Title

Advancing high quality longitudinal data collection: Implications for the HEALthy Brain and Child Development (HBCD) Study design and recruitment.

Authors

Si, Yajuan

Bandoli, Gretchen

Cole, Katherine

et al.

Publication Date

2024-10-01

DOI

10.1016/j.dcn.2024.101432

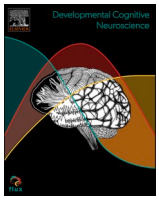
Peer reviewed

Developmental Cognitive Neuroscience 69 (2024) 101432

Contents lists available at ScienceDirect

Developmental Cognitive Neuroscience

journal homepage: www.elsevier.com/locate/dcn



Advancing high quality longitudinal data collection: Implications for the HEALthy Brain and Child Development (HBCD) Study design and recruitment

Yajuan Si [a,*], Gretchen Bandoli [b], Katherine M. Cole [c], M. Daniele Fallin [d], Elizabeth A. Stuart [e], Kelly K. Gurka [f], Keri N. Althoff [g], Wesley K. Thompson [h], & the HBCD Design Workgroup and Biostatistics Workgroup

[a] Survey Research Center, Institute for Social Research, University of Michigan, Ann Arbor, United States
[b] Department of Pediatrics, University of California San Diego, United States
[c] Division of Extramural Research, the National Institute on Drug Abuse, United States
[d] Rollins School of Public Health, Emory University, United States
[e] Department of Biostatistics, Johns Hopkins Bloomberg School of Public Health, United States
[f] Department of Epidemiology, University of Florida, United States
[g] Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, United States
[h] Laureate Institute for Brain Research, United States

ARTICLE INFO

Keywords:
HBCD
External and internal validity
Adaptive enrollment
Longitudinal trajectory

ABSTRACT

The HEALthy Brain and Child Development (HBCD) Study, a multi-site prospective longitudinal cohort study, will examine human brain, cognitive, behavioral, social, and emotional development beginning prenatally and planned through early childhood. The HBCD Study aims to reflect the sociodemographic diversity of pregnant individuals in the U.S. The study will also oversample individuals who use substances during pregnancy and enroll similar individuals who do not use to allow for generalizable inferences of the impact of prenatal substance use on trajectories of child development. Without probability sampling or a randomization-based design, the study requires innovation during enrollment, close monitoring of group differences, and rigorous evaluation of external and internal validity across the enrollment period. In this article, we discuss the HBCD Study recruitment and enrollment data collection processes and potential analytic strategies to account for sources of heterogeneity and potential bias. First, we introduce the adaptive design and enrollment monitoring indices to assess and enhance external and internal validity. Second, we describe the visit schedule for in-person and remote data collection where dyads are randomly assigned to visit windows based on a jittered design to optimize longitudinal trajectory estimation. Lastly, we provide an overview of analytic procedures planned for estimating trajectories.

1. Introduction

The HEALthy Brain and Child Development (HBCD) Study aims to recruit a U.S. cohort of pregnant and postpartum individuals ages 18 years or older and follow the parent-child dyads until the child is at least ten years of age. This multi-site study will facilitate addressing the following objectives: 1) Characterize typical neurodevelopmental trajectories, 2) Assess how biological and environmental exposures affect these trajectories, 3) Assess how gene/epigenetic/environment interactions influence trajectories, 4) Assess effects of early life exposure to opioids, marijuana, alcohol, and/or other substances on neurodevelopment, 5) Identify key developmental windows during which the impact of exposures (including variables associated with COVID-19 and high levels of maternal stress) influence later neurodevelopmental outcomes, 6) Identify key developmental windows during which protective influences are most impactful on these trajectories, and 7) Assess the impact of early caregiver-child relationships on later developmental outcomes.

* Correspondence to: Survey Research Center, Institute for Social Research, University of Michigan, Ann Arbor, ISR 4014, 426 Thompson St, Ann Arbor, MI 48104, United States.
E-mail address: yajuan@umich.edu (Y. Si).

https://doi.org/10.1016/j.dcn.2024.101432

Available online 10 August 2024

With the study objectives in mind, the enrolled cohort must (1) reflect the sociodemographic diversity of the target U.S. birthing population (individuals aged 15–50 years in the US who gave birth within the year, based on fertility data from the 2016–2020 American Community Survey (ACS) as a proxy), (2) include pregnant individuals who used specific substances (opioids, marijuana, alcohol, tobacco) during pregnancy, and (3) include pregnant people who did not use substances during pregnancy, who are demographically and behaviorally similar to those who used substances to enhance internal validity for causal inference in this non-experimental study.

2. The HBCD study population

The HBCD Study is designed to advance our understanding of neuroscience from a population perspective, similar to the Adolescent Brain Cognitive Development (ABCD) Study (Garavan, et al., 2018). Due to similar challenges faced by the ABCD Study, it is not feasible for the HBCD Study to implement a probability sampling survey, a conventional way to enroll representative study populations (often referred to as "samples"). Probability sample surveys often start from a list frame of eligible population units, all of which are assigned with known, non-zero probabilities to be selected into the sample. A sampling frame of U.S. pregnant individuals does not exist nor can it be constructed. Additionally, probability sample surveys have recently experienced rapidly declining response rates and increased costs (de Leeuw et al., 2018). For example, the Monitoring the Future (MTF, Schulenberg et al., 2021) study has used school-based recruitment to study patterns of drug use among 12th grade students and establish a panel of teens who are followed into young adulthood. MTF response rates have rapidly declined in recent years (Patrick et al., 2023). Due to these challenges, the HBCD Study uses a quota- and volunteer-based enrollment strategy with monitoring so that modifications to enrollment can be made to reach the goal of a study cohort to ensure participants represent the sociodemographic diversity of the U.S. population of pregnant individuals and ensure a sufficient sample size to assess prenatal substance use effects, controlling for important potential confounders (i.e., adaptive enrollment). Multiple strategies have been implemented to recruit, engage, and retain underserved and hard-to-reach populations (Cole et al.; Jones Harden et al.; Hillard et al.; Anunziata et al.).

