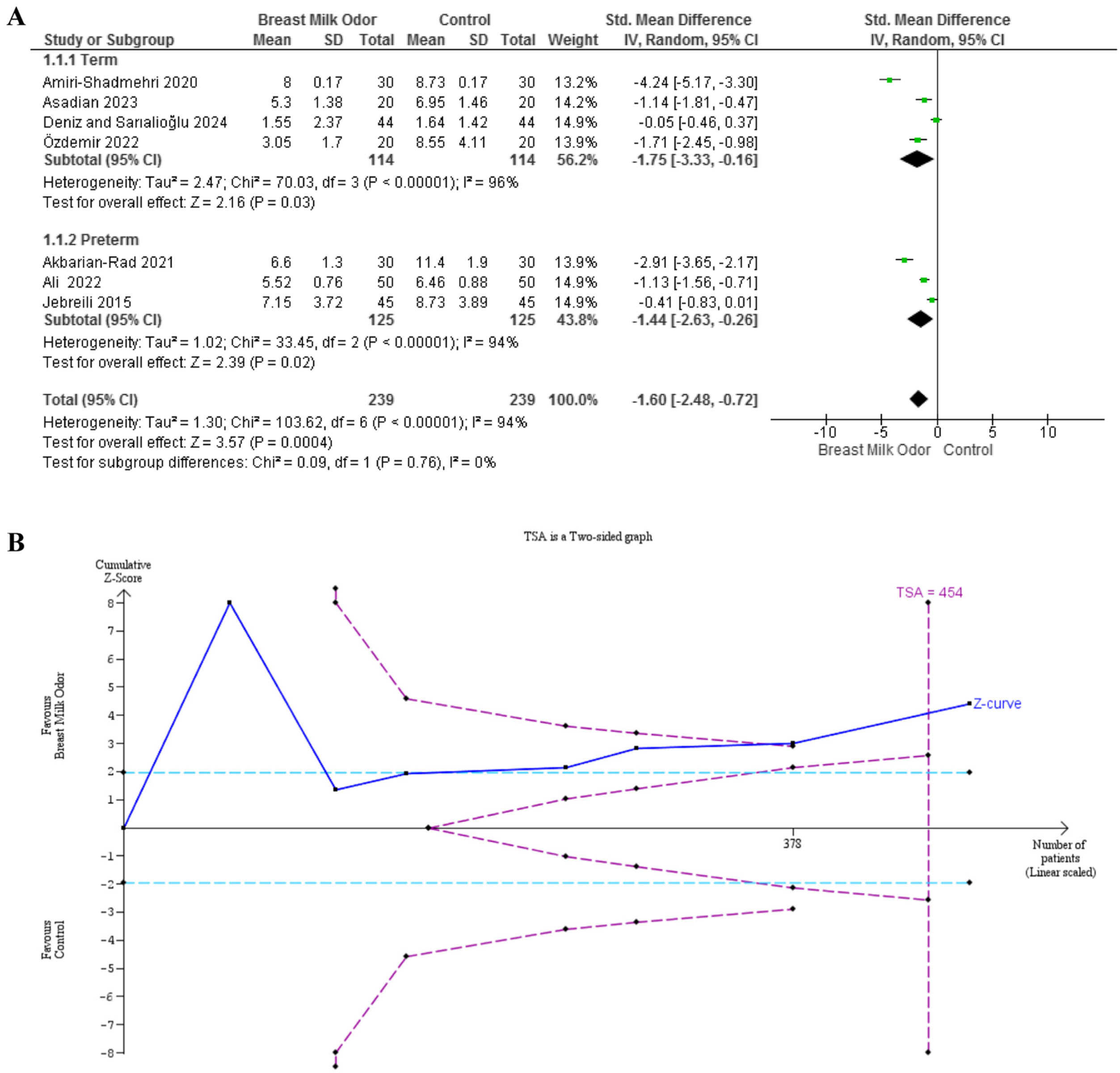

Fig. 3 Effect of Breast Milk Odor Intervention on Neonatal Pain (**a**) and Trial Sequential Analysis of Neonatal Pain (**b**)

