**How diverse are large multi-site schizophrenia studies? Modelling race, ethnicity and gender parity in COGS2**

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**Background**

Multi-center studies are increasingly necessary to advance psychiatric neuroscience and evaluate novel interventions for patients with schizophrenia. However, successfully translating results even from large, well-powered cohorts to usual-care clinical contexts remains challenging. Race, ethnicity, and gender disparities in recruitment of patients with schizophrenia (SZ) are some of the many factors that contribute to this generalizability barrier. Here, we report on race, ethnicity and gender diversity in the Consortium on the Genetics of Schizophrenia 2 (COGS2) study, and quantify the extent of additive sampling necessary to achieve racial, ethnicity, and gender parity.

**Methods**

The analysis cohort included 841 healthy control subjects (HCS) and 1060 SZ subjects between ages 18 and 65 from four of the five sites in: Los Angeles, New York, Philadelphia, and Seattle. We generated a Diversity Index using methodology from National Equity Atlas and previously published entropy index calculation to characterize the diversity within this sample. We categorized subjects into 24 categories based on combinations of race (Caucasian Americans, African-American, American Indian/Alaska Native, Asian, Pacific Islander/Native Hawaiian, and Multiracial/Other), ethnicity (Hispanic/Latino or non-Hispanic/Latino), and gender (Male/Female) from demographic information assessed at study entry and generated Diversity Index values for both HCS and SZ subjects for each city. These proportions and Diversity Indexes were compared to age-matched American Community Survey (ACS) census data for each of the above cities from 2010-2014. We carried out a simulation algorithm which sequentially expanded the COGS2 cohort by 50% by randomly resampling from the already recruited cohort, excluding subjects who were already oversampled in COGS2 based ACS data. The algorithm was allowed to resample until all 24 category proportions were within 2.5% of ACS data, and simulations were repeated 1,000 times.

**Results**

Analyses revealed multiple groups were over- or underrepresented in both HCS and SZ cohorts, compared to ACS demographic data. Compared to the HCS cohort, the SZ cohort had overrepresentation of African-American non-Hispanic/Latino females and African-American Hispanic/Latino males, and underrepresentation of Asian-American and Caucasian non-Hispanic females. On average the HCS cohort required 22.7 additive resamples (standard deviation, s.d. = 6.27) to approximate ACS race, ethnicity and gender proportions of the cities in which they were conducted, while SZ required 46.8 additive resamples (s.d.=11.0). For the SZ cohort to approximate the HCS race, ethnicity and gender proportions, 17.6 additive resamples were required (s.d= 6.69).

**Conclusion**

Data highlights the extent to which both HCS and SZ subjects differ in demographic composition compared to the city populations in which they are recruited. While demographic discrepancies have been observed in many large multi-site SZ trials, our results suggest relying on usual recruitment and ascertainment strategies would be inadequate for achieving demographic parity: COGS2 would need to be expanded by a factor of >10 for HCS and >20 for SZ to achieve representative racial, ethnic, and gender diversity. Ongoing analyses will investigate whether primary outcomes in COGS2 would be altered in simulated cohorts which are adequately diverse. Our findings emphasize the need for nuanced and targeted approaches for recruitment in large SZ multi-site studies.