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Age matters in pediatric pain care: Bayesian meta-reanalysis of virtual reality trials

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BACKGROUND: Immersive virtual reality proved effective in pediatric procedural pain and anxiety management, yet the extent to which age modifies these effects remains uncertain. Notably, the two most recent and widely cited meta-analyses (Eijlers et al., 2019 and Tas et al., 2022) reported conflicting conclusions.

METHODS: We performed a Bayesian meta-reanalysis of the above mentioned meta-analyses. We extracted standardized mean differences (SMD) for pain ($n = 21$) and anxiety ($n = 10$), plus study-level age, sex distribution, quality score, and procedure type. Primary outcomes were pooled SMDs; the secondary outcome was the age effect estimated with a Bayesian random-effects meta-regression. We report pooled effects, age slope (ΔSMD/year), heterogeneity, 95% credible intervals (CrI), and posterior probabilities (P[β_age>0]).

RESULTS: Virtual reality is strongly associated with reductions in both pain (SMD −0.69, CrI −0.93 to −0.47) and anxiety (SMD −0.75, CrI −1.05 to −0.49). Age was associated with variation in effect size for both pain: 0.10 ΔSMD/year (CrI 0.02–0.19; $P[\beta_{age} > 0] = 0.988$), and anxiety: 0.13 ΔSMD/year (CrI 0.02–0.25; $P[\beta_{age} > 0] = 0.991$), indicating attenuation of benefit with increasing age.

CONCLUSION: Immersive virtual reality proves effective in pediatric procedural pain and anxiety management, with benefits diminishing with increasing age. Bayesian evidence synthesis should be increasingly applied to pediatric research, where studies are small and highly heterogeneous.

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IMPACT:

- Immersive virtual reality significantly reduces procedural pain and anxiety in children, but its effectiveness decreases with increasing age.
- This Bayesian meta-reanalysis reconciles conflicting findings from prior frequentist meta-analyses, showing that age is a key determinant of non-pharmacological pain management efficacy.
- Findings advocate for age-specific implementation of immersive virtual reality and encourage adoption of Bayesian evidence synthesis methods to better inform pediatric clinical guidelines where studies are small and heterogeneous.

INTRODUCTION

Procedures in pediatric practice are inherently painful and anxiety-inducing. Suboptimal management of these symptoms can intensify procedural anxiety, discourage healthcare engagement, and impair subsequent adherence later in life.[1,2] Among non-pharmacological strategies, immersive virtual reality has proven effective for pediatric procedural analgesia and anxiolysis.[3,4] However, whether this efficacy vary by age remains insufficiently characterized, and published findings are inconsistent.[3–5]

Age is a known core determinant of non-pharmacological strategies effectiveness, as developmental differences in pain perception, coping strategies, and attentional capacity shape responsiveness to these techniques.[6–8] Notably, age is already a central determinant in pediatric pain assessment, with tools well calibrated to developmental stage (e.g., Numerical Rating Scale for ≥6 years, Wong-Baker Faces for ≥3 years, and observational scales such as FLACC for younger children.[9]) By contrast, comparable age-specific frameworks are not available for non-pharmacological pain management, contributing to between-study heterogeneity and risking both dilution of true benefits in some age groups and overestimation in others.

Moreover, pediatric and neonatal research is shaped by intrinsic constraints—including small sample sizes, diverse care environments, high heterogeneity, and strict ethical requirements—that restrict randomization and consent.[10,11] Under these conditions, conventional frequentist analyses can be unstable and underpowered, particularly for study-level moderators such as mean age. A Bayesian framework offers several advantages in this setting: rather than increasing statistical power per se, it provides an alternative inferential approach that enables partial pooling,

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propagates uncertainty in moderators, and yields probabilistic statements about effect sizes and their direction. These features support more informative interpretation in small, heterogeneous datasets without relying on dichotomous significance thresholds.[12,13]

A Bayesian framework directly addresses these needs by enabling partial pooling, propagating measurement error in moderators, and formally incorporating prior evidence (e.g., from earlier trials or meta-analyses).[14,15] This approach closely mirrors clinical decision-making - where prior knowledge is central - unlike conventional frequentist statistics approaches, which lack mechanism to incorporate prior evidence.[16] These features are particularly important in evidence synthesis (meta-analysis and meta-regression), which guides practice and must use models that match the realities of pediatric and neonatal data.[17–19] When such modeling choices are neglected, studies can reach conflicting conclusions, impeding clear recommendations.

