Assessing the Cumulative Exposure Response in Alzheimer's Disease Studies

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Abstract

To assess long-term cumulative benefit of a treatment, the relationship between cumulative drug exposure and outcomes could be explored to understand dose response. However, cumulative exposure corresponds to the longitudinal profile of an outcome, which is heavily confounded with natural disease progression and missing data. A model-based approach is developed to account for the confounding factors. In particular, the observed measures are adjusted by the projected disease progression at the corresponding time points before exposure response is assessed. The proposed approach introduces new insights to the interpretation of study data. In the case study used to demonstrate the method, there seem to be various degrees of efficacy trend favoring higher level of cumulative exposure in active drug, based on selected clinical and biomarker endpoints.

Key Words: Cumulative exposure response, disease progression model, dropout effect, MMRM

1. Introduction

During drug development, two of the most typical questions are "how high" the dose or "how long" the treatment duration needs to be. These questions are naturally answered by assessing the relationship between cumulative drug exposure and cumulative treatment effect. However, in clinical trials, understanding the real cumulative treatment effect is often difficult because cumulative exposure, corresponding to the longitudinal profile of the observed outcome, is often a mixture of multiple factors:

- Drug effect: the actual treatment difference over placebo
- Natural disease progression: the deterioration observed under naive treatment
- Missing data impact: early dropouts may have shown greater deterioration

This complexity is particularly clear for a clinical trial of the neurodegenerative disease. For example, clinical trials for the Alzheimer's disease (AD) are usually conducted with elderly patients and last for years. During the course of a lengthy AD trial, the disease condition of the trial participants, who often have complex concomitant medical conditions due to age, deteriorates dramatically. These factors often cause a large portion of early dropouts and invalidate the direct interpretation of the cumulative exposure. As a result, when assessing the effect of cumulative exposure, it is critical to adjust the impact of these confounding factors.

We have proposed a model-based approach to account for the confounding factors. This approach provides a way to adjust for (remove) the impact of the confounding factors and undercover the true treatment benefit associated with the drug exposure. This method introduces important new insights to the interpretation of study data. In particular, in the case study used to demonstrate the method, there seem to be various degrees of efficacy

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trend favoring higher level of cumulative exposure in active drug, based on selected clinical and biomarker endpoints.

The rest of the paper is organized as follows: in Section 2 the proposed approach is introduced with details; in Section 3 a case study is presented to illustrate its use; Section 4 concludes and offers some discussion.

2. Method

Before introducing the details of the proposed approach, let us consider an example of two hypothetical subjects who have received active treatment in an AD clinical trial. The trial plans to record 6 consecutive post-baseline cognitive measurements but only 1 of these 2 subjects finished the trial (the other early terminated after the 5th measurement). The observed longitudinal outcomes of these 2 subjects are displayed by the solid curves in Figure 1. Due to informative dropout, subject 2 exhibited slightly faster deterioration as compared to subject 1. In addition, assume the real disease progression for these 2 subjects without treatment are given by the dashed lines of the corresponding color, then the real drug response is represented by the distance between the observation (solid curve) and the potential disease progression under naïve treatment (dashed curve). This provides a simple