Table 2 Meta-Regression results for risk factors associated with outcomes

Variable	Coefficient	Standard Error	P-value	95% CI
Pain				
Cesarean delivery percent	0.086	0.033	**0.010**	[0.020 to 0.152]
Male neonate percent	0.026	0.052	0.613	[-0.075 to 0.127]
Oxygen saturation (SPO2)				
Cesarean delivery percent	-0.146	0.141	0.298	[-0.422 to 0.129]
Male neonate percent	0.167	0.197	0.394	[-0.218 to 0.553]
Heart Rate				
Cesarean delivery percent	0.339	0.593	0.568	[-0.824 to 1.502]
Male neonate percent	0.868	1.184	0.463	[-1.453 to 3.190]

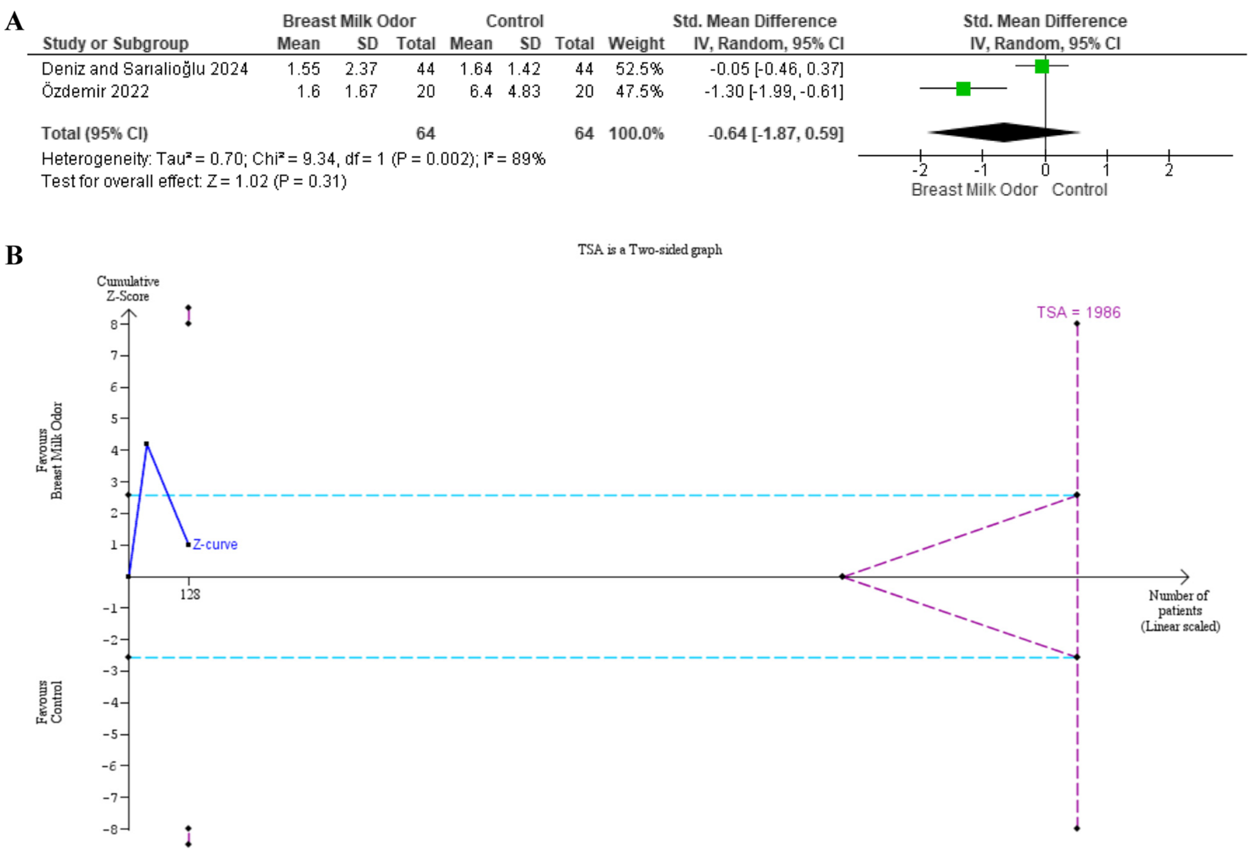

Fig. 4 Effect of Breast Milk Odor Intervention on Neonatal Stress (a) and Trial Sequential Analysis of Neonatal Stress (b)

