

Placebo effect model in asthma clinical studies: longitudinal meta-analysis of forced expiratory volume in 1 second

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Abstract

Objective Our objective was to describe the time course of the placebo effect in asthma and quantitatively investigate the affective factors of the placebo effect for the placebo response simulation during the asthma clinical study design. **Methods** We conducted a systemic search of public data sources for the study-level forced expiratory volume in 1 second (FEV₁) to build the placebo effect model for studies by oral or inhaled administrations simultaneously. The administration routes, types of inhalation device, mean patient age, mean male proportion, baseline FEV₁, disease severity, year of publication, inhaled corticosteroid status during the treatment, and dropout rate were tested as covariates. **Results** There are 34 literature sources containing 178 mean values for FEV₁ presenting the individual observations from about 3,703 patients. The exponential models adequately

described the time course of placebo effect with the typical value of the maximum placebo effect ($P_{\max}$) of 0.060 L. Dropout rate incorporated in the residual error model and the disease severity (mild to moderate and moderate to severe) at baseline were covariates that remained in the final model. **Conclusions** The placebo effect is adequately described by an exponential model over time. By incorporating the dropout rate in the residual error model, the estimation precision was improved. The model could predict the placebo response profile in mild to severe asthmatic patients for the asthma clinical study design and could also be a structure model of the placebo effect for the pure drug effect evaluation in the asthma clinical trials.

Keywords Asthma · Placebo effect · Longitudinal · Meta-analysis · FEV₁

Feng Guo and Wei Lu contributed equally to the concept and design of this study and can be considered to be co-corresponding authors.

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Introduction

Placebo groups are often conducted as controls to investigate the influence of the clinical trial beyond randomized treatment. The placebo effect has been discussed for decades in many fields. Its existence has been proved in many studies, such as those investigating pain, depression, and Parkinson's disease, and besides the psychological effect, the physiological mechanisms regarding the placebo effect also play a role in the placebo response [1–3]. Obviously, study design and adherence to protocol may also influence the observed placebo effect, where benefits of participating in a study or too short a washout time before randomization may be influences. The objective existence of the placebo effect in asthma patients has been proven in a previous patient-level study by measuring forced expiratory volume in 1 second (FEV₁) after methacholine challenge, which demonstrated the necessity of placebo arms in antiasthma trials for establishing the actual drug effect [4]. Researchers also verified that there was measurable placebo response in asthma patients by a meta-analysis based on the change from baseline (CFB) outcomes at the end of the study period in studies published before 1996 [5]. However, the time course of the placebo response in asthma clinical trials has not been investigated. This is important for the simulation of placebo effect during the design of clinical trials for asthma studies.

Longitudinal model-based meta-analysis is an efficient method to investigate and learn from the information collected in previous trials. Across various therapeutic areas, it has been used for an overall understanding of disease progression, drug effect, or comparison of pharmacokinetic characteristics in different populations [6–9]. One important advantage is the ability to quantitatively describe the common characteristics of the summarized level of data from previous studies, which is suitable for investigating the main trend of the placebo response with time in asthma clinical trials.

The aim of our study was to quantitatively describe the time course of the placebo effect and its affective mediators in asthma clinical trials in order to guide asthma study design. We hypothesized that different routes of administration, dosage forms, disease status, and patient demographic characteristics may affect the placebo effect. The objective outcome of FEV₁ was chosen as the endpoint of interest because it is regarded as the gold standard for airflow evaluation in the asthma clinical trials [10]. Moreover, objective outcomes were more reliable than subjective ones (e.g., patient self-reports) for objective evaluation of the placebo response [11].

Methods

Study selection

Studies published before May 2011 were screened after a systemic search of public data sources (PubMed, Embase, Clinicaltrial), which was conducted using the terms “asthma,” “clinical trial,” and “placebo.” Inclusion criteria were:

1. Double-blind randomized, multidose clinical trials in patients with chronic asthma who were older than 12 years.
2. Males, and non-breast-feeding and nonpregnant females;
3. Placebos taken orally or inhaled from a metered-dose inhaler (MDI) or dry-powder inhaler (DPI).
4. Longitudinal trough FEV₁ data were provided in tables or graphics.
5. Number of patient in the placebo group should be more than ten.
6. if a crossover study design, only data from the first period was analyzed.