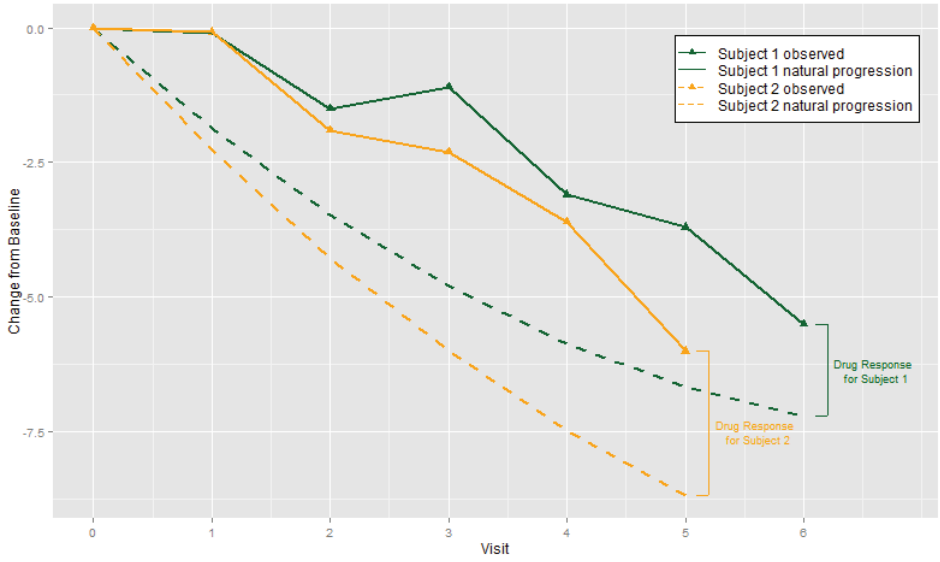

Figure 1: Subject level response adjustment

formulation of the observed outcome as

$$R_{\text{Observed}}(t) = E(t) + P(t) + m(t)\ ,\ t = 1, 2, ..., T\ , \tag{1}$$

where R is the response, E is the real effect of cumulative exposure, P is the natural disease progression, and m is the potential missing data impact. By Equation 1, the true effect of drug exposure is given by

$$E(t) = R_{\text{Observed}}(t) - P(t) - m(t) = R_{\text{Adjusted}}(t)\ ,\ t = 1, 2, ..., T\ , \tag{2}$$

This leads to the proposed 3-step approach in evaluating the real effect of cumulative exposure:

1. A disease progression model is constructed to represent the natural disease progression over the time course of the trial, where subject-level characteristics and dropout timing are taken into consideration

2. The observed outcome measures are adjusted by the projected disease progression at the *corresponding time points*

3. The resulting model-adjusted outcome measures are linked with the level of cumulative exposure (ie, total area under the entire concentration curve)

2.1 Disease progression model

A disease progression model reflects the amount of deterioration over time under naive treatment. Being used as the basis of the adjustment made to the observed data, the disease progression model is a critical part of the approach. While a disease progression model can be established following multiple approaches, a good choice that can be used for the purpose of this exposure response analysis needs to satisfy several requirements:

- Characterizes the longitudinal profile of the progression. This means, regardless of the actual structure of the disease progression model, it needs to have a term that reflects the time course of the measurements

- Differentiates patients with distinct disease severity. This means, in addition to the time component, the disease progression model needs to incorporate the impact of several subject-level variables (eg, age, baseline disease severity, etc) that are believed to impact the rate of progression. By doing this, the projected disease progression for subjects with different characteristics would be different and the model can be used to provide subject-level projection of the disease progression

- Recognizes dropout effect. Due to informative dropouts, subjects who early terminated from the study usually demonstrate higher level of deterioration as compared to those who stayed longer in the study. By recognizing the dropout effect, the dropout model should be able to differentiate the path of disease progression between a study terminator and a study completer. With that, consider 2 patients with identical characteristics but one completed the study but one early terminated before completion, the dropout model should give different projected disease worsening paths for these 2 subjects

The disease progression model we considered is essentially a mixed-effect model for repeated measures (MMRM). In any study with longitudinal measurements, such model can be established by using all observed response of the placebo-treatment subjects. In particular, our MMRM includes the observed response as the dependent variable, and a set of model covariates such as subject demographics (eg, age), baseline disease severity, time (visit) corresponding to each observed response, time to dropout, and several interaction terms as appropriate.

2.1.1 Model-based adjustment

After a disease progression model is constructed, all observed response could be adjusted by subtracting the model-projected disease progression. Several points should be noted when using the model to adjust

- For any given subject, the model-projected disease progression should be calculated using that particular subjects information as required by the disease progression model, including time to dropout. With that, each subject is compared with her/his own path of natural disease progression
- While the disease progression model provides the entire path of the disease progression for any given subject, the adjustment should be made only at the corresponding time point
- Observed response from placebo-treated subjects could be adjusted, too. Because the disease progression model itself is constructed using the placebo data, the adjusted response of placebo-treated subjects should represent a set of random noise that centers at 0

2.1.2 Exposure response modeling

The relationship of interest is the one between adjusted response and corresponding cumulative exposure level. Once every single observed response has been adjusted, an analysis that links the cumulative exposure and adjusted response at corresponding time point could be performed. Such analysis could be as simple as a correlation analysis based on a particular time point, or as complicated as a model that includes all information as an analysis for repeated measures (multiple records provided by the same subject).