This is the case of age effect on virtual reality effectiveness within the two recent and most widely cited meta-analyses on the argument: while Eijlers and colleagues[5] found a significant effect of age on both pain and anxiety outcome, the meta-analysis update three years later[4] identified opposite results.

Studies in the meta-analysis update[4] were highly heterogeneous in terms of age, enrolling participants from 3 to 21 years. This represents an exceptionally broad range that amplifies both clinical and methodological variability, increasing the risk of ecological bias and regression-dilution. Moreover, the frequentist meta-regression modeled age alone, omitting potentially significant covariates, such as sex, procedure type, and study quality. Accordingly, the discrepancy with the original meta-analysis[5] might reflect the limited ability to accommodate the several sources of heterogeneity in a frequentist framework with small numbers.

In the current study, the meta-analysis update[4] was then re-analyzed using Bayesian hierarchical models that better accommodate heterogeneity constraints. We estimated the pooled treatment effects of virtual reality on pain and anxiety, and assessed whether age modifies these effects through meta-regression, with the aim to provide clear age-informed, clinically actionable guidance for nonpharmacological pain care in pediatrics.

METHODS

Data and outcomes

The same exact studies used in the most recent update of the pediatric virtual reality meta-analysis[4] were re-analyzed, to make results directly comparable. For each study (i) the standardized mean difference (SMD) and its 95% confidence interval (*CI*) for pain ($n = 21$) and anxiety ($n = 10$) were abstracted. By convention in the original dataset, negative SMD values favor virtual reality (lower pain/anxiety). From each CI the standard error - which quantifies study precision and determines analytic weight - was computed as:

$$s_i \approx \frac{UCL_i - LCL_i}{2x1.96}$$

Study-level mean age (*age*), its standard deviation, sample size, the proportion of male participants, the study quality score (as reported in the original publication),[4] and the procedure type (e.g., venous access, burn care, etc.), were also extracted as candidate covariates.

Study aims

- Primary aim: estimate the effect of virtual reality on pain and anxiety using a Bayesian random-effects meta-analysis.
- Secondary aim: evaluate whether age modifies virtual reality effectiveness via Bayesian meta-regression.

Primary aim: virtual reality efficacy

A Bayesian random-effects model, which assumes each study estimates its own true effect (θ_i) and those true effects vary around an overall mean (μ), was used. For each study (i), the reported SMD (y_i) was included as a noisy measurement of that study unknown true effect (θ_i), and its standard error (s_i) served to capture its statistical imprecision: $y_i \sim N(\theta_i, s_i^2)$.

Rather than forcing all studies to share one common effect, we served a random effect model allowing θ_i to differ, as study-level settings, procedures, and populations vary:

$$\theta_i = \mu + v_i, v_i \sim N(0, \tau^2)$$

Here, μ is the overall mean effect across comparable settings; v_i is that study deviation from the mean; and τ (tau) is the between-study heterogeneity that captures clinical/methodological diversity across studies: when τ is large, studies disagree more; when τ is small, they are more consistent with μ and θ_i getting closer.

Overall, using this approach two sources of variability were accounted for: between-study heterogeneity (τ), reflecting clinical and methodological differences, and within-study sampling variability (s_i), reflecting the uncertainty of each study's estimated effect.