Fig. 1 depicts the HBCD Study design to accomplish the three recruitment goals through a single-cohort strategy with a focus on: 1) external validity, i.e., sociodemographic representation of the general U. S. population of individuals who recently gave birth, and 2) internal validity, i.e., enhanced enrollment of pregnant people who use substances during pregnancy (SU) and similar pregnant people who do not (snSU). To monitor external validity of the study cohort during recruitment and enrollment, we compare the currently enrolled study cohort to that of the proxy target population (i.e., U.S. individuals ages 15–50 years in 2020 who have given birth in the past 12 months) by the following key characteristics: race, ethnicity, education, household income, urbanicity, and residence area deprivation index (ADI, Kind and Buckingham, 2018). Using the *Adaptive Enrollment Dashboard*, we assess the distributions of the currently enrolled study cohort characteristics with that of the target population to inform the need to, and timing of, modifications to the site-specific targets to achieve overall external validity. Any remaining differences in the enrolled study and the target population at the end of the enrollment period will be remedied with weighting approaches to enhance the generalizability of the study cohort.

2.1. External validity: the target, source, and enrollment

A large-scale study cohort that reflects the demographic characteristics of the target population is necessary to characterize the population average neurodevelopmental trajectory and the natural heterogeneity by race, ethnicity, education, household income, urbanicity, ADI, and interactions of these generalizability characteristics. This unified framework to monitor the study cohort during enrollment is necessary to ensure these key study aims can be achieved. Generalizing inference from HBCD findings to the target population requires determining the representativeness of the study cohort compared to the target population. The source population includes pregnant people within the recruitment catchment areas of the 27 geographically diverse HBCD sites that are mainly academic medical research centers and hospitals (Nelson et al.; Volkow et al.). Each site defined catchment areas (by county or zip codes) of potential participants, considering factors like driving distances to the research center. Thirty one percent of the targeted U.S. population lives within the HBCD consortium-wide catchment areas.

The aggregated U.S. Census and ADI data (specifically, individual demographic characteristics from the five-year (2015–2019) ACS data, tract-level urbanicity indicators in 2019 from the U.S. Census, and

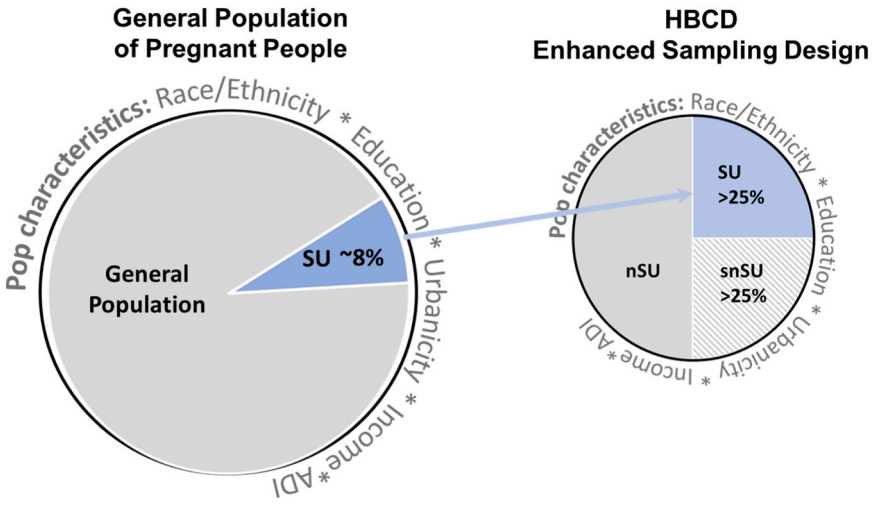


Fig. 1. The HEALthy Brain and Child Development (HBCD) Study enrolls a diverse cohort of pregnant individuals, with over-sampling of substance users during pregnancy and a sufficient number of demographically and behaviorally similar pregnant individuals who do not use substances to allow for investigation of the study aims. Abbreviations: SU= substance use (i.e., pregnant individuals who use substances during pregnancy). nSU = non-substance using (i.e., pregnant individuals who do not use substances during pregnancy). snSU=similar, non-substance using (i.e., similar to those who use substances with respect to potential confounders).

block-level 2019 ADI values) for each site's catchment area were used to estimate initial enrollment targets, by race, ethnicity, education, household income, urbanicity, and ADI. Urbanicity and ADI characterize the neighborhood environment of the sites' catchment areas.

Urbanicity includes urban areas or urban clusters from the Census tract level using data from the 2019 U.S. tract data and 2019 U.S. UAC10 data. The ADI is a summary index measuring multi-dimensional socioeconomic factors of income, education, employment, and housing quality to the Census block group level. We chose these characteristics because they are likely predictive of the analytic outcome and the sample inclusion mechanism (Little and Vartivarian, 2005; Si, 2024). The site-specific targets are formed to match the population distributions of these key characteristics in their corresponding catchment area. Site investigators reviewed the initial enrollment targets and provided feedback regarding the feasibility of reaching the targets based on the pregnant people they believed they could access in the catchment area. Small modifications were made to the initial targets to improve the likelihood the site could reach their targeted characteristics of enrolled participants. The modified targets were used for the site's enrollment goals; aggregation of these site-specific targets reflects the consortium-wide targeted characteristics of enrolled participants.

The demographic characteristics of the target population were compared to the consortium-wide targeted characteristics of enrolled participants (Table 1). Compared to the target population, the anticipated HBCD Study cohort based on the sites' catchment areas may in the end have a greater proportion of Black individuals, with an annual household income higher than $100 K, and a college education (or higher degree). The anticipated HBCD Study cohort may be more urban and residing in areas with lower area deprivation. At the conclusion of the HBCD Study enrollment period, weights will be estimated to ensure inferences from the HBCD Study cohort are generalizable to the target population of U.S. birthing women, particularly to rectify underrepresentation of residents in rural areas and with higher material deprivation.

Table 1
Distribution of key generalizability variables in the U.S. population and HBCD Study recruitment targets.