However, it worth to point out that, since the adjustment is made based on the matching time point, the adjusted response is no longer impacted by time. In other words, an adjusted response at visit 5 can now be compared to an adjusted response at visit 6, and the only factor that differentiates these 2 records would be the cumulative exposure level. For example, as we will further discuss in the case study in Section 3, the final exposure-response analysis is performed by using each subjects last available measurement, which could be observed at different time points due to early dropouts.

3. A case study

As a case study, we considered data from 2 recently finished phase 3 clinical studies in testing the safety and efficacy of bapineuzumab IV in patients with mild to moderate AD.

3.1 Bapineuzumab

While the real cause of Alzheimers disease is still unknown, the mostly commonly accepted explanation is given by the amyloid hypothesis which suggests that the disease develops when clumps of abnormal proteins (beta amyloid) grow in the brain. Bapineuzumab is a humanized monoclonal antibody, which binds to and clears beta amyloid peptide, and is designed to provide antibodies to beta amyloid directly to the patient.

Two phase 3 placebo-controlled clinical trials were conducted to evaluate the safety and efficacy of bapineuzumab in patients with mild to moderate AD. The first study (Study ELN115727-301 or simply Study 301) enrolled only patients who are apolipoprotein E $\varepsilon 4$ gene noncarriers. Patients were to receive 6 quarterly IV injections of placebo or bapineuzumab at 0.5 mg/kg or 1.0 mg/kg dose levels. The second study (Study ELN115727-302 or simply Study 302) enrolled only patients who are apolipoprotein E $\varepsilon 4$ gene carriers. Enrolled patients followed the same dosing scheme as Study 301 patients, but only 1 bapineuzumab dose (0.5 mg/kg) was tested. An open label extension study (Study ELN115727-351 or simply Study 351) was conducted where completers of

the double-blind parent studies (Study 301 or Study 302) may be enrolled to receive only bapineuzumab. A diagram is given in Figure 2 to illustrate the sample size in each study. The co-primary clinical endpoints were cognitive and functional ability as measured by

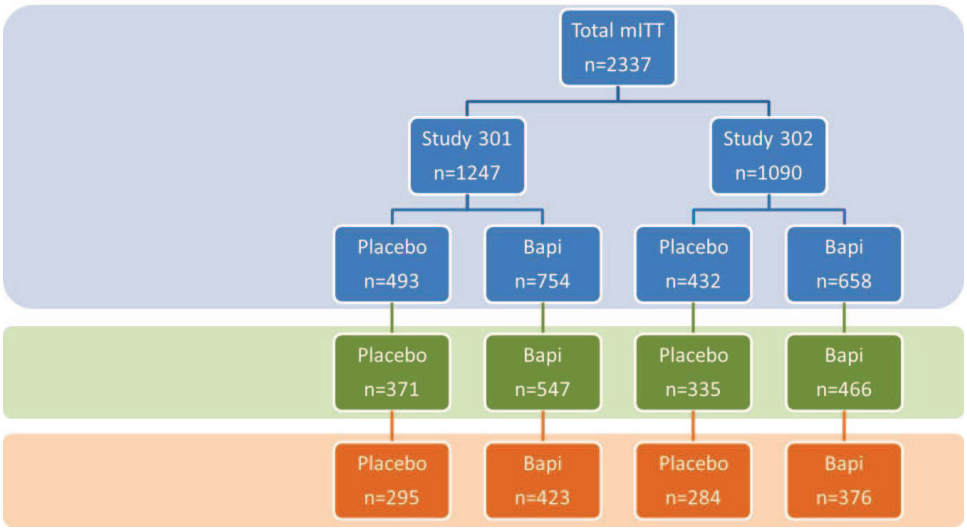

Figure 2: Sample size in bapineuzumab IV phase 3 studies

ADAS-Cog/11 total score and DAD total score. In addition, brain amyloid load was also assessed via PET imaging. Finally, compared to placebo, bapineuzumab did not demonstrate statistically significant treatment effect based on co-primary clinical endpoints, but demonstrated statistically significant treatment effect based on the PET imaging biomarker in ApoE $\varepsilon 4$ carriers.

