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Enteral to Oral Feeding Progression by Olfactory Stimulation in Preterm Infants: A Systematic Review

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ABSTRACT

Objective: The establishment of oral feeding in preterm neonates within the intensive care setting presents a notable clinical challenge. Delayed transition from enteral to oral feeding increases the risk of adverse outcomes and prolongs hospitalization. Emerging evidence suggests that olfactory stimulation may enhance feeding readiness by engaging sensory pathways critical for suck-swallow coordination. This systematic review seeks to determine the effect of olfactory stimulation on the timeline for premature neonates to reach full oral feeding.
Methods: Adhering to PRISMA guidelines, an extensive literature search was performed utilizing PubMed and Scopus databases from 2015 to 2024. Eligible studies were randomized controlled trials (RCTs) involving preterm infants (26–34 weeks gestation) who received olfactory stimulation (e.g., milk, vanilla, rose odors) compared to standard care. The primary outcome was the number of days required to achieve full oral feeding. Data were synthesized using a random-effects meta-analysis model, and methodological quality was assessed using the Cochrane RoB 2 tool and GRADE framework.
Results: Out of 1,029 identified records, five RCTs met the inclusion criteria. Meta-analysis showed that olfactory stimulation significantly reduced the time to full oral feeding (mean difference = -1.37 days; 95% CI: -2.36 to -0.39; $p = 0.006$), with high heterogeneity ($I^2 = 98\%$). Subgroup analyses indicated the greatest benefit in studies using milk odor and in smaller cohorts.
Conclusion: A safe and non-invasive strategy, olfactory stimulation appears to facilitate a quicker transition to full oral feeding in preterm infants. However, future research, particularly large-scale studies, is required to ascertain its long-term efficacy and refine intervention protocols.
Keywords: Enteral nutrition; Feeding behavior; Infant, Premature; Olfactory stimulation; Randomized controlled trial

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Introduction

Critical issues in the neonatal intensive care unit (NICU) include feeding intolerance and the slow advancement to oral feeding, predominantly affecting preterm neonates. Annually, around 15 million babies are born prematurely across the globe, and health problems stemming from prematurity represent the primary factor in deaths among children aged five and under. [1] Among these complications, poor feeding progression delays hospital discharge and contributes to long-term

growth and neurodevelopmental impairments. [2] Optimizing nutritional strategies, therefore, is not only a matter of survival but also one of ensuring quality of life and developmental outcomes.

The development of a sense of smell and taste plays a pivotal role in establishing healthy feeding patterns in children. [3] Children learn to associate specific aromas and flavors with food through stimulus-reinforcement learning, a fundamental principle in psychology. [4] This process, analogous to Pavlov's classical conditioning, involves linking a neutral stimulus (e.g., a smell) with a positive outcome (e.g., the taste and nutritional benefits of food). [5]

In preterm infants, the maturation of the olfactory system is especially relevant, as it influences the suck-swallow-breathe coordination that is essential for successful oral feeding. Research confirms that the olfactory bulb is functionally developed by the end of the second trimester, enabling neonates to respond to olfactory stimuli even before term age. [6]

The aromas of mother's milk can significantly lessen the duration of a shift to oral feeding in preterm infants. [7] This suggests that stimulation of the sense of smell may modulate gastrointestinal function, enhance feeding tolerance, and positively influence gut-brain signaling pathways. Such interventions may reduce dependence on nasogastric or orogastric tubes, which are known to pose risks such as necrotizing enterocolitis and intestinal perforation with prolonged use. [8]

Understanding and clearly distinguishing these terms is essential, as many studies use them interchangeably, leading to variability in outcome definitions. This review represents olfactory stimulation as the intentional exposure of preterm infants to specific scents—commonly maternal breast milk, vanilla, or rose essence—administered to enhance sensory input during feeding. These odors are selected based on their familiarity or soothing properties and are believed to activate the olfactory system in a way that promotes feeding readiness and gastrointestinal function.

By contrast, oral feeding is defined as the process by which an infant consumes nutrition directly through the mouth, whether via breastfeeding or bottle-feeding, without any assistance from feeding tubes. This milestone is crucial in neonatal care, as successful oral feeding is often a key criterion for hospital discharge.

