INFERENCE FOR INDIVIDUAL MEDIATION EFFECTS AND INTERVENTIONAL EFFECTS IN SPARSE HIGH-DIMENSIONAL CAUSAL GRAPHICAL MODELS

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We consider the problem of identifying intermediate variables (or mediators) that regulate the effect of a treatment on a response variable. While there has been significant research on this classical topic, little work has been done when the set of potential mediators is high-dimensional. A further complication arises when these mediators are interrelated (with unknown dependencies). In particular, we assume that the causal structure of the treatment, the pre-treatment covariates (or confounders), the potential mediators and the response is a (possibly unknown) directed acyclic graph (DAG). High-dimensional DAG models have previously been used for the estimation of causal effects from observational data. In particular, methods called IDA and joint-IDA have been developed for estimating the effects of single interventions and multiple simultaneous interventions, respectively. In this paper, we propose an IDA-type method, called MIDA, for estimating so-called ‘individual’ mediation effects from high-dimensional observational data under our setting. Although IDA and joint-IDA estimators have been shown to be consistent in certain sparse high-dimensional settings, their asymptotic properties such as convergence in distribution and inferential tools in such settings have remained unknown. In this paper, we prove high-dimensional consistency of MIDA for linear structural equation models with sub-Gaussian errors. More importantly, we derive distributional convergence results for MIDA in similar high-dimensional settings, which are applicable to IDA and joint-IDA estimators as well. To the best of our knowledge, these are the first such distributional convergence results facilitating inference for IDA-type estimators. These results are built on our novel theoretical results regarding uniform bounds for linear regression estimators over varying subsets of high-dimensional covariates, which may be of independent interest. Finally, we empirically validate our asymptotic theory and demonstrate the usefulness of MIDA in the identification of large mediation effects via extensive simulations, and we also illustrate a practical application of MIDA in genomics with a real dataset.

1. Introduction. Although confirmatory causal inference from high-dimensional observational data is impossible due to identifiability issues, this topic has received great attention in the recent past. Intervention experiments are considered to be the gold-standard for making
causal inference. However, experimental data cannot always be generated given the considerable ethical concerns, time constraints, and the high costs associated with performing appropriate experiments. Another major problem that can arise in many scientific disciplines is that the sheer number of causal hypotheses is simply too large to test experimentally. Good examples are gene knockout experiments, where potential candidate genes for the knockout experiments typically lie in the order of thousands. In such a situation, causal predictions from observational data can be extremely useful in prioritizing intervention experiments [Maathuis et al., 2010; Stekhoven et al., 2012; Le et al., 2017].

There has been a lot of recent progress in estimating causal effects from high-dimensional observational data based on a graphical model framework. Most of these methods assume that the data are generated from an unknown linear structural equation model (LSEM) with independent Gaussian errors, and that the causal relationships among the variables can be represented by a directed cyclic graph (DAG). Under these assumptions, high-dimensional consistency results have been derived for the estimation of the causal graph and causal effects. In particular, Maathuis et al. [2009] proposed Interventional calculus when the DAG is Absent (IDA) for estimating the total causal effect of a variable on another variable, and they proved a high-dimensional consistency result for their IDA estimator. The IDA method has been further extended to the joint-IDA by Nandy et al. [2017] for estimating the effects of multiple simultaneous interventions as well, and a similar high-dimensional consistency result for the joint-IDA estimator has been proved therein.

The IDA method estimates a multi-set of causal effects as follows. The first step is to estimate a partially directed graph, called Completed Partially Directed Acyclic Graph (CPDAG), from high-dimensional observational data. This can be done by applying a structure learning algorithm such as the PC algorithm [Spirtes et al., 2000; Colombo and Maathuis, 2014], greedy equivalence search (GES) [Chickering, 2002b] and adaptively restricted greedy equivalence search (ARGES) [Nandy et al., 2018]. High-dimensional consistency results for these structure learning algorithms have been proved in Kalisch and Bühlmann [2007]; Colombo and Maathuis [2014]; Nandy et al. [2018], e.g. The reason behind estimating a partially directed graph here instead of the underlying directed graph is that the true causal DAG is not identifiable from observational data alone without making further stringent assumptions. A CPDAG uniquely represents a Markov equivalence class of DAGs that can generate the same joint distribution of the variables. The IDA method estimates a possible causal effect for each DAG in the Markov equivalence class represented by the estimated CPDAG and combines them to produce a multi-set (where each element can have multiple copies) of causal effects. The authors also noted that the listing of all DAGs in the Markov equivalence class from a given CPDAG is typically computationally infeasible for large graphs with thousands of variables, and provided computational shortcuts to obtain the multi-set of possible effects without listing all DAGs in the Markov equivalence class of the estimated CPDAG. It is common practice to summarize the multi-set of possible effects by its average or the minimum absolute value.

Despite all these recent advances in estimating total causal effects and/or learning the underlying causal structure, very little work has been done on the corresponding problem of causal mediation analysis in high-dimensional settings. Such problems, however, are of considerable relevance in the modern ‘big data’ era, with a growing interest across various scientific disciplines in understanding the role of ‘networks’ of multiple intermediate variables (or mediators) in simultaneously regulating the causal effect of a treatment on a response. Inspired by such motivations, we consider here the problem of identifying mediators in settings where the set of potential mediators are: (i) high dimensional, and more importantly, (ii) possibly interrelated with unknown dependencies. Both aspects combined make our setting considerably challenging and distinct compared to most of the existing classical mediation...
literature. The latter aspect, in particular, creates unique challenges and necessitates revisiting the very definition of mediation effects in such settings, compared to existing definitions that typically apply only for conditionally independent mediators. In this regard, we first propose a novel definition of the mediation effect in the presence of multiple mediators (see Section 2.4, and in particular, Definition 2.2 therein).

Classical mediation analysis has a rich literature. A simpler problem considering only one potential mediator has been well studied within the framework of LSEMs [Judd and Kenny, 1981; James et al., 1982; Sobel, 1982; Baron and Kenny, 1986; MacKinnon et al., 2002]. The goal of causal mediation analysis with a single mediator is to understand what portion of the total causal effect of a treatment on a response can be attributed to the potential mediator. In fact, the total effect in this case can be decomposed as a sum of the direct effect and the indirect effect, where the indirect effect is the effect of the treatment on the response that goes through the potential mediator. Similarly, in the case of multiple potential mediators, we are interested in understanding what portion of the total effect of the treatment, $X_t$, on the response, $X_p$, can be attributed to a potential mediator, $X_j$. We refer to it as the individual mediation effect (Defn. 2.2) with respect to $X_j$. Note that with possibly interrelated mediators, the total effect of the treatment on the response may not be decomposed as the sum of all individual mediation effects and the direct effect here, unless the potential mediators are conditionally independent of each other given the treatment.

The estimation and testing for mediation effects in causal models with conditionally independent mediators have also been considered in both classical settings [Preacher and Hayes, 2008; Boca et al., 2014], as well as in high-dimensional settings [Zhang et al., 2016]. For causal models with conditionally dependent mediators, VanderWeele and Vansteelandt [2014] discussed estimation methods for the total effect of all mediators (or the total indirect effect), while Huang and Pan [2016] proposed to estimate the individual effects with respect to a transformed set of conditionally independent variables in high-dimensional settings. In contrast to these existing works, we are interested in separately evaluating the importance of each potential mediator, allowing for (unknown) inter-dependencies. The identification of mediators corresponding to large individual mediation effects can be very useful in a variety of scientific applications, including genomics, where it is often of interest to understand how an influential genotype regulates a phenotype of interest through gene expressions.

Our contributions. In this paper, we propose an IDA-type estimation method, called MIDA (see Section 3.2), for estimating the causal mediation effect of a treatment variable on a response variable through an intermediate variable (a.k.a. mediator) in high-dimensional settings. In particular, we consider a treatment (a.k.a. exposer) $X_t$, a set of pre-treatment covariates (a.k.a. confounders) $\{X_1, \ldots, X_{t-1}\}$, a response variable $X_p$, and a set of potential mediators $\{X_{t+1}, \ldots, X_{p-1}\}$ that could be high-dimensional. A pre-treatment covariate can be a common cause of the treatment variable and the response, and also a common cause of the potential mediators and the response. We assume that the causal relationships among the variables in $X = \{X_1, X_2, \ldots, X_p\}$ can be represented by a DAG (possibly unknown), where $X_i$ and $X_j$ are connected by a directed edge if and only if $X_i$ is a direct cause of $X_j$.

As is the case with IDA-type estimators, MIDA relies on the estimation of an underlying CPDAG, and it produces a multi-set of possible mediation effects, which we summarize by taking the average. We prove the consistency of MIDA for certain sparse high-dimensional LSEMs with sub-Gaussian errors (Theorem 4.1). Furthermore, we provide unified distributional convergence results for IDA-type estimators in similar high-dimensional settings (Theorems 6.1–6.2, Corollaries 6.1–6.2), thus facilitating inference for such estimators. These results have been built on a novel uniform non-asymptotic theory for linear regression over varying subsets of high-dimensional covariates (Theorem 5.1) which may be of independent interest. This is a critical tool in our case for handling the possibly large multi-set of causal
effects obtained from the estimated CPDAG which poses the key challenge in our theory for inference. The theory notably also does not depend on the nature of the CPDAG estimation procedure as long as it is consistent. To the best of our knowledge, we propose the first estimation method for mediation effects when the data are generated from an unknown DAG, as well as the first high-dimensional distributional convergence results and inferential tools for IDA-type estimators of both interventional effects as well as mediation effects. Our contributions in the latter regard thus extend beyond just inference for mediation effects.

Finally, we note that while we work with the CPDAG here, the underlying causal DAG is identifiable in the following special cases: (i) when all error variables in the LSEM are non-Gaussian [Shimizu et al., 2006, 2011] and (ii) when all error variables in the LSEM are Gaussian with equal error variances [Peters and Bühlmann, 2014; Shi and Li, 2020]. In these cases, MIDA can still be applied with the estimated DAG (instead of the estimated CPDAG) to obtain mediation effects (instead of a multi-set of possible mediation effects). However, these additional assumptions cannot be verified from observational data typically, and hence, a more conservative approach of estimating the CPDAG is recommended. Note also that the equal error variance assumption cannot be achieved by normalizing the data to have equal variances for all observed variables since the assumption is on the underlying data generating error variables instead of the observed variables (see Definition 2.1).

Organization. The rest of this paper is organized as follows. Section 2 provides some necessary background material. In Section 3, we propose the MIDA algorithm for estimating individual mediation effects from observational data. In Section 4, we prove consistency of MIDA in sparse high-dimensional LSEMs with sub-Gaussian errors and also discuss the modifications required to relax the linear sub-Gaussian assumption. Our non-asymptotic theoretical results on linear regression over varying subsets of high-dimensional covariates are given in Section 5 which can be read independently. Section 6 discusses the distributional convergence results and inferential tools for MIDA and IDA-type estimators. Section 7 contains simulation results, where we demonstrate the usefulness of MIDA and our asymptotic theory for the identification of non-zero mediation effects. In Section 8, we apply MIDA to a real dataset generated from a collection of yeast segregants, and we end with a concluding discussion in Section 9. All proofs, additional technical materials, and additional numerical results are collected in the Supplement (Appendices A–D).

2. Preliminaries. We begin with a few basic definitions and notations.

2.1. Graph Terminology. We consider graphs \( \mathcal{H} = (X, E) \) with vertex (or node) set \( X = \{X_1, \ldots, X_p\} \) and edge set \( E \). There is at most one edge between any pair of vertices and edges may be either directed \( (X_i \rightarrow X_j) \) or undirected \( (X_i - X_j) \). If \( \mathcal{H} \) contains only (un)directed edges, it is called (un)directed. If \( \mathcal{H} \) contains directed and/or undirected edges, it is called partially directed. A pair of nodes \( \{X_i, X_j\} \) are adjacent if there is an edge between \( X_i \) and \( X_j \). If \( X_i \rightarrow X_j \), then \( X_i \) is a parent of \( X_j \). We denote the set of all parents of \( X_j \) in \( \mathcal{H} \) by \( \text{Pa}_{\mathcal{H}}(X_j) \), and all adjacent nodes of \( X_j \) in \( \mathcal{H} \) by \( \text{Adj}_{\mathcal{H}}(X_j) \). A path between \( X_i \) and \( X_j \) is a sequence of distinct nodes \( \{X_i, \ldots, X_j\} \) such that all successive pairs of nodes are adjacent. A directed path from \( X_i \) to \( X_j \) is a path between \( X_i \) and \( X_j \) where all edges are directed towards \( X_j \). A directed path from \( X_i \) to \( X_j \) together with the edge \( X_j \rightarrow X_i \) forms a directed cycle. A (partially) directed graph that does not contain a directed cycle is called a (partially) directed acyclic graph or (P)DAG.

2.2. Linear Structural Equation Models (LSEMs).
**Definition 2.1.** Let $\mathcal{G}_0 = (X, E)$ be a DAG and let $B_{\mathcal{G}_0}$ be a $p \times p$ matrix such that $(B_{\mathcal{G}_0})_{ij} \neq 0$ if and only if $X_i \in Pa_{\mathcal{G}_0}(X_j)$. Let $\epsilon = (\epsilon_1, \ldots, \epsilon_p)^T$ be a zero mean random vector of jointly independent error variables. Then $X = (X_1, \ldots, X_p)^T$ is said to be generated from a linear structural equation model (LSEM) characterized by the pair $(B_{\mathcal{G}_0}, \epsilon)$ if

\begin{equation}
(X - \mu) \leftarrow B_{\mathcal{G}_0}^T (X - \mu) + \epsilon, \quad \text{where } \mu := \mathbb{E}(X). \tag{2.1}
\end{equation}

If $X$ is generated from an LSEM characterized by the pair $(B_{\mathcal{G}_0}, \epsilon)$, then we call $\mathcal{G}_0$ the *causal DAG*. The symbol “$\leftarrow$” in (2.1) emphasizes that the expression should be understood as a generating mechanism rather than as a mere equation. We emphasize that we assume here that there are no hidden confounders (see Section 4.1 for more discussion on this case), and hence the joint independence of the error terms. In the rest of the paper, we refer to LSEMs without explicitly mentioning the independent error assumption.

### 2.3. Markov Equivalence Class of DAGs

The causal DAG $\mathcal{G}_0$ is (typically) not identifiable from (observational data from) the distribution of $X$. A DAG encodes conditional independence relationships via the notion of *d-separation* (Pearl [2000], Theorem 1.2.4, page 18). In general, several DAGs can encode the same conditional independence relationships, and such DAGs form a *Markov equivalence class*. Two DAGs belong to the same Markov equivalence class if and only if they have the same skeleton and the same v-structures [Verma and Pearl, 1990]. A Markov equivalence class of DAGs can be uniquely represented by a *completed partially directed acyclic graph* (CPDAG) [Spirtes et al., 2000; Chickering, 2002a], which is a graph that can contain both directed and undirected edges. A CPDAG satisfies the following: $X_i \rightarrow X_j$ in the CPDAG if $X_i \rightarrow X_j$ in every DAG in the Markov equivalence class, and $X_i \leftarrow X_j$ in the CPDAG if the Markov equivalence class contains a DAG for which $X_i \leftarrow X_j$ as well as a DAG for which $X_i \leftarrow X_j$. CPDAGs can be estimated from observational data using various algorithms [Spirtes et al., 2000; Chickering, 2002b; Tsamardinos et al., 2006; Nandy et al., 2018].

### 2.4. Problem Setup

We assume that $X = \{X_1, \ldots, X_p\}$ is generated from an LSEM characterized by the pair $(B_{\mathcal{G}_0}, \epsilon)$ as in (2.1), where $\{X_1, \ldots, X_{t-1}\}$ is a set of pre-treatment covariates (a.k.a. confounders), $X_t$ is the *treatment* variable, $\{X_{t+1}, \ldots, X_{p-1}\}$ is a set of potential mediators and $X_p$ denotes the *response* variable. Note that we do allow the case $t = 1$ here to represent the absence of pre-treatment covariates. We assume that no potential mediator is a direct cause of a variable in $\{X_1, \ldots, X_t\}$, i.e. $(B_{\mathcal{G}_0})_{ji} = 0$ for all $i \leq t$, for each $j = t + 1, \ldots, p - 1$. Further, we assume that the response variable $X_p$ is not a direct cause of any other variable in $X$, i.e. $(B_{\mathcal{G}_0})_{pj} = 0$ for all $j < p$. Finally, the *observed data* consists of $n$ independent and identically distributed (i.i.d.) realizations of $X$, where throughout we allow for a *high-dimensional* setting with $p$ allowed to diverge with the sample size $n$.

In order to define the total causal effect of a variable $X_i$ on another variable $X_k$, we consider a hypothetical outside *intervention* to the system where we set a variable $X_i$ to some value $x_i$ uniformly over the entire population. This can be denoted by Pearl’s do-operator: $\text{do}(X_i = x_i)$ [Pearl, 2009], which corresponds to removing the edges into $X_i$ in $\mathcal{G}_0$ (or equivalently, setting the $i$-th column of $B_{\mathcal{G}_0}$ equal to zero) and replacing $\epsilon_i$ by the constant $x_i$. The post-interventional expectation of $X_k$ is denoted by $\mathbb{E}[X_k \mid \text{do}(X_i = x_i)]$.

Under the LSEM assumption, $\mathbb{E}[X_k \mid \text{do}(X_i = x_i)]$ is a linear function of $x_i$ and the **total causal effect** of $X_i$ on $X_k$ is defined as [Maathuis et al., 2009]

$$\theta_{ik} := \frac{\partial}{\partial x_i} \mathbb{E}[X_k \mid \text{do}(X_i = x_i)].$$
To provide a graphical interpretation of $\theta_{ik}$, we define the effect of $X_{i_0}$ to $X_{i_{k+1}}$ through a directed path $\{X_{i_0}, X_{i_1}, \ldots, X_{i_k}, X_{i_{k+1}}\}$ as $\prod_{\ell=0}^k (B_{G_0})_{i_\ell, i_{\ell+1}}$. Then the total causal effect $\theta_{ik}$ is given by the sum of the effects of $X_i$ to $X_k$ through all directed paths from $X_i$ to $X_k$. This is known as the path method for computing the total causal effects in an LSEM [Wright, 1921].

We denote a joint-intervention on $X_i$ and $X_j$ by $do(X_i = x_i, X_j = x_j)$. Again, the post-interventional expectation $E[X_k \mid do(X_i = x_i, X_j = x_j)]$ is a linear function of $(x_i, x_j)$ and the effect of $X_i$ on $X_k$ in the joint intervention $do(X_i = x_i, X_j = x_j)$ is defined as [Nandy et al., 2017]

$$\theta_{ik}^{(i,j)} := \frac{\partial}{\partial x_i} E[X_k \mid do(X_i = x_i, X_j = x_j)].$$

Note that $\theta_{ik}^{(i,j)}$ can be interpreted as the total causal effect of $X_i$ on $X_k$ when we set $X_j = x_j$ uniformly over the entire population, that is, the portion of the total effect of $X_i$ on $X_k$ that does not go through $X_j$.

Finally, we define the individual mediation effect of a potential mediator $X_j$ ($j = t + 1, \ldots, p - 1$) to be the portion of total effect of the treatment variable $X_t$ on the response $X_p$ that goes through $X_j$.

**Definition 2.2.** The individual mediation effect, $\eta_j$, with respect to a potential mediator $X_j$ ($j = t + 1, \ldots, p - 1$) is defined as

$$\eta_j := \frac{\partial}{\partial x_t} E[X_p \mid do(X_t = x_t)] - \frac{\partial}{\partial x_t} E[X_p \mid do(X_t = x_t, X_j = x_j)].$$

**Remark 2.1.** The individual mediation effect can be interpreted as the change in the total causal effect of $X_t$ on $X_p$ when the potential mediator $X_j$ is knocked out from the causal graph $G_0$ by the intervention $do(X_j = x_j)$. Note that Definition 2.2 as well as this interpretation of the individual mediation effect holds for a general structural equation model: $X_i \leftarrow f_i(X_{Pa_i}(X_i), \epsilon_i)$ for $i = 1, \ldots, p$. While under the linearity assumption $\eta_j$ does not depend on the intervention values $x_t$ and $x_j$, in a more general setting $\eta_j(x_t, x_j)$ can be a non-trivial function of $(x_t, x_j)$.