3.2 Cumulative exposure analysis

The proposed cumulative exposure analysis was performed as a post hoc analysis, in exploration of whether or not higher level of cumulative exposure has potentially larger treatment benefit. Figure 3 shows a simple scatter plot of cumulative drug exposure in AUC (ug/mL $\times$ day) and the observed response, defined as change from baseline in ADAS-Cog/11 total score at the last visit. Two trend lines are superimposed to indicate the clear upward trend in both ApoE $\varepsilon 4$ carriers and noncarriers. For ADAS-Cog/11 total score, larger value means greater impairment, therefore Figure 3 seems to suggest that higher level of exposure causes greater amount of deterioration.

Such counter-intuitive observation is a direct consequence of confounding factors discussed in Section 1. To see this, it should be noted that subjects with high level of cumulative exposure are generally those who stayed longer in the study. However, due to natural disease progression, subjects who stayed longer in the study had a longer time period for disease deterioration. This natural disease progression is strong enough to significantly offset the drug effect, and thus cause an apparent upward trend when looking at the responses with adjusting for the confounding factor. Therefore, this dataset serves as a good example to apply the proposed 3-step exposure response analysis method, which is illustrated in detail in the next 3 subsections.

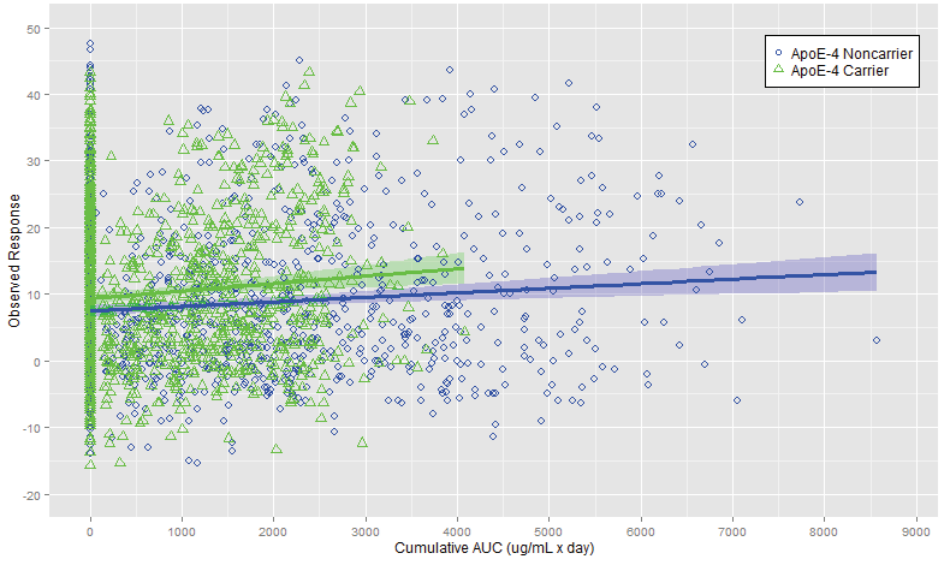

Figure 3: Observed response (ADAS-Cog/11 total score) vs. cumulative exposure AUC

3.2.1 Disease progression model

A mixed-effect model for repeated measures (MMRM) was used to build the disease progression model. The model used only placebo data (with slight modification for Study 351) and included the following terms:

- visit schedule
- baseline age
- randomization strata
- baseline value of the corresponding variable
- time to dropout
- baseline value vs. visit interaction

In addition, to appreciate the difference in disease progression between different patient populations, the model was constructed separately for ApoE $\varepsilon 4$ carriers and ApoE $\varepsilon 4$ noncarriers, and for treatment phase (double-blind period or open label extension period).

The estimated model terms for the double-blind period based on ADAS-Cog/11 total score are given in Table 1. It worth to note that, while not being statistically significant, the coefficient for the term "time to dropout" was negative for both the noncarrier and carrier populations. This intuitively reflects the fact that subjects who early terminated from the study often demonstrated greater amount of deterioration (for ADAS-Cog/11, larger score means greater impairment).