	Group	Target population[1]	HBCD recruitment goals based on the consortium-wide catchment area
Size	Total	3987,092	1232,329
Race	White	68.1 %	61.4 %
	Black or African American	14.6 %	21.3 %
	American Indian and Alaska Native	1 %	1.4 %
	Asian	6.5 %	6 %
	Native Hawaiian and Other Pacific Islander	0.3 %	0.1 %
	Two or more races	3.3 %	4.3 %
	Other	6.2 %	5.5 %
Ethnicity	Hispanic or Latino	22 %	18.2 %
Education	High school or equivalent graduate or lower	34.7 %	33.1 %
	Some college or associate's degree	30.9 %	28.9 %
	Bachelor's degree	21.3 %	22.3 %
	Graduate or professional degree	13.1 %	15.8 %
Household income	<10k	6 %	6 %
	10–75k	41.8 %	40.6 %
	75–100k	14.3 %	14.3 %
	100–200k	27.6 %	28.1 %
	200k	10.4 %	10.9 %
Urbanicity[2]	Urban	55.7 %	62.5 %
Area Deprivation Index[3]	<=25	24.5 %	29.6 %
	25–50	24.5 %	26.5 %
	50–75	24.5 %	23.3 %
	75–100	26.6 %	20.7 %

1. The 2015–2019 American Community Survey (ACS, weighted) of U.S. women ages 15–50-year-old who had given birth in the past 12 months is the target population.
2. The urban indicator is on the tract level that we construct based on two census data sources: 2019 U.S. tract data (https://www2.census.gov/geo/tiger/TIGER2019/TRACT/) and 2019 U.S. UAC10 data (https://www2.census.gov/geo/tiger/TIGER2019/UAC/).
3. The calculation is based on the block-level 2019 Area Deprivation Index values (https://www.neighborhoodatlas.medicine.wisc.edu).

2.2. Internal validity: people who do and do not use substances while pregnant

Overall, during pregnancy the prevalence of addictive substance use, including opioids, cannabis, alcohol, and tobacco, in the U.S. was at least 10 % in 2020 (Substance Abuse and Mental Health Services Administration, 2020). To ensure adequate power to investigate individual and polysubstance use exposures during pregnancy on maternal and child health outcomes, a study cohort enriched with people using substances during pregnancy is required. Opioids, marijuana, alcohol, and tobacco were identified as the substances of interest. A target of 25 % of the total study cohort was set for the enrollment of people who use any of these substances during pregnancy. Individual substance targets were also established including 12 % opioid use, 12 % marijuana use, 12 % alcohol use, and 12 % tobacco use, which includes polysubstance use between the four substances. Prenatal substance use is assessed via multiple modes at enrollment including self-report, electronic health record (EHR) diagnosis of substance-related syndromes in child participants, and research-based biochemical assays, with specified threshold definitions of exposure for each substance (Gurka et al.). These criteria are used solely to define minimum prenatal use of substances to ensure that the consortium enrolls a study cohort enhanced for opioid use and other substances of interest during pregnancy. Importantly, individuals with any substance use below these criteria are still enrolled, ensuring a wide range of exposures for analysis.

To ensure internal validity of causal inferences in a non-experimental study design comparing child outcomes in those who were and were not exposed to substances *in utero*, we will identify study participants who did not use substances during pregnancy (unexposed) that had similar characteristics to those who did (exposed). This comparison group is needed to achieve internal validity. Even when analytic tools are used to address confounding, there must be enough overlap of confounder variables between exposed and unexposed participants to assure valid inference, and ideally extensive measurement of the potential confounders to be able to adjust for them (Rosenbaum and Rubin, 1983; Stuart, 2010).

Given that people who use substances during pregnancy may have a relatively rare constellation of characteristics on key confounders, the general population of unexposed participants (nSU) may not provide sufficient comparison. HBCD must ensure enough similar, non-substance using participants (snSU concept in Fig. 1). For this reason, HBCD is actively monitoring the enrollment of the unexposed group with respect to confounder distributions to ensure sufficient overlap with the substance using group. This is operationalized via predicted propensity score (PS) of using substances (individual and overall use) during pregnancy. The PS for substance use is estimated for all participants, regardless of actual exposure status, from models that include measured variables considered to be likely confounders for many of the key scientific questions about the relationship of substance use during pregnancy and developmental outcomes.

2.3. The adaptive enrollment dashboard

During the HBCD Study recruitment/enrollment period, (a) external validity is monitored by comparing characteristics of the enrolled study

cohort with the target population and (b) internal validity is monitored by visualizing the confounder balance across the substance using and non-substance using participants. The external and internal validity-relevant comparisons are visualized in the Adaptive Enrollment Dashboard (accessible to study investigators) and updated daily (Fig. 2).

The dashboard is monitored by multiple groups of investigators, including the Design Working Group. Threats to external and internal validity of the study visualized in the dashboard as well as site-specific differences in their targets and enrolled participants are addressed with modifications to recruitment.

The distributions of race, ethnicity, education, and household income from the 2015–2019 ACS data of U.S. women ages 15–50 years old who had given birth in the past 12 months are coded in the dashboard as external validity targets. These measurements from the enrolled HBCD Study participants are visualized as the difference between their observed distribution and the target proportion (Fig. 3). The geographic characteristics of urbanicity and ADI distribution are also visualized. In addition to the marginal distributions of the characteristics of the target and enrolled study cohort, joint distributions based on important high-order interaction terms can also be visualized.

The study is designed to recruit individuals to help maximize internal and external validity, as described above. However, given the anticipated differences in the HBCD Study cohort and the target population, it is likely that additional analytic approaches will help enhance the external validity of the ultimate analyses. In particular, weights developed through raking (e.g., iterative proportional fitting) or post-stratification based on the generalizability variables can further strengthen the external validity of HBCD findings. Weighting improves external validity but potentially reduces precision with increased variance. The dashboard will incorporate weighting adjustments and monitor their performance by illustrating the weighted summary statistics, including the weighted proportions of the generalizability variable categories, and the design effect, defined as the ratio of weighted variance estimates to unweighted variances, measuring the precision loss due to weighting. Effectively, the Adaptive Enrollment Dashboard can monitor the bias and variance tradeoff of the weighting approaches. When the weighted summary statistics from the HBCD Study cohort do not match those of the target population, or the design effect is substantial, recruitment and enrollment strategies will be modified. Site-specific modifications to enrollment targets follow the principle that consortium-wide external validity according to the chosen characteristics is the priority. If one site has difficulty recruiting individuals with some characteristics, for example, rural participants, the modification could be moving this site's rural target to another site that has been successfully recruiting individuals from rural areas and increasing the latter site's rural target numbers.

Similarly for internal validity, the Adaptive Enrollment Dashboard will compare the PS distributions and characteristics of the enrolled people who use substances (individual and overall use) during pregnancy and enrolled people who do not. The larger the overlapping area, the more similar the two groups are on key confounders. For each confounder variable, the dashboard provides visualization of that variable's distribution before and after a PS adjustment when comparing the individuals using that substance and those not using that substance. The PS adjustment methods include inverse PS weighting and matching. Ideally, the PS adjusted confounder distributions should be more similar than those before the adjustment. Simultaneous monitoring both PS overlapping and covariate balance is key to achieving internal validity with successfully enrollment of the exposed and unexposed groups who are demographically and behaviorally similar.