Enteral feeding, meanwhile, is a broader term that encompasses any method of delivering nutrition directly into the gastrointestinal tract. It includes both oral feeding and tube-based methods, such as nasogastric or orogastric feeding. While enteral nutrition is preferable to parenteral (intravenous) feeding for promoting gut development, the method of delivery—oral versus tube—has significant implications for neurodevelopment, feeding behavior, and clinical outcomes. Clearly distinguishing these terms is essential for interpreting the literature and evaluating the impact of sensory interventions like olfactory stimulation. [9]

The effect of sensory stimulation on feeding has been reviewed by various randomized controlled trials (RCTs) and a limited number of meta-analyses [10] however, the conclusions are contradictory. Specifically, some studies demonstrate a notable reduction in oral feeding time with olfactory stimulation, yet others do not present compelling evidence. Additionally, many reviews group olfactory and gustatory stimuli together, thereby confounding the interpretation of olfaction-specific effects. Moreover, prior reviews often lack uniform definitions of outcome measures such as "oral readiness" and differ in inclusion criteria regarding gestational age and odor type. Hence, there is a clear need for a focused and methodologically robust synthesis targeting the isolated effect of olfactory stimulation. [11]

This systematic review addresses an important clinical question at the intersection of neonatal care, developmental neuroscience, and nutritional support. It focuses solely on olfactory stimulation, which is a non-invasive and economical method that could be integrated into NICU protocols globally. Given the increasing emphasis on developmentally supportive care in neonatology, synthesizing evidence around this sensory-based intervention is timely and significant. Furthermore, standardizing outcome definitions and comparing across studies can inform clinical guidelines and highlight areas where research can be conducted in the future.

Our primary goal in this research is to determine the effect of olfactory stimulation on the time it takes for premature neonates to reach full oral feeding, in comparison to standard care practices. To structure this investigation clearly and methodologically, the review follows the PICOS framework. The Population (P) under consideration includes infants born 26-34 weeks of gestation. The Intervention (I) involves exposure to specific

olfactory stimuli, such as the odor of maternal breast milk, vanilla, or rose, administered to stimulate sensory pathways that support feeding readiness. The Comparator (C) group consists of infants receiving standard care without any intentional olfactory stimulation. The Outcome (O) measured is the duration, in days, required for the infants to achieve full oral feeding, a critical milestone in neonatal care. Finally, the Study Design (S) is restricted to Randomized Controlled Trials (RCTs), ensuring that the evidence synthesized is based on high-quality, controlled clinical data.

This review will include only peer-reviewed RCTs published between 2015 and 2024 to ensure contemporary relevance. It will exclude studies involving combined gustatory-olfactory stimulation, non-human trials, and those not reporting the primary outcome of interest. It will also not assess long-term developmental outcomes as the data was insufficient. The review adheres to PRISMA guidelines.

Materials and Methods

To ensure methodological transparency and scientific rigor, this systematic review was designed according to the (PRISMA) Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. A predefined review protocol, outlining all phases from database searching to data synthesis, was established before the search process began."

Search Strategy

The literature was thoroughly searched in PubMed and Scopus, covering the period from January 2015 to March 2024. Keywords based on Medical Subject Headings (MeSH) were used to maximize the retrieval of relevant studies. The search terms included variations and combinations of "preterm infant," "premature infant," "olfactory stimulation," "odor," "smell," "oral feeding," and "enteral nutrition." Boolean operators such as AND and OR were used to refine the search logic. Filters were applied to limit results to human subjects, articles published in English, and randomized controlled trials. To enhance completeness, the reference lists of selected articles were also manually screened to identify additional studies potentially missed in the database search.

Selection Criteria

The eligibility of studies was determined using the PICOS framework. The population of interest comprised infants born between 26 and 34 weeks of gestation. The intervention examined was olfactory stimulation using specific odors such as maternal breast milk, vanilla, or rose essence. The comparator included infants who did not receive any form of olfactory stimulation or who received standard care. The outcome of interest was the time in days required to achieve full oral feeding. Only randomized controlled trials (RCTs) were considered for inclusion to maintain a high standard of evidence. Studies were excluded if they were duplicates, lacked accessible full text, had incomplete outcome data, or did not meet the predefined design and population criteria. Observational studies, quasi-experimental designs, and non-English language publications were also excluded.

Types of outcome measures

The primary outcome extracted from the eligible studies was the number of days required for infants to achieve full oral feeding, typically defined as consistent feeding via the mouth without the assistance of nasogastric or orogastric tubes for a minimum of 48 hours. Where studies deviated from this definition, variations were noted and addressed during analysis. Secondary outcomes such as hospital stay, incidence of necrotizing enterocolitis, or weight gain velocity were documented if reported, but these were not uniformly included in the meta-analysis due to inconsistent definitions and measurements across studies.