3.2.2 Adjusted response

Based on the MMRM-based disease progression model specified in Section 3.2.1, each subject's last observed outcome is adjusted by subtracting the model projected disease progression at the corresponding time point. For example, subject 1 was a study completer,

Table 1: Fitted disease progression model for ADAS-Cog/11 total score

ApoE ε4 Noncarrier		ApoE ε4 Carrier	
Model Terms	Coeff. Estimate (SE)	Model Terms	Coeff. Estimate (SE)
Intercept	5.6499 (2.2179)	Intercept	7.8834 (2.6256)
Baseline	0.2271 (0.0481)	Baseline	0.2300 (0.0558)
Age	-0.0443 (0.0216)	Age	-0.0470 (0.0273)
Time to dropout	-0.0196 (0.0117)	Time to dropout	-0.0265 (0.0125)
MMSE: Low	2.8437 (0.5386)	MMSE: Low	1.9702 (0.5427)
AD Med: No	-1.9626 (0.7593)	AD Med: No	-1.2737 (0.9078)
ApoE Allele: 1	NA (NA)	ApoE Allele: 1	-0.6596 (0.5268)
Week: 13	1.1309 (0.9812)	Week: 13	0.2257 (1.2464)
Week: 26	-0.0966 (0.8937)	Week: 26	-1.4345 (1.1145)
Week: 39	-0.5595 (0.7890)	Week: 39	-1.7955 (1.0306)
Week: 52	-1.5227 (0.7093)	Week: 52	-0.3949 (0.9196)
Week: 65	-0.0160 (0.7082)	Week: 65	-1.3741 (0.8406)
Baseline $\times$ Week: 13	-0.3528 (0.0443)	Baseline $\times$ Week: 13	-0.3349 (0.0505)
...	...	...	...
Baseline $\times$ Week: 65	-0.0597 (0.0311)	Baseline $\times$ Week: 65	-0.0103 (0.0347)

therefore his projected response at the 6th post-baseline visit was subtracted from his last observed response. One the other hand, subject 2 early terminated after the 4th dose, therefore her projected response at the 3rd post-baseline visit was subtracted from her last observed response.

Figure 4 illustrates a scatter plot of cumulative drug exposure in AUC (ug/mL $\times$ day) and the adjusted response. Two trend lines are also superimposed to demonstrate the downward trend within both ApoE ε4 carrier and noncarrier populations.

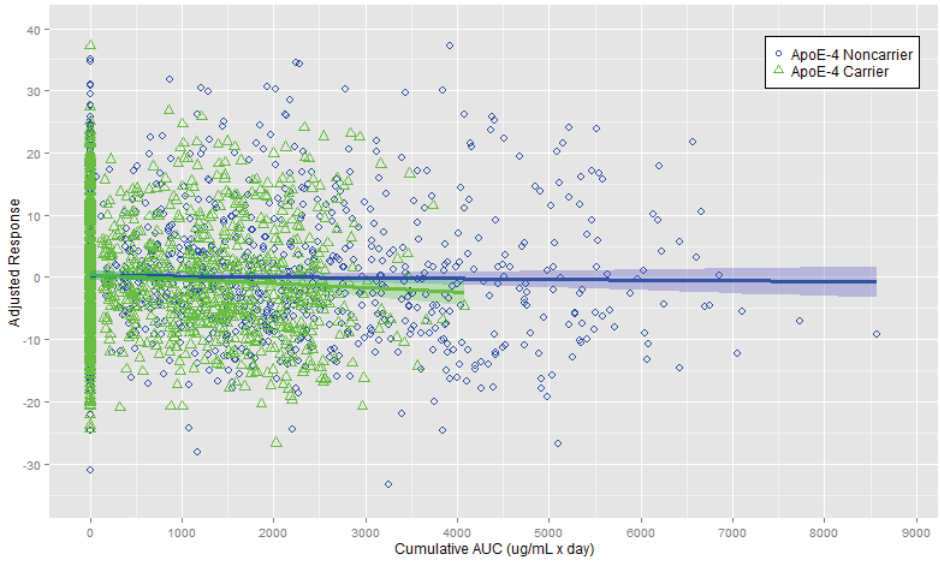

Figure 4: Adjusted response (ADAS-Cog/11 total score) vs. cumulative exposure AUC

3.2.3 Cumulative exposure response modeling

Based on the scatter plot (Figure 4), for simplicity, a linear regression was performed to demonstrate the relationship between cumulative drug exposure and the adjusted response

$$R_{\text{Adjusted}} = \alpha + \beta \cdot E \, . \tag{3}$$

However, it should be noted that other approaches might be preferred under various considerations. For example, from a typical dose-response point of view, an EMax type of model might be fit to recognize the potential "ceiling effect" of high exposure level

$$R_{\text{Adjusted}} = \alpha + \frac{\beta \cdot E}{\gamma + E} \, . \tag{4}$$

Also, a nonparametric approach (eg, LOESS) might be applied if a specific parametric shape of the dose response cannot be identified at priori.