The ultimate goal of monitoring the internal and external validity of the enrolled HBCD Study cohort is to inform site-specific modifications to recruitment and enrollment targets to bolster the external and internal validity of inferences from the study cohort at the conclusion of the recruitment/enrollment phase.

3. Longitudinal design

Longitudinal data are crucial for addressing the HBCD Study aims to characterize within-person change over time and to estimate neurodevelopmental trajectories. However, given the limitations of study participation burden and cost, it was not possible to obtain a dense set of assessments across the entire age-span of interest (birth to ten years of age). Therefore, visit timing was a primary consideration in designing the longitudinal component of the study. It is important to note that there will be more remote and in-person visits as the study progresses and the participants grow older, but their timing and the assessments to be collected have yet to be completely decided as of the writing of this paper. We thus describe the visit design up to 17 months adjusted age for the child participants; we use the term "adjusted age" to refer to the number of months from estimated due date (EDD), rather than the number of months from birth.

The HBCD Study visit schedule, planned as a combination of in-person and remote visits across the first decade of life, supports a complex and comprehensive protocol that includes assessments of children's physical (Cioffredi et al.; Pini et al.), emotional, cognitive (Kable et al.), and neurobiological development (Elinor et al.; Dean et al.; Fox et al.) and measurements of parental health and well-being, prenatal substance use exposures (Gurka et al.), caregiver-child relationships (Edwards et al.), and other social and environmental factors

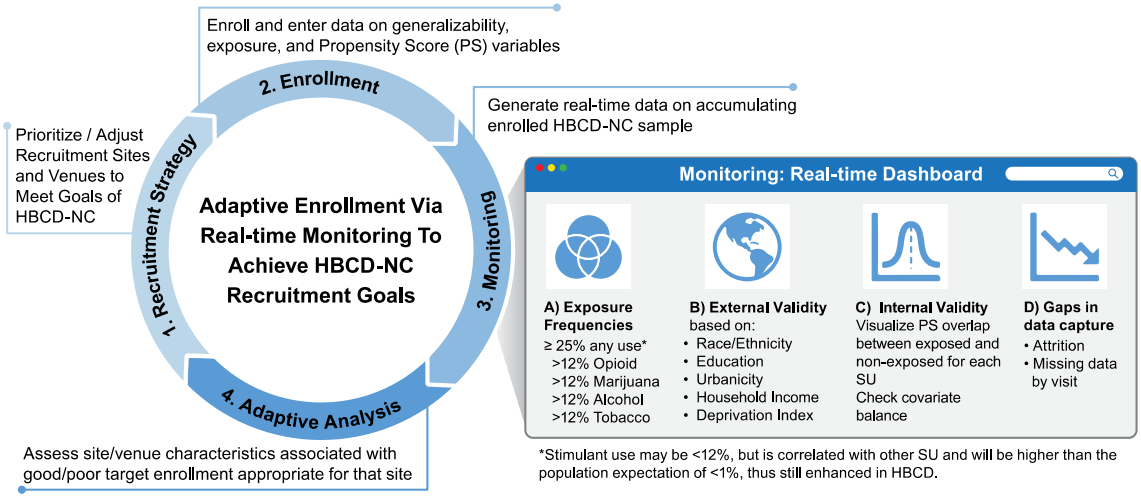


Fig. 2. Adaptive Enrollment Dashboard in the HBCD Study.

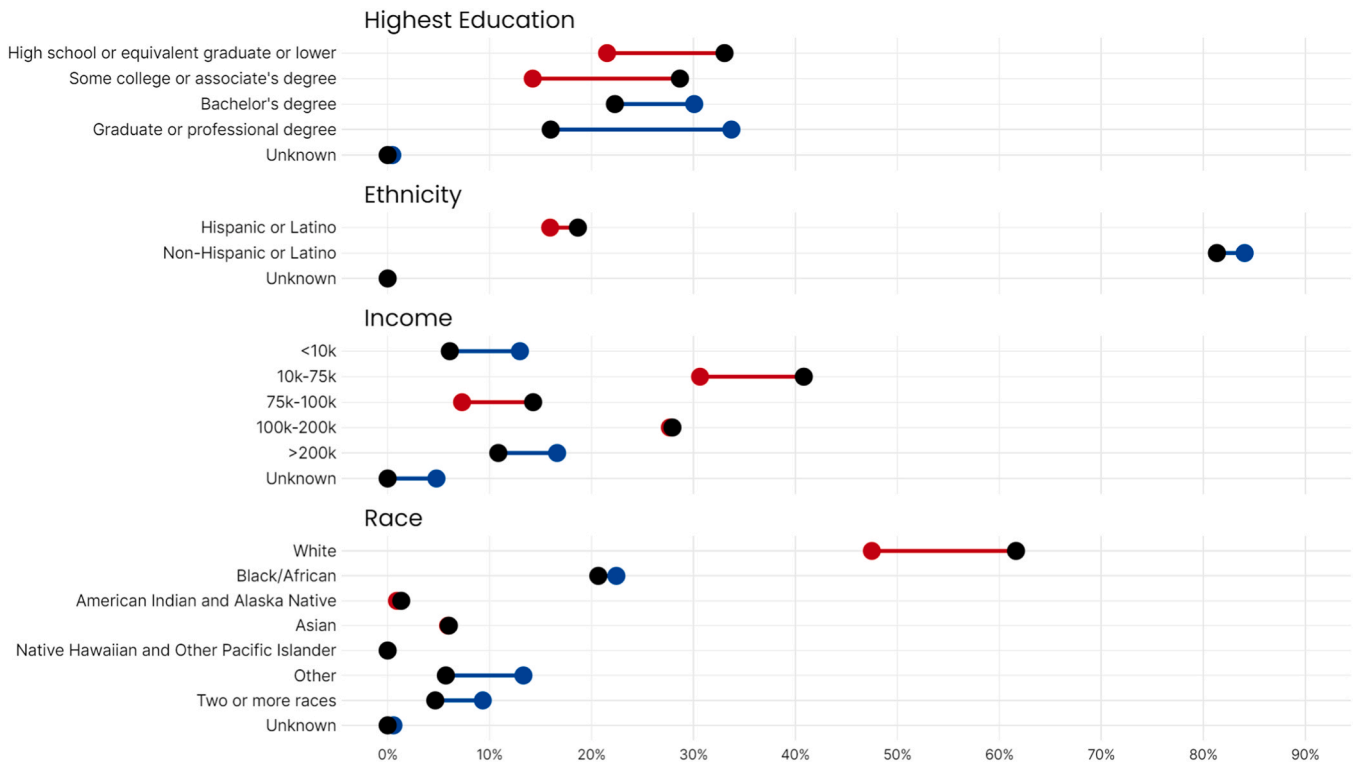


Fig. 3. An example of the visualization of differences in the enrolled HBCD Study cohort and the target population (Black dots: target; red dots: recruitment lower than targets; blue dots: recruitment higher than targets).

that may impact child development outcomes (Cioffredi et al.).