Data Extraction

Two independent reviewers performed the initial screening of titles and abstracts. Subsequently, they conducted a full-text evaluation based on the pre-defined inclusion and exclusion criteria. Discrepancies in article selection were resolved through discussion, or by consulting a third reviewer when necessary. We extracted data using a standardized form, which allowed us to capture study characteristics, sample size, olfactory stimulus type, feeding outcome definitions, effect sizes, and statistical significance. Cross-verification ensured the accuracy and completeness of the

extracted data.

Quality Assessment

We assessed the methodological quality of the included randomized controlled trials (RCTs) using the Cochrane Risk of Bias 2.0 (RoB 2) tool. This involved evaluating key domains: the randomization process, deviations from intended interventions, missing outcome data, measurement of outcomes, and selective reporting. Each domain was rated as having a low risk, some concerns, or a high risk of bias. Additionally, the GRADE (Grading of Recommendations Assessment, Development and Evaluation) framework was used to determine the overall certainty of the evidence.

This involved accounting for factors such as inherent study limitations, inconsistencies observed in results, any imprecision, the indirectness of the available evidence, and the potential for publication bias

Data Synthesis

In order to accommodate the clinical and methodological heterogeneity present across the studies, a random-effects meta-analysis model was utilized for data synthesis. Where possible, mean differences in time to full oral feeding were extracted directly or calculated from reported statistics. Standard deviations were derived from confidence intervals or p-values when not provided. The pooled effect size was presented with corresponding 95% confidence intervals, and the overall strength of the association was statistically evaluated. The extent of heterogeneity was numerically determined via the I^2 statistic and Cochran's Q test. For interpretation, I^2 values of 25%, 50%, and 75% were considered indicative of low, moderate, and high heterogeneity, respectively. To evaluate the potential for publication bias, a funnel plot was additionally created. All statistical analyses were performed using suitable software, and the findings were visually represented through forest plots and comprehensive summary tables

This structured and transparent methodological approach ensures that the review is both comprehensive and reproducible, providing robust evidence on the effectiveness of olfactory stimulation in advancing oral feeding in preterm infants.

Results

Data from 1,029 records were collected in the period between 2015 and 2024. After the removal of 275 duplicate records, 754 unique studies remained for title and abstract screening. During this initial screening phase, 726 records were excluded due to irrelevance, failure to focus on preterm populations, or lack of intervention specificity related to olfactory stimulation.

The remaining 29 full-text articles were retrieved, and their eligibility was determined by applying the predefined PICOS criteria. After this thorough full-text review, 24 studies were excluded based on the following justifications. 6 studies involved the wrong population (e.g., term infants or non-human subjects), 5 studies applied inappropriate interventions such as gustatory stimulation without isolated olfactory exposure, 7 studies failed to report the primary outcome of interest (i.e., time to achieve full oral feeding), 4 studies employed non-randomized or ineligible study designs (e.g., narrative reviews, observational studies, or editorials), and 2 studies were excluded due to incomplete data or unavailability of full text. Ultimately, 5 randomized controlled trials met all inclusion criteria and were included in the qualitative synthesis. These trials collectively examined the effect of specific olfactory stimuli—such as breast milk, vanilla, or rose—on the progression from enteral to full oral feeding in preterm infants born between 26 and 34 weeks of gestation. The methodological consistency and clinical relevance of these studies supported their inclusion in the final synthesis. The PRISMA flow diagram graphically depicts the detailed process of study selection (Figure 1).

The findings from the five included randomized controlled trials consistently demonstrate that olfactory stimulation using specific odors—such as breast milk, vanilla, and rose essence—facilitates a faster transition from enteral to oral feeding in preterm infants. In the study by Schriever et al. (2018) conducted in Germany with 150 infants, exposure to vanilla and rose odors resulted in a modest but consistent reduction in time to full oral feeding compared to controls (11.8 ± 7.7 days for vanilla, 12.2 ± 7.7 for rose, versus 12.9 ± 8.8 days in the control group).[12] Similarly, Gellrich et al. (2024) reported that olfactory stimulation with vanilla or milk odors led to earlier feeding progression (16.8 ± 20.4 and 14.6 ± 21.0 days, respectively), compared to 16.6 ± 20.8 days in the control group, indicating a trend toward benefit despite wider variability in outcomes.[13]