The certainty of the evidence

The evidence for pain was assessed as having low certainty due to concerns about risk of bias and inconsistency. For other outcomes, the certainty was rated as very low because of risk of bias, inconsistency, and imprecision. The details are shown in Table 3.

Discussion

This systematic review offers evidence demonstrating that the odor of breast milk significantly alleviates pain in neonates, yielding a marked reduction in pain responses compared to standard care practices. The analgesic effect is complemented by improvements in critical physiological parameters, such as heart rate and SpO_2, which are vital indicators of neonatal well-being. While the decrease in stress levels observed in the neonates is noteworthy, it is essential to acknowledge that this change was not statistically significant, indicating a need for further exploration in this area.

The meta-analysis revealed a high degree of heterogeneity among the included studies, suggesting that various factors may influence outcomes. This variability necessitated subgroup analyses to delve deeper into the specific contexts affecting pain perception and physiological responses in neonates. The subgroup analyses revealed that the type of procedure performed can have a substantial impact on both pain and SpO_2 outcomes. Notably, the treatment effects of breast milk odor appear to be consistent across both term and preterm neonates, suggesting that this intervention may be universally beneficial regardless of gestational age. This consistency is crucial for clinical practice, as it indicates that breast milk odor could be a viable pain management strategy for all newborns undergoing medical procedures.

The meta-regression analyses shed light on additional factors influencing neonatal pain experiences. Specifically, higher rates of cesarean deliveries may be associated with increased pain experiences in neonates, potentially due to the effects of surgical delivery on the infant's physiological state. The stress of an operative birth, coupled with potential alterations in maternal-infant bonding during recovery, could contribute to an increased pain response in these infants [44, 45].

Weng et al. (2024) conducted a systematic review and meta-analysis of 35 RCTs involving 2,134 preterm infants in the NICU, exploring non-pharmacological