Under the linearity assumption, the individual mediation effect $\eta_j$ is given by the sum of the effects of $X_t$ to $X_p$ through all directed paths from $X_t$ to $X_p$ that go through $X_j$. It follows from Theorem 3.1 of Nandy et al. [2017] that $\eta_j$ equals the product of the total causal effect of $X_t$ on $X_j$ and the total causal effect of $X_j$ on $X_p$. We formalize this in the proposition below.

**Proposition 2.1.** Let $X$ be generated from an LSEM. The individual mediation effect $\eta_j$ with respect to a potential mediator $X_j$ is then given by

$$\eta_j = \theta_{tj} \theta_{jp} \quad (j = t + 1, \ldots, p - 1),$$

where for any $(i, k)$, $\theta_{ik}$ denotes the total causal effect of $X_i$ on $X_k$.

It is important to note that this ‘product-type’ representation of the mediation effect $\eta_j$ does not correspond, in general, to the product of regression coefficients obtained from regressing the mediator vs. the treatment, and the response vs. the mediator, as in ‘marginal’ mediation analyses under conditionally independent mediators. We illustrate this further in Examples 1–2 below. (Example 2 is in Section 3.1 and is a continuation of Example 1.)
where the first element is $i$, the treatment variable $X_2$, the potential mediators $\{X_3, \ldots, X_6\}$ and the response variable $X_7$. The edge weights represent the coefficients of the following LSEM: $X_1 \leftarrow \epsilon_1$, $X_2 \leftarrow 1.6X_1 + \epsilon_2$, $X_3 \leftarrow 0.7X_2 + 1.4X_4 + \epsilon_3$, $X_4 \leftarrow 1.4X_1 + \epsilon_4$, $X_5 \leftarrow 1.2X_2 + 0.9X_3 + \epsilon_5$, $X_6 \leftarrow 1.1X_5 + \epsilon_6$, and $X_7 \leftarrow 0.6X_3 + 0.8X_4 + 1.8X_6 + \epsilon_7$. The error variables can be assumed to have any distribution for deriving the total causal effects and the individual mediation effects, since the total causal effects in an LSEM do not depend on the distributions of the error variable. The total causal effects of the treatment variable on the potential mediators, the total causal effects of the potential mediators on the response variable, and the individual mediation effects are given in Table 1. Note that the equality of $\eta_5$ and $\eta_6$ represents the fact that the change in the total causal effect of $X_2$ on $X_7$ for knocking out $X_5$ from the causal graph is the same as the change for knocking out $X_6$.

**EXAMPLE 1.** We consider a simple case with $p = 7$, $t = 2$. The DAG in Figure 1 represents the causal structure among the pre-treatment covariate $X_1$, the treatment variable $X_2$, the potential mediators $\{X_3, \ldots, X_6\}$ and the response variable $X_7$. The edge weights represent the coefficients of the following LSEM: $X_1 \leftarrow \epsilon_1$, $X_2 \leftarrow 1.6X_1 + \epsilon_2$, $X_3 \leftarrow 0.7X_2 + 1.4X_4 + \epsilon_3$, $X_4 \leftarrow 1.4X_1 + \epsilon_4$, $X_5 \leftarrow 1.2X_2 + 0.9X_3 + \epsilon_5$, $X_6 \leftarrow 1.1X_5 + \epsilon_6$, and $X_7 \leftarrow 0.6X_3 + 0.8X_4 + 1.8X_6 + \epsilon_7$. The error variables can be assumed to have any distribution for deriving the total causal effects and the individual mediation effects, since the total causal effects in an LSEM do not depend on the distributions of the error variable. The total causal effects of the treatment variable on the potential mediators, the total causal effects of the potential mediators on the response variable, and the individual mediation effects are given in Table 1. Note that the equality of $\eta_5$ and $\eta_6$ represents the fact that the change in the total causal effect of $X_2$ on $X_7$ for knocking out $X_5$ from the causal graph is the same as the change for knocking out $X_6$.

![Fig 1: Example of a weighted DAG representing the data generating process.](image)

**TABLE 1**

*Individual mediation effects: Illustration for the DAG in Example 1.*

| j | $\theta_{ij}$ | $\theta_{ij7}$ | $\eta_j$ |
|---|---|---|---|
| 3 | 0.7 | 0.6 + 0.9 $\times$ 1.1 $\times$ 1.8 | 1.6674 |
| 4 | 0 | 0.8 + 1.3 $\times$ 0.6 + 1.3 $\times$ 0.9 $\times$ 1.1 $\times$ 1.8 | 0 |
| 5 | 0.7 $\times$ 0.9 + 1.2 | 1.1 $\times$ 1.8 | 3.6234 |
| 6 | 0.7 $\times$ 0.9 $\times$ 1.1 $\times$ 1.2 $\times$ 1.1 | 1.8 | 3.6234 |

2.5. Notations and the ‘Faithfulness’ Assumption. We denote the vector of potential mediators $(X_{t+1}, \ldots, X_{p-1})^T$ by $X'$ and the corresponding subgraph of $G_0$ by $G_0'$ (obtained by deleting the nodes $X_{(1, \ldots, t)} \cup X_p$ and the corresponding edges from $G_0$). Let $B_{G_0'}$ be the submatrix of $B_{G_0}$ that corresponds to $X'$ and let $\epsilon' = (\epsilon_{t+1}, \ldots, \epsilon_{p-1})^T$. Further, we denote the CPDAG representing the Markov equivalence class of $G_0'$ by $C_0'$ and the Markov equivalence class by MEC($C_0'$). We assume that the conditional distribution of $X'$ given $\{X_1, \ldots, X_t\}$ is *faithful* to $G_0$. The faithfulness condition states that every independence constraint that holds in the distribution is encoded by $G_0'$ (see, e.g., Definition 3.8 of Koller and Friedman [2009]). This assumption is a necessary condition for learning causal structures from observational data [Spirtes et al., 2000; Chickering, 2002a], and we do not need the faithfulness assumption when the underlying causal structure is known or given.

We will often treat sets as vectors and vice versa, where we consider an arbitrary ordering of the elements in a vector unless specified otherwise. For example, $(i, S, k)$ denotes a vector where the first element is $i$, the last element is $k$, but elements of the set $S$ are ordered arbitrarily in $(i, S, k)$. We denote the covariance matrix of $X$ by $\Sigma_0$. For any set $S \subseteq \{1, \ldots, p\}$, we denote the corresponding random vector $\{X_r : r \in S\}$, i.e. the restriction of $X$ onto $S$, by $X_S$. Further, we denote Cov$(X_{S_i}, X_{S_j})$ by $(\Sigma_0)_{S_i,S_j}$. For simplicity, we denote $(\Sigma_0)_{(i)j}$ and $(\Sigma_0)_{iS}$ by $(\Sigma_0)_{ij}$ and $(\Sigma_0)_{iS}$ respectively.
We denote the \( i \)-th column of the \( k \times k \) identity matrix by \( e_i, k \). For \( i \neq k \) and any set \( S \subseteq \{1, \ldots, p\} \setminus \{i, k\} \), we denote the coefficient of \( X_i \) in the linear regression of \( X_k \) on \( X_{\{i\}\cup S} \) by \( \beta_{ik|S} \) or by \( \beta_{ik|X_k} \). For simplicity, we denote \( \beta_{ik|\emptyset} \) by \( \beta_{ik} \). Note that \( \beta_{ik|S} \) is model-free, i.e. it is well-defined regardless of whether or not the conditional expectation \( E[X_k | X_{\{i\}\cup S}] \) is a linear function of \( \{X_i\}\cup X_S \). For any vector \( \nu = (\nu_j)^d_{j=1} \in \mathbb{R}^d \), for any \( d \geq 1 \), \( \|\nu\|_r := \left( \sum_{j=1}^{d} |\nu_j|^r \right)^{1/r} \), for any \( r \geq 1 \), and \( \|\nu\|_\infty := \max\{|\nu_j| : j = 1, \ldots, d\} \) denote the \( L_r \) and \( L_\infty \) norms of \( \nu \), respectively.

Using (3.1), the individual mediation effect \( \eta_j \)’s can be expressed as follows.

**Lemma 3.1.** Let \( X \) be as in Section 2.4. Then, \( \forall j = t + 1, \ldots, p - 1, \)

\[
\eta_j = \theta_{ij} \theta_{jp} = \beta_{ipj} X_{\{1, \ldots, t - 1\}} \beta_{j|\text{Pa}_0(X_i)} X_{\{1, \ldots, t\}}.
\]

**Example 2.** To illustrate Lemma 3.1, we reconsider Example 1 and let \( \Sigma = \text{Cov}(X) \). Using (3.1), the individual mediation effect \( \eta_j \)’s can be computed as in Table 2. Furthermore, it is easy to verify that a naive method that ignores the causal graph among the mediators and computes the individual mediation effects as \( \beta_{2j|\{1\}} \times \beta_{j7|\{1, 2\}} \) would be inaccurate for \( j = 3, 5, 6 \).

| \( j \) | \( \eta_j = \theta_{2j} \times \theta_{j7} \) |
|---|---|
| 3 | \( \beta_{23|\{1\}} \times \beta_{37|\{1, 2\}} = e_{2, 3}^T (\Sigma_{\{1, 2\}})^{-1} \Sigma_{\{1, 2\}} e_{3, 7} = e_{2, 3}^T (\Sigma_{\{1, 2\}})^{-1} (\Sigma_{\{1, 2\}})^{-1} \Sigma_{\{1, 2\}} e_{3, 7} \) |
| 4 | \( \beta_{24|\{1\}} \times \beta_{47|\{1, 2\}} = e_{2, 4}^T (\Sigma_{\{1, 2\}})^{-1} \Sigma_{\{1, 2\}} e_{4, 7} = e_{2, 4}^T (\Sigma_{\{1, 2\}})^{-1} (\Sigma_{\{1, 2\}})^{-1} \Sigma_{\{1, 2\}} e_{4, 7} \) |
| 5 | \( \beta_{25|\{1\}} \times \beta_{57|\{1, 2\}} = e_{2, 5}^T (\Sigma_{\{1, 2\}})^{-1} \Sigma_{\{1, 2\}} e_{5, 7} = e_{2, 5}^T (\Sigma_{\{1, 2\}})^{-1} (\Sigma_{\{1, 2\}})^{-1} \Sigma_{\{1, 2\}} e_{5, 7} \) |
| 6 | \( \beta_{26|\{1\}} \times \beta_{67|\{1, 2\}} = e_{2, 6}^T (\Sigma_{\{1, 2\}})^{-1} \Sigma_{\{1, 2\}} e_{6, 7} = e_{2, 6}^T (\Sigma_{\{1, 2\}})^{-1} (\Sigma_{\{1, 2\}})^{-1} \Sigma_{\{1, 2\}} e_{6, 7} \) |

**Table 2**

*Individual mediation effects via covariate adjustments for the DAG in Example 1.*
3.2. The MIDA Estimator. Our goal is to estimate \( \epsilon_j = \theta_{ij}\theta_{jp} \), based on i.i.d. data from the distribution of \( X \), for \( j = t + 1, \ldots, p - 1 \). Note that if \( \mathbf{P}a_{G_0}(X_j) \) were known, then we could estimate \( \epsilon_j \) by plugging in the sample regression coefficients \( \hat{\beta}_{tj}|X_{(1, \ldots, t-1)} \) and \( \hat{\beta}_{jp}|\mathbf{P}a_{G_0}(X_j) \cup X_{(t, \ldots, t)} \) in (3.1).

When \( G_0^t \) is unknown, we need to estimate it from the data. However, a causal DAG is (usually) not identifiable from observational data without further assumptions. But we can estimate the CPDAG representing the corresponding Markov equivalence class (see Section 2.3). In particular, we can estimate the CPDAG \( C_0^t \) that represents the Markov equivalence class of \( G_0^t \). Consequently, \( \theta_{ij} \) and \( \epsilon_j \) are also not identifiable from observational data (with unknown \( G_0^t \)). Therefore, following the IDA approach of Maathuis et al. [2009] and Nandy et al. [2017], we aim to estimate the following identifiable version \( \epsilon_j(C_0^t) \) of \( \epsilon_j \) defined as

\[
\epsilon_j(C_0^t) := \beta_{tj}|X_{(1, \ldots, t-1)} \times \text{aver}(\Theta_{jp}(C_0^t)), \quad \text{where}
\]

\[
\Theta_{jp}(C_0^t) := \{\beta_{jp}|\mathbf{P}a_{C_0^t}(X_j) \cup X_{(t, \ldots, t)} : \mathcal{G} \in \text{MEC}(C_0^t)\}
\]

is a multi-set of possible causal effects of \( X_j \) on \( X_p \), and \( \text{aver}(A) \) denotes the average of all numbers (respecting any multiple occurrences) in the multi-set \( A \). We will empirically verify that \( \epsilon_j(C_0^t) \) serves as a reasonable proxy for \( \epsilon_j \) in sparse high-dimensional settings (see Section 7 for more details).

In order to estimate the CPDAG \( C_0^t \), we first remove the effect of \( X_{(1, \ldots, t)} \) on each potential mediator \( X_j \) by replacing the data that corresponds to \( X_j \) by the residuals of the regression of \( X_j \) on \( X_{(1, \ldots, t)} \). Then, we apply any suitable structure learning algorithm on this transformed data for estimating \( C_0^t \), followed by estimating \( \epsilon_j(C_0^t) \). The steps of our MIDA approach are formalized next in Algorithm 3.1. For any \( i, k \) and \( X_S \subseteq X \), let \( \hat{\beta}_{ki}|X_S \) denote the estimated regression coefficient of \( X_i \) in the linear regression of \( X_k \) on \( X_{(i) \cup S} \).

---

**Algorithm 3.1 MIDA**

**Input:** \( n \) i.i.d. observations of \( X \) (data)

**Output:** Estimates of \( \epsilon_j(C_0^t) \) for \( j = t + 1, \ldots, p - 1 \)

1: for \( j = t + 1, \ldots, p - 1 \), obtain the vector of residuals \( r_j = (r_j^{(1)}, \ldots, r_j^{(n)}) \) from the regression of \( X_j \) on \( X_{(1, \ldots, t)} \);
2: apply any suitable structure learning algorithm (such as (AR)GES or PC) on the data \( \{r_{t+1}, \ldots, r_{p-1}\} \) to obtain an estimate \( \hat{C}_0^t \) of the CPDAG \( C_0^t \);
3: for each \( j = t + 1, \ldots, p - 1 \), obtain a multi-set of possible causal effects \( \hat{\Theta}_{jp}(C_0^t) := \{\hat{\beta}_{jp}|\mathbf{P}a_{\hat{C}_0^t}(X_j) \cup X_{(t, \ldots, t)} : \hat{\mathcal{G}} \in \text{MEC}(\hat{C}_0^t)\} \) based on the original data;
4: return \( \hat{\epsilon}_j(C_0^t) := \hat{\beta}_{tj}|X_{(1, \ldots, t-1)} \times \text{aver}(\hat{\Theta}_{jp}(C_0^t)) \) for \( j = t + 1, \ldots, p - 1 \).

**LEMMA 3.2.** Let \( X \) be as in Section 2.4 and let \( X', G_0^t, B_{G_0^t} \), and \( \epsilon' \) be as in Section 2.5. Then, the conditional expectation \( \mathbb{E}[X'|X_{(1, \ldots, t)}] \) is linear in \( X_{(1, \ldots, t)} \). Further, \( X^t := X' - \mathbb{E}[X'|X_{(1, \ldots, t)}] \) satisfies: \( X^t = B_{G_0^t}^T X + \epsilon' \), and the distribution of \( X^t \) is faithful to \( G_0^t \).

**LEMMA 3.3.** Let \( \hat{\rho}_{ik}|S \) denote the sample partial correlation between \( X_i \) and \( X_k \) given \( X_S \) and \( \hat{\rho}_{ik}|S \) the sample partial correlation between \( X_i^t \) and \( X_k^t \) given \( X_S^t \) computed based on the residuals \( r_j \)’s defined in Algorithm 3.1. Then, for all \( i, k \in \{t + 1, \ldots, p - 1\}, i \neq k \) and \( S \subseteq \{t + 1, \ldots, p - 1\} \setminus \{i, k\} \),

\[
\hat{\rho}_{ik}^{2|S} = \hat{\rho}_{ik}^{2|S \cup \{1, \ldots, t\}}.
\]
Lemmas 3.2–3.3 justify the estimation of $C^*_0$ from the residuals $r_j$'s in Algorithm 3.1. This is because both the (AR)GES and PC algorithms are designed to estimate the CPDAG corresponding to a faithful DAG of an LSEM based on the squared sample partial correlations. In particular, (AR)GES sequentially adds and deletes edges based on the $\log(1 - \hat{\rho}^2_{ik|S})$ values (see Lemma 5.1 and Section 6 of Nandy et al. [2018]) and the PC algorithm uses the $\log(1 + |\hat{\rho}_{ik|S}|)$ values (see Section 2.2.2 of Kalisch and Bühlmann [2007]).

The main difference between $\hat{\Theta}_{jp}(C^*_0)$ above and the corresponding original IDA estimator of Maathuis et al. [2009] is that we always include $X_{\{1,\ldots,t\}}$ in the adjustment set, leveraging the fact that $X_j$ is not a direct cause of the treatment variable $X_t$ and the confounders $X_{\{1,\ldots,t-1\}}$. Further, note that computing MEC($\hat{C}^*_0$) can be computationally infeasible for a large CPDAG $\hat{C}^*_0$ [Maathuis et al., 2009]. This computation bottleneck can be relieved by directly obtaining the multi-set of parent sets $\mathcal{P}_A_{\hat{C}^*_0}(X_j) = \{\mathcal{Pa}_G(X_j) : G \in \text{MEC}(\hat{C}^*_0)\}$ from $\hat{C}^*_0$ without computing MEC($\hat{C}^*_0$) via Algorithm 3 of Nandy et al. [2017]. We note that the output of Algorithm 3 of Nandy et al. [2017] and $\mathcal{P}_A_{\hat{C}^*_0}(X_j)$ may not be the same multi-set, but Theorem 5.1 of Nandy et al. [2017] guarantees that they are equivalent multi-sets in the sense that they have the same distinct elements and the ratio of the multiplicities of any two elements in the output of Algorithm 3 of Nandy et al. [2017] equals the ratio of their multiplicities in $\mathcal{P}_A_{\hat{C}^*_0}(X_j)$. Therefore, using the output of Algorithm 3 of Nandy et al. [2017] instead of MEC($\hat{C}^*_0$) makes no difference in obtaining $\text{aver}(\hat{\Theta}_{jp}(\hat{C}^*_0))$. Thus, for simplicity, we can safely pretend that we use MEC($\hat{C}^*_0$) for computing $\text{aver}(\hat{\Theta}_{jp}(\hat{C}^*_0))$ in the rest of the paper.

4. Consistency in High-Dimensional Settings. We now consider an asymptotic scenario where the sample size $n$ and the number of potential mediators $(p - t - 1)$ in $X$ grows to infinity. (We consider $t \geq 1$ to be fixed.) We prove high-dimensional consistency of the MIDA estimators $\hat{\nu}_j(C^*_0)$ defined in Algorithm 3.1, whenever the CPDAG $\hat{C}^*_0$ is estimated consistently. We note here that such high-dimensional consistency in the CPDAG estimation holds under the following assumptions, and some additional assumptions (e.g., see Kalisch and Bühlmann [2007]; Nandy et al. [2018]), when $\hat{C}^*_0$ is estimated using (AR)GES or PC (see Lemmas 3.2 and 3.3 and the subsequent discussion).

ASSUMPTION 4.1 (LSEM with sub-Gaussian error variables). $X$ is generated from a linear SEM $(B_{G_0}, \epsilon)$ with sub-Gaussian error variables satisfying $\max_{1 \leq i \leq p} ||\epsilon_i||_{\psi_2} \leq C_1$ for some absolute constant $C_1 > 0$, where $|| \cdot ||_{\psi_2}$ denotes the sub-Gaussian norm given in Definition B.1 (in Appendix B of the Supplement).

ASSUMPTION 4.2 (High-dimensional setting). $p = O(n^a)$ for some $a \geq 0$.