Studies in patients with acute asthma, exercise-induced asthma, allergen-induced asthma, or aspirin-exacerbated respiratory disease (aspirin-induced asthma) were excluded. Figure 1 shows the study selection flow process.

Data extraction

We extracted the longitudinal data from tables or graphics in each selected clinical study and summarized the characteristics of each, including authors, year of publication, number of randomized patients (sample size) in placebo arms, inhaled dosage forms, duration of treatment, baseline FEV₁, mean patient age, proportion of males, percentage of predicted FEV₁ (disease severity), history of inhaled corticosteroid (ICS), and dropout rate (percentage that discontinued before the end of study period) in the placebo arms. We used FEV₁ as the endpoint for modeling because the normalized methods (change or percentage change from baseline FEV₁) are less suitable for longitudinal analysis [12]. Data for CFB, percentage change from baseline FEV₁ (%CFB), and raw FEV₁ were extracted using GetData Graph Digitizer. FEV₁ was derived from %CFB and CFB via mean baseline FEV₁ provided in each study.

Structural model development

FEV₁ data from oral and inhaled studies were log-transformed and analyzed simultaneously. We hypothesized that the placebo effect would change with time and achieve a plateau. Thus, we described the placebo effect profiles

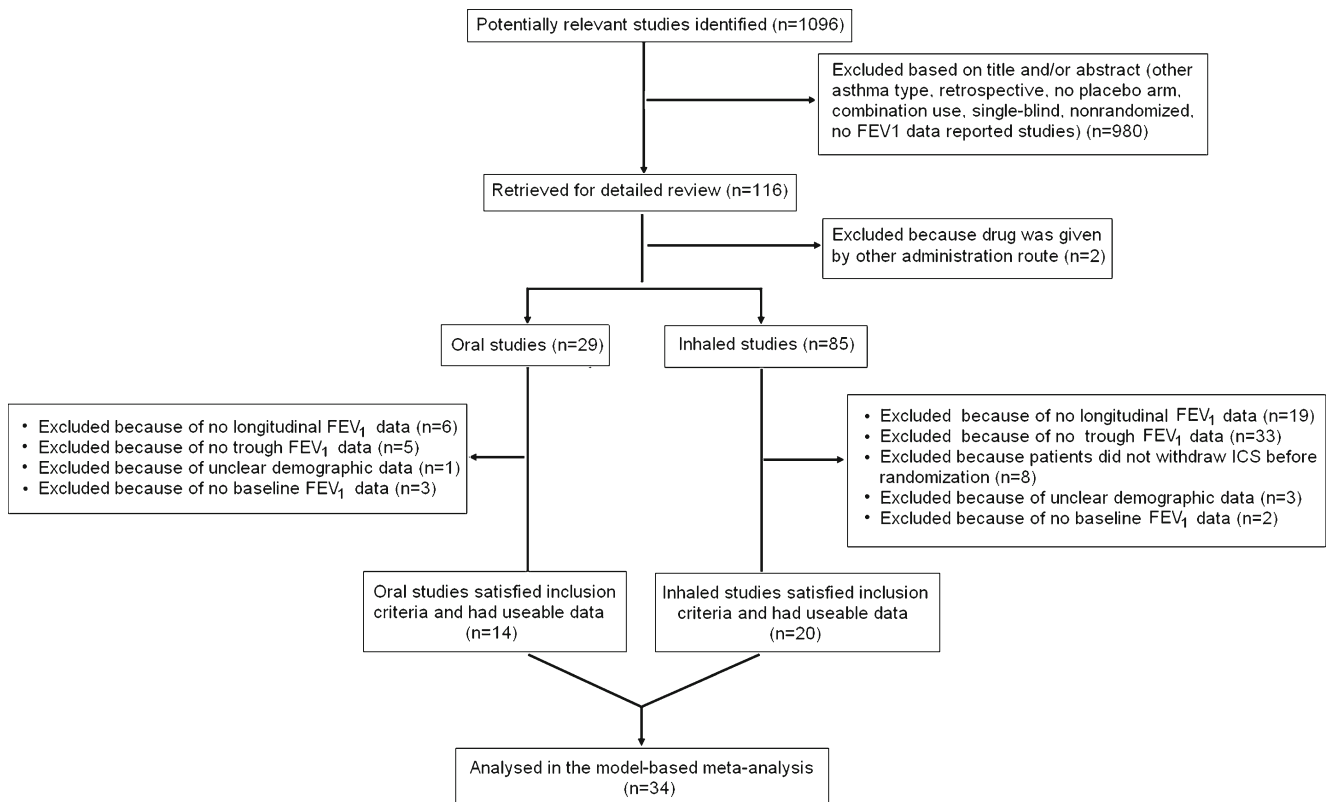


Fig. 1 Quality of Reporting of Meta-analyses (QUOROM) flow diagram indicating study selection for meta-analysis

with the Sigmoid and non-Sigmoid $E_{\max}$ and exponential models with time as the independent variable.