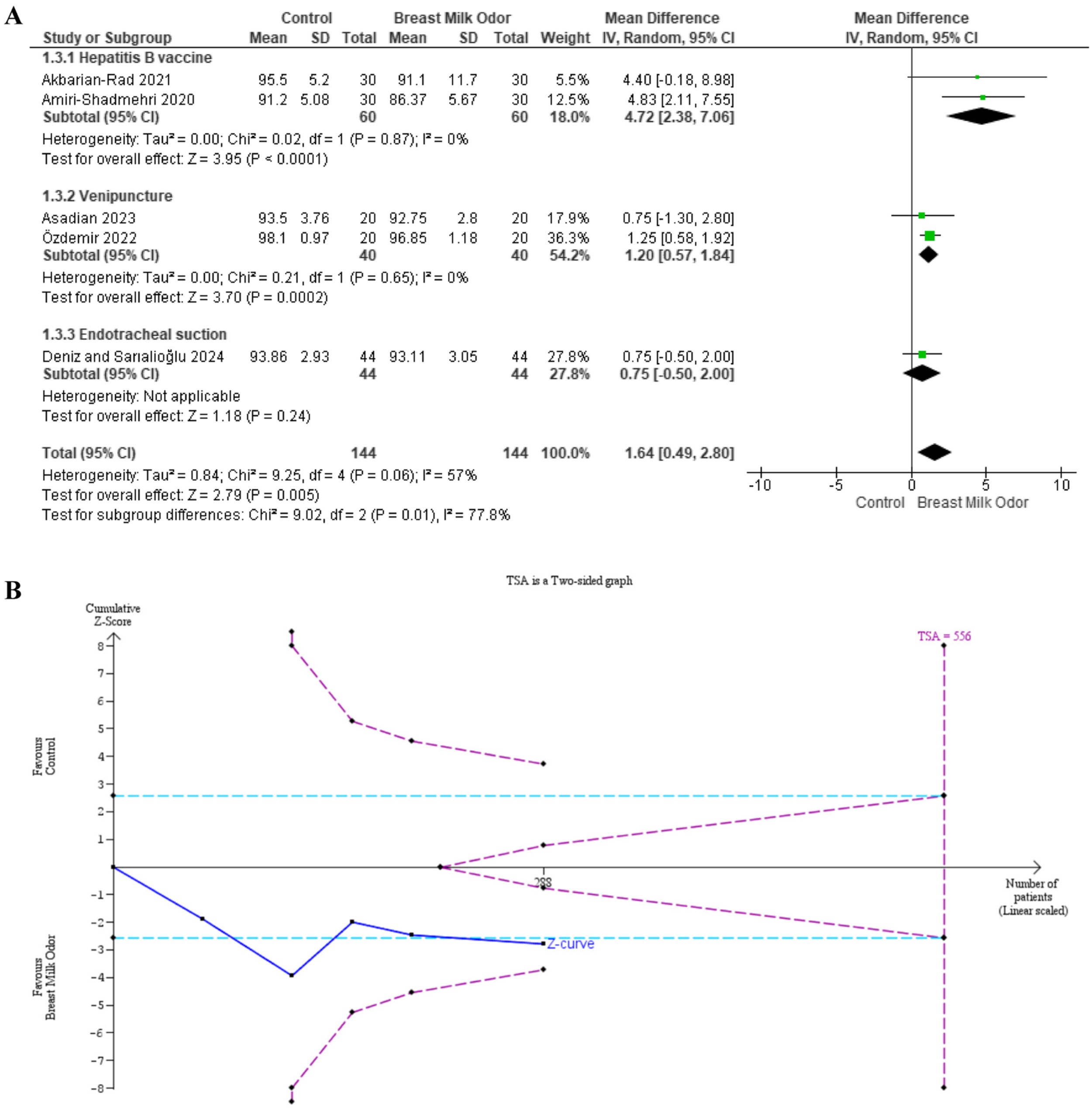

Fig. 5 Effect of Breast Milk Odor Intervention on Neonatal Oxygen Saturation (SpO_2) (**a**) and Trial Sequential Analysis of Neonatal SpO_2 (**b**)

therapies for pain management. The analysis included various interventions like olfactory stimulation, non-nutritive feeding combined with oral sucrose, fetal positioning, audio stimulation, and tactile stimulation. The results highlighted significant differences in efficacy among these therapies, with combined interventions being more effective in pain reduction and fetal positioning improving oxygen saturation. However, no improvement in heart rate was observed. This underscores the need for novel non-pharmacological therapies to complement existing treatments [46].

In 2023, Ilmiasih et al. reviewed non-pharmacological interventions affecting infant pain scores, analyzing 19 RCTs published between 2015 and 2022. Interventions included sweet oral solutions, skin stimulation, position changes, auditory, and olfactory stimulation. The findings suggested that combined non-pharmacological strategies are more effective than single interventions,