ASSUMPTION 4.3 (Sparsity condition). Let $q := \max_{1 \leq j \leq p - 1} |\text{Adj}_{\hat{C}^*_0}(X_j)|$ denote the maximum degree in $C^*_0$. Then, $q = O(n^{1-b_1})$ for some $0 < b_1 \leq 1$.

ASSUMPTION 4.4 (Structure learning consistency). The estimated CPDAG $\hat{C}^*_0$ in Algorithm 3.1 is a consistent estimator of $C^*_0$ i.e. $\mathbb{P}(\hat{C}^*_0 \neq C^*_0) \rightarrow 0$.

ASSUMPTION 4.5 (Bounds on the eigenvalues of covariance matrices). For any $(q + t + 2) \times (q + t + 2)$ principal submatrix $\Sigma$ of $\Sigma_0 = \text{Cov}(X)$,

$$C_2 \leq 1/||\Sigma^{-1}||_2 \leq ||\Sigma||_2 \leq C_3,$$
for some absolute constants $C_2, C_3 > 0$, where $\|\cdot\|_2$ denotes the spectral norm (as defined in Section 2.5) and $q$ is as defined in Assumption 4.3 above.

**THEOREM 4.1** (Uniform consistency of MIDA). Let $\hat{\eta}_j(\hat{C}_0) = \hat{\beta}_{1j} \mathbf{x}_{\{1,\ldots,t-1\}} \times \text{aver}(\hat{\Theta}_{jp}(\hat{C}_0))$ denote the output of Algorithm 3.1. Then, under Assumptions 4.1–4.5, we have:

1. $\max_{t<j<p} \left| \text{aver}(\hat{\Theta}_{jp}(\hat{C}_0)) - \text{aver}(\Theta_{jp}) \right| \xrightarrow{P} 0$, and
2. $\max_{t<j<p} | \hat{\eta}_j(\hat{C}_0) - \eta_j(C_0) | \xrightarrow{P} 0$.

Note that the high dimensional consistency results for (joint-)IDA estimators were proven only for LSEMs with Gaussian errors [Maathuis et al., 2009; Nandy et al., 2017]. Theorem 4.1 thus extends the existing high-dimensional consistency results for IDA estimators to LSEMs with sub-Gaussian errors. Finally, it is worth noting again that the results above do not depend on the nature of the CPDAG estimation method as long as it is consistent.

### 4.1. Discussion on Assumption 4.1

We demonstrate the adaptivity of the high-dimensional consistency result above for the MIDA estimator, with respect to some of the recent efforts in relaxing the linearity assumption for the IDA-type estimators [Nandy et al., 2017; Frot et al., 2019]. We outline here the modifications needed to relax Assumption 4.1, but we refrain from a mere repetition of the existing theoretical analyses for the sake of brevity.

Relaxing linearity. The linear sub-Gaussian setting is a key requirement for the high-dimensional inference results for MIDA presented in Section 6 later. However, the high-dimensional consistency result given here can indeed be extended beyond the linear sub-Gaussian setting by combining some existing results [Harris and Drton, 2013; Han and Liu, 2017; Nandy et al., 2017, 2018; Frot et al., 2019]. In particular, we can establish a high-dimensional consistency result under only the assumption that $X$ follows a transelliptical distribution (Definition 2.2 of Han and Liu [2017]), i.e. $(f_1(X_1), \ldots, f_p(X_p))^T$ has an elliptical distribution (e.g., Gaussian) for some increasing (or decreasing) functions $f_1, \ldots, f_p$. When the distribution of $(f_1(X_1), \ldots, f_p(X_p))^T$ is multivariate Gaussian, the distribution of $X$ is called nonparanormal. Under the nonparanormal assumption, Harris and Drton [2013] proved a high-dimensional consistency result for the so-called Rank PC algorithm, and Nandy et al. [2017] extended this result to a modified version of the (joint-) IDA estimator. The high-dimensional consistency of (AR)GES under the nonparanormal distribution, as well as the more general transelliptical distribution, has been proved in Nandy et al. [2018]; Frot et al. [2019].

A high-dimensional consistency result for a modified version ‘(M)IDA’ of MIDA under the transelliptical assumption can be obtained by combining the structure learning consistency result of Frot et al. [2019] with the proofs of Theorem 7.1 of Nandy et al. [2017] and our Theorem 4.1. The required modification for (M)IDA is to simply apply Algorithm 3.1 on a transformed sample rank correlation matrix $\sin((\pi/2)\hat{T})$ instead of the sample covariance matrix $\hat{\Sigma}$ itself, where the sine function is applied element-wise and $\hat{T}$ is the Kendall’s rank correlation matrix. To this end, note that the first three steps of Algorithm 3.1 are equivalent to applying the (AR)GES algorithm on the covariance matrix

\[(4.1) \quad \hat{\Sigma} \mathbf{x}_{\{t+1,\ldots,p-1\}} \mathbf{x}_{\{t+1,\ldots,p-1\}} - \hat{\Sigma} \mathbf{x}_{\{t+1,\ldots,p-1\}} \mathbf{x}_{\{1,\ldots,t\}} \Sigma_{\{t+1,\ldots,p-1\}}^{-1} \mathbf{x}_{\{t+1,\ldots,p-1\}} \hat{\Sigma} \mathbf{x}_{\{1,\ldots,t\}} \mathbf{x}_{\{1,\ldots,t\}}^T \mathbf{x}_{\{1,\ldots,p-1\}}^T.
\]

Handling the case of hidden confounders. Finally, recall that the independence of the error variables in Definition 2.1 corresponds to the no hidden (or unmeasured) confounder (that
is a common cause of more than one observed variable) assumption. This assumption has been relaxed in Frot et al. [2019]. In particular, the authors considered a setting with a few hidden variables that have a direct effect on many of the observed variables and derived a consistent method for estimating the underlying CPDAG corresponding to the observed variables. The main idea is to apply a low-rank plus sparse decomposition [Chandrasekaran et al., 2012] of the inverse covariance matrix to remove the influence of the hidden confounders before applying a structure learning method that assumes the absence of hidden confounders. Furthermore, the authors proposed to use the estimated CPDAG and an estimate of the conditional covariance matrix given the hidden confounders to obtain IDA-type estimators of total causal effects under the linear sub-Gaussian assumption or the transelliptical assumption. The same techniques can be applied to the covariance matrix in (4.1) or the corresponding transformed rank correlation matrix to obtain a consistent MIDA estimator in the presence of a small number of highly influential hidden variables.

5. Linear Regression over Varying Subsets of High-Dimensional Covariates. This section considers linear regression over varying subsets of high-dimensional covariates in a general setting, and derives uniform bounds and first order expansions for the resulting estimators. These results are used in Section 6 to derive the asymptotic distributions of the estimators of interventional and mediation effects. While derived primarily for establishing the (uniform) asymptotic normality and inferential tools for our proposed estimators, these results are applicable far more generally to any setting involving linear regressions over varying (non-random) subsets of high-dimensional regressors, and may be of independent interest. For notational simplicity and clarity of exposition, we therefore derive them under more general and standard notations where \( Y \) and \( X \) denote a generic response and a (high-dimensional) covariate vector, respectively. All our results here are non-asymptotic.

Basic setup and definitions. Let \( D_n := \{Z_i \equiv (Y_i, X_i)\}_{i=1}^n \) denote the observed data consisting of \( n \) i.i.d. realizations of \( Z := (Y, X) \), where \( Y \in \mathbb{R} \), \( X \in \mathbb{R}^p \) and \( p \equiv p_n \) is allowed to diverge with \( n \). Neither \( Y \) nor \( X \) is needed to be centered (i.e. zero-mean) and/or continuous. Let \( \mu_Y := \mathbb{E}(Y) \), \( \mu := \mathbb{E}(X) \) and \( \Sigma := \mathbb{E}\{(X - \mu)(X - \mu)^T\} \equiv \text{Cov}(X) \), where we assume \( \Sigma \succ 0 \). Further, let \( \bar{Y} := n^{-1} \sum_{i=1}^n Y_i \), \( \bar{X} := n^{-1} \sum_{i=1}^n X_i \) and \( J := \{1, \ldots, p\} \).

Let \( \Omega_J \) denote the collection of all possible subsets of \( J \). For any \( S \in \Omega_J \) with \( |S| = s \leq p \), and any vector \( v = (v_i)_{i=1}^p \in \mathbb{R}^p \), let \( v_S \in \mathbb{R}^s \) denote the restriction of \( v \) onto \( S \), i.e. for \( S = \{i_1, \ldots, i_s\} \subseteq J \), \( v_S = (v_{i_1})_{j=1}^s \). Let \( X_S, \{X_{S,i}\}_{i=1}^n, \mu_S \) and \( \bar{X}_S \) respectively denote the restrictions of \( X, \{X_i\}_{i=1}^n \), \( \mu \) and \( \bar{X} \) onto \( S \). Let \( \Sigma_S := \text{Cov}(X_S) \) and \( \Sigma_{S,Y} := \text{Cov}(Y, X_S) \), and define:

\[
\hat{\Sigma}_S := \frac{1}{n} \sum_{i=1}^n (X_{S,i} - \bar{X}_S)(X_{S,i} - \bar{X}_S)^T, \quad \hat{\Gamma}_S := (\bar{X}_S - \mu_S)(\bar{X}_S - \mu_S)^T,
\]

\[
\hat{\Sigma}_{S,Y} := \frac{1}{n} \sum_{i=1}^n (Y_i - \bar{Y})(X_{S,i} - \bar{X}_S), \quad \hat{\Gamma}_{S,Y} := (\bar{Y} - \mu_Y)(\bar{X}_S - \mu_S).
\]

Varying subset linear regression estimator(s). Let \( S \subseteq \Omega_J \) denote any collection of subsets of \( J \) with \( \max\{s := |S| : S \in \Omega_J\} \leq q_n \), for some \( q_n \equiv q_{n,S} \leq \min(n, p_n) \), and let \( L_n \equiv L_{n,S} := |S| \). We now consider linear regression(s) of \( Y \) on \( X_S \), for all \( S \in \Omega_J \), via the ordinary least squares (OLS) estimator, \( \hat{\beta}_S \), defined, along with its corresponding target parameter, \( \beta_S \), as follows.

\[
\beta_S := \arg\min_{\beta \in \mathbb{R}^p} \mathbb{E}\{(Y - \mu_Y)(X_S - \mu_S)^T \beta\}^2 \equiv \Sigma_S^{-1} \Sigma_{S,Y}, \quad \text{and}
\]

\[
\hat{\beta}_S := \arg\min_{\beta \in \mathbb{R}^p} \mathbb{E}\{(Y - \mu_Y)(X_S - \mu_S)^T \beta\}^2 \equiv \hat{\Sigma}_S^{-1} \hat{\Sigma}_{S,Y}.
\]
\[
\hat{\beta}_S := \arg \min_{\beta \in \mathbb{R}^s} \frac{1}{n} \sum_{i=1}^n \{(Y_i - \bar{Y}) - (X_{S,i} - X_S)^T \beta\}^2 \equiv \sum_S^{-1} \hat{\Sigma}_{S,Y}.
\]

Since we are only interested in the regression coefficients, we circumvent the need for any nuisance intercept terms by appropriately centering \(Y\) and \(X_S\) in both (5.1) and (5.2). The existence and uniqueness of \(\beta_S\) and \(\hat{\beta}_S\) in (5.1)–(5.2) are both guaranteed for any \(S \in S\) since \(\Sigma > 0\), so that \(\Sigma_S\) is invertible, and \(\hat{\Sigma}_S\) is invertible almost surely (a.s.) as \(|S| \equiv s \leq n\). Further, note that throughout the formulations in (5.1)–(5.2), we make no assumptions on the existence of a true linear model between \(Y\) and \(X_S\) for any \(S\). The target parameter \(\beta_S\) is well-defined regardless of any such model assumptions and simply denotes the coefficients in the best (in the \(L_2\) sense) linear predictor of \(Y\) given \(X_S\). Our framework is thus completely model free in this sense.

**Decomposition of \((\hat{\beta}_S - \beta_S)\)**. For notational simplicity, define: \(\tilde{X}_S := X_S - \mu_S\) and \(\tilde{Y} := Y - \mu_Y\), the centered versions of \(X\) and \(Y\); and let \(\psi_S(Z) := \tilde{X}_S(\tilde{Y} - \tilde{X}_S^T \beta_S)\), where we note that \(\mathbb{E}\{\psi_S(Z)\} = 0\) by the definition of \(\beta_S\) in (5.1). Using the estimating equations (5.1)–(5.2), it is then straightforward to show that \(\hat{\beta}_S - \beta_S\), for any \(S \in S\), satisfies a deterministic decomposition:

\[
\hat{\beta}_S - \beta_S = \frac{1}{n} \sum_{i=1}^n \Psi_S(Z_i) + T_{n,S} + R_{n,S}, \quad \text{where}
\]

\[
\Psi_S(Z) := \Sigma_S^{-1} \psi_S(Z) \equiv \Sigma_S^{-1} \tilde{X}_S(\tilde{Y} - \tilde{X}_S^T \beta_S) \quad \text{with} \quad \mathbb{E}\{\Psi_S(Z)\} = 0,
\]

\[
T_{n,S} := \frac{1}{n} (\Sigma_S^{-1} - \Sigma_S^{-1}) \sum_{i=1}^n \psi_S(Z_i) \quad \text{and} \quad R_{n,S} := \sum_S^{-1} (\Gamma_S \beta_S - \Gamma_{S,Y}).
\]

For a single \(S\) and under classical asymptotics (i.e. \(s\) is fixed and \(n \to \infty\)), standard results from \(M\)-estimation theory [Van der Vaart and Wellner, 1996; Van der Vaart, 1998, e.g.] imply that under mild conditions, \(\hat{\beta}_S\) is a \(\sqrt{n}\)-consistent and asymptotically normal (CAN) estimator of \(\beta_S\) and admits an **asymptotically linear expansion** (ALE): \(\hat{\beta}_S - \beta_S = n^{-1} \sum_{i=1}^n \Psi_S(Z_i) + o_p(n^{-1/2})\), with an **influence function** (IF): \(\Psi_S(Z)\), so that \(\sqrt{n}(\hat{\beta}_S - \beta_S)\) is asymptotically normal with mean 0 and variance: \(\text{Cov}\{\Psi_S(Z)\}\). Further, even when \(s \equiv |S|\) is allowed to diverge, it is also well known (e.g., see Portnoy [1984, 1985, 1986, 1988]) that under suitable regularity conditions and if \(s = o(n)\), \(\|\hat{\beta}_S - \beta_S\|_2 = O_p(\sqrt{s/n})\) and \(\|\hat{\beta}_S - \beta_S - n^{-1} \sum_{i=1}^n \Psi_S(Z_i)\|_2 = o_p(s/n)\), so that whenever \(s = o(\sqrt{n})\), \(\hat{\beta}_S\) is a CAN estimator of \(\beta_S\) and admits an ALE with IF \(\Psi_S(Z)\). However, these results are all asymptotic in nature, and more importantly, apply only to a single set \(S\).

**Contributions.** Our main challenges lie in the fact that we have a **family** of estimators based on a collection of subsets \(\{X_S\}_{S \in S}\) of \(X\), where \(|S|\) itself is possibly large and further, for each \(S \in S\), \(X_S\) may be high-dimensional with \(s \leq q_n\) allowed to diverge with \(n\). Under such a setting, we aim to provide inferential tools for our family of estimators \(\{\hat{\beta}_S\}_{S \in S}\) and their derived functionals. We achieve this by providing (uniform) ALEs for \(\{\hat{\beta}_S\}_{S \in S}\) in Theorem 5.1, whereby we control the remainder terms \(T_{n,S}\) and \(R_{n,S}\) in (5.3) uniformly over \(S \in S\) based on non-asymptotic bounds for \(\sup_{S \in S} \|T_{n,S} + R_{n,S}\|_2\) that establishes their uniform convergence rates (Remark 5.1). Note that the potentially diverging sizes of \(S\) and each \(S \in S\) necessitate such non-asymptotic analyses. Lastly, apart from the (second order) error terms \(T_{n,S}\) and \(R_{n,S}\), we also provide uniform convergence rates of the first order term: \(n^{-1} \sum_{i=1}^n \Psi_S(Z_i)\) in (5.3) under the \(L_2\) norm, thereby establishing the rate of
sup_{S \in \mathcal{S}} \| \hat{\beta}_S - \beta_S \|_2. Further, for linear functionals of \{ \beta_S \}_{S \in \mathcal{S}}, we also provide results on \sqrt{n}\text{-consistency and asymptotic normality for the corresponding linear functionals of the estimators } \{ \hat{\beta}_S \}_{S \in \mathcal{S}} (Remark 5.2). Such results would be useful for establishing our results in Section 6 regarding asymptotic distribution of the IDA based estimators.

5.1. Uniform ALEs for OLS: Non-Asymptotic Bounds and Uniform Convergence Rates for All Terms in (5.3). We first state our main assumptions and define a few related quantities that will appear in our results. We present our main result in Theorem 5.1 below. Its proof (given in Appendix A.6) also involves two useful supporting lemmas, Lemma A.2 and Lemma A.3, which may be of independent interest. These lemmas are also given in Appendix A.6.

ASSUMPTION 5.1 (Main assumptions and some definitions). (i) We assume that \( \bar{Y} \equiv Y - \mu_Y \) is sub-Gaussian and \( X_S \equiv X_S - \mu_S \) is sub-Gaussian uniformly in \( S \in \mathcal{S} \), and also that \( \Sigma_S \) is well conditioned uniformly in \( S \in \mathcal{S} \). Specifically, for some constants \( \sigma_Y, \sigma_{X,S} \in [0, \infty) \) and \( \lambda_{\inf,S}, \lambda_{\sup,S} \in (0, \infty) \),

\[
\| Y - \mu_Y \|_{\psi_2} \leq \sigma_Y, \quad \sup_{S \in \mathcal{S}} \| X_S - \mu_S \|_{\psi_2}^* \leq \sigma_{X,S}, \quad \text{and}
\]

\[
(5.4) \quad 0 < \lambda_{\inf,S} \leq \inf_{S \in \mathcal{S}} \lambda_{\min}(\Sigma_S) \leq \sup_{S \in \mathcal{S}} \lambda_{\max}(\Sigma_S) \leq \lambda_{\sup,S} < \infty,
\]

where \( \| \cdot \|_{\psi_2} \) and \( \| \cdot \|_{\psi_2}^* \) denote the sub-Gaussian norms as in Definitions B.1–B.2, respectively. Let us further define the constant \( K_S := C_1 \sigma_{X,S}^2 \frac{\lambda_{\sup,S}}{\lambda_{\inf,S}} > 0 \), where \( C_1 \) is the same absolute constant as in Lemma B.6 (and also same as the constant given in Theorem 4.7.4 and Exercise 4.7.3 of Vershynin [2018]).

(ii) Let \( Z_S := (Y, X_S) \), \( \nu_S := \mathbb{E}(Z_S) \) and \( \Xi_S := \text{Cov}(Z_S) \). Then, we also assume that \( \Xi_S \) is well-conditioned uniformly in \( S \in \mathcal{S} \). Specifically, for some constants \( \tilde{\lambda}_{\inf,S}, \tilde{\lambda}_{\sup,S} \in (0, \infty) \),

\[
0 < \tilde{\lambda}_{\inf,S} \leq \inf_{S \in \mathcal{S}} \lambda_{\min}(\Xi_S) \leq \sup_{S \in \mathcal{S}} \lambda_{\max}(\Xi_S) \leq \tilde{\lambda}_{\sup,S} < \infty.
\]

Further, let \( \tilde{\sigma}_{Z,S} := \sigma_Y + \sigma_{X,S} \) and define the constant \( K_S := C_1 \tilde{\sigma}_{Z,S}^2 \frac{\tilde{\lambda}_{\sup,S}}{\tilde{\lambda}_{\inf,S}} > 0 \), where \( C_1 > 0 \) is the same absolute constant as in part (i) above.