In Bayesian statistics, a key step is the specification of prior distributions for model parameters. A prior is a probability distribution expressing what is known before analyzing the current data (e.g., based on earlier trials or meta-analyses). The current data then update this prior via Bayes' rule to yield the posterior, which reflects both prior knowledge and new evidence.[20] Priors may be weak/neutral (allowing the data to dominate) or informative (anchored to credible external evidence). Good practice is to assess sensitivity to different prior choices so that conclusions do not hinge on any single specification.[21,22] Accordingly, both a weakly informative and an informative prior model were run. The weakly informative model specified a Normal(0,1) prior for the overall effect, while the informative model used a normal distribution based on the pooled estimate from the earlier meta-analysis.[5] For heterogeneity, a weakly-informative half-normal prior with scale 0.5 on the SMD scale was used. Results are reported as posterior means with 95% credible intervals (CrI) for the overall virtual reality effect (μ) and for τ.

Secondary aim: age influence

To test whether age explains between-study differences in virtual reality effectiveness, a Bayesian random-effects meta-regression was served.

Covariates standardization. Before modeling, continuous study-level moderators were standardized (*z-scored*) to place them on a common, unit-free scale. By standardizing continuous covariates around their overall means, the model's intercept corresponds to the expected virtual reality effect for a "*typical*" study with average age and average sex proportion. This improved sampling stability and efficiency of the model. Moreover, z-scoring allows the same priors to be used across coefficients, making effects directly comparable and interpretable, without altering substantive inferences. Sex proportion for each study was also standardized.

Model specification. Each study true effect (θ_i) was allowed to vary around a meta-analytic mean through a random intercept: $\theta_i = \alpha + \beta \overline{age^*_{z(i)}} + \gamma_1 sex_{z(i)} + m(quality_i) + \delta(type_i) + b_{0i}$

Here, α is the overall mean virtual reality effect, β is the age slope with $\overline{age^*_{z(i)}}$ the unknown (z-standardized) age true value,

Table 1. Prior distributions for model parameters.

Parameter	Prior	Notes
Intercept α	Student-$t(3, \mu_0, sd_{map})$	Centered on pooled effect from the previous meta-analysis[5]
Age slope β (informative)	Normal($\mu_{age,z}$, $1.4xsd_{age,z}$)	Based on previous meta-analysis age effect ($\mu_{age,z}$) and standard error ($sd_{age,z}$) inflated for conservatism
Age slope β (broader weakly informative)	Normal($\mu_{age,z}$, $2.8xsd_{age,z}$)	Sensitivity analysis with increased prior uncertainty
Age slope β (zero-centered weakly regularizing)	Normal(0,1)	Sensitivity analysis assuming no prior age effect
Other fixed effects	Normal(0,1)	Weakly regularizing priors providing mild shrinkage
Random-effect SD τ	Half-Student-$t(3, 0, 0.5)$	Prior on between-study heterogeneity

Summary of prior specifications used in the Bayesian models, including sensitivity analyses for the age effect under informative, weakly informative, and zero-centered priors.

$sex_{z(i)}$ is the (z-standardized) study's male proportion, the study quality score is included as a monotonic effect $m(quality_i)$ is a monotonic effect for the quality score, $\delta(type_i)$ adjusts for procedure type, and b_{0i} is the study-specific deviation (random intercept). The study quality score was modeled using a monotonic effect, which assumes that higher quality levels are associated with systematically increasing or decreasing effects without imposing equal spacing between categories. This approach is appropriate for ordinal variables where the ordering is meaningful but the distances between levels are not.[23] The random model allows each study to have its own deviation from the overall mean effect through b_{0i}, and assume these offsets vary randomly across studies with mean 0 and spread τ: $b_{0i} \sim N(0, \tau^2)$ where τ represents the between-study heterogeneity. Within the model, standardized mean age was considered normally distributed around each study unknown true mean age ($\overline{age^*_{z(i)}}$) with spread on its standard error $se^{\overline{age}}_{z(i)}$ as: $age_{z(i)} \sim N\left(age^*_{z(i)}, \left(se^{(\overline{age})}_{z(i)}\right)^2\right)$.