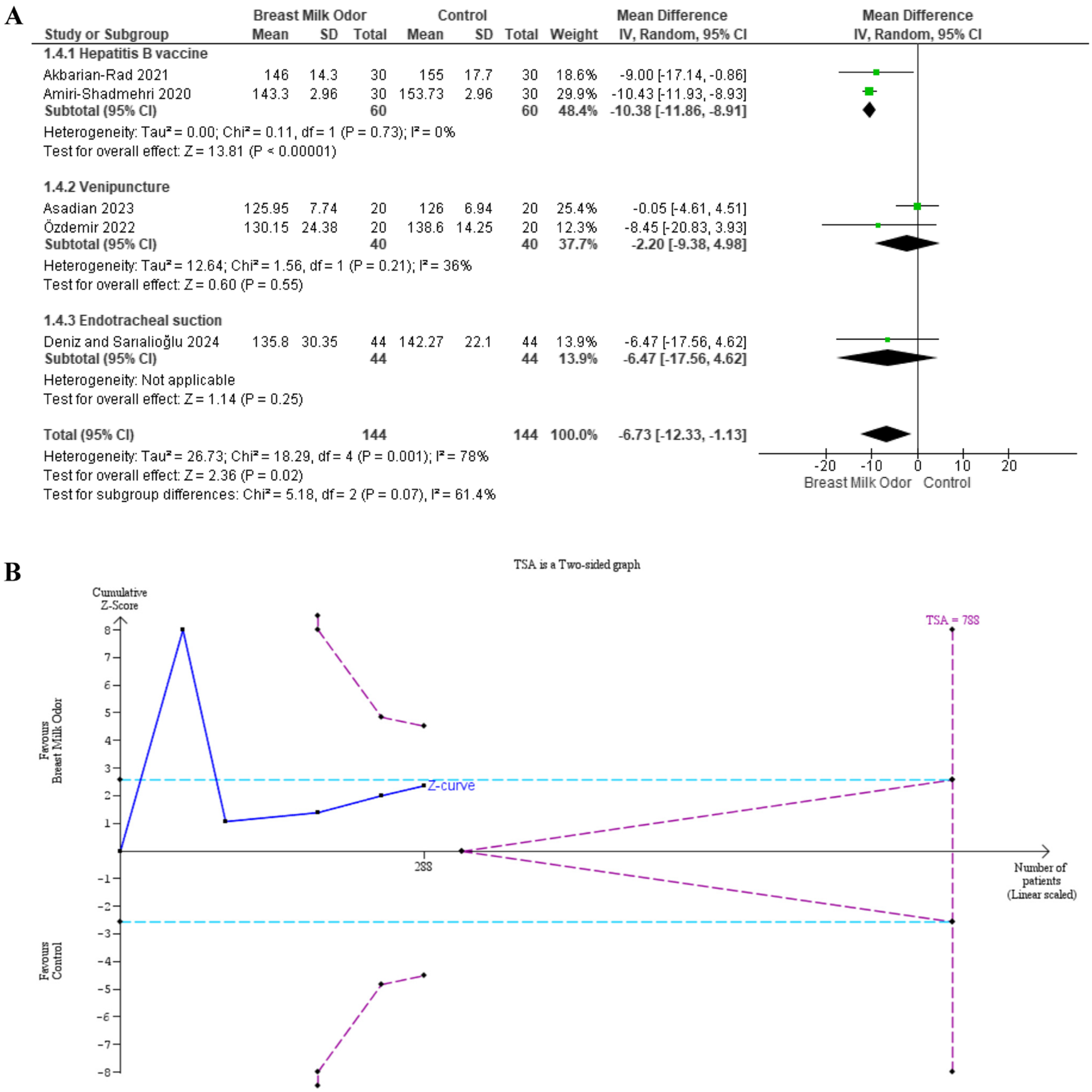

Fig. 6 Effect of Breast Milk Odor Intervention on Neonatal Heart Rate (**a**) and Trial Sequential Analysis of Neonatal Heart Rate (**b**)

particularly emphasizing the impact of breast milk odor [47].

Guo et al. (2020) investigated the efficacy and safety of combined non-pharmacological interventions for recurrent procedural pain in preterm infants. Their systematic review included eight RCTs, concluding that combined interventions generally outperformed conventional care. However, the diversity of interventions limits the ability to formulate definitive guidelines, highlighting the need for further research with larger sample sizes [48]. De Clifford-Faugere et al. (2020) systematically analyzed olfactory stimulation interventions, finding that familiar odors effectively reduced pain and crying duration in infants. Despite these promising results, the evidence quality was deemed low, necessitating more rigorous studies to confirm these findings and ensure safety [49].