THEOREM 5.1 (Uniform bounds and convergence rates for all the terms in (5.3)). Consider any \( \mathcal{S} \subseteq \Omega \) with \( | \mathcal{S} | := L_n \equiv L_{n,S} \) and \( \sup_{S \in \mathcal{S}} | \mathcal{S} | \leq q_n \equiv q_{n,S} \leq \min(n, p_n) \), and suppose Assumption 5.1 holds. Let \( r_n := q_n + \log L_n \), \( \bar{r}_n := r_n + 1 \) and \( C_S := \sqrt{2\sigma_Y \lambda_{\inf,S}} \). For any \( c > 0 \), let \( \bar{c} := c + 1 \) and define:

\[
\epsilon_{n,1}(c, r_n) := c \bar{K}_S \left( \sqrt{\frac{r_n}{n}} + \frac{r_n}{n} \right), \quad \epsilon_{n,2}(c, r_n) := c \bar{K}_S \left( \sqrt{\frac{\bar{r}_n}{n}} + \frac{\bar{r}_n}{n} \right);
\]

\[
\eta_{n,1}(c, r_n) := 32c \bar{K}_S \frac{r_n}{n} + \frac{\lambda_{\sup,S}}{n}, \quad \eta_{n,2}(c, r_n) := 32c \bar{K}_S \frac{\bar{r}_n}{n} + \frac{\lambda_{\sup,S}}{n}; \quad \text{and}
\]

\[
\delta_n(c, r_n) := \bar{K}_S^* \left( \sqrt{\frac{\bar{r}_n}{n}} + \frac{33r_n}{n} \right) + \frac{2 \lambda_{\sup,S}}{n \lambda_{\inf,S}};
\]
where \((K_S, \overline{K}_S, \lambda_{\text{sup}, S}, \lambda_{\text{inf}, S}, \overline{\lambda}_{\text{sup}, S}, \overline{\lambda}_{\text{inf}, S}, \sigma_Y)\) are as in Assumption 5.1 and \(K^*_S := 2\lambda_{\text{inf}, S}^{-2}K_S\). Further, let \(c^* > 0\) be any constant that satisfies:

\[
(c^* + 1)K_S \left( \sqrt{\frac{r_n}{n}} + \frac{33\lambda_{\text{sup}, S}}{n} \right) + \lambda_{\text{sup}, S} \leq \lambda_{\text{inf}, S}.
\]

(i) Then, for any such constant \(c^* > 0\), and for any \(c > 0\), we have the following bounds. With probability at least \(1 - 8\exp(-cr_n) - 4\exp(-c^*r_n)\),

\[
\sup_{S \in \mathcal{S}} \|T_{n,S}\|_2 \leq \delta_n(c, r_n) \{\lambda_{\text{inf}, S} \{\lambda_{\text{inf}, S} + \lambda_{\text{sup}, S} \} \} \lesssim c_S^2 r_n, \quad \text{and}
\]

\[
\sup_{S \in \mathcal{S}} \|R_{n,S}\|_2 \leq \{\delta_n(c, r_n) + \lambda_{\text{inf}, S}^{-1}\} \{\lambda_{\text{inf}, S} + \lambda_{\text{sup}, S} \} \lesssim c_S r_n.
\]

(ii) Further, for any \(c > 0\), the first order term \(n^{-1} \sum_{i=1}^n \Psi_S(Z_i)\) in (5.3) satisfies the following bound. With probability at least \(1 - 4\exp(-cr_n)\),

\[
\sup_{S \in \mathcal{S}} \left\| \frac{1}{n} \sum_{i=1}^n \Psi_S(Z_i) \right\|_2 \leq \lambda_{\text{inf}, S}^{-1} \{\lambda_{\text{inf}, S} + \lambda_{\text{sup}, S} \} \lesssim c_S \sqrt{\frac{r_n}{n}}.
\]

Here, \(c_S\) denotes a generic constant (possibly different in each bound) depending only on \(S\), and \(\lesssim\) denotes inequality up to multiplicative constants.

Remark 5.1. The two bounds in result (i) of Theorem 5.1 also imply, in particular, that with high probability,

\[
\sup_{S \in \mathcal{S}} \left\| \bar{\beta}_S - \beta_S \right\|_2 = \sup_{S \in \mathcal{S}} \|T_{n,S} + R_{n,S}\|_2 \lesssim \frac{r_n}{n},
\]

thereby establishing (non-asymptotically) that the uniform (in \(S \in \mathcal{S}\)) convergence rate (under the \(L_2\) norm) of the second order terms in the ALE (5.3) of \(\bar{\beta}_S - \beta_S\) is \(O_{\mathbb{P}}(r_n/n)\).

Further, the bound in result (ii) also establishes (non-asymptotically) the uniform (in \(S \in \mathcal{S}\)) convergence rate (under the \(L_2\) norm) of the first order term in the ALE (5.3) to be \(O_{\mathbb{P}}(\sqrt{r_n/n})\). Consequently, it establishes that \(\sup_{S \in \mathcal{S}} \left\| \bar{\beta}_S - \beta_S \right\|_2 = O_{\mathbb{P}}(\sqrt{r_n/n} + r_n/n)\).

Remark 5.2 (ALEs and asymptotic normality for linear functionals of \(\{\bar{\beta}_S\}_{S \in \mathcal{S}}\)). Let \(A_S := \{a_S \in \mathbb{R}^s : S \in \mathcal{S}\}\) denote any collection of (known) vectors with \(\sum_{S \in \mathcal{S}} a_S^2 = O(1)\). Consider the linear functional of \(\{\bar{\beta}_S\}_{S \in \mathcal{S}}\) given by: \(\beta(A_S) := \sum_{S \in \mathcal{S}} a_S^T \bar{\beta}_S\), and its corresponding estimator: \(\hat{\beta}(A_S) := \sum_{S \in \mathcal{S}} a_S^T \hat{\beta}_S\). Then, as a direct consequence of Theorem 5.1, \(\hat{\beta}(A_S) - \beta(A_S)\) satisfies the following ALE:

\[
\sqrt{n} \{\hat{\beta}(A_S) - \beta(A_S)\} = \frac{1}{\sqrt{n}} \sum_{i=1}^n \xi_{A_S}(Z_i) + R_{n,A_S} =: \sqrt{n}S_{n,A_S} + R_{n,A_S},
\]

where \(\xi_{A_S}(Z) := \sum_{S \in \mathcal{S}} a_S^T \Psi_S(Z)\) and \(R_{n,A_S} := \sum_{S \in \mathcal{S}} a_S^T (T_{n,S} + R_{n,S})\),

with \(|R_{n,A_S}| \leq \sup_{S \in \mathcal{S}} \|T_{n,S} + R_{n,S}\|_2 \left( \sum_{S \in \mathcal{S}} \|a_S\|_2 \right) = O_{\mathbb{P}} \left( \frac{r_n}{\sqrt{n}} \right). \quad \square
\]

Thus, \(\sqrt{n} \{\hat{\beta}(A_S) - \beta(A_S)\} = \sqrt{n}S_{n,A_S} + o_{\mathbb{P}}(1)\), as long as \(r_n = o(\sqrt{n})\) and \(\sum_{S \in \mathcal{S}} \|a_S\|_2 = O(1)\). Note that \(S_{n,A_S}\) is an average of the centered i.i.d. random variables \(\{\xi_{A_S}(Z_i)\}_{i=1}^n\).
Hence, \( n^{3/2}/\sigma_{AS} \), when appropriately scaled to have unit variance, is expected to converge to a \( N(0, 1) \) distribution under suitable Lyapunov-type moment conditions on \( \xi_{AS}(Z) \). We characterize this more explicitly through a stronger non-asymptotic statement as follows.

Let \( \sigma_{\xi_{AS}}^2 := \mathbb{E}[(\xi_{AS}(Z))^2] \equiv \text{Var} \{ \xi_{AS}(Z) \} \) and \( \rho_{\xi_{AS}} := \left[ \mathbb{E} \{ |\xi_{AS}(Z)|^3 \} \right]^{1/3} \), so that \( 0 < \sigma_{\xi_{AS}} \leq \rho_{\xi_{AS}} \), and assume that \( \sigma_{\xi_{AS}} = \Omega(1) \) and \( \rho_{\xi_{AS}} = O(1) \), so that \( \rho_{\xi_{AS}}/\sigma_{\xi_{AS}} = O(1) \) (verifications of these conditions are discussed in the Supplement; see Appendix C). Finally, let \( F_{n,AS}(x) := \mathbb{P}\left( \sqrt{n}S_{n,AS}/\sigma_{\xi_{AS}} \leq x \right) \) denote the cumulative distribution function (CDF) of \( \sqrt{n}S_{n,AS}/\sigma_{\xi_{AS}} \), and let \( \Phi(x) := \mathbb{P}(Z \leq x) \), where \( Z \sim N(0, 1) \), denote the standard normal CDF, for all \( x \in \mathbb{R} \). Then, the Berry-Esseen theorem [Shevtsova, 2011] implies:

\[
\sup_{x \in \mathbb{R}} \left| F_{n,AS}(x) - \Phi(x) \right| \leq 0.48\rho_{\xi_{AS}}^3/(\sqrt{n}\sigma_{\xi_{AS}}^3) = O(n^{-1/2}).
\]

As a consequence, we also have: \( \sqrt{n}S_{n,AS}/\sigma_{\xi_{AS}} \overset{d}{\to} N(0, 1) \) as \( n \to \infty \).

Therefore, as long as \( r_n = o(\sqrt{n}) \), \( \sum_{S \in S} \| a_S \|_2 = O(1) \), \( \sigma_{\xi_{AS}} = \Omega(1) \) and \( \rho_{\xi_{AS}} = O(1) \), we have:

\[
\sqrt{n}\left\{ \hat{\beta}(AS) - \beta(AS) \right\}/\sigma_{\xi_{AS}} = \sqrt{n}S_{n,AS}/\sigma_{\xi_{AS}} + o_P(1) \quad \text{and} \quad \sqrt{n}S_{n,AS}/\sigma_{\xi_{AS}} \overset{d}{\to} N(0, 1).
\]

Invoking Slutsky’s theorem, we finally have:

\[
\sqrt{n}\left\{ \hat{\beta}(AS) - \beta(AS) \right\}/\sigma_{\xi_{AS}} \overset{d}{\to} N(0, 1).
\]

Furthermore, for any consistent estimator \( \hat{\sigma}_{\xi_{AS}} \) of \( \sigma_{\xi_{AS}} \), it also holds, via another application of Slutsky’s theorem, that

\[
\sqrt{n}\left\{ \hat{\beta}(AS) - \beta(AS) \right\}/\hat{\sigma}_{\xi_{AS}} \overset{d}{\to} N(0, 1) \text{ as } n \to \infty.
\]

Lastly, as mentioned above, verification of the moment conditions: \( \rho_{\xi_{AS}} = O(1) \) and \( \sigma_{\xi_{AS}} = \Omega(1) \) is discussed in Appendix C of the Supplement, where we provide fairly mild and general sufficient conditions for both to hold.

As we conclude, it is worth mentioning that some results on ‘uniform-in-model’ bounds, similar in flavor to those presented in this section, were also obtained independently in the recent work of Kuchibhotla et al. [2018] on post-selection inference in linear regression, although their results are not directly comparable to ours. Their analysis is targeted towards more general settings, but their results are more involved and less tractable. Our approach, on the other hand, is simpler and the results are more explicit and ready-to-use for application purposes. Further, our results automatically account for any data-dependent centering of \( Y \) and \( X \), unlike theirs, and the bounds in our main result (i.e., Theorem 5.1) are also more flexible in the sense that they directly involve the cardinality of \( S \), as opposed to their bounds which generally aim at a worst-case analysis with \( S \) assumed to include all subsets of \( X \) having cardinality bounded by some \( k \leq p \). Our bounds are therefore adaptive in \( |S| \) and lead to sharper rates when \( |S| \) is not too large (or at least not growing as fast as the worst case) which is often the case in practice.

6. Asymptotic Properties in High-Dimensional Settings: Inference for MIDA. Using the results from Section 5, we now develop inferential tools for MIDA (these also apply generally to any IDA-type estimator). We first prove asymptotic linearity of MIDA under Assumptions 4.1–4.5 in Section 6.1 (Theorem 6.1), and then derive its asymptotic normality under some additional assumptions in Section 6.2 (Corollaries 6.1–6.2 and Theorem 6.2), followed by construction of confidence intervals, hypothesis tests (\( p \)-values) etc. for the mediation effects in Section 6.3. We emphasize that the results derived below do not depend on the nature of the CPDAG estimation method as long as it’s consistent (Assumption 4.4).

6.1. Asymptotic Linearity. For \( j \in \{ t + 1, \ldots, p - 1 \} \), we define

\[
E_{n,jp}(\hat{C}_j, C'_j) := \text{aver}(\hat{\Theta}_{jp}(\hat{C}_j)) - \text{aver}(\hat{\Theta}_{jp}(C'_j)), \quad \text{where}
\]

\[
E_{n,jp}(\hat{C}_j, C'_j) := \frac{1}{n} \sum_{i=1}^{n} \left[ \hat{C}_j(X_i, Z_i) - C'_j(X_i, Z_i) \right].
\]
of $X$ subsets of high-dimensional covariates, since uniform non-asymptotic theory developed in Section 5 for linear regression over $E$ (possibly diverging) sequence $\{a_n\}$ (e.g., $a_n = n$),

$$\Pr \left( a_n \bigg| E_{n,jp}(\hat{C}_0, C'_0) \bigg) > \epsilon \right) \leq \Pr(\hat{C}_0 \neq C'_0) \rightarrow 0 \quad \text{as } n \rightarrow \infty,$$

so that $E_{n,jp}(\hat{C}_0, C'_0) = o_\Pr(a_n^{-1})$ for any $t + 1 \leq j \leq p - 1$. This result allows us to use the uniform non-asymptotic theory developed in Section 5 for linear regression over non-random subsets of high-dimensional covariates, since

$$\text{aver}(\hat{\Theta}_{jp}(C'_0)) - \text{aver}(\Theta_{jp}(C'_0)) = E_{n,jp}(\hat{C}_0, C'_0) + \left\{ \text{aver}(\hat{\Theta}_{jp}(C'_0)) - \text{aver}(\Theta_{jp}(C'_0)) \right\}.$$

To present our results, we first define the residual of the linear regression of $X_i$ on $S \subseteq \{1, \ldots, p\} \setminus \{i\}$, for any $1 \leq i \leq p$, as

$$R_{i|S} := X_i - \mu_i - (\Sigma_0)_iS [(\Sigma_0)SS]^{-1} (X_S - \mu_S).$$

Note that $(\Sigma_0)_iS [(\Sigma_0)SS]^{-1}$ is the vector of regression coefficients in the linear regression of $X_i$ on $X_S$. For $j \in \{t + 1, \ldots, p - 1\}$, we now define

$$Z_{jp} := \frac{1}{L_j} \sum_{\ell=1}^{L_j} e_{1|S, l}^T \left( (\Sigma_0)_{S, S}^{-1} \right) (X_{S, l} - \mu_{S, l}) R_{p|S, l},$$

where $\{X_{S, 1}, \ldots, X_{S, L_j}\}$ is the multi-set of vectors $\{(X_j, X_{\{1, \ldots, t\}}, Pa_{G'}(X_j))^T : G' \in \text{MEC}(C'_0)\}$ containing $L_{\text{distinct}, j}$ distinct elements. Further, we define

$$Z_{tj} := e_{1|t}^T \left( (\Sigma_0)_{\{1, \ldots, t\}, \{1, \ldots, t\}}^{-1} \right) (X_{\{1, \ldots, t\}} - \mu_{\{1, \ldots, t\}}) R_{\{1, \ldots, t\}}.$$

For any random variable (or vector) $Z$, we will denote its $n$ i.i.d. copies by $Z^{(1)}, \ldots, Z^{(n)}$.

Finally, we define $q_j := |\text{Adj}_{C'_0}(X_j)|$ for $t + 1 \leq j \leq p - 1$. Note that by Assumption 4.3, we have $q_j \leq q = O\left(n^{1-b_1}\right)$ for some $0 < b_1 \leq 1$.

**Theorem 6.1 (Asymptotic linearity of $\text{aver}(\hat{\Theta}_{jp}(\hat{C}'_0))$ and $\hat{\eta}_j(\hat{C}'_0)$).** Under Assumptions 4.1–4.5, we have for any $t < j < p$,

$$\text{aver}(\hat{\Theta}_{jp}(\hat{C}'_0)) - \text{aver}(\Theta_{jp}(C'_0)) = E_{n,jp}(\hat{C}'_0, C'_0) + \frac{1}{n} \sum_{r=1}^{n} Z_{r}^{(r)} + O_{\Pr}\left( \frac{q_j + \log(L_{\text{distinct}, j})}{n} \right),$$

and

$$\hat{\eta}_j(\hat{C}'_0) - \eta_j(C'_0) = \hat{\theta}_{tj} E_{n,jp}(\hat{C}'_0, C'_0) + \frac{1}{n} \sum_{r=1}^{n} \left( \theta_{tj} Z_{r}^{(r)} + \text{aver}(\Theta_{jp}(C'_0)) Z_{tj}^{(r)} \right) + \left( \frac{1}{n} \sum_{r=1}^{n} Z_{tj}^{(r)} \right) \left( \frac{1}{n} \sum_{r=1}^{n} Z_{tj}^{(r)} \right) + \hat{\theta}_{tj} O_{\Pr}\left( \frac{q_j + \log(L_{\text{distinct}, j})}{n} \right) + \text{aver}(\hat{\Theta}_{jp}(C'_0)) O_{\Pr}(1/n).$$

Note that all sums above are zero-mean i.i.d. sums as $\mathbb{E}(Z_{jp}) = \mathbb{E}(Z_{tj}) = 0.$
6.2. Asymptotic Normality. In order to establish the asymptotic normality of the estimator of the total causal effect and that of the individual mediation effects, we impose the following stronger sparsity condition.

**Assumption 6.1 (Sparsity condition).** Let $q_j$ and $L_{\text{distinct},j}$ be as above, for any $t + 1 \leq j \leq p - 1$. Then, we assume that

$$n^{-1/2}\{q_j + \log(L_{\text{distinct},j})\} \rightarrow 0, \text{ as } n \rightarrow \infty.$$ 

We note that such stronger sparsity assumptions of a similar flavor are frequently adopted in the literature, albeit for different but related problems, for deriving asymptotic normality results and confidence intervals in high-dimensional settings [Portnoy, 1988; Van de Geer et al., 2014; Javanmard and Montanari, 2014; Zhang and Zhang, 2014]. To compare results and confidence intervals in high-dimensional settings [Portnoy, 1988; Van de Geer, 2008], we impose the stronger sparsity condition.

**Assumption 6.2 (Non-degenerate conditional distributions).** The conditional variances satisfy the following lower bounds: for any $t < j < p$,

1. $\text{Var}(X_j \mid \text{Adj}_{C_0}(X_j) \cup X_{\{1, \ldots, t\} \cup \{X_j\}}) > v,$ and
2. $E[\text{Var}(X_j \mid \text{Adj}_{C_0}(X_j) \cup X_{\{1, \ldots, t\}})] > v, \text{ for some constant } v > 0.$

We note that Assumption 6.2 resembles Assumption (F) of Maathuis et al. [2009]. Further, note that Assumption 6.2 follows from Assumption 4.5 when the error variables are normally distributed. This is because $X$ is generated from an LSEM with normally distributed error variables implies that the joint distribution of $X$ is multivariate Gaussian with covariance matrix $\Sigma_0$. Hence, for any $1 \leq i \leq p$ and $S \subseteq \{1, \ldots, p\} \setminus \{i\}$ such that $|S| \leq q + t + 2$,

$$\text{Var}(X_i \mid X_S) = (\Sigma_0)_{ii} - (\Sigma_0)_{iS}(\Sigma_0)_{S}^{-1}(\Sigma_0)_{Si} \geq \lambda_{\min}(\Sigma_0)_{(S,i)(S,i)} \geq C_2,$$

where the first inequality follows from the interlacing property of eigenvalues of a Hermitian matrix $A$ and eigenvalues of the Schur complement of any principal submatrix of $A$ (see, for example, Corollary 2.3 of Zhang [2005]), and the last inequality follows from Assumption 4.5.