Figure 5 shows the exposure response for ADAS-Cog/11 total score based on simple linear regression. The 2 trend lines are identical to the trend lines in Figure y but, to better illustrate the trend signal, scatter plot is not provided. Several vertical reference lines are also provided to show the cumulative exposure level of a study completer from each treatment group with typical body weight. The exposure response in both patient populations exhibit certain level of downward trend, suggesting stronger treatment effect associated with higher level of cumulative drug exposure.

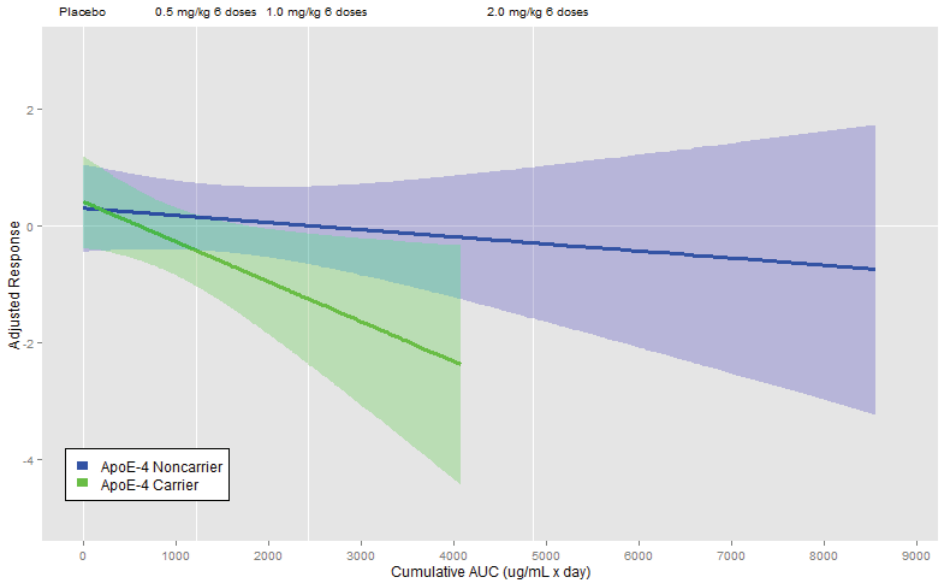

Figure 5: Adjusted response in ADAS-Cog/11 by cumulative AUC

Similarly, Figure 6 shows the exposure response for PET amyloid load (Florbetapir PET global cortical average SUVr). Similar to that of the ADAS-Cog/11 total score, the exposure response for PET amyloid load also exhibits a downward trend for both patient populations, with the signal in the ApoE e4 carrier population a bit stronger.

4. Summary and discussion

In this paper we introduced a model-based approach to assess the treatment effect of cumulative drug exposure. Such approach accounts for several confounding factors that are