Norouziasl et al. (2020) reviewed various pain management techniques, concluding that while breast milk odor can alleviate pain during medical procedures, the overall analgesic effect requires more comprehensive

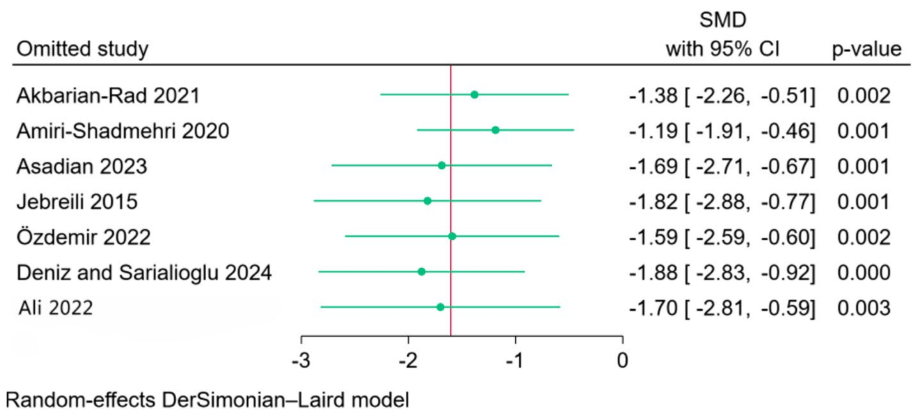

Fig. 7 Leave-One-Out Meta-Analysis of the Effects of Breast Milk Odor Intervention on Neonatal Pain

Table 3 Assessment of evidence certainty utilizing GRADE framework

chemical variability and detection by Outcomes	Number of Participants [Studies]	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Certainty of Evidence
Pain	478 [6 RCTs, 1 Quasi-experimental]	Serious [a]	Serious [b]	Not serious	Not serious	None	⊕⊕⊖⊖Low
Oxygen saturation (SPO_2)	288 [5 RCTs]	Serious [c]	Serious [d]	Not serious	Serious [e]	None	⊕⊖⊖⊖Very low
Heart Rate	288 [5 RCTs]	Serious [c]	Serious [f]	Not serious	Serious [e]	None	⊕⊖⊖⊖Very low
Stress	128 [2 RCTs]	Not serious	Serious [g]	Not serious	Very serious [e]	None	⊕⊖⊖⊖Very low

A: Among the seven studies, three exhibited a low risk of bias, while four presented some concerns regarding bias

B: Heterogeneity was assessed as high ($I^2 = 94\%$, $p < 0.001$)

C: Of the five studies, two demonstrated a low risk of bias, and three had some concerns regarding bias

D: Heterogeneity was assessed as high ($I^2 = 57\%$, $p = 0.06$)

E: The evidence was downgraded due to a wide confidence interval

F: Heterogeneity was assessed as high ($I^2 = 78\%$, $p = 0.001$)

G: Heterogeneity was assessed as high ($I^2 = 89\%$, $p = 0.002$)

investigation [50]. Hatfield et al. (2019) supported this by demonstrating that behavioral and environmental therapies, including oral sucrose and kangaroo care, significantly reduce pain responses in preterm infants [51]. Lago et al. (2017) emphasized the effectiveness of non-pharmacological strategies, especially for needle-related pain, advocating for evidence-based guidelines [52]. Similarly, Aguilar Cordero et al. (2015) found that approaches like sweet solutions and breastfeeding were beneficial for both preterm and full-term infants, while also calling for more extensive research to evaluate long-term effects [53]. Shayani et al. (2023) highlighted that combined non-pharmacological interventions, such as massage and swaddling, effectively reduce pain and stress in infants, confirming their applicability in various healthcare settings [54]. In a quasi-experimental study by Rashwan et al., 62 mechanically ventilated infants were randomly assigned to two groups: an experimental group that received a warm, maternally scented simulated hand (MSSH) during invasive procedures, and a control group. The findings indicated that infants wrapped in the MSSH experienced significantly lower levels of discomfort and pain compared to those receiving standard care. The study concluded that using a warm MSSH can enhance comfort and reduce pain and discomfort in premature infants, particularly when their mothers are not physically present [55]. Tavlar compared the scent of breast milk to maternal heartbeat sounds and breastfeeding during heel prick procedures. The study found that newborns in the breast milk scent group exhibited high levels of stress, those in the maternal heartbeat sound group showed mild stress, and those in the breastfeeding group experienced no stress. Breast milk scent was not found to be an effective method for stress control [56].