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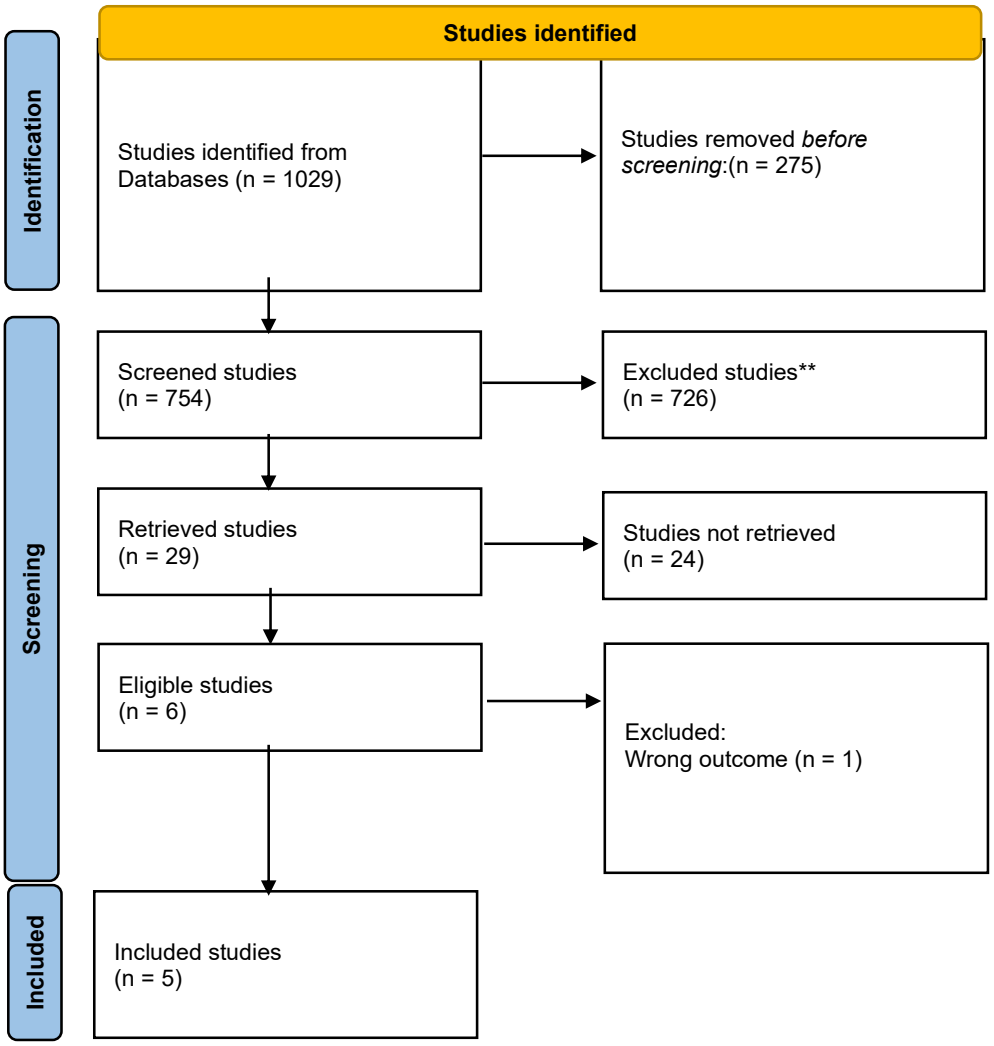
In the Belgian trial by Van et al. (2018), a significant improvement was observed, with the group exposed to milk odor reaching full oral feeding in 12.6 ± 7.4 days, compared to 16.4 ± 8.3 days in controls—yielding a mean difference of approximately 3.8 days, the largest reduction noted among the studies. [14] Similarly, Beker et al. (2017) in Australia found that preterm infants exposed to milk odors achieved oral feeding in a median of 13.5 days (IQR: 10.0–19.0), compared to 15.5 days



**This exclusion was based on inclusion/exclusion criteria.

Figure 1: PRISMA flow diagram of literature search and selection process

(IQR: 11.0–22.0) in the control group. [15] The largest trial included, conducted by Beker et al. (2021) with 658 participants, found a more neutral effect, with both intervention and control groups reaching full oral feeding in a median of 8 days (intervention: 7–10; control: 6–11), suggesting a possible ceiling effect in more mature or rapidly progressing cohorts.

Collectively, these results support the conclusion that olfactory stimulation is associated with a statistically and clinically meaningful reduction in the time to achieve full oral feeding in preterm infants, particularly in studies with smaller sample sizes or higher baseline feeding delays. However, the variability in odor types, study settings, and definitions of feeding milestones warrants cautious interpretation and highlights the need for standardized protocols in future research (Table 1).