Fig. 4 presents the planned longitudinal visits. Visit 1 is prenatal and occurs between gestational week 13 and birth. There will be a relatively small proportion of participants who will be enrolled after childbirth and hence will not have a Visit 1. In addition to a prenatal in-person visit, there will be three in-person (Visits 2, 3, and 4) postnatal visits and one remote (Visit 5) visit in approximately the first one and a half years of life. All three of these in-person visits will collect magnetic resonance imaging (MRI), whereas electroencephalographic (EEG) data will be collected in Visits 3 and 4. Planning of visit structure and protocols following remote Visit 5 is ongoing as of the writing of this paper. Frequency of assessments will decrease following Visit 5, at some point likely settling into annual in-person visits.

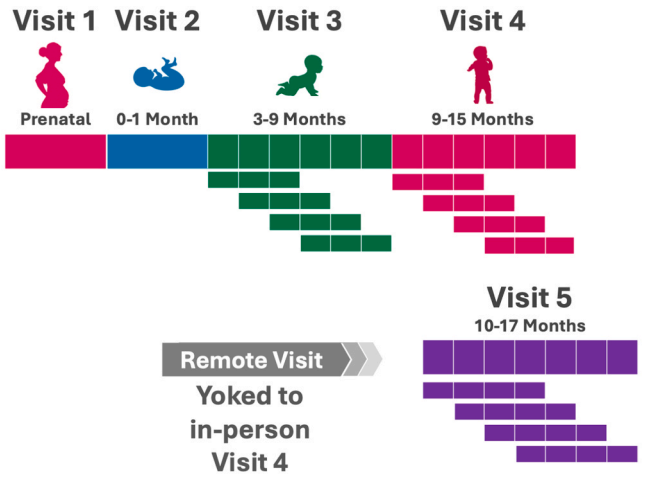


Fig. 4. Longitudinal follow-up visits. Note: The visit schedules are only current as of the time of manuscript submission and may change during the piloting study and implementation refinement.

The design of the study sought to balance intense data collection during the rapid period of child growth and development with participant and site burden in the data collection process. Thus, the study will use a 'jittered' design and randomly assign participants into jittered micro-bins (Fig. 4) beginning at Visit 3 to provide maximal data coverage with minimal operational burden. Another important benefit of this "jittered design" is the variable length of time between visits across participants, thus optimizing the ability to estimate within-person developmental trajectories at the individual level from relatively sparse longitudinal data with minimal assumptions regarding the shape of these trajectories (Staniswalis and Lee, 1998).

There were additional considerations in implementing this longitudinal design to balance rigorous analysis of the resulting data, and participant burden. First, once a participant has been assigned to a particular micro-bin for a given visit, they are allowed to schedule the visit any time in that micro-bin; however, all of the components of the visit are required to be finished within 30 days of each other; if there are both MRI and EEG assessments during the visit, they are required to be scheduled within 14 days of each other. These requirements were put in place to enable treating them as more-or-less contemporaneous for statistical analyses relating these measures to each other. Given the rapid rate of infant development, it is likely unrealistic to assume assessments spread out over several months are contemporaneous and hence would require more complex analytical strategies to relate to each other.

A second consideration was ensuring that visits did not occur too close together. Thus, the randomization into micro-bins was restricted so that the next in-person visit would not occur less than two months later. This maximizes the utility of the longitudinal assessments by allowing for a meaningful amount of time to pass between collections of the same assessments (e.g., MRI) while also allowing time for rescheduling components of a visit if necessary, without impinging on the next in-person visit.

3.1. Visit structure

Visit 1 is an in-person visit that occurs during pregnancy, with the exception of 10 % of the sample that can be enrolled postnatally if limited prenatal care visits occurred (< 4 visits). Sites are directed to ideally enroll participants around 20 weeks of gestation. Visit 2, the first postnatal visit, is intended to occur from 0 to 1 months post EDD. There will be a proportion of Visit 2's that occur before this (for babies born before their EDD) and after this (in the 2–3 months post-EDD period) if, for various reasons, it is not possible to schedule a visit from 0 to 1 months post EDD.

The possible micro-bin sizes for Visits 3 and 4 are larger, and the procedure for scheduling these was carefully designed to fill them out as uniformly as possible across participants. Visit 3 happens from [3,9) months (where the notation $[x, y)$ implies the visit times t can be equal or larger than x but strictly smaller than y), and Visit 4 happens from [9,15) months. These bin sizes are likely to be fairly large compared to the rapid developmental change occurring in infants in these age ranges.

To fully assess developmental change, it was decided to obtain a uniform distribution of participant ages from 3 to 17 months during both in-person and remote visits. This is being accomplished by randomizing participants into smaller 90-day windows (so called "micro-bins") within each of the larger bins. For example, Visit 3 is subdivided into [3, 6), [4,7), [5,8), and [6,9) month micro-bins. Likewise, Visit 4 is subdivided into [9−12), [10,13), [11,14), and [12,15) month micro-bins (see Fig. 4). As soon as the EDD is established for a given child, that child is randomly assigned to a random micro-bin for each of Visits 3 and 4. This randomization will ensure a uniform distribution of ages for in-person visits from [3,15) months.

Remote Visit 5, occurring between [10−17) months, is yoked to the previous in-person visit (i.e., Visit 4) and scheduled to occur between 30 and 60 days after its completion. The rationale for this is to facilitate analyses where measures from both the in-person and remote visits are included (e.g., in a regression where an MRI feature may be used to predict a behavioral outcome collected during the remote visit). More details are provided below.

Note, the visit schedules are only current as of the time of manuscript submission and may change during the piloting study and implementation refinement.