The exponential model was as follows:

$$FEV_1 = \theta_{base} + P_{\max} \cdot (1 - e^{-k \times t}) \quad (1)$$

where θ_{base} presents the population baseline FEV_1 ; $P_{\max}$ is the maximum placebo effect; k is the rate constant for onset of the placebo effect.

Random-effect model

An additive interstudy variability was used for $P_{\max}$, which allows both positive and negative placebo effect; exponential and proportional interstudy variability were tried for other parameters. Off-diagonal interstudy variability block was used to investigate whether there was a correlation between parameters. The additive residual error (proportional residual error model after transforming back to the normal FEV_1) weighed by the sample size of each placebo arm was calculated as follows:

$$Y = Ln(F) + \frac{SD}{\sqrt{n}} \cdot \varepsilon \quad (2)$$

where Y is the log-transformed observed data; F is the individual prediction based on the model; SD is the standard

deviation of residual error; n is the sample size of each placebo arm (the number of patients in each placebo arm at the randomization); and ε is the residual error with variance fixed to 1.

Model selection criteria

Structural model selection was based on both the visual diagnostic plots and the objective function value (OFV) difference. Models with lower OFV, acceptable parameter precision, and good fitness of the observations were selected. A model with OFV 3.84 (for hierarchical models with 1 df; corresponding to $\alpha=0.05$) lower than the other, was accepted as a better model. The goodness of fit was evaluated by graphic assessment, such as plots of observed versus predicted, individual prediction plot, and plots of conditional weighted residuals versus time or predicted.

Covariate evaluation

The potential continuous covariates, including mean age, baseline FEV_1 , proportion of male patients, proportion of ICS-withdrawn patients, duration of treatment, and dropout rate were assessed in the analysis. Both linear and power relationships were investigated in the continuous covariate modeling. The proportions of ICS-withdrawn patients were

Table 1 Characteristics of placebo groups from the selected asthma clinical studies [17–50]