Lin et al. examined the effectiveness of breast milk scent alone or in combination with breast milk taste in terms of changes on biological responses to pain during heel prick blood sampling procedures. The mean heart rate changes in infants who received both breast milk scent and taste were lower than those in the control group [57]. Cirik and Efe aimed to compare the effects of non-pharmacological methods, both alone and in combination, on the pain profile scores and physiological parameters (heart rate, oxygen saturation) of infants. Their findings revealed that swaddling combined with expressed breast milk resulted in a lesser drop in oxygen saturation compared to routine care. This suggests that swaddling, similar to our method of covering, positively influences physiological responses [58]. A study conducted by Rad et al. examined the effect of inhaling breast milk scent on the behavioral responses to pain caused by vaccination in premature infants. The results indicated that fetal-maternal odors could reduce stress responses, such as crying and motor activity, in newborns undergoing traumatic procedures [26].

Huda et al. conducted a systematic review and network meta-analysis examining non-pharmacological interventions involving parents to reduce pain in newborns during invasive procedures. The analysis included 35 randomized controlled trials with 4,790 participants, highlighting effective methods such as breastfeeding, mother holding, and a combination of these with music therapy. These interventions significantly alleviated neonatal pain, suggesting that healthcare professionals should engage parents in administering these treatments to improve pain management in the Neonatal Intensive Care Unit (NICU) [59]. Çamur and Erdoğan conducted a systematic review and meta-analysis on the analgesic effects of breastfeeding alone, expressed breast milk, and breast milk odor on newborns undergoing painful procedures. Analyzing nine RCTs with 720 newborns, the study found that these interventions significantly reduced pain and improved heart rate and oxygen saturation during and after procedures. The results suggest that breastfeeding and breast milk are effective non-pharmacological options for managing pain in newborns [60]. Lastly, Maayan-Metzger (2018) studied the effects of maternal milk odor on stress indicators, finding that it significantly lowers salivary cortisol levels in preterm infants, suggesting a calming effect [2].

Odors can trigger the release of neurotransmitters, such as endorphins, in infants. Neurotransmitters are released in infants to alleviate painful stimuli, leading to a drop in stress levels [61]. Alternatively, non-pharmacological therapies such as cholecystokinin can stimulate neuropeptide systems. Cholecystokinin is a regulatory compound that enhances the ability to adjust to stress. Olfactory odor stimulation can change the autonomic balance towards a state of parasympathetic dominance, resulting in relaxation and decreased pain [62]. Cortisol, is crucial for stress response and immune function, but prolonged elevation can harm preterm infants. Stress-reducing interventions like music therapy and gentle touch help regulate cortisol levels. Elevated cortisol disrupts autonomic balance, reducing heart rate variability and altering respiratory patterns, highlighting the need for stress management in preterm infants [63–66].

Strengths and limitations

This systematic review highlights for the first time the analgesic effects of breast milk odor on neonates through a comprehensive search that assessed studies published in English, Persian, and Turkish. By drawing from a diverse range of studies, it demonstrates the potential of breast milk odor as a non-pharmacological strategy for pain and stress management. Detailed subgroup analyses based on specific medical procedures and gestational status (term vs. preterm) provide a nuanced understanding of how these factors influence pain perception. The application of advanced statistical techniques, including meta-regression and Trial Sequential Analysis, enhances the rigor of the findings, while sensitivity analyses offer robust evidence supporting the analgesic effects of breast milk odor in neonates.