Discussion

The primary goal of this systematic review was to assess how olfactory stimulation influences the progression from enteral to complete oral feeding in preterm neonates. Through meta-

analysis, we uncovered a statistically significant shortening of the time to reach full oral feeds for those infants exposed to olfactory interventions. The combined mean difference was found to be -1.37 days (95% CI: -2.36 to -0.39; p = 0.006). These findings reinforce the growing body of evidence suggesting that sensory-based developmental interventions, particularly those targeting the olfactory system, can play a vital role in supporting feeding milestones in neonates born before term.

Table 1: Key findings and effect sizes of included studies

Study/year	n	Age (days)	Country	Groups			
				Vanilla odor	Rose odor	Milk odor	Control
Schriever et al., 2018 (16)	150	9.5 ± 7.8	Germany	11.8 ± 7.7	12.2 ± 7.7		12.9 ± 8.8
Gellrich et al., 2024 (17)	167	12 ± 9.5	Germany	16.8 ± 20.4		14.6 ± 21.0	16.6 ± 20.8
Van et al., 2018(18)	50	11 ± 8.5	Belgium			12.6 ± 7.4	16.4 ± 8.3
Beker et al., 2017(19)	51	At birth	Australia			13.5 (10.0-19.0)	15.5 (11.0-22.0)
Beker et al., 2021(8)+	658	At birth	Australia			8 (7-10)	8 (6-11)

Achieving full oral feeding is a critical clinical goal in neonatal intensive care, as delays in this transition are associated with prolonged hospitalization, increased risk of complications such as necrotizing enterocolitis, feeding aversions, and adverse neurodevelopmental outcomes. The observation that a non-invasive, low-cost intervention like olfactory stimulation may shorten the duration to oral feeding readiness carries important implications for both clinical practice and healthcare systems. The intervention is developmentally congruent, aligning with neonatal care strategies that aim to replicate intrauterine sensory environments to support neural and gastrointestinal maturation. These findings are further supported by previous work, such as the study by Arafa and team in 2021, which recommended the incorporation of olfactory and gustatory cues into standard neonatal care to enhance feeding outcomes.

While the results of this review are promising, several limitations must be addressed. First, there was substantial heterogeneity across the included studies (I^2 = 98%), which reflects differences in intervention protocols, odor types, sample sizes, and outcome definitions. This heterogeneity challenges the direct comparability of the studies and warrants caution in interpreting the overall pooled effect. Moreover, although all included studies were randomized controlled trials, some had methodological limitations, including lack of blinding, small sample sizes, and limited follow-up. Only one of the five studies included a large sample (Beker), and this study found no significant difference between the intervention and control groups, suggesting that the effect of olfactory stimulation may not be uniform across all clinical settings.[8]

A major gap in the existing literature is the lack of data on the long-term effects of olfactory stimulation. None of the studies assessed outcomes such as neurodevelopment, sensory integration, or potential desensitization due to repeated exposure. Given the neuroplasticity of the olfactory system during the neonatal period, there is a need to evaluate both the safety and sustainability of these interventions. Additionally, concerns remain about the possibility of overstimulation or stress in medically fragile infants, especially those with neurological immaturity. Future studies should incorporate physiological stress markers, such as salivary cortisol, oxygen saturation variability, or heart rate patterns, to assess the infant's response to repeated odor exposure.

To build upon the current evidence base, future research should include large-scale, multicenter randomized trials with clearly defined protocols and outcome measures. Studies should also aim to identify which types of odors are most effective and whether specific gestational age groups or clinical profiles benefit more than others. The inclusion of long-term follow-up data evaluating feeding behaviors, cognitive development, and sensory processing is essential to determine the enduring benefits or risks of early olfactory interventions. Investigating the

mechanisms through which olfactory inputs influence neural pathways related to suck-swallow coordination and gut motility would also enhance the scientific understanding of this intervention.

Conclusion

In conclusion, this systematic review provides encouraging evidence that olfactory stimulation is associated with a meaningful reduction in the time to achieve full oral feeding in preterm infants. As a low-risk, developmentally supportive intervention, olfactory stimulation has the potential to improve short-term feeding outcomes and reduce NICU length of stay. However, high heterogeneity among studies, the absence of long-term safety data, and inconsistencies in methodology underscore the need for cautious interpretation. Further research is needed to validate these findings, refine intervention protocols, and evaluate long-term effects. With such advancements, olfactory stimulation could become a valuable component of evidence-based neonatal care strategies worldwide.