Author	Dosage forms	N ^a	Duration (week)	Mean Age (yrs)	Baseline FEV ₁ (L)	Male (%)	FEV ₁ Pred ^b (%)	Dropout rate (%)	ICS withdrawn ^c (%)	ICS withdrawn ^d	All adults ^e	Disease severity ^f
Israel et al. [17]	CAP	47	4	32	2.29	76.6	58	6	100	Y	Y	1
Persson et al. [18]	TAB	162	4	45	2.05	54.3	62	6	68	Y	Y	2
Israel et al. [19]	TAB	135	13	33	2.26	46.7	60	14	0	N	Y	1
Liu et al. [20]	TAB	122	25	34	2.35	44.3	64	12	0	N	N	2
Barnes et al. [21]	CAP	44	4	38	2.44	65.9	67	2	70.5	N	N	1
Grossman et al. [22]	CAP	22	4	36	2.49	45.5	68	0	45 ^g	Y	N	1
Altman et al. [23]	CAP	58	6	36	2.40	77.6	59	19	21	N	N	2
Nathan et al. [24]	TAB	223	13	32	2.37	40.8	67	17	100	Y	N	2
Noonan et al. [25]	TAB	69	3	36	2.00	49.3	61	4	26	Y	N	2
Reiss et al. [26]	TAB	273	12	31	2.50	46.9	69	14	23.4	Y	N	1
Malmstrom et al. [27]	TAB	257	12	36	2.20	42.8	66	16	0	N	N	2
Yoo et al. [28]	CAP	99	4	45	2.44	54.5	73	NA	47	Y	N	1
Nelson et al. [29]	IR-TAB*	97	12	35	2.40 ^e	55.7	58	17	100	Y	N	2
	CR-TAB**	198	12	34	2.40 ^e	44.9	59	28	100	Y	N	2
Lu et al. [30]	TAB	46	2	32	2.52	56.5	65	NA	19	N	Y	2
Physicians[31]	MDI	61	14	35	2.34	67.2	65	15	36	Y	N	1
Pearlman et al. [32]	MDI	249	14	35	2.34	67.2	65	14	45 ^g	Y	N	1
Chunchalin et al. [33]	MDI	39	4	45	2.60	51.3	77	5	11.9	Y	Y	1
Fernandes et al. [34]	DPI	20	8	36	2.20	20.0	78	0	100	Y	Y	1
Yang et al. [35]	DPI	26	4	44	NA	34.6	84	NA	15.4	Y	N	1
Nayak et al. [36]	DPI	87	12	35	2.61	47.1	73	25	100	Y	N	1
Kemp et al. [37]	DPI	74	12	32	2.55	58.1	71	24	0	N	Y	1
Bronsky et al. [38]	MDI	87	8	36	2.62	46.0	NA	42	100	Y	Y	1
Ramsdell et al. [39]	MDI	48	6	32	2.67	44.0	NA	25	39.1	Y	Y	1
Ohta et al. [40]	MDI	169	16	49	2.11	42.7	76	17	100	N	Y	2
ZuWallack et al. [41]	DPI	79	12	NA	2.46	58.0	67	51	45 ^g	Y	N	1
Selroos et al. [42]	DPI	15	12	37	3.21	72.0	87	33	0	N	Y	1
Banov et al. [43]	DPI	87	12	35	2.50	56.3	71	11	0	N	Y	1
Nathan et al. [44]	DPI	84	12	37	2.22	44.0	63	44	45 ^g	Y	N	1
Meltzer et al. [45]	MDI	147	12	39	2.63	36.1	79	32	100	Y	N	1
McFadden et al. [46]	DPI	104	18	36	2.87	42.3	83	25	45	Y	Y	1
Berger et al. [47]	MDI	177	16	37	2.45	43.5	73	23	0	N	N	1
Kerwin et al. [48]	DPI	124	12	40	2.10	33.9	65	48	100	Y	Y	1
Bernstein et al. [49]	MDI	61	6	34	2.69	50.0	NA	18	54	Y	Y	1

Table 1 (continued)

Author	Dosage forms	N ^a	Duration (week)	Mean Age (yrs)	Baseline FEV ₁ (L)	Male (%)	FEV ₁ Pred ^b (%)	Dropout rate (%)	ICS withdrawn ^c (%)	ICS withdrawn ^d	All adults ^e	Disease severity ^f
Ekstrom et al. [50]	DPI	113	12	47	NA	51.3	60	11	89	N	Y	1

FEV₁ forced expiratory volume, DB double blind, PG parallel group, PC placebo controlled, CX crossover, RCT randomized clinical trials, TAB tablets, CAP capsules, MDI metered-dose inhaler, DPI dry-powder inhaler, IR-TAB immediate release tablets, CR-TAB controlled release tablets, NA not available

^a Number of patients in the placebo arm at randomization

^b Predicted FEV₁ read directly from tables in the literature

^c Percentage of patients who inhaled corticosteroid (ICS) before being included in the treatment

^d Patients taking ICS before treatment stopped taking ICS during treatment

^e Patient population included adolescents (age 12–18 years)

^f Disease severity: 1 = mild to moderate asthma, 2 = moderate to severe asthma

^g Imputed value by median of available values

the percentage of patients on ICS treatment before screening who were subsequently withdrawn from this treatment during the run-in and treatment periods. We imputed the proportion of ICS-withdrawn patients with the median value for other studies that showed no ICS-withdrawn data but the description of withdrawing ICS was found in the paper. Besides the proportion of patients withdrawn from ICS during the study, withdrawn status during the study was also tested simply as a binary covariate. Patient age ranges were treated as a binary covariate to indicate whether all patients were adults in each placebo arm. Disease severity was presented as mild to moderate or moderate to severe according to patient selection. Year of publication was also used as a categorical covariate to test whether there was difference between clinical trials published before and after 2000. Different administration routes (oral vs. inhaled) and inhaled administration devices (i.e., MDI vs. DPI) were tested as a categorical covariate during the covariate modeling. Dropout rate was tested by incorporating the weight of sample size directly into residual error (Eq. 3), where the number of completers is used instead of the number randomized:

$$Y = Ln(F) + \frac{SD}{\sqrt{n \cdot (1 - R_{drop})}} \cdot \varepsilon \quad (3)$$

where R_{drop} is the percentage dropout rate at the end of the treatment period.