Model priors. To assess robustness of the findings, alternative prior specifications were evaluated. The full prior specification for all model parameters, including hyperparameters, is reported in Table 1.

Briefly, the intercept (α) was assigned a Student-t prior centered on the pooled effect from the previous meta-analysis.[5] For the age slope (β), three alternative priors were examined in sensitivity analyses: an informative prior based on previous meta-analytic evidence, a broader weakly informative prior with increased uncertainty, and a zero-centered weakly regularizing prior.

All additional fixed effects were assigned weakly regularizing Normal(0,1) priors. Between-study heterogeneity (τ) was modeled using a half-Student-t(3, 0, 0.5) prior.

Model fit. Models were fitted in *brms* (version 2.22.0) using *Stan* via the *cmdstanr* backend. Hamiltonian Monte Carlo sampling was performed with 8 parallel chains, each run for 8000 iterations (2000 warm-up and 6000 post-warm-up), yielding 48,000 posterior draws per model. The *adapt_delta* parameter was set to 0.99 and *max_treedepth* to 12 to ensure stable sampling.

Convergence was assessed using the potential scale reduction factor ($\widehat{R}$), with values < 1.01 considered indicative of convergence, and by visual inspection of trace plots. Effective sample sizes (bulk and tail ESS) were also examined. Hamiltonian Monte Carlo diagnostics, including divergent transitions and treedepth saturation, were evaluated.

Posterior predictive checks were performed to assess model fit by comparing observed data with simulated draws from the posterior predictive distribution, using graphical diagnostics. Additional diagnostic details are provided in the Supplementary Materials.

Age effect report. To facilitate clinical interpretation, age results are reported back on the per-year scale via: $\beta_{year} = \frac{\beta_z}{s_{age}}$ where β_z is the regression coefficient for the z-scored mean age.

In the meta-regression, β is the change in SMD per 1-year increase in cohort mean age. As in the original data more negative SMD means more virtual reality benefit:

- $P(\beta > 0)$)—the SMD shifts toward positive as age increases: older cohorts benefit less from virtual reality (attenuation).
- $P(\beta < 0)$)—the SMD becomes more negative with age: older cohorts benefit more (amplification).

Posterior probabilities were used to quantify the strength of evidence for the direction of the association. Values near 0.5 (posterior probability 50%), indicate no directional evidence (i.e., age does not affect the outcome under analysis), while values near extremes (1-0) indicate strong evidence for attenuation or amplification, respectively.

Sensitivity analyses. To analyze whether the prior specification matters, the three model including different priors (informative, weakly-informative, non-informative) fits were compared through leave-one-study-out cross-validation: each time, one study is held out, the model predicts it from the others, and we score the prediction. Pareto smoothed importance sampling aggregates these scores to tell us which prior leads to better out-of-sample predictions: when the difference in expected predictive fit (ΔELPD) is smaller than its standard error, the models are practically indistinguishable.

To maximize reproducibility and limit risks of overfitting or multicollinearity—given that the frequentist meta-analysis update[4] fit a random-effects meta-regression with age as the sole moderator—an analogous Bayesian random-effects meta-regression including only age was also compiled: $\theta_i = \alpha + \beta\overline{age^*_{z(i)}} + b_{0i}$ and compared model results with the full model specified above.