3.2. Pre-visit, in-person, and after-visit alignment

The first four visits of the HBCD Study are done primarily in person (Fig. 5), and include MRI, EEG, and interactive social and cognitive assessments (e.g., individually administered play tasks); however, a proportion of surveys, questionnaires, and additional elements may be completed remotely prior to the visit or within a visit. Then, starting with Visit 4, each in-person visit is planned to have an accompanying yoked remote visit (e.g., Visit 4 *in-person* + Visit 5 *remote*) that occurs one to two months following the end of the in-person visit. This structure creates several timepoints for the administration of assessment relative to collection of in-person (i.e., brain) data: pre-visit (remote), in-person visit, yoked visit (remote). To minimize participant burden during in-person visits any study elements that could be done remotely was administered in either a pre-visit or yoked visit.

Careful consideration went into planning the timing of administration of the various elements of the HBCD Study protocol across the visit schedule. One of the primary aims of the HBCD Study is to characterize subject-level neurodevelopmental trajectories using MRI and EEG data to better understand how various prenatal and early life experiences and exposures may alter these trajectories to impact child outcomes such as physical, emotional, and cognitive development. The temporal order of exposure–brain–outcome is thus a critical feature of the protocol design. Where feasible, order of administration of remote assessments was aligned with the structure described above, so that exposures were assessed in the pre-visit and outcomes were assessed in the yoked remote visit. When an exposure was considered as relatively stable and/or ongoing (e.g., exposures to environmental toxicants due to residential location) it was approved to be administered within the yoked remote visit. An additional consideration was to ensure that any element that

Fig. 5. The HBCD Study visit schedule includes a combination of in-person and remote visits across the first decade of life, to collect data on children's physical, emotional, cognitive, and neurobiological development, and measurements of prenatal and early life experiences. In-person visits focus on collecting interactive assessments of social and cognitive development, biospecimens, biosensor data, and neurobiological information (MRI, EEG). Remote visits include surveys and questionnaires completed on an internet-enabled electronic device.

was presented at a particular time (i.e., yoked visit) remained in that window if repeated longitudinally so it would have the same timing relative to in-person data throughout the study.

4. Analytical strategies

There will likely be an enormous range of analytical strategies applied to the HBCD data once they publicly available. This is ultimately highly desirable, especially if these analyses are made reproducible by code sharing (e.g., via GitHub), an important act all investigators using these data should strongly consider doing. Thus, we do not wish to imply that certain analyses are favored over others here. However, certain analytical strategies were paramount in the consideration of the HBCD consortium during the design phase of the study.

First, as described above, external and internal validity were of paramount importance. We have designed and been monitoring the HBCD Study recruitment and enrollment to improve the data quality and reduce potential error and burden in the adjustment during the analysis. To take advantage of the generalizability of the sample analysis of HBCD data should account for the design by either including the weights or the generalizability variables given in Table 1. The literature recommends the use of population weighting in descriptive summaries, and their role in analytic models depends on the model specification (Si et al., 2024). Similarly, propensity score weighting adjusts for the observed differences between exposed and unexposed groups in observational comparisons, such as comparing children exposed to substances prenatally and those who were not. In the HBCD data analysis, it could be the case that we have to combine both population weighting and propensity score weighting to achieve both external and internal validity (as in Dong et al., 2020). Weighting is attractive because it can be applied all outcomes and analyses. In addition to weighting, matching and outcome regression methods can also be used for confounder adjustment. Outcome prediction models could potentially improve efficiency because of introduced model structure, but they are outcome specific. Hybrid approaches combine weighting and outcome prediction approaches, such as doubly robust estimators, have become popular.

The estimation of individual developmental trajectories was central when designing the longitudinal visit structure. Mixed-effects models will be commonly utilized to accomplish this, with nesting within child (and within family for twins/siblings who are both included in the study). The jittered visit design was chosen to optimize the ability to estimate individual developmental trajectories with minimal assumptions as to their shape (Staniswalis and Lee, 1998), Non-parametric curve estimation of longitudinal data is commonly-termed Functional Data Analysis (FDA, Ramsay and Silverman, 1997; Morris, 2015), which consists of a large and growing body of methods which can be applied to HBCD longitudinal data once they are available. For example, FDA methods have been adapted to perform mediation analysis where brain function is a mediator of exposures on behavioral outcomes (Lindquist, 2012).

5. Conclusions

The HBCD Study will collect unprecedented data of pregnant and postpartum people and their live born children from birth to early childhood to enable characterization of natural variability and trajectories of child development. The study cohort will reflect the sociodemographic diversity of pregnant people in the study catchment areas and include an enhanced group of people who use substances during pregnancy and a demographically and behaviorally similar group who do not use substances during pregnancy. Careful design and close monitoring in the recruitment and enrollment aim to achieve the generalizability and the assessment validity of the impact of prenatal substance use on neurodevelopmental trajectories of children. The longitudinal design of in-person and remote data collection visits randomly assigns individuals based on a jittered design to allow for optimal longitudinal trajectory estimation and valid assessments of various exposure effects on developmental trajectories. All HBCD data will be made available to the scientific community and facilitate open science to allow a comprehensive integrative study of multi-dimensional factors, e.g., biological and environmental exposures and gene/epigenetic/environment interactions, and their interactive influences on child developmental trajectories.

Papers with federal co-authors

Dr. Cole substantially participated in the preparation, review, and approval of the manuscript, consistent with her roles as Acting Project Director and Scientific Program Manager for the HBCD Consortium study and was substantially involved in U24DA055330 consistent with her role as Scientific Officer. The views and opinions expressed in this manuscript are those of the authors only and do not necessarily represent the views, official policy or position of the U.S. Department of Health and Human Services or any of its affiliated institutions or agencies.

CRediT authorship contribution statement

Yajuan Si: Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis, Conceptualization. **Gretchen Bandoli:** Writing – review & editing, Conceptualization. **Katherine M. Cole:** Writing – review & editing, Writing – original draft, Visualization, Conceptualization. **M. Daniele Fallin:** Writing – review & editing, Visualization, Methodology, Conceptualization. **Elizabeth A. Stuart:** Writing – review & editing, Methodology. **Kelly K. Gurka:** Writing – review & editing. **Keri N. Althoff:** Writing – review & editing, Visualization, Conceptualization. **Wesley K. Thompson:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Conceptualization.

Declaration of Competing Interest

None.

Data Availability

Data will be made available on request.