**Corollary 6.1 (Asymptotic normality of the estimator(s) of the total causal effect(s)).** Under Assumptions 4.1–4.5, 6.1 and 6.2, we have

$$\sqrt{n}\left\{\text{aver}(\hat{\Theta}_{jp}(C_0)) - \text{aver}(\Theta_{jp}(C_0))\right\} \frac{d}{\sqrt{E[Z_{jp}^2]}} \rightarrow \mathcal{N}(0, 1), \quad (t < j < p).$$

**Remark 6.1.** Although we state Corollary 6.1 for our particular LSEM setting where $B_{jk} = B_{kj} = 0$ for all $k \in \{1, \ldots, t\}$ and $j \in \{t + 1, \ldots, p - 1\}$, we emphasize that the same result also continues to hold for the original IDA estimator $\hat{\Theta}_{ik}(\hat{C}_0) = \{\hat{\beta}_{ik}\mid \text{Pa}_G(X_i) : G \in \text{MEC}(C_0)\}$, corresponding to the full CPDAG $C_0$, for any $1 \leq i, k \leq p$, under the assumptions of Corollary 6.1.
COROLLARY 6.2 (Asymptotic normality of the estimator(s) of the mediation effect(s)).
Under Assumptions 4.1–4.5, 6.1 and 6.2, we have
\[
T_{n,jp} := \frac{\sqrt{n} \left( \hat{\eta}_j(C'_0) - \eta_j(C'_0) \right)}{\sqrt{\mathbb{E}[(\theta_{tj}Z_{jp} + \text{aver}(\Theta_{jp}(C'_0))Z_{tj}^2)]}} \xrightarrow{d} \mathcal{N}(0,1), \quad (t < j < p),
\]
provided at least one of \( \theta_{tj} \) and \( \text{aver}(\Theta_{jp}(C'_0)) \) is non-zero.

To derive an asymptotic distribution of \( \hat{\eta}_j \) even allowing for both \( \theta_{tj} \) and \( \text{aver}(\Theta_{jp}(C'_0)) \) to be zero, we consider a modification, \( \tilde{T}_{n,jp} \), of \( T_{n,jp} \) as follows.

\[
(6.1) \quad \tilde{T}_{n,jp} := \frac{\sqrt{n} \left( \hat{\eta}_j(C'_0) - \eta_j(C'_0) \right)}{\sqrt{\hat{\theta}_{tj}^2 \mathbb{E}[Z_{jp}^2] + \text{aver}(\hat{\Theta}_{jp}(C'_0))^2 \mathbb{E}[Z_{tj}^2] + 2\hat{\theta}_{tj} \text{aver}(\hat{\Theta}_{jp}(C'_0)) \mathbb{E}[Z_{jp}Z_{tj}]}}.
\]

In contrast to \( T_{n,jp} \), the denominator of the modified version \( \tilde{T}_{n,jp} \) involves only the estimators \( \hat{\theta}_{tj} \) and \( \text{aver}(\hat{\Theta}_{jp}(C'_0)) \) which are expected to be non-zero (a.s.), thereby ensuring that \( \tilde{T}_{n,jp} \) is well-defined regardless of whether or not the corresponding true parameters \( \theta_{tj} \) and \( \text{aver}(\Theta_{jp}(C'_0)) \) are both zero.

THEOREM 6.2 (Asymptotic limit of \( \tilde{T}_{n,jp} \)). Let \( \tilde{T}_{n,jp} \) be as in (6.1) and let \( \rho = \frac{\mathbb{E}[Z_{tj}Z_{jp}]}{\sqrt{\mathbb{E}[Z_{tj}^2] \mathbb{E}[Z_{jp}^2]}} \) be the correlation coefficient between \( Z_{tj} \) and \( Z_{jp} \). Further, let \( (W_1,W_2)^T \) be a random vector that has a zero-mean bivariate Gaussian distribution with the covariance matrix \( \left( \begin{array}{cc} 1 & \rho \\ \rho & 1 \end{array} \right) \). Then, under Assumptions 4.1 - 4.5, 6.1 and 6.2, we have for any \( t < j < p \),
\[
\tilde{T}_{n,jp} \xrightarrow{d} \left\{ \begin{array}{ll}
W(\rho) := \frac{W_1W_2}{\sqrt{W_1^2 + W_2^2 + 2\rho W_1W_2}} & \text{if } \theta_{tj} = \text{aver}(\Theta_{jp}(C'_0)) = 0, \\
\mathcal{N}(0,1) & \text{otherwise}.
\end{array} \right.
\]

Theorem 6.2 therefore provides a unified result on the asymptotic distribution of \( \tilde{T}_{n,jp} \), accounting for all possible cases regarding the true values of \( \theta_{tj} \) and \( \text{aver}(\Theta_{jp}(C'_0)) \). To our knowledge, results of this flavor, that also allow for both the parameters to be zero, are generally rare in the relevant literature on inference for product-type mediation effect parameters. We provide further discussions on Theorem 6.2, and its implications and uses in inference, in Section 6.3 next (see, in particular, the last two paragraphs and the discussion involving Figure 2 therein), where we also discuss how it can be used to obtain valid confidence intervals and \( p \)-values for testing the mediation effects \( \eta_j(C'_0) \) via a unified approach, without requiring any knowledge of which case we are under, i.e. whether or not \( \theta_{tj} \) and \( \text{aver}(\Theta_{jp}(C'_0)) \) are both truly zero.

6.3. Confidence Interval and Hypothesis Testing. To construct a confidence interval (CI) for \( \eta_j(C'_0) \) based on \( \tilde{T}_{n,jp} \), we need to estimate the denominator in the right hand side of (6.1).
To this end, we define for \( t < j < p \),
\[
\hat{R}_{i|S} := X_i - \hat{\mu}_i - (\hat{\Sigma}_0)_{i|S} \left[ (\hat{\Sigma}_0)_{SS} \right]^{-1} (X_S - \hat{\mu}_S) \quad (1 \leq i \leq p),
\]
\[
\hat{Z}_{tj} := \mathbf{e}_{1,t}^T \left[ (\hat{\Sigma}_0)_{\{1,...,t\}\{1,...,t\}} \right]^{-1} (X_{\{1,...,t\}} - \hat{\mu}_{\{1,...,t\}}) \hat{R}_{j|\{1,...,t\}}, \quad \text{and}
\]
\[
\hat{Z}_{jp} := \frac{1}{L_j} \sum_{\ell=1}^{L_j} \mathbf{e}_{1,|S_{j|\ell}|}^T \left[ (\hat{\Sigma}_0)_{\hat{S}_{j|\ell}\hat{S}_{j|\ell}} \right]^{-1} (X_{\hat{S}_{j|\ell}} - \hat{\mu}_{\hat{S}_{j|\ell}}) \hat{R}_{p|\hat{S}_{j|\ell}}, \quad \text{where}
\]
\( \hat{\mu} \) is the sample mean and \( \hat{\Sigma}_0 \) is the sample covariance matrix of \( \mathbf{X} \), and \( \{ \mathbf{X}_{\mathcal{S}_1}, \ldots, \mathbf{X}_{\mathcal{S}_{L_j}} \} \) is the multi-set of vectors \( \{(X_j, X_1, \mathbb{P}_{a_j}(X_j))^T : G' \in \text{MEC}(\mathcal{C}_0')\} \).

Finally, we define for any \( t + 1 \leq j \leq p - 1 \),

\[
T_{n,jp}(\eta_j(C'_0)) := \frac{\sqrt{n} \left( \hat{\eta}_j(C'_0) - \eta_j(C'_0) \right)}{\sqrt{\frac{1}{n} \sum_{r=1}^{n} \left\{ \text{aver}(\hat{\Theta}_{jp}(C'_0)) \left( \hat{Z}_{ij}^{(r)} + \hat{\theta}_{ij} \hat{Z}_{jp}^{(r)} \right) \right\}^2}}
\]

Owing to the consistency of \( \hat{C}_0' \), and that of any \( q \times q \) sub-matrix of \( \hat{\Sigma}_0 \) (for \( q \) as in Assumption 4.3), it follows that \( T_{n,jp} \) and \( T_{n,jp} \) have the same asymptotic distribution. Therefore, using Corollary 6.2 (or Theorem 6.2), when at least one of \( \theta_{ij} \) and \( \text{aver}(\hat{\Theta}_{jp}(C'_0)) \) is non-zero, an asymptotically correct 100 \( (1 - \alpha) \) CI for \( \eta_j(C'_0) \) is given by

\[
\hat{\eta}_j(C'_0) \pm \Phi^{-1}(1 - \alpha/2) \sqrt{\frac{1}{n} \sum_{r=1}^{n} \left\{ \text{aver}(\hat{\Theta}_{jp}(C'_0)) \left( \hat{Z}_{ij}^{(r)} + \hat{\theta}_{ij} \hat{Z}_{jp}^{(r)} \right) \right\}^2},
\]

where \( \Phi(\cdot) \) denotes the CDF of a standard normal distribution.

When both \( \theta_{ij} \) and \( \text{aver}(\hat{\Theta}_{jp}(C'_0)) \) are zero, the CI ideally needs to be computed using the probability distribution of \( W(\mu) \) (as defined in Theorem 6.2). However, Figure 2 shows that the distribution of \( W(\mu) \) is much more concentrated around zero compared to the standard normal distribution. This suggests that a unified approach for constructing the CI is to use (6.3) for all values of \( \text{aver}(\hat{\Theta}_{jp}(C'_0)) \) and \( \theta_{ij} \). The resulting CI would be conservative (but nonetheless still valid) when both \( \theta_{ij} \) and \( \text{aver}(\hat{\Theta}_{jp}(C'_0)) \) are zero, or are very close to zero.

Again, when at least one of \( \theta_{ij} \) and \( \text{aver}(\hat{\Theta}_{jp}(C'_0)) \) is non-zero, then owing to Theorem 6.2, the \( p \)-value for testing the null hypothesis, \( H_0 : \eta_j(C'_0) = 0 \), against the two-sided alternative, \( H_1 : \eta_j(C'_0) \neq 0 \), can be computed as:

\[
2 \left[ 1 - \Phi \left( \frac{|T_{n,jp}(\eta_j(C'_0))|}{\sqrt{\frac{1}{n} \sum_{r=1}^{n} \left\{ \text{aver}(\hat{\Theta}_{jp}(C'_0)) \left( \hat{Z}_{ij}^{(r)} + \hat{\theta}_{ij} \hat{Z}_{jp}^{(r)} \right) \right\}^2}} \right) \right], \quad (t + 1 \leq j \leq p - 1).
\]

When both \( \theta_{ij} \) and \( \text{aver}(\hat{\Theta}_{jp}(C'_0)) \) are zero, the \( p \)-value corresponding to the two-sided test ideally should be \( \mathbb{P}(|W(\mu)| > |T_{n,jp}(\eta_j(C'_0))|) \). In the next section (on simulation studies), we will use the \( p \)-values to rank the mediators according to their individual mediation effects. For this purpose, however, we propose to use the Gaussian \( p \)-values in all cases. We justify this choice in the second part of Figure 2 which shows that the CDF of \( |W(\mu)| \) dominates the CDF of the absolute value of a standard Gaussian random variable (i.e. \( 2\Phi(x) - 1 \), for any \( x > 0 \)). This implies conservative (that is higher than expected), but nonetheless still valid, \( p \)-values when both \( \theta_{ij} \) and \( \text{aver}(\hat{\Theta}_{jp}(C'_0)) \) are zero, or are very close to zero.

7. Simulations. We conducted extensive simulation studies to examine the performance of our proposed MIDA estimator and associated inferential tools under various settings, which we describe below in Section 7.1, followed by presenting the results in Section 7.2.

7.1. Simulation Settings. For each of the three basic settings given in Table 3, we use the \texttt{R}-package \texttt{pcalg} [Kalisch et al., 2012] to simulate \( m \) random weighted DAGs \( \{G^{(1)}, \ldots, G^{(m)}\} \) with \( p - 2 \) vertices \( \{X_2, \ldots, X_{p-1}\} \) and \( (p - 2)d/2 \) edges on average, where each pair of nodes in a randomly generated DAG has the probability \( d/(p-2) \) of being adjacent (implying that the expected degree of each node is \( d \)). From each DAG \( G^{(r)} \), we obtain the DAG \( G^{(r)} \), with \( p \) vertices \( \{X_1, X_2, \ldots, X_{p-1}, X_p\} \) by randomly adding directed
Fig 2: The left subfigure compares the probability density function of the random variable \( W(\rho) \) (as in Theorem 6.2) with that of the standard Gaussian density (dashed line). The right subfigure compares the cumulative distribution function (CDF) of \(|W(\rho)|\) with the CDF of the absolute value of a standard Gaussian random variable (dashed line).

edges from \( X_1 \) to \( X_j \) with probability 0.2 for \( j = 2, \ldots, p \) and from \( X_j \) to \( X_p \) with probability 0.1 for \( j = 1, \ldots, p - 1 \). The edge weights are drawn independently from a uniform distribution on \([-1, -0.5] \cup [0.5, 1]\). Here we assume the absence of any pre-treatment covariates, i.e. we set \( t = 1 \).

TABLE 3

Simulation settings. Here, \( p \) denotes the number of potential mediators (plus two more to account for the treatment and the response), \( d \) denotes the average degree in the causal DAG on the potential mediators, and \( m \) denotes the number of randomly generated DAGs for a pair \((p, d)\).

| Setting | \( p \) | \( d \) | \( m \) |
|---------|--------|--------|--------|
| 1       | 252    | 3      | 20     |
| 2       | 502    | 3.5    | 10     |
| 3       | 1002   | 4      | 5      |

Let \( B_{G^{(r)}} \) denote the weight matrix of the weighted DAG \( G^{(r)} \), i.e. \((B_{G^{(r)}})_{ij} \neq 0 \) if and only if the edge \( X_i \rightarrow X_j \) is present in \( G^{(r)} \) and it then equals the corresponding edge weight. For \( r = 1, \ldots, m \), the weight matrix \( B_{G^{(r)}} \) and a random vector \( e^{(r)} = (e_1^{(r)}, \ldots, e_p^{(r)})^T \) define a distribution on \( X^{(r)} = (X_1^{(r)}, \ldots, X_p^{(r)})^T \) via the linear structural equation model

\[
X^{(r)} = B_{G^{(r)}}^T X^{(r)} + e^{(r)}.
\]

We choose \( e_1^{(r)}, \ldots, e_p^{(r)} \) to be zero-mean Gaussian random variables with variances independently drawn from a \( \text{Uniform}[0.5, 1] \) distribution. Finally, we standardize all the variables to have: \( \text{Var}(X_i^{(r)}) = 1 \), for all \( i = 1, \ldots, p \).

For each setting, we generate 200 random samples \( \{D_{n1}^{(r)}, \ldots, D_{n200}^{(r)}\} \) of size \( n \in \{500, 1000, 5000\} \) from the joint distribution of \( X^{(r)} \) for \( r = 1, \ldots, m \). For each \( r \in \{1, \ldots, m\} \), we compute estimates and the corresponding \( p \)-values for \( \eta_{ij}^{(r)} \) based on the data.
$\mathcal{D}_{nk}$ using Algorithm 3.1 when the graph used in line 3 is either: (i) an estimated CPDAG obtained by applying the ARGES algorithm \cite{nandy2018}, or (ii) the true CPDAG $\mathcal{C}^0(r)$, or (iii) the true DAG $\mathcal{G}^0(r)$, or (iv) the empty graph. Note that the last case (empty graph) corresponds to a naive method that assumes that the potential mediators are conditionally independent given the treatment variable.

7.2. Results. As a finite sample validation of the asymptotic results obtained in Section 6, we record (from each replication) whether the true parameter value $\eta_j^{(r)}$ lies within the 95% standard Gaussian confidence interval given by (6.3) with $\alpha = 0.05$. To present the results, we split \{$\eta_j^{(r)}: r \in \{1, \ldots, m\}, j \in \{2, \ldots, p-1\}$\} into three equally sized groups according to the quantiles of $|\max(\theta_{ij}^{(r)}, \text{aver}(\Theta_{jp}^{(r)}))|$’s distribution, and report the median empirical coverage probabilities in each group. Table 4 shows that these 95% asymptotic confidence intervals exhibit an extremely high coverage in the first group where most of $|\max(\theta_{ij}^{(r)}, \text{aver}(\Theta_{jp}^{(r)}))|$ equal zero, as well as in the second group where most of $|\max(\theta_{ij}^{(r)}, \text{aver}(\Theta_{jp}^{(r)}))|$ are very close to zero. This is due to the fact that the correct asymptotic distribution of $T_{np}^{(r)}$ (see Theorem 6.2 and relevant discussions in Section 6.3) in these cases is much more concentrated around zero than the distribution of a standard Gaussian random variable. The third group with reasonably high values of $|\max(\theta_{ij}^{(r)}, \text{aver}(\Theta_{jp}^{(r)}))|$ exhibits the correct coverage when the CPDAG is known, but we do see some minor loss of coverage (and/or little higher standard errors) when the CPDAG is estimated due to finite sample graph estimation errors.

Next, we investigate the effect of graph estimation error in identifying the set of true mediators: $S^{(r)} := \{X_j^{(r)}: \eta_j^{(r)} \neq 0, j = 2, \ldots, p-1\}$. Figure 3 shows the averaged (over 200 iterations) Precision-Recall curves for estimating the target set $\bigcup_{r=1}^{m} S^{(r)}$ based on (i) the ranking of the absolute values of estimates of $\bigcup_{r=1}^{m} \{\eta_1^{(r)}, \ldots, \eta_p^{(r)}\}$ and (ii) the ranking of the corresponding $p$-values (in the reverse order). As we would expect, the methods based on the true DAG performs the best. Although it is unrealistic to assume that the true graph is known, we include it in our results to gain insight into the loss due to estimating the true CPDAG instead of the true DAG. We note that the methods based on the estimated CPDAG and based on the true CPDAG perform equally well, and they outperform the naive method based on the empty graph. Finally, Figure 3 also demonstrates that we can achieve substantial performance gain by using $p$-values instead of the raw estimates. This further exemplifies the importance and benefit of our inferential tools developed in Section 6 for IDA-type estimators that enables one to obtain these $p$-values in the first place.