RESULTS

Primary aim: virtual reality efficacy

Across studies, virtual reality was associated with reduction in both outcomes, similarly to results identified in the frequentist meta-analysis.[4] For pain, the pooled posterior under the weakly informative prior was −0.66 (95% CrI −0.90 to −0.43) and −0.69 (95% CrI −0.93 to −0.47) using the informative prior based on previous meta-analysis results. For anxiety, the pooled posterior was −0.73 (95% CrI −1.03 to −0.45) with a weakly informative

prior and −0.75 (95% CrI −1.05 to −0.49) with the informative prior. Estimated between-study heterogeneity (τ) indicated moderate dispersion of true effects: 0.41 (95% CrI 0.23–0.63) for pain and 0.32 (95% CrI 0.09–0.61) for anxiety. Results were insensitive to the choice of prior on the overall mean effect. For pain, the posterior mean pooled effect changed from −0.67 to −0.70, while heterogeneity remained at 0.42. For anxiety, the posterior mean pooled effect changed from −0.74 to −0.76 and heterogeneity remained at 0.33, indicating minimal sensitivity to the prior specification. Results are graphically summarized in Fig. 1.

Secondary aim: age influence

Unlike the frequentist meta-analysis,[4] the Bayesian meta-regression found strong evidence that the virtual reality effect was smaller in studies with higher mean age in both outcomes, aligning with the original meta-analysis result.[5] For pain, the age slope was 0.10 SMD per year (95% CrI 0.02–0.19), with 98.8% high directional evidence: $P(\beta_{age} > 0) = 0.988$. For anxiety, the slope was 0.13 SMD per year (95% CrI 0.02–0.25; $P(\beta_{age} > 0) = 0.991$), likewise indicating attenuation in older groups. Results for posterior draws are reported in Fig. 2. Beyond age, no covariate showed a credible association with the virtual reality effect. Between-study heterogeneity indicated moderate dispersion ($\tau_{pain} = 0.36$ and $\tau_{anxiety} = 0.20$). Results proved robust to prior specification: informative, weakly informative, and non-informative priors produced near-identical posteriors—the age slope varied by <0.02, $P(\beta_{age} > 0)$ by ≤0.03, and τ by <0.03—with no meaningful differences in predictive accuracy by Pareto-smoothed leave-one-out cross-validation. Findings were also stable across specifications, both the age slope and heterogeneity were essentially unchanged.

All models showed good convergence, with $\hat{R}$ values equal to 1.00 and high effective sample sizes for all parameters. No divergent transitions or treedepth saturations were observed. Posterior predictive checks indicated good agreement between observed data and model-implied distributions. Details are provided in Supplementary Materials.

DISCUSSION

In this Bayesian meta-reanalysis, immersive virtual reality yielded clinically meaningful reductions in procedural pain and anxiety. Meta-regression showed a clear age gradient, with smaller effects observed in studies with higher mean age. These results reconcile discrepant conclusions in recent syntheses[4,5] by demonstrating that study-level mean age was strongly associated with differences in observed effect sizes.

This difference is methodological: frequentist and Bayesian analyses pose distinct questions and handle uncertainty in different ways. The frequentist update asked a yes/no question—"*Is there enough evidence to rule out no age effect (at the 0.05 threshold)?*"—so a *p*-value just above 0.05 is labeled "*non-significant*" even when there is substantial (but not quite sufficient) evidence for an age effect. With few, heterogeneous studies and age available only as a study-level average, that test was underpowered, and it returned "*not significant*". By contrast, the Bayesian analysis asks a more clinical question—"*How likely is it that virtual reality benefit decreases with age, and by how much?*"—and combines all relevant uncertainty (between-study variability and imprecision in the age moderator), yielding a graded probability and an effect size rather than a dichotomous *p*-value. Clinically, decisions rarely hinge on a threshold; for example, if there is a high probability that a treatment works, it would reasonably implemented even if a frequentist *p*-value does not cross 0.05.

Uncertainty handling is central in meta-regression because variability arises from multiple sources—clinical setting, methods, and reporting—not just sampling error. In the meta-analysis update, a study-level random-effects meta-regression using method-of-moments showed substantial heterogeneity ($I^2 \approx$ 60–70%) and non-significant age slopes for pain and anxiety. In small sizes, high-heterogeneity settings, such tests are underpowered and especially vulnerable to regression dilution when the moderator is an aggregated mean age measured with error—an ecological fallacy the authors themselves acknowledge.[4,5] Accordingly, the difference in conclusions reflects framework and power, not conflicting data: a dichotomous *p*-value can miss a clinically relevant trend that a Bayesian probability statement detects and quantifies.