The introduction of any covariates contributing to the drop of >3.84 (χ^2 , $\alpha=0.05$, $df=1$) in the OFV was kept in the model during forward inclusion. During the backward elimination procedure, a covariate was removed from the model if the OFV increased <6.63 (χ^2 , $\alpha=0.01$, $df=1$) during the exclusion. The model estimation was performed using NONMEM 7 (Level 1.2, ICON Development Solutions, Ellicott City, MD, USA) with the FOCE interaction method. Diagnostic graphics of NONMEM output were performed using the R (version 12.2.2) with the package Xpose (version 4.3.2) [13, 14]. The 95% confidence intervals (CI) of parameter estimates based on 1,000 bootstrap iterations and the visual predictive check (VPC) for evaluation of the prediction of the model on 1,000 simulations were performed using PsN (version 3.4.2) [15]. The complete modeling process was conducted on the interface software Piraña (version 2.4.0) [16].

Results

Characteristics of selected studies

There were 34 selected literature sources containing 178 values of FEV₁ (including FEV₁ calculated from CFB) presenting individual observations from about 3,703 patients. Of the 34 studies, 14 were conducted by oral

Table 2 Parameter estimation of the placebo effect model in asthma studies

Parameters	Values	Relative standard error (%)	95% confidence interval
θ_{base} , mild-moderate (L)	2.50	1.9	2.43-2.59
θ_{base} , moderate-severe (L)	2.18	2.7	2.07-2.30
Maximum placebo effect [P_{max} (L)]	0.060	27.5	0.033-0.091
k (week ⁻¹)	0.806	28.5	0.459-1.389
ω_{Baseline} (L ²)	0.0079	28.4	0.0046-0.011
$\omega_{P_{\text{max}}}$ (L ²)	0.0093	32.5	0.0051-0.016
ω_k (week ⁻²)	0.294	21.8	0.158-0.462
Correlation coefficient ($\omega_{\text{baseline}}-\omega_k$)	-0.775	-	-
Standard deviation	0.108	7.5	0.0927-0.121

administration; nine of the remaining 20 inhaled studies were by MDI and 11 by DPI. Detailed information of each study is listed in Table 1. Mean patient age values, mean proportion of male patients, and baseline FEV₁ were 36.9 (31–49.2) years, 50.5% (20–77.6%), and 2.40 (2.00–3.21) L, respectively. Most trials selected were conducted in Western countries, and the majority of study participants was white. Mean dropout rate for the oral studies was 12.6% (0–27.8%) and for inhaled studies 24.5% (0–51%); which was twice as high as for oral studies. Six of the 20 inhaled studies had a dropout rate >30%, which was higher than the highest dropout rate in oral studies.

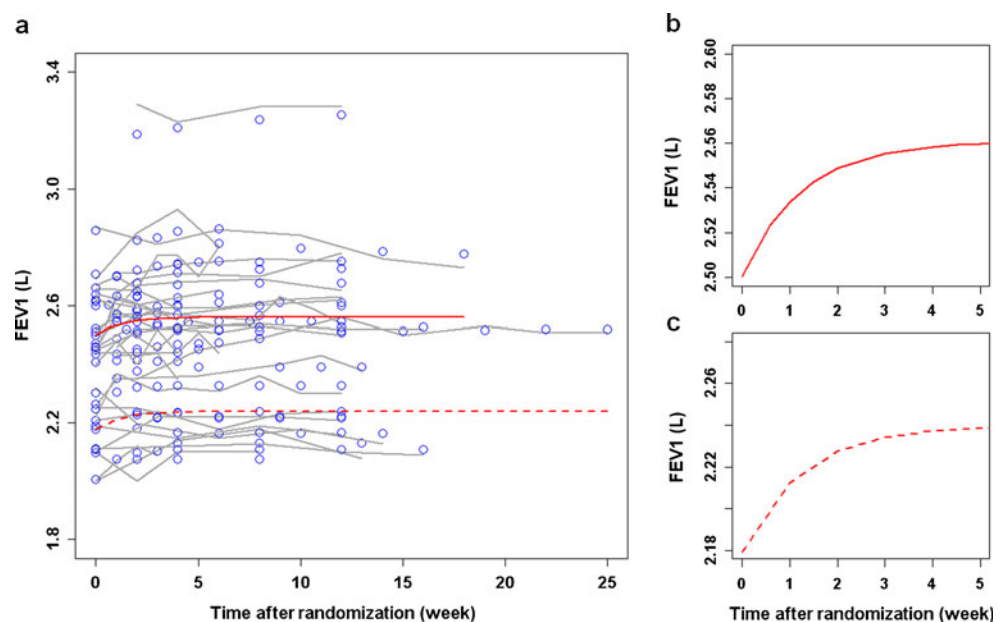
Placebo effect in asthma clinical studies