The harmonic mean of precision and recall is known as F-score, and it is a popular way of combining precision and recall into a single performance measure that ranges between 0 and 1. By adopting this notion of a performance measure, we aim to choose a set of top mediators that maximizes the F-score. We achieve this in practice through a heuristic p-value based thresholding approach; the results are presented in Table 5. Table 5 demonstrates that we can achieve a nearly optimal F-score (i.e. the best achievable F-score for our method on a given dataset) by a thresholding of $p$-values at a level of 0.01 for $n = 5000$, and at a level of 0.1 for $n \in \{500, 1000\}$. We acknowledge that this heuristic $p$-value thresholding technique does not possess any theoretical justification, but it seems to work surprisingly well for estimating the target set $\bigcup_{r=1}^{m} \mathcal{G}^{(r)}$ in our simulation settings. We also provide discussions on some alternative approaches (including a Benjamini-Hochberg false discovery rate control procedure and its modifications) in Section 9 and in Appendix D of the Supplement.
**Table 4**

Median empirical coverage probabilities (coverage) and average lengths (size) of the 95% confidence intervals when the CPDAG is known and when the CPDAG is estimated. For each of the simulation settings, the results are divided into three groups (L ← Low, M ← Medium and H ← High) of roughly equal sizes based on \( |\max(\theta^{(r)}_{tj}, \text{aver}(\theta^{(r)}_{jp}))| \)'s values. The numbers in the brackets denote the corresponding standard deviations of the coverages.

| \(p\) | \(n\) | Known CPDAG | Estimated CPDAG |
|------|------|------------|-----------------|
|      |      | Coverage   | Size            | Coverage   | Size            |
|      |      | (\(0.00\)) | 0.01            | (\(0.00\)) | 0.01            |
| 500  | 100  | 100        | 0.00            | 100        | 0.00            |
| 252  | 1000 | 100        | 0.01            | 100        | 0.01            |
| 500  | 100  | 100        | 0.00            | 100        | 0.00            |
| 502  | 1000 | 100        | 0.01            | 100        | 0.01            |
| 500  | 100  | 100        | 0.00            | 100        | 0.00            |
| 1002 | 1000 | 100        | 0.01            | 100        | 0.01            |
| 5000 | 100  | 100        | 0.00            | 100        | 0.00            |
| 500  | 100  | 99.0       | 1.48            | 99.0       | 1.48            |
| 252  | 1000 | 98.0       | 2.22            | 98.0       | 2.97            |
| 5000 | 100  | 96.0       | 2.22            | 96.0       | 2.97            |
| 500  | 100  | 99.5       | 0.74            | 99.5       | 0.74            |
| 252  | 1000 | 98.5       | 2.22            | 98.5       | 2.22            |
| 5000 | 100  | 96.5       | 2.22            | 96.5       | 2.97            |
| 500  | 100  | 98.5       | 2.22            | 98.5       | 2.22            |
| 252  | 1000 | 97.5       | 2.97            | 97.5       | 2.97            |
| 5000 | 100  | 96.0       | 2.22            | 96.0       | 2.22            |
| 500  | 100  | 95.0       | 1.48            | 94.0       | 2.97            |
| 252  | 1000 | 95.0       | 1.48            | 94.0       | 2.97            |
| 5000 | 100  | 95.0       | 1.48            | 94.0       | 2.97            |
| 500  | 100  | 95.5       | 1.48            | 94.5       | 2.22            |
| 252  | 1000 | 95.0       | 1.48            | 94.5       | 2.22            |
| 5000 | 100  | 95.0       | 1.48            | 94.5       | 2.22            |
| 500  | 100  | 95.0       | 1.48            | 94.5       | 2.22            |
| 1002 | 1000 | 95.0       | 1.48            | 94.5       | 2.22            |
| 5000 | 100  | 95.0       | 1.48            | 94.5       | 2.22            |

**8. Application.** We demonstrate the applicability of our MIDA estimator in real data using a data set collected on 104 yeast segregants created by crossing of two genetically diverse strains, BY and RM [Brem and Kruglyak, 2005]. The data set includes the growth yields of each segregant grown in the presence of different chemicals or small molecule drugs [Perlstein et al., 2007]. These segregants have different genotypes that contribute to rich phenotypic diversity. One key question is to understand how genetic variants contribute to the phenotypic variability. One possible path is through regulation of gene expression variations. Besides genotype data, 6189 yeast genes are profiled in rich media and in the absence of any chemical or drug using expression arrays [Brem and Kruglyak, 2005]. We use the same data preprocessing steps as Chen et al. [2009] to create a list of candidate gene expression features based on their potential regulatory effects, including transcription factors, signalling molecules, chromatin factors and RNA factors and genes involved in vacuolar transport, endosome, endosome transport and vesicle-mediated transport. We further filter out genes with standard deviation (s.d.) ≤ 0.2 in expression level, resulting in a total of 813 genes in our analysis.
We are interested in identifying the genes whose expression levels mediate the effect of genetic variants on yeast growth yield after being treated with hydrogen peroxide. In particular, the genetic variant M2_477206_486640 is highly associated with the yeast growth yield ($p$-value = 0.00032). Our goal is to identify the gene expressions that mediate the effect of this genetic variant. At a nominal $p$-value of 0.05, MIDA identified six genes that may mediate the effects of the genetic variant M2_477206_486640 on yeast growth (see Table 6). Due to relatively small sample sizes, these genes are not significant after we adjust for multiple comparisons. However, although we cannot claim any statistically significant result here, we demonstrated how MIDA can be used to prioritize future biological experiments by identifying a set of candidate genes. The candidate selection is performed by thresholding the $p$-values, as this turned out to be most effective method in our simulation study.

Interestingly, the estimated signs of the mediation effects in Table 6 agree with known biology. Among these genes, over-expression of DBP8 [Daugeron and Linder, 2001] leads to vegetative and decreased rate of growth. In contrast, lower expression of the GPA1 gene typ-
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Table 5

Averaged (over 200 iterations) recall, precision and F-score for estimating the target set $\bigcup_{r=1}^{p_{n}} S^{(r)}$ based on p-value thresholding, where we used estimated CPDAGs for computing the value of our IDA-based estimators and the corresponding p-values for thresholding. The numbers in the brackets denote the corresponding standard deviations.

| $p$ | $n$ | Target size | Estimated size | Recall (p) | Precision (p) | Achieved F-score (p) | Optimal F-score (p) |
|-----|-----|-------------|----------------|------------|---------------|----------------------|---------------------|
| 252 | 500 | 568.0 (18.1) | 0.61 (0.02) | 0.54 (0.02) | 0.57 (0.01) | 0.59 (0.01) |
|     | 1000 | 503 | 673.6 (19.3) | 0.74 (0.02) | 0.55 (0.01) | 0.63 (0.01) | 0.69 (0.01) |
|     | 5000 | | 560.7 (11.4) | 0.82 (0.01) | 0.73 (0.01) | 0.77 (0.01) | 0.79 (0.01) |
| 502 | 500 | 445.8 (17.2) | 0.38 (0.02) | 0.52 (0.02) | 0.44 (0.02) | 0.46 (0.01) |
|     | 1000 | 613 | 569.6 (17.8) | 0.54 (0.02) | 0.58 (0.02) | 0.56 (0.01) | 0.56 (0.01) |
|     | 5000 | | 505.8 (10.5) | 0.68 (0.01) | 0.83 (0.01) | 0.75 (0.01) | 0.75 (0.01) |
| 1002 | 500 | 390.7 (17.5) | 0.24 (0.01) | 0.48 (0.02) | 0.32 (0.01) | 0.38 (0.01) |
|     | 1000 | 788 | 502.6 (18.1) | 0.35 (0.01) | 0.55 (0.02) | 0.43 (0.01) | 0.45 (0.01) |
|     | 5000 | | 455.0 (14.2) | 0.5 (0.01) | 0.87 (0.02) | 0.63 (0.01) | 0.67 (0.01) |

Table 6

Analysis of yeast growth yield in the presence of hydrogen peroxide. The gene expression mediators for the genetic variant M2_477206_48664 that were identified by MIDA with a nominal p-value < 0.05. The gene names, their estimated mediation effects and the corresponding 95% confidence intervals are presented below.

| Gene ID | Gene name | Estimated effect | 95% confidence interval | p-value |
|---------|-----------|------------------|-------------------------|---------|
| YNR047W | YNR047W | -0.0532 (0.0233) | (-0.0988, -0.0077) | 0.022 |
| YHR136C | SPL2 | 0.0257 (0.0116) | (0.0029, 0.0485) | 0.027 |
| YHR184W | SSP1 | 0.0468 (0.0229) | (0.0019, 0.0916) | 0.041 |
| YAL035W | FUN12 | 0.0757 (0.0375) | (0.0022, 0.1491) | 0.043 |
| YHR005C | GPA1 | 0.0766 (0.0381) | (0.0020, 0.1512) | 0.044 |
| YHR169W | DBP8 | -0.1035 (0.0526) | (-0.2067, -0.0003) | 0.049 |

9. Discussion. In this paper, we have considered the problem of mediation analysis in the setting where we have high-dimensional and possibly interacting mediators. DAGs are used to characterize the possible interaction effects among the high dimensional mediators and to define the individual mediation effects based on linear structural equation models. We have developed an IDA-based procedure, MIDA, to estimate the individual mediation effects, which takes into account the uncertainty of the estimated DAGs. We have also derived the asymptotic distributions of the estimates of both interventional effects as well as individual mediation effects, under the assumption of sub-Gaussian errors for the LSEMs, which facilitates inference based on these estimators, and to the best of our knowledge, are the first such results available in the literature. We have illustrated the methods in simulation studies with promising performance, as well as using a real data set on yeast in order to identify the possible gene expression mediators of a genetic variant for yeast growth in the presence of drugs. The methods can also be applied to the problem of identifying the important gene expression or methylation mediators that mediate the effects of genetic variants identified through genome-wide association studies on disease phenotypes.

Another crucial contribution of this work lies in the results of Section 5 on uniform ALEs and non-asymptotic control of error terms for linear regression estimators based on varying subsets of high dimensional covariates that serve as the backbone of our results on the...
asymptotic distribution of the MIDA estimators. These results are applicable quite generally in several other problems, and should therefore be of independent interest.

**FDR control for MIDA.** Our simulations have shown that the confidence intervals based on MIDA provide correct coverage when the mediation effects are not too small. In high dimensional settings with thousands of possible mediators, large sample sizes are needed in order to accurately estimate the individual mediation effects. In order to estimate the set of true mediators \( \{X_j : \eta_j \neq 0\} \), as an alternative to our heuristic \( p \)-value based thresholding approach proposed in Section 7.2, one can also apply the Benjamini-Hochberg (BH) false discovery rate (FDR) control procedure at some desired level \( \alpha \) (e.g., \( \alpha = 0.1 \)). However, the theoretical guarantee of the BH procedure does \textit{not} apply in our case due to the fact that the true DAG is not identifiable. Instead, the BH procedure (asymptotically) guarantees to control FDR for estimating \( \{X_j : \theta_{tj} \text{aver}(\Theta_{jp}) \neq 0\} \), and only when the true CPDAG is known. Furthermore, Table 5 suggests that it might be unreasonable and too optimistic to enforce a high precision level such as 0.9 (equivalently, FDR control at level \( \alpha = 0.1 \)) in the challenging problem of estimating the set of true mediators in high-dimensional settings. For these reasons, we recommend the estimation of the target set by maximizing the F-score because of its adaptive capability of automatically adjusting to the best achievable precision level (or, least FDR level) for the problem at hand.

We also empirically observed (see Figure A in Appendix D of the Supplement) that the BH procedure becomes very \textit{conservative} for estimating \( \{X_j : \theta_{tj} \text{aver}(\Theta_{jp}) \neq 0\} \), mainly because the \( p \)-value corresponding to the test \( \theta_{tj} \text{aver}(\Theta_{jp}) = 0 \) has a non-uniform and left-skewed distribution when both \( \theta_{tj} \) and \( \text{aver}(\Theta_{jp}) \) are 0 (see also the last paragraph of Section 6.3). One way to mitigate this issue is to apply a heuristic \textit{screening procedure}. We explored this approach in our simulation studies to first obtain a potential set of mediators for which the total effect of the treatment on the mediator is non-zero, and then apply the BH procedure on this selected set. We provide further discussions on this approach in Appendix D of the Supplement. The simulation results presented therein show that this strategy can significantly improve the FDR controlling compared to a direct application of the BH procedure based on the \( p \)-values.

**Supplement: Appendices A–D.** In the supplement, we provide: (i) proofs of all theoretical results in the main paper (Appendix A); (ii) additional technical tools, including definitions and key supporting lemmas that are required in all the proofs (Appendix B); (iii) discussions on verifying the moment conditions required in the last part of Remark 5.2 (Appendix C); and (iv) additional numerical results regarding FDR controlling for MIDA (Appendix D).

**A. Proofs of All Results.**

**A.1. Proof of Proposition 2.1.** By Theorem 3.1 of Nandy et al. [2017], we have,

\[
\theta_{tp}^{(t,j)} = \theta_{tp} - \theta_{tj}\theta_{jp}.
\]

Hence, \( \eta_j = \theta_{tp} - \theta_{tp}^{(t,j)} = \theta_{tj}\theta_{jp} \).

**A.2. Proof of Lemma 3.1.** The linearity assumption implies that the total causal effect of \( X_i \) on \( X_k \) can be expressed as the coefficient of \( X_i \) in the linear regression of \( X_k \) on \( X_i \cup X_S \) [Maathuis et al., 2009; Nandy et al., 2017] for a set of covariates \( X_S \subseteq X \setminus \{X_i, X_k\} \) that satisfies Pearl’s back-door criterion (see Definition 3.3.1 of Pearl [2000]). Using this, we obtain

\[
\theta_{tj} = \beta_{tj\mid x_{(1,\ldots,t)}} \quad \text{and} \quad \theta_{jp} = \beta_{jp\mid \text{Pa}_0(x_j) \cup X_{(1,\ldots,t)}}.
\]
Recall that $G_0'$ denotes the DAG on the set of potential mediators. Then the result follows from the fact that $Pa_{G_0}(X_j) \cup \{X_1, \ldots, X_t\} = Pa_{G_0}(X_j) \cup \{X_1, \ldots, X_t\}$, followed by an application of Proposition 2.1.

A.3. Proof of Lemma 3.2. The conditions $(B_{G_0})_{ji} = 0$ for all $i \leq t$ imply that $X_{\{1,\ldots,t\}} - \mu_{\{1,\ldots,t\}} = (I - (B_{G_0})_{\{1,\ldots,t\}\{1,\ldots,t\})^{-1}\epsilon_{\{1,\ldots,t\}}$. Therefore, it follows from the independence of the error variables that

$$
E[\epsilon \mid X_{\{1,\ldots,t\}}] = (\epsilon_{\{1,\ldots,t\}}, 0, \ldots, 0)^T
$$

$$
= e_{\{1,\ldots,t\},p}^T (I - (B_{G_0})_{\{1,\ldots,t\}\{1,\ldots,t\}) (X_{\{1,\ldots,t\}} - \mu_{\{1,\ldots,t\}}),
$$

where $e_{\{1,\ldots,t\},p}^T$ denotes the first $t$ columns of a $p \times p$ identity matrix.

Let $A$ denote the $(p-t-1) \times p$ matrix such that $X' - \mu' = A(X - \mu)$, where $\mu' := E(X')$. Then, we have,

$$
E[(X' - \mu') \mid X_{\{1,\ldots,t\}}] = A E[(X - \mu) \mid X_{\{1,\ldots,t\}}]
$$

$$
= A(I - B_{G_0}^T)^{-1} E[\epsilon \mid X_{\{1,\ldots,t\}}]
$$

$$
= A(I - B_{G_0}^T)^{-1} e_{\{1,\ldots,t\},p}^T (I - (B_{G_0})_{\{1,\ldots,t\}\{1,\ldots,t\}) (X_{\{1,\ldots,t\}} - \mu_{\{1,\ldots,t\}}).
$$

This completes the proof of the linearity property of the conditional expectation $E[X' \mid X_{\{1,\ldots,t\}}]$.

Next, note that for each $j \in \{t + 1, \ldots, p - 1\}$,

$$
E[X_j \mid X_{\{1,\ldots,t\}}] = \mu_j + \sum_{k=1}^p (B_{G_0})_{kj} E[X_k \mid X_{\{1,\ldots,t\}}] + E[\epsilon_j \mid X_{\{1,\ldots,t\}}]
$$

$$
= \mu_j + \sum_{k=t+1}^{t} (B_{G_0})_{kj} X_k + \sum_{k=t+1}^{p-1} (B_{G_0})_{kj} E[X_k \mid X_{\{1,\ldots,t\}}].
$$

The last equality follows from the fact that $(B_{G_0})_{pj} = 0$ and $E[\epsilon_j \mid X_{\{1,\ldots,t\}}] = E[\epsilon_j] = 0$. This implies

$$
X_j - E[X_j \mid X_{\{1,\ldots,t\}}] = \sum_{k=t+1}^{p-1} (B_{G_0})_{kj} (X_k - E[X_k \mid X_{\{1,\ldots,t\}}]) + \epsilon_j,
$$

for all $j \in \{t + 1, \ldots, p - 1\}$. This completes the proof of $X^* = B_{G_0}^T X^* + \epsilon'$.

Finally, we show that the faithfulness of the distribution of $X^*$ to $G_0'$ follows from the faithfulness of the distribution of $X$ to $G_0$. Suppose $X^*_i$ and $X^*_k$ are conditionally independent given $X^*_S$ for some set $S \subseteq \{t + 1, \ldots, p - 1\} \setminus \{i, k\}$. In order to establish faithfulness of $X^*$ to $G_0'$, we need to show that $X_i$ and $X_k$ are d-separated by $X_S$ in $G_0'$, that is $X_S$ blocks every path between $X_i$ and $X_k$ in $G_0'$. A path in a graph is a sequence of distinct nodes such that all pairs of successive nodes in the sequence are adjacent in the graph, and $S$ blocks a path in $G_0'$ if the path contains a non-collider that is in $X_S$, or the path contains a collider that has no descendant in $X_S$, where $(X_r, X_s, X_t)$ a collider in a graph $G$ if $\{X_r, X_t\} \subseteq Pa_G(X_s)$.

Since there is no directed path from $X_i$ or $X_k$ to a node in $X_{\{1,\ldots,t\}}$, no node in $X_{\{1,\ldots,t\}}$ can be a collider on a path between $X_i$ and $X_k$. Further, since $(B_{G_0})_{pj} = 0$ for all $j$, $X_p$...
cannot be non-collider on any path in $G_0$. These imply $X_i$ and $X_k$ are d-separated by $X_S$ in $G'_0$ if and only if $X_i$ and $X_k$ are d-separated by $X_S \cup X_{\{1,\ldots,t\}}$ in $G_0$, since all paths between $X_i$ and $X_k$ in $G_0$ that are not present in $G'_0$ must go through $X_{\{1,\ldots,t\}}$ or $X_p$. Therefore, it is sufficient to show that $X_i$ and $X_k$ are d-separated by $X_S \cup X_{\{1,\ldots,t\}}$ in $G_0$. This is equivalent to show that the partial correlation between $X_i$ and $X_k$ given $X_S \cup X_{\{1,\ldots,t\}}$, denoted by $\rho_{ik|S\cup\{1,\ldots,t\}}$, is zero, as the distribution of $X$ is generated from a LSEM and faithful to $G_0$ (see Spirtes et al. [1998]; Nandy et al. [2018]).

Note that the fact that $X_i^\dagger$ and $X_k^\dagger$ are conditionally independent given $X_S^\dagger$ implies that the partial correlation between $X_i^\dagger$ and $X_k^\dagger$ given $X_S^\dagger$, denoted by $\rho_{ik|S}^\dagger$, is zero. This completes the proof, since Lemma 3.3 ensures that $\rho_{ik|S\cup\{1,\ldots,t\}}^2 = \rho_{ik|S}^\dagger$.

\[ \square \]

**A.4. Proof of Lemma 3.3.** Let $\Sigma^\dagger := \text{Cov}(X^\dagger)$. Then, note that the linearity of conditional expectation $E[X | X_1]$ (Lemma 3.2) implies

$$
\Sigma^\dagger = \Sigma_{(t+1,\ldots,p-1)(t+1,\ldots,p-1)} - \Sigma_{(t+1,\ldots,p-1),(1,\ldots,t)}\Sigma_{(1,\ldots,t)(1,\ldots,t)}^{-1}\Sigma_{(1,\ldots,t)(t+1,\ldots,p-1)}.
$$

Recall that if $\sigma^2_{i|S} := \Sigma_{ii} - \Sigma_{iS}(\Sigma_{SS})^{-1}\Sigma_{Si}$ is the variance of the residuals in the linear regression (based on $\Sigma^\dagger = \text{Cov}(X^\dagger)$) of $X_i^\dagger$ on $X_S^\dagger$ and $\sigma^2_{i|S\cup\{k\}}$ is the variance of the residuals in the linear regression of $X_i^\dagger$ on $X_{S\cup\{k\}}^\dagger$, then it holds that [Yule, 1907]

\[ \sigma^2_{i|S\cup\{k\}} = (1 - \rho^2_{ik|S})\sigma^2_{i|S}. \]

By applying the identity for expressing the Schur complement of a $(r-1) \times (r-1)$ principal submatrix of a $r \times r$ matrix as the ratio of determinants, we obtain

$$
\sigma^2_{i|S} = \frac{|\Sigma^\dagger_{(i,S)(i,S)}|}{|\Sigma_{SS}|} = \frac{|\Sigma_{(i,S)(i,S)} - \Sigma_{(i,S)(1,\ldots,t)}\Sigma_{(1,\ldots,t)(1,\ldots,t)}^{-1}\Sigma_{(1,\ldots,t)(i,S)}|}{|\Sigma_{SS} - \Sigma_{S(1,\ldots,t)}\Sigma_{(1,\ldots,t)(1,\ldots,t)}^{-1}\Sigma_{(1,\ldots,t)S}|}
= \frac{|\Sigma_{(i,S,1,\ldots,t)(i,S,1,\ldots,t)}| \cdot |\Sigma_{(1,\ldots,t)(1,\ldots,t)}|}{|\Sigma_{(1,\ldots,t)(1,\ldots,t)}| \cdot |\Sigma_{(S,1,\ldots,t)(S,1,\ldots,t)}|} = \sigma^2_{i|S\cup\{1,\ldots,t\}},
$$

where $\sigma^2_{i|S\cup\{1,\ldots,t\}}$ is the variance of the residuals in the linear regression (based on $\Sigma = \text{Cov}(X)$) of $X_i$ on $\{X_r : r \in S \cup \{1, \ldots, t\}\}$. Similarly, we have $\sigma^2_{i|S\cup\{k\}} = \sigma^2_{i|S\cup\{1,\ldots,t\}\cup\{k\}}$. Hence, from A.1, we have

$$
1 - \rho^2_{ik|S} = \frac{\sigma^2_{i|S\cup\{k\}}}{\sigma^2_{i|S}} = \frac{\sigma^2_{i|S\cup\{1,\ldots,t\}\cup\{k\}}}{\sigma^2_{i|S\cup\{1,\ldots,t\}}} = 1 - \rho^2_{ik|S\cup\{1,\ldots,t\}}.
$$

\[ \square \]

**A.5. Proof of Theorem 4.1.** We first state and prove a lemma that will be useful in the main proof. The proof is then presented in several parts.