Acknowledgements

Data/Processes/Plans/Concepts (select as appropriate) used in the preparation of this article were obtained from the HEALthy Brain and Child Development (HBCD) Study (https://hbcdstudy.org/). This is a multisite, longitudinal study designed to recruit over 7000 families and follow them from pregnancy to early childhood. The HBCD Study is supported by the National Institutes of Health and additional federal partners under award numbers U01DA055352, U01DA055353, U01DA055366, U01DA055365, U01DA055362, U01DA055342, U01DA055360, U01DA055350, U01DA055338, U01DA055355, U01DA055363, U01DA055349, U01DA055361, U01DA055316, U01DA055344, U01DA055322, U01DA055369, U01DA055358, U01DA055371, U01DA055359, U01DA055354, U01DA055370, U01DA055347, U01DA055357, U01DA055367, U24DA055325, U24DA055330. A full list of supporters is available at https://hbcdstudy.org/about/federal-partners/. A listing of participating sites and a complete listing of the study investigators can be found at https://hbcdstudy.org/study-sites/. HBCD consortium investigators designed and implemented the study and/or provided data but did not necessarily participate in the analysis or writing of this report. This manuscript reflects the views of the authors and may not reflect the opinions or views of the NIH or HBCD consortium investigators.

References

Anunziata, F., Cisneros, C., Castillo, M.I.N., Perez, A., Rodriguez, V., De La Cruz, S., Estrada, K., Durbal, A., Jaramillo, M., Marquez, L.E., Nunez, J., Peralta-Carcelen, M., Wisnowski, J.L., & the HBCD Spanish Language Committee. ¿Donde están? Hispanic/Latine inclusion, diversity and representation in the HEALthy and (HBCD) Study. *Developmental Cognitive Neuroscience*.

Cioffredi, L., Yerby, L.G., Burris, H.H., Cole, K.M., Engel, S.M., Murray, T.M., Slopen, N., Volk, H.E., Acheson, A., & the HBCD Social and Environmental Determinants Workgroup. Assessing prenatal and early childhood social and environmental determinants of health in the HEALthy Brain and Child Development Study. *Developmental Cognitive Neuroscience*.

Cioffredi, L., Garner, B., Maxwell, J.R., Merhar, S., Peralta-Carcelen, M., Scott, L.S., Sisodia, M., DeMauro, S.B., & the HBCD Physical Health Workgroup. Infant and early childhood physical health assessments in the HEALthy Brain and Child Development (HBCD) Study. *Developmental Cognitive Neuroscience*.

Cole, K.M., Jordan, C.J., Parkinson, M., Estrada, K., Hoffman, E.A., Croff, J.M., Freund, M.P., Howlett, K.D., & the HBCD Communications, Engagement, and Dissemination Workgroup. Communications, engagement, and dissemination strategies for the HBCD Study. *Developmental Cognitive Neuroscience*.

de Leeuw, E., Hox, J., & Luiten, A. (2018). International nonresponse trends across countries and years: An analysis of 36 years of labour force survey data. In Survey Insights: Methods from the Field. ⟨https://surveyinsights.org/?p=10452⟩.

Dean, D.C., Tisdall, M.D., Wisnowski, J.L., Fezko, E., Gagoski, B., Alexandar, A.L., Edden, R.A.E., Gao, W., Hendrickson, T.J., Howell, B.R., Huang, H., Humphreys, K.L., Riggins, T., Sylvester, C.M.,, Weldon, K.B., Yacoub, E., Ahtam, B., Beck, N., Banerjee, S., Boroday, S., Caprihan, A., Caron, B., Carpenter, S., Chang, Y., Chung, A.W., Cieslak, M., Clarke, W.T., Dale, A., Das, S., Davies-Jenkins, C.W., Dufford, A.J., Evans, A.C., Fesselier, L., Ganji, S.K., Gilbert, G., Graham, A.M., Gudmundson, A.T., McGregor, M.H., Harms, M.P., Hilbert, T., Hui, S.C.N., Irfanoglu, M.O., Kecskemeti, S., Kober, T., Kuperman, J.M., Lamichhane, B., Landman, B.A., Lecour-Bourcher, X., Lee, E.G., Li, X., MacIntyre, L., Madjar, C., Manhard, M.K., Mayer, A.R., Mehta, K., Moore, L.A., Murali-Manohar, S., Navarro, C., Nebel, M.B., Newman, S.D., Newton, A.T., Noeske, R., Norton, E.S., Oeltzschner, G., Organo-Carcy, R., Ou, X., Ouyang, M., Parrish, T.B., Pekar, J.J., Pengo, T., Pierpaoli, C., Poldrack, R.A., Rajagopalan, V., Rettmann, D.W., Rioux, P.,.Rosenberg, J.T., Salo, T., Satterwaite, T.D., Scott, L.S., Shin, E., Simegn, G., Simmons, W.K., Song, Y., Tikalsky, B.J., Tkach, J., van Zijl, P.C. M., Vannest, J., Versluis, M., Zhao, Y., Zöllner, H.J., Fair, D.A.,Smyser, C.D., Elison, J.T., & the HBCD MRI Workgroup. Quantifying brain development in Quantifying Brain Development in HEALthy Brain and Child Development (HBCD) Study: The Magnetic Resonance Imaging and Spectroscopy Protocol. Dean III, DC et al., Submitted to Developmental Cognitive Neuroscience.

Dong, N., Stuart, E.A., Lenis, D., Quynh Nguyen, T., 2020. Using propensity score analysis of survey data to estimate population average treatment effects: a case study comparing different methods. Eval. Rev. 44 (1), 84–108.

Edwards, R.C., Planalp, E.M., Enlow, M.B., Akshoomoff, N., Bodison, S.C., Brennan, M.B., Ciciolla, L., Eiden, R.D., Fillipi, C.A., Gustafsson, H.C., McKelvey, L.M., Morris, A.S., Peralta-Carcelen, M., Poehlmann, J., Wakschlag, L.S., Wilson, S., & the HBCD Child Behavior and Caregiver-Child Interaction Workgroup. Capturing the complexity of child behavior and caregiver-child relationships in the HEALthy Brain and Child Development (HBCD) Study using a rigorous and equitable approach. *Developmental Cognitive Neuroscience*.

Elinor, L.S., Ryan, B., Ludmila, B., Pat, L., Joseph, J., Sheldon, M., Croff, J.M., Thomason, M., Lo, J.O., MacIntyre, L., Shrivastava, S., Cioffredi, L., Edlow, A.G., Howell, B.R., Chaiyachati, B.H., Lashley-Simms, N., Molloy, K., Lam, C., Stoermann, A., Trinh, T., Ambalavanan, N., Neiderhiser, J.M., & the HBCD Biospecimens Workgroup. Biospecimens in the HEALthy Brain and Child Development (HBCD) Study: Rationale and protocol. *Developmental Cognitive Neuroscience*.