The placebo effect in asthma clinical trials was adequately described by the exponential model (Eq. 1) compared with the sigmoid and E_{max} model. In the final model, no potential covariates other than disease severity (mild to moderate or moderate to severe) on baseline

FEV₁, and dropout rate on weight in the residual error portion (Eq. 3) remained. The population value of the P_{max} was estimated as 0.060 L, and the rate constant k to achieve the plateau P_{max} was 0.806 week⁻¹. The parameter estimated with the 95% CI based on the bootstrap is listed in Table 2. Baseline FEV₁ for mild to moderate asthmatics was 2.50 L and for moderate to severe patients 2.18 L. Interstudy variability of the baseline negatively correlated with that of the rate constant k , with a correlation coefficient of -0.775. The proportional residual error was 10.8% in the final model.

When exploring whether clinical study designs and clinical spirometry tests in different time periods would have influence on the P_{max} , the impact of the year of publication was tested on the P_{max} , and no statistical significance was seen. Disease status (i.e., disease severity and percentage of predicted FEV₁), mean patient age, and the proportion of males were also considered as the covariates on θ_{base} , as well as on k and P_{max} , but only the

Fig. 2 Goodness of fit plots and prediction of the final placebo effect model. *Left panel:* observed forced expiratory volume in 1 second (FEV₁) (grey lines), time course of individual predictions (blue circles), and time course of median population predicted FEV₁ in mild to moderate (red solid line) and in moderate to severe patients (red dashed line) (a). *Right panel:* zoom of the median population predicted FEV₁ curve in mild to moderate asthmatic patients (b) and in moderate to severe patients (c) in the range of 0–5 weeks



impact of disease severity (mild to moderate or moderate to severe) on θ_{base} was statistically significant. The proportion withdrawn from ICS as a linear relationship and as a binary covariate was tested on P_{max} . No significance was found. Compared with no consideration of dropout rate on the residual error, replacing the randomized sample size by the number of completers (Eq. 3) obtained a similar OFV and more precise parameter estimation. Using the number of completers for weighting the residual error is also appealing, as studies with high dropout rates (i.e., from an actually smaller sample size) are down-weighted in parameter estimations.

Evaluation of the placebo effect model

The time course of FEV₁ and population and individual predicted FEV₁ in the studies are shown in Fig. 2. The individual predicted FEV₁ presented a good fit in relation to the observation FEV₁. Meanwhile, the median population predicted FEV₁ of mild to moderate and moderate to severe asthma demonstrated that the placebo effect achieved the plateau from different baseline FEV₁. Evaluation of the placebo model prediction is shown as VPC plots in Fig. 3, where 95% CI of the 5%, median, and 95% predicted percentiles covered the corresponding observed percentiles, which indicated that the model had an adequate prediction capability.

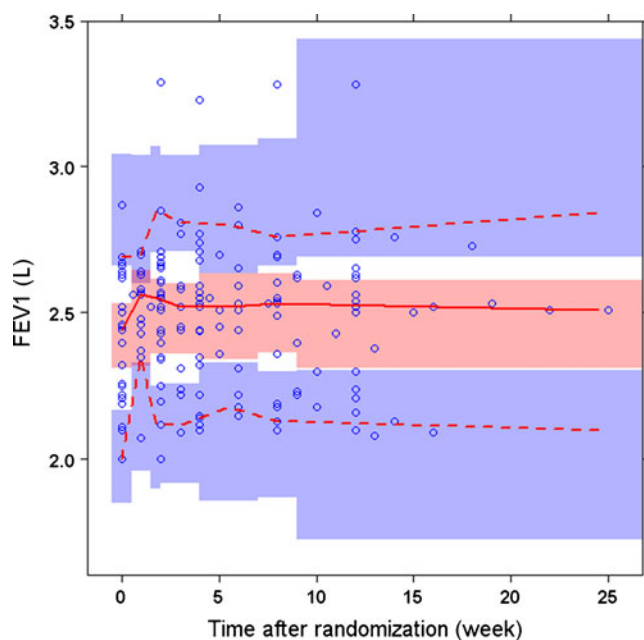


Fig. 3 Visual predictive check (VPC) for the final placebo effect model with the observed median forced expiratory volume in 1 second (FEV₁) (red solid line) and observed 5% and 95% percentiles (red dash lines) superimposed on the observations (blue circles). The 95% confidence intervals (CI) are shown in the blue shading for the 5% and 95% predicted percentiles and in the red shading for the predicted median

