Project 2

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Introduction

The purpose of this analysis is to develop an analysis plan and perform sample size calculations for a research grant involving Alzheimer's disease (AD). The goal of the grant is to examine the relationship between inflammation, AD pathology, and cognitive decline over time. The research team would like to have an analysis plan and sample size justification for two particular aims. The aims are as follows:

1. Evaluate longitudinal associations between markers of peripheral inflammation, cognition, and brain structure in Amnestic Mild Cognitive Impairment (aMCI).

2. Examine how markers of peripheral inflammation impact the relationship between AD pathology and clinical progression of aMCI.

The investigative team is interested in a longitudinal evaluation (from baseline to one year follow-up) of innate immune system-associated mechanisms of cognitive decline in aMCI.

Analysis Plan

We will develop several regression models for each aim. There will be a regression model for each cytokine/chemokine (IL-6; TNF-alpha; MCP-1; Eotaxin- 1; Beta-2 microglobulin; and ACT) to predict change in memory as measured by the California Verbal learning Test II (CVLT), and a separate regression model for each cytokine/chemokine to predict AD-signature cortica. thickness. Each of these models will adjust for age and sex, and cytokine/chemokine baseline values. Additionally, for Aim 1, we are interested in the same linear models, but rather adjusting for the change in chemokine and cytokine level as a covariate instead of baseline value. For all models now and going forward, to adjust for multiple comparisons of cytokines/chemokines, we will use the standard Bonferroni correction.[1] Addressing Aim 2, will be a linear

model to predict change in memory from baseline to one year (CVLT), with the interaction of amyloid deposition and cytokine/chemokine level, and adjusting for age, and sex (one for each cytokine/chemokine). As with Aim 1, we are also interested in predicting one year change in AD-signature cortical thickness, with the interaction of amyloid deposition and cytokine/chemokine baseline level, and adjusting for age, and sex, for each cytokine/chemokine. Amyloid deposition is to be treated as an indicator variable, for those with deposition below the median (low-) and those with deposition higher than the median (high-). Within these models we will examine as covariates: demographics (i.e. age; education), functional (i.e. Clinical Dementia Rating, CDR), behavioral (i.e. Geriatric Depression Scale, GDS), medication use (i.e. nonsteroidal anti-inflammatory drugs, NSAIDs), cardiovascular risk metrics (i.e. body mass index, BMI; blood pressure; history of hypercholesterolemia), APOE genotype, and diagnostic information. We would also like to keep the model a reasonable size while adjusting for these covariates. We will manage the model size by doing backward selection for variables that contribute significantly to expalined variance in the outcome. In addition to all models mentioned above we are also interested in the models decribed above that include all cytokines/chemokines in the model.

Sample Size Justification

This study was powered initially using the association described in Aim 1., the association between basiline cytokine and chemokine levels, and change in memory from baseline. To detect a correlation of 0.25, using a Bonferroni correction[1] to correct for six chemokines and cytokines, and adequate power of 80%. This sample-size calculation yielded a sample size of 186.

Using a sample size of 186 for Aim 2, where there are 93 in each of the low and high amyloid deposition groups (low and high), and a correlation of 0 for the low amyloid group and a correlation of 0.4 for the high amyloid group, yielded a power of only 58%. In order to account for 80% power in Aim 2, the sample size was recalculated. For each of the low- and high-amyloid deposition groups, we now need 138 subjects. This was calculated using the same Type-I error rate as before.

After recalculation, and accounting for 10% attrition, the final necessary sample size is 304 subjects, where 121 will be healthy controls (HC) and 183 will be aMCI. All sample size and power calculations were done using G * Power.[2]

Budget Justification

The total estimate 5-year statistical support budget is $389,000, with larger amounts allocated for the first and last years (Table 1.). The job of the Senior Biostatistician is to be the statistical support team supervisor. In the first year the Senior on the team will be attending meetings, and advising the Junior Biostatistician and Research Assistant, as well as any potential supervision of the Data Manager. The senior biostatistician is also responisble for assembling the statistical team, and onboarding new members as positions change hands. The Junior Biostatistician will be the primary analyst on all analyses as outlined above, with support from the Research Assistant, and supervision from the Senior Biostatiscian. The Data Manager will require little supervision, and may require some support from the Research Assistant. The data manager is only needed for the first two and final years. Their goal is to establish a well documented database in the first year, and onboard all other team memebers to use of that database. In the final year the Data manager is available as needed. The research assistant provides support as needed to all other members, and is expected to gain practical domain knowledge in addition to learning and honing statistical skills.

Please note that each member of the statistical support team expects to be supported both financially, and academically by inclusion as co-authors in any manuscripts where contributions were made. Manuscript writing will be done primarily by the Junior and Research Assistant, with editorial supervision from the Senior Biostatistician.

	Year 1	Year 2	Year 3	Year 4	Year 5
Senior Biostatistician					
Salary ($)	115000	115000	115000	115000	115000
Benefits	32200	32200	32200	32200	32200
Effort (%)	15	5	5	5	15
Cost	22080	7360	7360	7360	22080
Junior Biostatistician					
Salary ($)	80000	80000	80000	80000	80000
Benefits	22400	22400	22400	22400	22400
Effort (%)	50	25	25	25	50
Cost	51200	25600	25600	25600	51200
Data Manager					
Salary ($)	65000	65000	NA	NA	65000
Benefits	18200	18200	NA	NA	18200
Effort (%)	50	25	NA	NA	5
Cost	41600	20800	NA	NA	4160
Research Assistant					
Salary ($)	31000	31000	31000	31000	31000
Benefits	13000	13000	13000	13000	13000
Effort (%)	50	25	25	25	50
Cost	22000	11000	11000	11000	22000
Total	136880	64760	43960	43960	99440

Table 1. Five year statistical support budget justification.

References

1. Faul, F., Erdfelder, E., Buchner, A., & Lang, A.-G. (2009). Statistical power analyzes using G * Power 3.1: Tests for correlation and regression analyzes. Behavior Research Methods , 41 , 1149-1160

2. Bonferroni, C. E. (1935). Il calcolo delle assicurazioni su gruppi di teste. Studi in onore del professore salvatore ortu carboni, 13-60.