Despite these strengths, the review faces several limitations. The relatively small number of included studies restricts the generalizability of the findings, and the inability to assess publication bias, coupled with high heterogeneity among studies, may complicate interpretations. Furthermore, the certainty of the evidence was low for all outcomes, and the geographical restriction of studies conducted primarily in Iran, Turkey, and Egypt limits the applicability of the findings to broader populations.

Implications of Practice and Research

The results of this systematic review have important implications for both research and clinical practice in neonatal pain management. The observed analgesic effects of breast milk odor represent a cost-effective and straightforward strategy that could be integrated into routine care, potentially improving the comfort of neonates during medical procedures. Clinicians are encouraged to consider the implementation of breast milk odor exposure as a complementary intervention alongside existing pain management protocols, especially in environments where pharmacological options may be limited or inappropriate. This strategy is consistent with the increasing focus on holistic, family-centered care within neonatal units, fostering a nurturing atmosphere that supports both the physiological and emotional well-being of infants.

Additionally, it would be beneficial to compare this method with other established approaches, such as non-nutritive sucking or sucrose, to provide a more comprehensive understanding of its efficacy in neonatal pain management. From a research standpoint, the review emphasizes the low certainty of evidence regarding pain relief and the very low certainty for outcomes related to SpO_2, heart rate, and stress levels. The findings from the TSA reveal insufficient statistical power to make definitive conclusions, particularly concerning SpO_2, heart rate, and stress outcomes. This highlights the necessity for further research to validate and build upon the current findings. Future studies should aim for larger, multicenter trials utilizing standardized methodologies to examine the long-term effects of breast milk odor on pain and stress in neonates. Additionally, exploring the underlying mechanisms behind the analgesic properties of familiar odors could yield significant insights for clinical applications. It will also be crucial to evaluate the long-term effects of maternal breast milk odor on infant development and stress responses to establish best practices in neonatal care.

Conclusion

This systematic review indicates that breast milk odor significantly reduces pain responses in neonates and improves critical physiological parameters such as heart rate and SpO_2. Although a decrease in stress levels was observed, it did not reach statistical significance. Our study advances prior research by comprehensively evaluating breast milk odor, employing rigorous methods to identify heterogeneity and systematically assess evidence certainty, addressing these shortcomings in key outcomes. The review highlights the need for further research due to the low to very low certainty of evidence surrounding key outcomes. Future studies should focus on rigorously designed trials—characterized by well-defined protocols, large sample sizes, control of selection and detection bias, and comprehensive data analysis—to confirm the analgesic effects of breast milk odor and its long-term impacts on neonatal health. Such research could enhance existing pain and stress management protocols for neonatal populations, including premature infants or those with medical complications, who may be particularly sensitive to pain and stressors in their environment.

Abbreviations

CI	Confidence interval
MD	Mean difference
MSSH	maternally scented simulated hand
NICU	Neonatal intensive care unit
PROSPERO	Prospective Register of Systematic Reviews
ROP	Retinopathy of prematurity
SID	Scientific Information Database
SMD	Standardized mean difference
TSA	Trial Sequential Analysis

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12887-025-05504-z.

Supplementary Material 1.

Acknowledgements
The authors express gratitude for the scientific support provided by the Clinical Research Development Unit of Taleghani Hospital, which is affiliated with Tabriz University of Medical Sciences in Tabriz, Iran.

Clinical trial number
Not applicable.

Authors' contributions
ShShL, Sİ, MMi and MMa played equal roles in various aspects of the study, including literature screening, evaluating the quality of the included studies, and authoring the manuscript. They were also involved in conducting the statistical procedures and interpreting the findings. The manuscript underwent an editing process with input from all the authors, who then approved the final version for submission.

Funding
None.

Data availability
Data were sourced from previous publications.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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Received: 6 November 2024 Accepted: 10 February 2025
Published online: 26 February 2025

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