Discussion

Studies on the placebo effect in pain have demonstrated that the placebo response is the result of the physiological mediations of the endogenous materials by the subjective expectancy, e.g., the activation of the endogenous opioid systems. Change in brain activity caused by cognitive factors, such as learning and expectation, that relieves pain may also affect respiratory function [51]. Thus, the placebo response in asthma clinical trials may be affected by patients' subjective cognition causing brain activity change. Even so, confounding the pure placebo effect are other influential and often study-specific factors, such as dropout (that may be related to lack of efficacy) and protocol violations in, e.g., the use of rescue medication and inadequate or absent washout.

Among the selected studies, the dropout rate in the inhaled clinical trials was obviously higher compared with oral administration trials. This may be the result of higher patient expectations in the administration route of inhalation or else a difference in study settings or included patients, e.g., previous use of ICS. Therefore, the dropout rate was considered in the sample size weighting for the residual error. Data from studies with more completers would contribute more to parameter estimation. With this incorporation of the dropout rate, we improved the precision of parameter estimation.

In this study, in which we assessed a larger number of studies, we obtained the same results as those of a previous meta-analysis of the placebo effect in asthma, that no significant difference was seen between different administration routes [5]. As the placebo effect was affected by drug forms in analysis of migraine and depression studies [52, 53], besides analyzing administration routes, we included the covariate of different inhaled dosage forms (i.e., MDI and DPI) as a binary to explore the effect from their different devices and different components. Placebos administered by MDIs consist of hydrofluoroalkane (HAF) propellant, and those administered by DPIs often contain inert lactose powder. However, the placebo effect of MDI and DPI on P_{max} were not statistically significant. Thus, no significant difference in placebo response was seen between different inhaled placebo components.

Among the predictors of placebo response previously investigated by Kemeny et al. [4], sex did not differ significantly between placebo responders and nonresponders, but younger patients on inhaled placebos improved more than older patients. Our data did not support this age trend on P_{max} , perhaps because we used trough FEV₁ values as endpoints, which would not show the immediate response from placebo shown in Kemeny's study [4]. However, we came to the same conclusion that the placebo effect existed and the magnitude of the placebo response was not negligible. This is supported by another individual-level study that reported that the placebo effect in asthma was "clinically meaningful" and can even "rival the effects of active medication" [11].

During covariate analysis, incorporation of predicted FEV₁ and disease severity on baseline reduced the OFV to the same extent, whereas predicted FEV₁ was not kept in the model because it was not entirely independent from observed baseline FEV₁. Therefore, the impact of disease severity on baseline FEV₁ remained in the final model. It is reasonable that studies in moderate to severe patients are more likely to have lower baseline FEV₁, which is about 0.3 L lower than that of mild to moderate asthmatics based on our model. Incorporation of disease severity on baseline improved the prediction of the model. One could directly predict a time course of placebo effect in patients with mild to severe asthma based on our model.

There are some limitations to our study. First, the limited number of clinical studies analyzed did not allowed us to split data into estimation and validation components, so the placebo effect model still needs external validation by individual-level data. Second, we only obtained combined information about disease severity (mild to moderate and moderate to severe) but no detailed proportion of different disease severities (mild, moderate, or severe), which would help with the more specific prediction of the placebo effect in patients with different disease severity levels.

Conclusions

In summary, the placebo effect based on published asthma clinical studies is adequately described by an exponential model over time. With incorporation of dropout rate in weighting for the residual error, precision of the final parameter estimation improved. With the quantitative incorporation of disease severity on baseline FEV₁, one can predict the time course of the placebo response in mild to severe asthmatic patients during clinical study design. Moreover, it could also be a structure model for the placebo effect during evaluation of the pure drug effect in asthma clinical trials.

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Conflict of interest The authors declare that they have no conflict of interest.

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