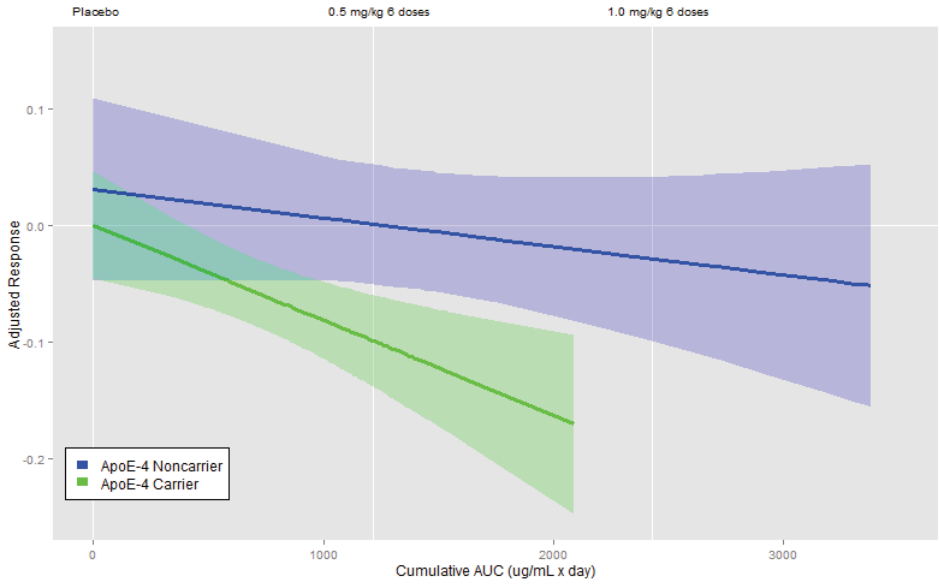

Figure 6: Adjusted response in PET GCA SUVr by cumulative AUC

typically experienced in longitudinal studies of chronic neurodegenerative disease. The proposed approach has 3 steps: first, a disease progression model is constructed to represent the natural disease progression over the time course of the trial, where subject-level characteristics and dropout timing are taken into consideration; then, the observed outcome measures are adjusted by the projected disease progression at the corresponding time points; finally, the resulting model-adjusted outcome measures are linked with the level of cumulative exposure (AUC). In the case study used to demonstrate the method, there seem to be various degrees of efficacy trend favoring higher level of cumulative exposure in active drug, based on selected clinical and biomarker endpoints.

While this approach is demonstrated for analyzing the effect of cumulative drug exposure, it can be in principal applied in all situations where the confounding impacts of time course need to be adjusted. The key component of the approach is the construction of disease progression model. Although such model can be established using different approaches, it is important to validate the appropriateness of the model via methods such as visual predictive checking (VPC). Figure 7 compares the observed ADAS-Cog/11 total score mean placebo response during parent and extension periods with that is suggested by the proposed disease progression model. The VPC suggests that the MMRM-based disease progression model well captures the natural disease deterioration in the overall population and when recognizing the baseline disease severity.

Finally, despite of its potentially wide application, the proposed approach has certain limitations that need to be emphasized

- Interpretation of cumulative exposure. The cumulative exposure (AUC) is jointly impacted by multiple factors (eg, dose level, number of doses, clearance, body weight, etc), therefore it is difficult to identify the marginal effect of a single factor. For example, when higher level of cumulative exposure is beneficial, unless additional control is applied, it is impossible to determine if the benefit comes from higher dose level or longer treatment duration.

- Due to the purpose and hence the design of the study, subjects' allocation to different

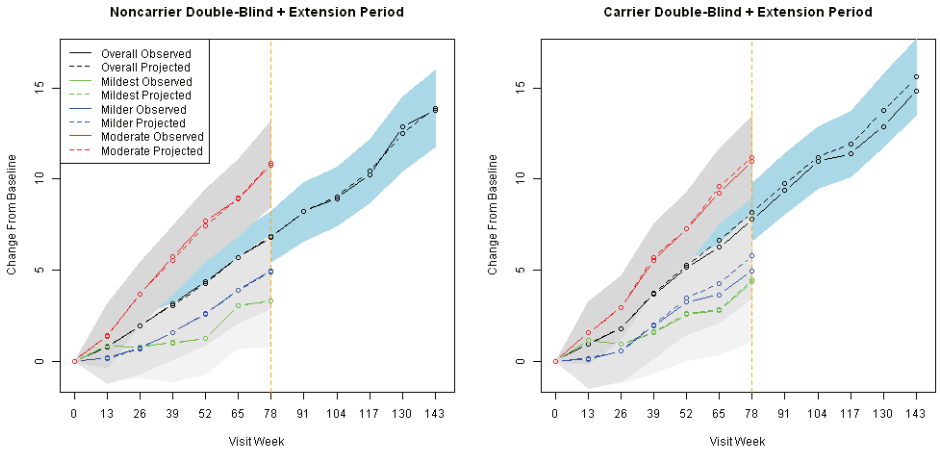

Figure 7: Visual predictive check: disease progression model (ADAS-Cog/11)

exposure levels is generally not random. For example, low cumulative exposure is to some extent confounded with early dropouts, while the efficacy performance of the early terminated subjects is observed to be worse than the general population.

- The adjustment of natural disease progression is performed based on a specific set of disease progression models. Therefore the results could be sensitive to model misspecification. For example, informative dropouts may create bias in modeling the disease progression. Although related factors (eg, time to dropout) are included in the disease progression model, this might not be sufficient in completely capturing the missing data impact, especially when missing data are missing not at random

- The exposure-response is modeled using specific parametric functions, which assume particular curve shapes and add certain restrictions and limitations in representing the relationship

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