We also expanded the original random model which used age as the only covariate, conditioning it on key study-level factors, such as sex, procedure type, and study quality. This is to mitigate confounding by case-mix and implementation differences, allowing the age effect to be interpreted as independent and thus more clinically actionable. Nonetheless, residual heterogeneity remained, suggesting that other unmeasured factors contribute to variability in virtual reality effectiveness across studies. These may include differences in virtual reality design (e.g., level of immersion, interactivity, and content), patient engagement, procedural context, operator expertise, and the use of co-interventions such as pharmacological analgesia or behavioral support. These factors are variably reported and cannot be fully accounted for in study-level meta-regression.

From a clinical perspective, virtual reality confirms itself as a valuable pain management approach, but the expected effect appears stronger in younger cohorts. Thus, for older children and adolescents, clinicians should consider optimizing its design (e.g., interactivity, task difficulty, agency) and combining it with other non- or pharmacological supports to sustain analgesic/anxiolytic impact.

Importantly, these findings argue for an urgent age-aware implementation of non-pharmacological pain management, mirroring the age-stratified approach already routine in pain assessment.

Limitations

Limitations of the current study center on the use of study-level (and not the unavailable individual-level) covariates, which constrains causal interpretation and invites ecological fallacy—patterns seen across study means may not reflect within-child relationships. Age was available largely as a study mean rather than harmonized strata, which introduces regression-dilution bias and likely attenuates true age effects. In addition, unmeasured design features—such as virtual reality hardware and immersion (field of view, interactivity, agency), session "dose" and timing, operator expertise, and co-interventions (topical anesthetics, distraction coaching)—were variably reported and could confound effect estimates. Mean age may also act as a proxy for other study-level characteristics, including differences in intervention design, cognitive engagement, or accompanying clinical practices, which cannot be fully disentangled in aggregate-data meta-regression. Outcome measurement also differed across studies (scales, timing), adding noise that a study-level meta-regression cannot fully absorb. Importantly, these findings are based on study-level data and therefore reflect between-study associations. As such, they may be strongly influenced by confounding factors such as differences in virtual reality design, engagement, or co-interventions across studies. Moreover, the persistence of heterogeneity after adjustment indicates that the model explains only part of the between-study variance, consistent with the presence of unmeasured or poorly captured moderators. Together, these factors limit the ability to isolate age effects from implementation differences and underscore the need for harmonized age bands and richer reporting in future trials.