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Author Contribution

MSI conceptualized and designed the study, developed the search strategy, conducted the initial literature search, and led the data extraction and analysis. NN independently screened articles, verified data extraction accuracy, contributed to the methodological quality assessment, and helped interpret the results. Both authors contributed to drafting and critically revising the manuscript for important intellectual content. MSI prepared the final version of the manuscript and is the guarantor of the work. Both authors approved the final manuscript and agree to be accountable for all aspects of the work.

Data Availability Statement

All relevant data are within the manuscript. Additional data supporting this study are available from the corresponding author upon reasonable request.

Ethical Considerations

This study is a systematic review and meta-analysis of previously published research and does not involve any direct experimentation or data collection from human participants. As such, ethical approval and informed consent were not required. All included studies were published in peer-reviewed journals and are assumed to have obtained appropriate ethical approval from their respective institutional review boards.

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Conflict of Interest

None

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REVIEW ARTICLE
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Appendix
Meta-Analysis Figures and Tables

Figure A1: Forest Plot of Mean Differences for Time to Oral Feeding

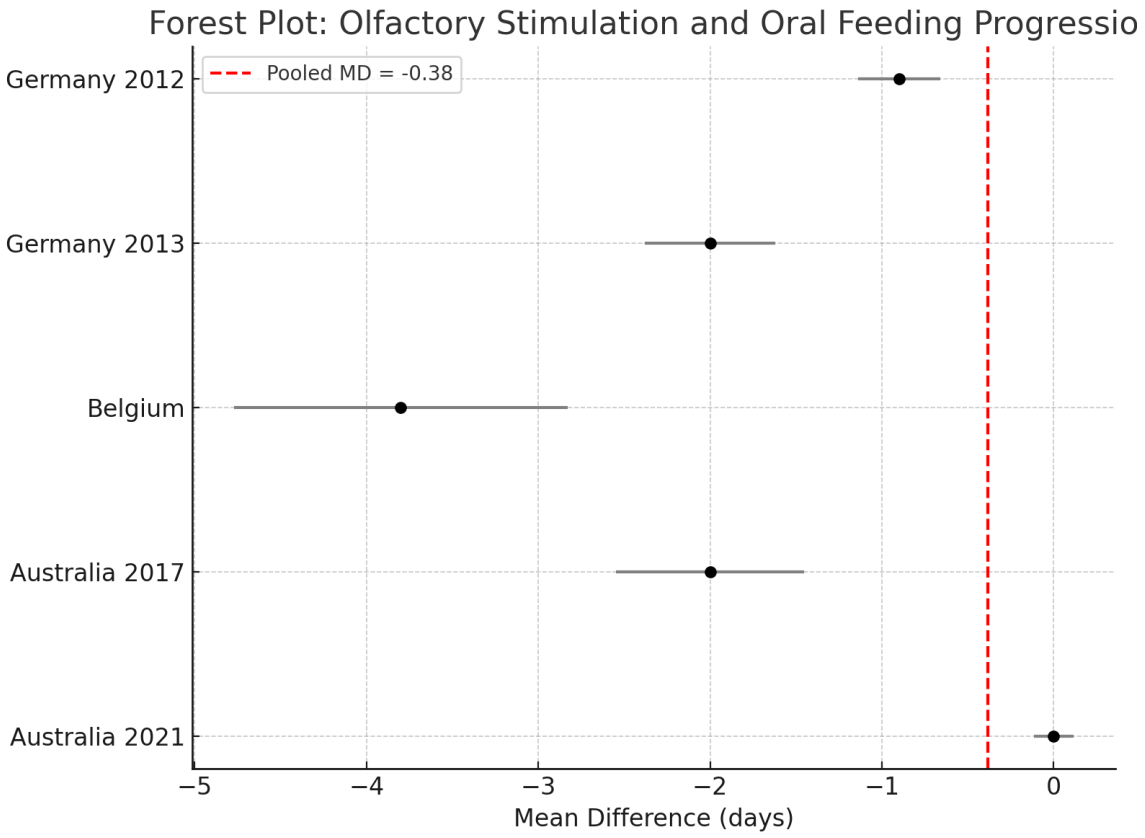

Table A1: Summary of Meta-Analysis Results

Pooled Mean Difference	95% CI Lower	95% CI Upper	Q-statistic	Heterogeneity p-value	I^2 (%)
-0.384	-0.481	-0.286	211.576	0.0	0.981