**LEMMA A.1.** Let $X$ be generated from a LSEM characterized by $(G_0, \epsilon)$. Then Assumptions 4.1, 4.3 and 4.5 imply that for any $S \subseteq \{1, \ldots, p\}$ such that $|S| \leq q + t + 2$,

$$
||X_S - \mu_S||^*_{\psi_2} \leq C_4,
$$

where $C_4 > 0$ is an absolute constant depending on $C_1$, $C_2$ and $C_3$ given by Assumptions 4.1 and 4.5, and $|| \cdot ||^*_{\psi_2}$ denotes the vector sub-Gaussian norm given by Definition B.2.
PROOF. Fix \( S \subseteq \{1, \ldots, p\} \) such that \(|S| \leq q + t + 2\). Let \( A \) be the \(|S| \times p\) matrix such that \( X_S - \mu_S = A(X - \mu) \). Therefore, we have, \( X_S - \mu_S = A(I - B_{G_0}^T)^{-1}\epsilon \). Hence,

\[
\|X_S - \mu_S\|_{\psi_2}^* = \sup_{\|v\|_2 = 1} \|v^T A(I - B_{G_0}^T)^{-1}\epsilon\|_{\psi_2}^*
\]

\[
= \sup_{\|v\|_2 = 1} \|v^T A(I - B_{G_0}^T)^{-1}\|_2 \left\| \frac{v^T A(I - B_{G_0}^T)^{-1}\epsilon}{\|v^T A(I - B_{G_0}^T)^{-1}\|_2} \right\|_{\psi_2}
\]

\[
\leq \|A(I - B_{G_0}^T)^{-1}\|_2 \|\epsilon\|_{\psi_2}^*,
\]

where the last inequality follows from the definitions of spectral norm and \( \| \cdot \|_{\psi_2}^* \) norm and the fact that \( \sup f(x) \geq \sup f(x) \sup g(x) \).

Since \( \epsilon_1, \epsilon_2, \ldots, \epsilon_p \) are independent zero-mean sub-Gaussian random variables satisfying \( \max_{1 \leq i \leq p} \| \epsilon_i \|_{\psi_2} \leq C_1 \), it follows from Lemma 5.24 of Vershynin [2012] that \( \| \epsilon \|_{\psi_2} \leq C_0 C_1 \), for some absolute constant \( C_0 \). Furthermore, since \( (\Sigma_0)_S = A(I - B_{G_0}^T)^{-1}D(I - B_{G_0}^T)^{-T}A^T \) for \( D := \text{Cov}(\epsilon) \), it follows from the sub-multiplicity property of the spectral norm that

\[
\|A(I - B_{G_0}^T)^{-1}\|_2 \leq \| (\Sigma_0)_S^{1/2} \|_2 \| D^{-1/2} \|_2 \leq \sqrt{C_3} \| D^{-1/2} \|_2,
\]

where the last inequality follows from Assumption 4.5.

Thus it remains to show that \( \| D^{-1/2} \|_2 \) is bounded. To this end, note that

\[
\| D^{-1/2} \|_2 = \frac{1}{\sqrt{\min_{1 \leq i \leq p} \text{Var}(\epsilon_i)}}.
\]

Finally, from the interlacing property of eigenvalues of a Hermitian matrix \( A \) and the eigenvalues of the Schur complement of any principal submatrix of \( A \) (see, e.g., Corollary 2.3 of Zhang [2005]), it follows that

\[
\text{Var}(\epsilon_i) = (\Sigma_0)_i - (\Sigma_0)_i P_{\mathcal{G}_0(i)} (\Sigma_0)_i P_{\mathcal{G}_0(i)}^{-1} P_{\mathcal{G}_0(i)} (\Sigma_0)_i P_{\mathcal{G}_0(i)}^{-1} P_{\mathcal{G}_0(i)}
\]

\[
\geq \lambda_{\min} \left( (\Sigma_0)_i (P_{\mathcal{G}_0(i)}) (P_{\mathcal{G}_0(i)} (\Sigma_0)_i) P_{\mathcal{G}_0(i)}^{-1} P_{\mathcal{G}_0(i)}^{-1} P_{\mathcal{G}_0(i)} \right)
\]

\[
\geq C_2,
\]

where \( P_{\mathcal{G}_0(i)} = \{ r : X_r \in P_{\mathcal{G}_0}(X_i) \} \). The last inequality follows from Assumption 4.5, since from Assumption 4.3, we have \( |P_{\mathcal{G}_0}(i)| \leq q \).

Combining the bounds for \( \text{Var}(\epsilon_i) \), \( \| D^{-1/2} \|_2 \) and \( \| A(I - B_{G_0}^T)^{-1} \|_2 \) above and applying them in the original bound for \( \|X_S - \mu_S\|_{\psi_2}^* \) yields the desired result. This completes the proof of Lemma A.1.

Proof of the first part of Theorem 4.1. Let \( A_n := \{ \hat{C}'(\lambda_n) = C_0 \} \). Since \( P(A_n) \rightarrow 0 \) (by Assumption 4.4) and \( \text{aver}(\hat{\Theta}_{jp}(C')) = \text{aver}(\hat{\Theta}_{jp}(C_0')) \) on the set \( A_n \), it is sufficient to show that for any \( \delta > 0 \),

\[
P \left( \max_{t < j < p} \left| \text{aver}(\hat{\Theta}_{jp}(C_0')) - \text{aver}(\hat{\Theta}_{jp}) \right| > \delta, \ A_n \right) \rightarrow 0.
\]

For \( j \in \{ t + 1, \ldots, p - 1 \} \), we denote the distinct elements in the multi-set \( \{ P_{\mathcal{G}}(X_j) \cup \{X_{\{1, \ldots, t\}} : \mathcal{G} \in \text{MEC}(C_0') \} \} \) by \( \{ X_{S_{j,1}}, \ldots, X_{S_{j,m_j}} \} \). By Assumption 4.3, we have \( m_j \leq 2^j \)
for all $j \in \{t+1, \ldots, p-1\}$. Therefore,

$$
\mathbb{P}\left( \max_{t<j<p} \left| \text{aver}(\hat{\Theta}_{jp}(C_0')) - \text{aver}(\Theta_{jp}) \right| > \delta, A_n \right) 
\leq \mathbb{P}\left( \max_{t<j<p} \max_{1 \leq r \leq m_j} |\hat{\beta}_{jp}x_{s_{jr}} - \beta_{jp}x_{s_{jr}}| > \delta, A_n \right) 
\leq (p-2)2^q \max_{t<j<p} \max_{1 \leq r \leq m_j} \mathbb{P}\left( |\hat{\beta}_{jp}x_{s_{jr}} - \beta_{jp}x_{s_{jr}}| > \delta \right).
$$

We complete the proof by showing that for all $j \in \{t+1, \ldots, p-1\}$ and $r \in \{1, \ldots, m_j\}$,

$$
\mathbb{P}(|\hat{\beta}_{jp}x_{s_{jr}} - \beta_{jp}x_{s_{jr}}| > \delta) \leq 2 \exp(-C_7 n \delta^2)
$$

for some absolute constant $C_7 > 0$. Note that this implies

$$
(p-2)2^q \max_{t<j<p} \max_{1 \leq r \leq m_j} \mathbb{P}(|\hat{\beta}_{jp}x_{s_{jr}} - \beta_{jp}x_{s_{jr}}| > \delta) 
\leq O(\exp((\log(2) + \log(p))q - C_7 n \delta^2)) \rightarrow 0,
$$

since from Assumptions 4.2 and 4.3, we have $p = O(n^a)$ and $q = O(n^{1-b_1})$ for some $0 \leq a < \infty$ and $0 < b_1 \leq 1$.

Fix $j \in \{t+1, \ldots, p-1\}$ and $r \in \{1, \ldots, m_j\}$. Let $\Sigma$ and $\Sigma'$ denote the submatrices of $\Sigma_0 = \text{Cov}(X)$ that corresponds to $(X_j, X_{S_{jr}}, X_p)$ and $(X_{nj}, X_{S_{jr}})$ respectively. Then $\beta_{jp}x_{s_{jr}} = e_1^T \Sigma^{-1} \sigma_p$, where $e_1$ denote the first column of an identity matrix of appropriate order and $\sigma_p$ denote the last column of $\Sigma$. Similarly, we define the corresponding sample covariance matrices $\hat{\Sigma}$ and $\hat{\Sigma}'$ to obtain $\hat{\beta}_{jp}x_{s_{jr}} = e_1^T \hat{\Sigma}'^{-1} \hat{\sigma}_p$, where $\hat{\sigma}_p$ denote the last column of $\hat{\Sigma}$. We show below that

$$
|e_1^T \hat{\Sigma}'^{-1} \hat{\sigma}_p - e_1^T \Sigma'^{-1} \sigma_p| \leq \frac{1}{C_2} ||\hat{\Sigma} - \Sigma||_2 + C_3 ||\Sigma'^{-1} - \Sigma'^{-1}||_2
$$

(A.2)

where for a matrix $A$, $||A||_2$ denotes its spectral norm, and $C_3$ and $C_2$ are given by Assumption 4.5. To this end, we first apply the inequality

$$
||a^T a_2 - b_1 b_2||_2 \leq ||b_1||_2 ||a_2 - b_2||_2 + ||b_2||_2 ||a_1 - b_1||_2 + ||a_1 - b_1||_2 ||a_2 - b_2||_2,
$$

with $a_1 = \Sigma'^{-1} e_1$, $a_2 = \sigma_p$, $b_1 = \Sigma^{-1} e_1$ and $b_2 = \sigma_p$, where for a vector $a$, $||a||_2$ denote its $\ell_2$ norm. Next, note that $||\Sigma'^{-1} e_1||_2 \leq ||\Sigma'^{-1}||_2 \leq 1/C_2$, where the last inequality follows from Assumption 4.5 and Cauchy’s interlacing theorem for eigenvalues of positive definite matrices, since $|S_{jr}| \leq q + t + 2$. Similarly, we have $||\sigma_p||_2 \leq C_3$. This completes the proof of (A.2).

From Lemma A.1, we have $||(X_j, X_{S_{jr}}^T, X_p)^T||_{\psi_2} < C_4$ for some constant $C_4 > 0$. Therefore, for any $\delta \in (0, 1)$ and sufficiently large $n$, we have

$$
\mathbb{P}(||\hat{\Sigma} - \Sigma||_2 > \delta) \leq 2 \exp(-C_5 n \delta^2),
$$

(A.3)

for some absolute constant $C_5 > 0$ depending on $C_4$ (see Corollary 5.50 of Vershynin [2012]). Similarly, for any $\delta \in (0, 1)$ and sufficiently large $n$, we have

$$
\mathbb{P}(||\hat{\Sigma}' - \Sigma'||_2 > \delta) \leq 2 \exp(-C_5 n \delta^2),
$$

(A.4)

We show below that a similar result holds for $||\hat{\Sigma}'^{-1} - \Sigma'^{-1}||_2$. To this end, we consider $\delta \leq C_2/2$ and $||\hat{\Sigma} - \Sigma||_2 \leq \delta$. Using the sub-multiplicility property of the spectral norm, we obtain

$$
||(\hat{\Sigma}' - \Sigma') \Sigma'^{-1}||_2 \leq ||\hat{\Sigma}' - \Sigma'||_2 ||\Sigma'^{-1}||_2 \leq \frac{\delta}{C_2} \leq 1/2 < 1.
$$
This implies $(\hat{\Sigma}' - \Sigma')\Sigma'^{-1} + I$ is invertible and the following inequality holds (see, for example, Section 5.8 of Horn and Johnson [1990]):

\begin{equation}
(A.5) \quad ||((\hat{\Sigma}' - \Sigma')\Sigma'^{-1} + I)^{-1} - I||_2 \leq \frac{||((\hat{\Sigma}' - \Sigma')\Sigma'^{-1}||_2}{1 - ||((\hat{\Sigma}' - \Sigma')\Sigma'^{-1}||_2} \leq 2 \frac{||((\hat{\Sigma}' - \Sigma')\Sigma'^{-1}||_2}{1 - \delta},
\end{equation}

where the second inequality follows from $||((\hat{\Sigma}' - \Sigma')\Sigma'^{-1}||_2 \leq 1/2$ and the third inequality follows from the sub-multiplicity property of the spectral norm, the assumption that $||\hat{\Sigma}' - \Sigma'||_2 \leq \delta$ and Assumption 4.5.

Therefore, $||\hat{\Sigma}' - \Sigma'||_2 \leq \delta < C_2/2$ implies

\begin{equation}
(A.6) \quad ||\hat{\Sigma}'^{-1} - \Sigma'^{-1}||_2 \leq ||\Sigma'^{-1} \cdot (((\hat{\Sigma}' - \Sigma')\Sigma'^{-1} + I)^{-1} - I)||_2 \leq ||\Sigma'^{-1}||_2 \frac{2\delta}{C_2} \leq \frac{2\delta}{C_2},
\end{equation}

where the second inequality follows from the sub-multiplicity property of the spectral norm and (A.5), and the third inequality follows from Assumption 4.5. By combining (A.4) and (A.6), we have, for any $\delta \in (0, C_2/2)$,

\begin{equation}
(A.7) \quad P(||\hat{\Sigma}'_{n-1} - \Sigma'_{n-1}||_2 > \delta) \leq 2 \exp(-C_5 n \delta^2),
\end{equation}

where $C_5 > 0$ is an absolute constant depending on $C_2$ and $C_5$. Finally, by combining, (A.2), (A.3) and (A.4), we obtain

\begin{equation}
(A.8) \quad P \left( |\hat{\beta}_{jp|X_{s,jr}} - \beta_{jp|X_{s,jr}}| > \delta \right) \leq 2 \exp(-C_7 n \delta^2),
\end{equation}

for some absolute constant $C_7 > 0$ depending on $C_3$, $C_2$ and $C_4$. This completes the proof of the first part of Theorem 4.1.

**Proof of the second part of Theorem 4.1.** First we recall that $\hat{\eta}_j(\lambda_n) = \hat{\beta}_{ij|x_{(1,\ldots,i)}} \times \text{aver}(\hat{\Theta}_{jp}(\lambda_n))$, and $\theta_{ij} = \beta_{ij|x_{(1,\ldots,i)}}$. Therefore, we have

\begin{equation}
(A.9) \quad |\hat{\eta}_j(\lambda_n) - \theta_{ij} \cdot \text{aver}(\Theta_{jp})| \leq |\theta_{ij}| \cdot |\text{aver}(\hat{\Theta}_{jp}(\lambda_n)) - \text{aver}(\Theta_{jp})| + |\text{aver}(\Theta_{jp})| \cdot |\hat{\beta}_{ij|x_{(1,\ldots,i)}} - \beta_{ij|x_{(1,\ldots,i)}}|.
\end{equation}

From the first part of Theorem 4.1, we have

\begin{equation}
(A.10) \quad \max_{t < j < p} \left| \text{aver}(\hat{\Theta}_{jp}(\lambda_n)) - \text{aver}(\Theta_{jp}) \right| \xrightarrow{\mathbb{P}} 0.
\end{equation}

Further, by similar argument as given in the proof of the second part of Theorem 4.1, we can show that

\begin{equation}
(A.11) \quad P \left( \max_{t < j < p} |\hat{\beta}_{ij|x_{(1,\ldots,i)}} - \beta_{ij|x_{(1,\ldots,i)}}| > \delta \right) \leq 2(p - 2) \exp(-C_7 n \delta^2) \rightarrow 0,
\end{equation}

where $C_7$ is as in (A.8).

Finally, note that for any $i, k \in \{t + 1, \ldots, p\}$ and $S \subseteq \{1, \ldots, p\} \ \backslash \ \{i, k\}$ such that $|S| \leq q + t + 2$, we have

\begin{equation}
(A.12) \quad |\beta_{ik|x_S}| = |e_i^T \Sigma'^{-1}\sigma_k| \leq ||\Sigma'^{-1}e_i||_2||\sigma_k||_2 \leq \frac{C_3}{C_2},
\end{equation}

where $\Sigma$ and $\Sigma'$ denote the submatrices of $\Sigma_0 = \text{Cov}(X)$ corresponding to $(X_i, X_S, X_k)$ and $(X_i, X_S)$ respectively, and $\sigma_k$ is the last column of $\Sigma$. Note that the first inequality in (A.12)
is Cauchy-Schwarz and the second inequality in (A.12) follows from Assumption 4.5 and Cauchy’s interlacing theorem for eigenvalues of positive definite matrices (we used similar arguments in the proof of the second part of Theorem 4.1).

Since (A.12) implies that $|\theta_j|$ and $|\text{aver}(\Theta_{i,j,p})|$ are bounded above by $C_3/C_2$ for all $j \in \{t+1, \ldots, p\}$, the second part of Theorem 4.1 now follows from (A.9), (A.10) and (A.11). This completes the proof of Theorem 4.1.  

\section*{A.6. Proof of Theorem 5.1.} We first state below two supporting lemmas that serve as essential ingredients in our proof of Theorem 5.1 and may also be of independent interest. Their proofs are given in Appendices A.7 and A.8.