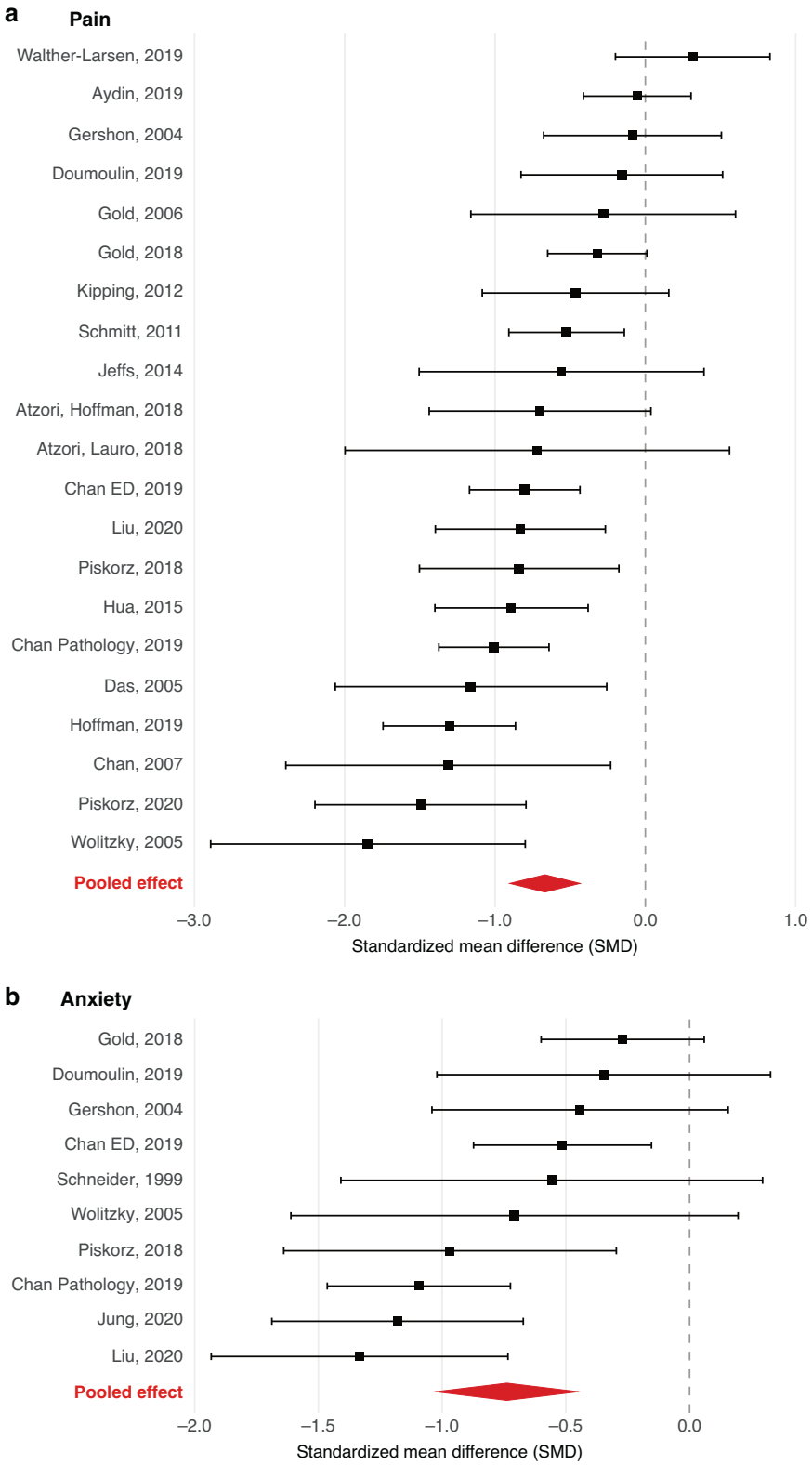

Fig. 1 Bayesian random-effects meta-analysis of the immersive virtual reality device on procedural pain in children and adolescents. **a** Presents results for pain, and **b** for anxiety. Points represent study-specific standardized mean differences (SMDs) with 95% credible intervals (CrI). The red diamond represents the pooled posterior mean effect with its 95% credible interval. Negative values indicate greater reduction in pain (**a**) or anxiety (**b**) with virtual reality compared to control.