Fox, N.A., Pérez-Edgar, K., Morales, S., Campbell, A.M., Cavanagh, J.F., Gabard-Durnam, L.J., Hudac, C.M., Key, A.P., Larson-Prior, L.J., Pedapati, E.V., Norton, E.S., Reetzke, R., Roberts, T.P., Rutter, T.M., Scott, L.S., Shuffrey, L.C., Antúnez, M., Boylan, M.R., Garner, B.M., Learnard, B., McNair, S., McSweeney, M., Natale Castillo, M.I., Norris, J., Nyabingi, O.S., Pini, N., Quinn, A., Stosur, R., Tan, E., Troller-Renfree, S.V., Yoder, L., & the HBCD Electroencephalography Workgroup. The development and structure of the HEALthy Brain and Child Development (HBCD) Study EEG protocol. *Developmental Cognitive Neuroscience*.

Garavan, H., Bartsch, H., Conway, K., Decastro, A., Goldstein, R.Z., Heeringa, S., Jernigan, T., Potter, A., Thompson, W., Zahs, D., 2018. Recruiting the ABCD sample: design considerations and procedures. Dev. Cogn. Neurosci. 32, 16–22.

Gurka, K.K., Burris, H.H., Ciciolla, L., Coles, C.D., Massey, S.H., Newman, S., Rajagopalan, V., Smith, L.M., Zilverstand, A., Bandoli, G., & the HBCD Pregnancy Exposures including Substances Workgroup. Assessment of maternal health and behavior during pregnancy in the HEALthy Brain and Child Development Study: Rationale and approach. *Developmental Cognitive Neuroscience*.

Harden, J.B., McKelvey, L.M., Poehlmann, J.A., Edwards, R., Anunziata, F., Beasley, L., Bomberger, M., Chinaka, O., De La Cruz, S., Gurka, K., Parkinson, M., & the HBCD Recruitment Retention and Community Engagement Workgroup. The HBCD experience: Recruiting and retaining diverse families in the HEALthy Brain and CHild Development Study (HBCD). *Developmental Cognitive Neuroscience*.

Hillard, F., Horan, H., Zgierska, A.E., Edwards, R.C., & the HBCD Navigator Workgroup. Establishing a model of peer support for pregnant persons with a substance use disorder as an innovative approach for engaging participants in longitudinal research. *Developmental Cognitive Neuroscience*.

Kable, J.A., Potter, A.S., Akshoomoff, N., Blasco, P.M., Bodson, S., Ciciolla, L., DeGray, S., Hulce, Z., Kuschner, E.S., Learnard, B., Luciana, M., Perez, A., Novack, M.A., Riggins, T., Shin, S.Y., Smith, S., Vannest, J., Zimak, E.H., & the HBCD Neurocognitive and Language Workgroup. Measurement of emerging neurocognitive and language skills in the HEALthy Brain and Child Development Study. *Developmental Cognitive Neuroscience*.

Kind, A.J., Buckingham, W.R., 2018. Making neighborhood-disadvantage metrics accessible—the neighborhood atlas. N. Engl. J. Med. 378 (26), 2456.

Lindquist, M.A., 2012. Functional causal mediation analysis with an application to brain connectivity. J. Am. Stat. Assoc. 107 (500), 1297–1309.

Little, R., Vartivarian, S., 2005. Does weighting for nonresponse increase the variance of survey means? Surv. Methodol. 31 (2), 161–168.

Morris, J.S., 2015. Functional regression. Annu. Rev. Stat. Appl. 2, 321–359.

Nelson, C.A., Frankeberger, J., & Chambers, C.D. An introduction to the HEALthy Brain and Child Development Study. *Developmental Cognitive Neuroscience*.

Patrick, M.E., Terry-McElrath, Y.M., Berglund, P., Pang, Y.C., Heeringa, S.G., & Si, Y. (2023). An updated weighting strategy for the Monitoring the Future Panel Study. Monitoring the Future Occasional Paper No. 98. Updated. Institute for Social Research.

Pini, N., Fifer, W.P., Oh, J., Nebeker, C., Croff, J.M., Smith, B.A., & the HBCD Novel Tech/Wearables Workgroup. Remote Data collection of infant activity and sleep patterns via wearable sensors in the HEALthy Brain and Child Development Study (HBCD). *Developmental Cognitive Neuroscience*.

Ramsay, J.O., Silverman, B.W., 1997. Functional Data Analysis. Springer, New York.

Rosenbaum, P.R., Rubin, D.B., 1983. The central role of the propensity score in observational studies for causal effects. Biometrika 70 (1), 41–55.

Schulenberg, J.E., Patrick, M.E., Johnston, L.D., O'Malley, P.M., Bachman, J.G., & Miech, R.A. (2021). Monitoring the Future national survey results on drug use, 1975-2020: Volume II, college students and adults ages 19-60. Ann Arbor: Institute for Social Research.

Si, Y. (2024). On the use of auxiliary variables in multilevel regression and poststratification. Statistical Science (forthcoming), ⟨https://arxiv.org/abs/2011.00360⟩.

Si, Y., Lee, S., Heeringa, S.G., 2024. Population weighting in statistical analysis. JAMA Intern Med 84 (1), 98–99.

Staniswalis, J.G., Lee, J.J., 1998. Nonparametric regression analysis of longitudinal data. J. Am. Stat. Assoc. 93 (444), 1403–1418.

Stuart, E.A., 2010. Matching methods for causal inference: a review and a look forward. Stat. Sci. 25 (1), 1–21.

Substance Abuse and Mental Health Services Administration (2020). Key substance use and mental health indicators in the United States: Results from the 2019 National Survey on Drug Use and Health. Seri:HHS Publication No. PEP20-07-01-001.

Volkow, N.D., Gordon, J.A., Bianchi, D.W., Chiang, M.F., Clayton, J.A., Klein, W.M., Koob, G.F., Koroshetz, W.J., Perez-Stable, E.J., Simoni, J.M., Tromberg, B.J., Woychik, R.P., Hommer, R., Sports, E.L., Xu, B., Zehr, J.L., Cole, K.M., Dowling, G.J., Freund, M.P., Howlett, K.D., Jordan, C.J., Murray, T.M., Pariyadath, V., Rankin, M. L., & Weiss, S.R.B. The HEALthy Brain and Child Development (HBCD) Study: NIH collaboration to understand the impacts of prenatal and early life experiences on brain development. *Developmental Cognitive Neuroscience*.