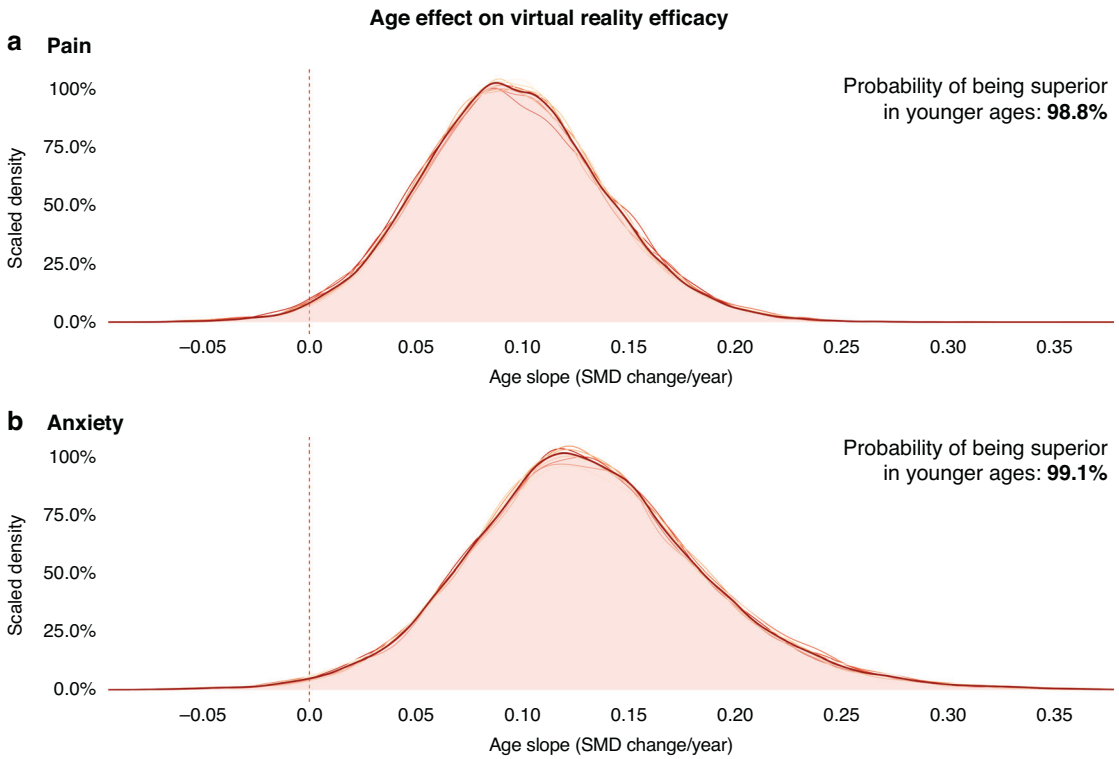

Fig. 2 Bayesian posterior age effect on virtual reality efficacy. The plot reports the Bayesian random-effects meta-regression posterior distributions of the age slope change in virtual reality effectiveness per one year increase in mean age. **a** Presents results for pain, and **b** for anxiety. The thin overlaid curves show the per-chain posterior densities from the eight Hamiltonian Monte Carlo chains, illustrating between-chain agreement and good mixing. The thick curve with its shaded area depicts the pooled posterior distribution of the age slope. The dashed red vertical line marks the null effect ($\beta_{age} = 0$). Shift toward positive values indicate attenuation of virtual reality benefit with increasing age.

CONCLUSION

This Bayesian meta-reanalysis confirms the effectiveness of immersive virtual reality in reducing procedural pain and anxiety in children. Through an accurate Bayesian approach, it reconciles disparate literature findings and demonstrates that efficacy declines with increasing age. These results argue for age-centered implementation and reporting of non-pharmacological approaches to pediatric procedural pain and anxiety. These results also support the wider adoption of Bayesian approaches to evidence synthesis—well suited to small and heterogeneous pediatric literature—in future reviews and guidelines.

DATA AVAILABILITY

This study is a reanalysis of previously published and publicly available data. All data used in this Bayesian reanalysis were extracted from the published systematic review and meta-analysis by Tas et al.[4] No new data were generated for this study.

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AUTHOR CONTRIBUTIONS

Enrico Cocchi conceived the study, designed the protocol, and supervised the project. Enrico Cocchi and Silvia Bloise directly accessed and verified the underlying data and analysis code. All authors had full access to all the data in the study and accept responsibility for the decision to submit for publication. Enrico Cocchi and Silvia Bloise did the literature search, study selection, and data extraction. Enrico Cocchi performed the statistical analyses and created the figures. Enrico Cocchi and Silvia Bloise interpreted the findings and provided clinical/policy contextualization. Enrico Cocchi drafted the manuscript; all authors critically revised it for important intellectual content and approved the final version.

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COMPETING INTERESTS

The authors declare no competing interests.

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