Recall the notations $\tilde{\Sigma}_S, \tilde{\Gamma}_S, \tilde{\Sigma}_{S,Y}, \tilde{\Gamma}_{S,Y}$ from Section 5 and further define:

\begin{align*}
\tilde{\Sigma}_S &:= \frac{1}{n} \sum_{i=1}^{n} (X_{S,i} - \mu_S)(X_{S,i} - \mu_S)^T \equiv \tilde{\Sigma} + \tilde{\Gamma}_S, \quad \text{and} \\
\tilde{\Sigma}_{S,Y} &:= \frac{1}{n} \sum_{i=1}^{n} (Y_i - \mu_Y)(X_{S,i} - \mu_S) \equiv \tilde{\Sigma}_{S,Y} + \tilde{\Gamma}_{S,Y}.
\end{align*}

\begin{lemma}
Suppose Assumption 5.1(i) holds for a given $S \subseteq \Omega, \mathcal{J}$ with $|S| := L_n \equiv L_{n,S}$ and $\sup_{S \in \mathcal{S}}|S| \leq q_n \equiv q_{n,S} \leq \min(n,p_n)$, and let $r_n := (q_n + \log L_n)$. Then, for any $c > 0$, the following bounds hold:

\begin{align}
\mathbb{P} \left\{ \sup_{S \in \mathcal{S}} \left\| \tilde{\Sigma}_S - \Sigma_S \right\|_2 > (c + 1)K_S \left( \sqrt{\frac{r_n}{n}} + \frac{r_n}{n} \right) \right\} \leq 2 \exp \left( -cr_n \right), \tag{A.13} \\
\mathbb{P} \left\{ \sup_{S \in \mathcal{S}} \left\| \tilde{\Gamma}_S \right\|_2 > 16(c + 1)K_S \left( \sqrt{\frac{r_n}{n}} + \frac{r_n}{n} \right) + \lambda_{\sup,S} \right\} \leq 2 \exp \left( -cr_n \right), \tag{A.14} \\
\mathbb{P} \left\{ \sup_{S \in \mathcal{S}} \left\| \tilde{\Sigma}_{S,Y} - \Sigma_{S,Y} \right\|_2 > (c + 1)K_S \left( \sqrt{\frac{r_n}{n}} + \frac{r_n}{n} \right) \right\} \leq 4 \exp \left( -cr_n \right), \tag{A.15}
\end{align}

Further, let $\tilde{r}_n := (r_n + 1)$, and suppose Assumption 5.1(ii) also holds. Then, for any $c > 0$, the following bounds hold:

\begin{align}
\mathbb{P} \left\{ \sup_{S \in \mathcal{S}} \left\| \tilde{\Sigma}_{S,Y} - \Sigma_{S,Y} \right\|_2 > (c + 1)K_S \left( \sqrt{\frac{r_n}{n}} + \frac{r_n}{n} \right) \right\} \leq 2 \exp \left( -cr_n \right), \tag{A.16} \\
\mathbb{P} \left\{ \sup_{S \in \mathcal{S}} \left\| \tilde{\Gamma}_{S,Y} \right\|_2 > 16(c + 1)K_S \left( \sqrt{\frac{r_n}{n}} + \frac{r_n}{n} \right) + \lambda_{\sup,S} \right\} \leq 2 \exp \left( -cr_n \right).
\end{align}

Lastly, the constants $\lambda_{\sup,S}$ and $\tilde{\lambda}_{\sup,S}$ may be chosen such that $\lambda_{\sup,S} \leq 2\sigma_{X,S}^2$ and $\tilde{\lambda}_{\sup,S} \leq 2\sigma_{Z,S}^2 \equiv 2(\sigma_Y + \sigma_{X,S})^2$. Moreover, $\sup_{S \in \mathcal{S}} \left\| \beta_S \right\|_2 \leq \text{Var}(Y)^{\frac{1}{2}} \lambda_{\inf,S}^{-1} \leq 2\sigma_Y^2 \lambda_{\inf,S}^{-1}$.

\begin{lemma}
Let $S$ and $r_n$ be as in Lemma A.2, and suppose Assumption 5.1(i) holds. Let $c^* > 0$ be any constant satisfying:

\begin{align}
(c^* + 1)K_S \left( \sqrt{\frac{r_n}{n}} + \frac{33r_n}{n} \right) + \frac{\lambda_{\sup,S}}{n} \leq \frac{1}{2} \lambda_{\inf,S}.
\end{align}

\end{lemma}
and let $K^*_S := 2\lambda_{\inf,S}^{-2}K_S$. Then, for any $c^* > 0$ as in (A.15) and for any $c > 0$, and defining $a_n(c, c^*, r_n) := \exp(-cr_n) + \exp(-c^*r_n)$, we have

\[
P \left\{ \sup_{S \in S} \left\| \hat{\Sigma}_S^{-1} - \Sigma_S^{-1} \right\|_2 > (c + 1)K^*_S \left( \frac{\sqrt{r_n/n}}{n} + \frac{33r_n}{n} \right) + 2\lambda_{\sup,S}^2 \right\}
\leq 4a_n(c, c^*, r_n) \equiv 4\exp(-cr_n) + 4\exp(-c^*r_n).
\]

The proof of Theorem 5.1 essentially follows from carefully combining all the results established in Lemmas A.2 and A.3. To this end, first note that under Assumption 5.1 and (A.16) (A.17) where (A.20) $P \equiv 4\exp(-cr_n) + 4\exp(-c^*r_n)$.

Next, noting that $\left\| \hat{\Sigma}_S - \Sigma_S \right\|_2 > \epsilon_n,1(c, r_n)$ for any $c > 0$ and any $c^* > 0$ satisfying condition (A.15),

\[
P \left\{ \sup_{S \in S} \left\| \hat{\Sigma}_S - \Sigma_S \right\|_2 > \epsilon_n,1(c, r_n) \right\} \leq 2\exp(-cr_n), \sup_{S \in S} \| \beta_S \|_2 \leq C_S,
\]

\[
P \left\{ \sup_{S \in S} \left\| \hat{\Sigma}_S, Y - \Sigma_S, Y \right\|_2 > \epsilon_n,2(c, r_n) \right\} \leq 2\exp(-c\tau_n) \leq 2\exp(-cr_n),
\]

\[
P \left\{ \sup_{S \in S} \left\| \hat{\Sigma}_S^{-1} - \Sigma_S^{-1} \right\|_2 > \delta_n(c, r_n) \right\} \leq 4\exp(-cr_n) + 4\exp(-c^*r_n),
\]

\[
P \left\{ \sup_{S \in S} \left\| \hat{\Gamma}_S, Y \right\|_2 > \eta_n,2(c, r_n) \right\} \leq 2\exp(-c\tau_n) \leq 2\exp(-cr_n), \text{ and}
\]

\[
P \left\{ \sup_{S \in S} \left\| \hat{\Gamma}_S \right\|_2 > \eta_n,1(c, r_n) \right\} \leq 2\exp(-cr_n), \sup_{S \in S} \left\| \Sigma_S^{-1} \right\|_2 \leq \lambda^{-1}_{\inf,S},
\]

where $\{ \epsilon_n, j(c, r_n), \eta_n, j(c, r_n) \}_{j=1}^2$ and $C_S$ are all as defined in Theorem 5.1. Note that for (A.19) and (A.20), we also used $\sqrt{r_n} \leq r_n$, and for (A.17) and (A.19), we used $r_n \leq \tau_n$.

Next, noting that $(\Sigma_S, Y - \Sigma_S, \beta_S) = 0$ for any $S \in S$, due to (5.1), we have:

\[
\sup_{S \in S} \left\| \Phi_{n,S} \right\|_2 \equiv \sup_{S \in S} \left\| (\hat{\Sigma}_S^{-1} - \Sigma_S^{-1}) \left\{ (\hat{\Sigma}_S, Y - \Sigma_S, Y) - (\hat{\Sigma}_S - \Sigma_S) \beta_S \right\} \right\|_2 
\leq \sup_{S \in S} \left\| \hat{\Sigma}_S^{-1} - \Sigma_S^{-1} \right\|_2 \sup_{S \in S} \left\| \Sigma_S, Y - \Sigma_S \right\|_2 
+ \sup_{S \in S} \left\| \hat{\Sigma}_S^{-1} - \Sigma_S^{-1} \right\|_2 \sup_{S \in S} \left\| \Sigma_S - \Sigma_S \right\|_2 \sup_{S \in S} \left\| \beta_S \right\|_2,
\]

where the inequality in (A.21) follows from multiple applications of Lemma B.4 (i). Using (A.16), (A.17) and (A.18) in (A.21), along with the union bound, we have: for any $c > 0$,

\[
P \left\{ \sup_{S \in S} \left\| \Phi_{n,S} \right\|_2 > \delta_n(c, r_n) \left\{ \epsilon_n,1(c, r_n)C_S + \epsilon_n,2(c, r_n) \right\} \right\}
\leq 8\exp(-cr_n) + 4\exp(-c^*r_n).
\]

This establishes the first of the two claims in result (i) of Theorem 5.1. □

Next, recall $R_{n,S} \equiv \hat{\Sigma}_S^{-1} \left( \hat{\Gamma}_S \beta_S - \hat{\Gamma}_S, Y \right)$, and hence using Lemma B.4 (i),

\[
\sup_{S \in S} \left\| R_{n,S} \right\|_2 \leq \sup_{S \in S} \left\| \hat{\Sigma}_S^{-1} \right\|_2 \left\{ \sup_{S \in S} \left\| \hat{\Gamma}_S \right\|_2 \sup_{S \in S} \left\| \beta_S \right\|_2 + \sup_{S \in S} \left\| \hat{\Gamma}_S, Y \right\|_2 \right\}.
\]
Hence, we have: for any $c > 0$, or equivalently, for any $\epsilon > 0$, the details are thus skipped here for brevity. The proof of Theorem 5.1 is now complete.

Finally, recall that $\Psi_S(z) = \Sigma_S^{-1} \psi_S(z)$ and $n^{-1} \sum_{i=1}^{n} \psi_S(z_i) \equiv \Sigma_{S,Y} - \Sigma_S \beta_S$. Further $(\Sigma_{S,Y} - \Sigma_S \beta_S) = 0$ for $S \in S$, due to (5.1). Hence, using Lemma B.4 (i), we have:

\[
\sup_{S \in S} \left\| \frac{1}{n} \sum_{i=1}^{n} \Psi_S(z_i) \right\|_2 = \sup_{S \in S} \left\| \Sigma_S^{-1} \{ (\Sigma_{S,Y} - \Sigma_S) \} \right\|_2 \\
\leq \sup_{S \in S} \left\| \Sigma_S^{-1} \right\|_2 \left( \sup_{S \in S} \left\| \Sigma_{S,Y} - \Sigma_S \right\|_2 + \sup_{S \in S} \left\| \Sigma_S - \Sigma_S \right\|_2 \right).
\]

Hence, we have: for any $c > 0$,

\[
\mathbb{P} \left[ \sup_{S \in S} \left\| \frac{1}{n} \sum_{i=1}^{n} \Psi_S(z_i) \right\|_2 > \lambda_{\text{inf},S}^{-1} \{ \epsilon_{n,1}(c,r_n) C_S + \epsilon_{n,2}(c,r_n) \} \right] \\
\leq 4 \exp(-c r_n) \quad \forall \; c > 0,
\]

where the final probability bound follows from applying (A.16), (A.17) and (A.20), along with the union bound, to the preceding bound. This establishes the result (ii) of Theorem 5.1.

Finally, all the ‘\(\lesssim\)’ type bounds claimed in results (i) and (ii) are quite straightforward and follow trivially from the definitions of $\{ \epsilon_{n,j}(c,r_n) \}_{j=1}^{2}$, $\{ \eta_{n,j}(c,r_n) \}_{j=1}^{2}$, $\delta_n(c,r_n)$ and $C_S$. The details are thus skipped here for brevity. The proof of Theorem 5.1 is now complete.

A.7. Proof of Lemma A.2. Applying Lemma B.6, under Assumption 5.1 (i), to the random vectors $\{ X_{S,i} - \mu_S \}_{i=1}^{n}$ for any $S \in S$, and recalling the definition of the constant $K_S > 0$ in (5.4) along with the fact that $s \leq q_n \; \forall \; S \in S$, it follows that for any $\epsilon \geq 0$ and for each $S \in S$,

\[
\mathbb{P} \left\{ \left\| \Sigma_S - \Sigma_S \right\|_2 > K_S \left( \sqrt{\frac{q_n + \epsilon}{n}} + \frac{q_n + \epsilon}{n} \right) \right\} \leq 2 \exp(-\epsilon),
\]

or equivalently, for any $\epsilon \geq 0$ and $S \in S$,

\[
\mathbb{P} \left\{ \left\| \Sigma_S - \Sigma_S \right\|_2 > K_S \left( \sqrt{\epsilon} + \epsilon \right) \right\} \leq 2 \exp(-\epsilon + q_n).
\]

Consequently, using (A.23) along with the union bound, we then have:

\[
\mathbb{P} \left\{ \sup_{S \in S} \left\| \Sigma_S - \Sigma_S \right\|_2 > K_S \left( \sqrt{\epsilon} + \epsilon \right) \right\} \\
\leq \sum_{S \in S} \mathbb{P} \left\{ \left\| \Sigma_S - \Sigma_S \right\|_2 > K_S \left( \sqrt{\epsilon} + \epsilon \right) \right\} \\
\leq 2 L_n \exp(-\epsilon + q_n) \equiv 2 \exp(-\epsilon + q_n + \log L_n) \quad \forall \; \epsilon \geq 0.
\]
Substituting $\epsilon$ in (A.24) above as: $\epsilon = (c + 1)(q_n + \log L_n)/n \equiv (c + 1)r_n/n$ for any $c \geq 0$, and noting that $\sqrt{c + 1} \leq (c + 1)$, we then have:\[\forall c \geq 0,\]

(A.25) $\mathbb{P}\left\{ \sup_{S \in \mathcal{S}} \left\| \tilde{\Sigma}_S - \Sigma_S \right\|_2 > (c + 1)K_S \left( \sqrt{\frac{r_n}{n}} + \frac{r_n}{n} \right) \right\} \leq 2 \exp(-cr_n).$

This therefore establishes the first claim (i) in (A.13).

Next, using Lemma B.3, along with Lemma B.2 (i) and the definition of $\| \cdot \|_{\psi_2}^\ast$ in B.2, it follows, under Assumption 5.1 (i), that for any $S \in \mathcal{S}$,

\[\|v^T (X_S - \mu_S)\|_{\psi_2} \leq (4\sigma_{X,S}/\sqrt{n}) \|v\|_2 \quad \text{for any } v \in \mathbb{R}^s, \quad \text{and thus},\]

\[\sup_{S \in \mathcal{S}} \|X_S - \mu_S\|_{\psi_2}^\ast \leq (4\sigma_{X,S}/\sqrt{n}).\]

Further, $\tilde{\Sigma}_{n,S} := \mathbb{E}\{(X_S - \mu_S)(X_S - \mu_S)^T\} \equiv \text{Cov}(X_S - \mu_S) = n^{-1}\Sigma_S$, so that $\|\tilde{\Sigma}_{n,S}\|_2 \equiv n^{-1}\lambda_{\text{max}}(\Sigma_S) \leq n^{-1}\lambda_{\text{sup},S}$. Hence, using Lemma B.6 again, this time applied to (a single observation of) $X_S - \mu_S$ for any $S \in \mathcal{S}$, we have: for any $c \geq 0$ and any $S \in \mathcal{S}$,

(A.26) $\mathbb{P}\left\{ \left\| \tilde{\Gamma}_S \right\|_2 > \frac{\lambda_{\text{sup},S}}{n} + \frac{16}{n}K_S \left( \sqrt{q_n + \epsilon} + q_n + \epsilon \right) \right\} \leq 2 \exp(-\epsilon),$

or equivalently, for any $\epsilon \geq 0$ and $S \in \mathcal{S}$,

Consequently, using (A.26) along with the union bound, similar to the arguments used earlier for obtaining (A.24), we have: for any $c \geq 0$,

(A.27) $\mathbb{P}\left\{ \sup_{S \in \mathcal{S}} \left\| \tilde{\Gamma}_S \right\|_2 > \frac{\lambda_{\text{sup},S}}{n} + \frac{16}{n}K_S \left( \sqrt{\epsilon} + \epsilon \right) \right\} \leq 2 \exp(-\epsilon + q_n + \log L_n).$

Substituting $\epsilon$ in (A.27) above as: $\epsilon = (c + 1)(q_n + \log L_n) \equiv (c + 1)r_n$ for any $c \geq 0$, and noting that $\sqrt{c + 1} \leq (c + 1)$, we then have:\[\forall c \geq 0,\]

(A.28) $\mathbb{P}\left\{ \sup_{S \in \mathcal{S}} \left\| \tilde{\Gamma}_S \right\|_2 > 16(c + 1)K_S \left( \sqrt{\frac{r_n}{n}} + \frac{r_n}{n} \right) + \frac{\lambda_{\text{sup},S}}{n} \right\} \leq 2 \exp(-cr_n).$

This establishes the second claim (ii) in (A.13).

Finally, the third claim in (A.13) follows from a simple application of the triangle inequality, along with combination (via the union bound) of the bounds in (A.25) and (A.28) with a slight adjustment applied to (A.28). Specifically, since $\tilde{\Sigma}_S \equiv \tilde{\Sigma}_S - \tilde{\Gamma}_S \forall S \in \mathcal{S}$, we have:

\[\sup_{S \in \mathcal{S}} \left\| \tilde{\Sigma}_S - \Sigma_S \right\|_2 \equiv \sup_{S \in \mathcal{S}} \left\| (\tilde{\Sigma}_S - \Sigma_S) + \tilde{\Gamma}_S \right\|_2 \leq \sup_{S \in \mathcal{S}} \left\| \Sigma_S - \Sigma_S \right\|_2 + \sup_{S \in \mathcal{S}} \left\| \tilde{\Gamma}_S \right\|_2 .\]

Hence, combining (A.25) and (A.28) through the union bound, and simplifying the resulting bound further by noting that $\sqrt{r_n/n} \leq r_n/n$, we then have:

(A.29) $\mathbb{P}\left\{ \sup_{S \in \mathcal{S}} \left\| \tilde{\Sigma}_S - \Sigma_S \right\|_2 > (c + 1)K_S \left( \sqrt{\frac{r_n}{n}} + \frac{33r_n}{n} \right) + \frac{\lambda_{\text{sup},S}}{n} \right\} \leq 4 \exp(-cr_n) \quad \text{for any } c \geq 0.$
This now establishes the third and final claim (iii) in (A.13).

To establish the claims (i) and (ii) in (A.14), we first recall the definitions of $Z_S, \nu_S$ and $\Xi_S$ from Assumption 5.1 (ii) and further, with $\{Z_{S,i}\}_{i=1}^n := \{(Y_i, X_{S,i})\}_{i=1}^n$, we define:

\[
\Xi_S := \frac{1}{n} \sum_{i=1}^n (Z_{S,i} - \nu_S)(Z_{S,i} - \nu_S)^T, \quad Z_S := \frac{1}{n} \sum_{i=1}^n Z_{S,i}
\]

and

\[
\tilde{Y}_S := (Z_S - \nu_S)(Z_S - \nu_S)^T.
\]

Then, note that the vectors $(\Sigma_{S,Y} - \Sigma_{S,Y})$ and $\tilde{Y}_{S,Y}$ are simply $s \times 1$ sub-matrices of the matrices $\Xi_S$ and $\tilde{Y}_S$, respectively. Hence, using Lemma B.4 (iii), we deterministically have: for any $S \in \mathcal{S}$,

\[
(A.30) \quad \left\|\Sigma_{S,Y} - \Sigma_{S,Y}\right\|_2 \leq \left\|\Xi_S - \Xi_S\right\|_2 \quad \text{and} \quad \left\|\tilde{Y}_{S,Y}\right\|_2 \leq \left\|\tilde{Y}_S\right\|_2.
\]

Next, under Assumption 5.1 (i), note that for any $u \equiv (a, v) \in \mathbb{R}^{s+1}$ with $a \in \mathbb{R}, v \in \mathbb{R}^s$, and for any $S \in \mathcal{S}$, we have: $\left\|u^T(Z_S - \nu_S)\right\|_{\psi_2} \equiv \left\|a\tilde{Y} + v^T\tilde{X}_S\right\|_{\psi_2} \leq \left\|a\right\|_{\psi_2} + \left\|v\right\|_{\psi_2} \leq \left\|u\right\|_2 (\sigma_Y + \sigma_X)$, where the steps follow through repeated use of Lemma B.1 (i), along with use of Lemma B.2 (i), Assumption 5.1 (i) and the definition of $\left\|\cdot\right\|_{\psi_2}$ in B.2. Using Definition B.2 again, we therefore have: $\sup_{S \in \mathcal{S}} \left\|Z_S - \nu_S\right\|_{\psi_2}^* \leq \sigma_{Z,S} \equiv (\sigma_Y + \sigma_X)$. Hence, similar to (A.23), applying Lemma B.6 to the random vectors $\{Z_{S,i} - \nu_S\}_{i=1}^n$ for any $S \in \mathcal{S}$, and recalling the definition of the constant $\tilde{K}_S > 0$ in Assumption 5.1 (ii) along with the fact that $\dim(Z_S) \leq q_n := q_n + 1 \forall S \in \mathcal{S}$, it follows that for any $\epsilon \geq 0$,

\[
P\left\{\left\|\Xi_S - \Xi_S\right\|_2 > \tilde{K}_S (\sqrt{\epsilon} + \epsilon)\right\} \leq 2 \exp(-n\epsilon + q_n) \quad \forall S \in \mathcal{S},
\]

and therefore, for any $c \geq 0$,

\[
P\left\{\sup_{S \in \mathcal{S}} \left\|\Xi_S - \Xi_S\right\|_2 > \tilde{K}_S (\sqrt{\epsilon} + \epsilon)\right\} \leq 2 \exp(-n\epsilon + q_n + \log L_n),
\]

where the last bound follows from using the union bound, similar to (A.24). Consequently, for any $\epsilon \geq 0$,

\[
P\left\{\sup_{S \in \mathcal{S}} \left\|\Sigma_{S,Y} - \Sigma_{S,Y}\right\|_2 > \tilde{K}_S (\sqrt{\epsilon} + \epsilon)\right\} \leq 2 \exp(-n\epsilon + q_n + \log L_n),
\]

and hence, for any $c \geq 0$,

\[
P\left\{\sup_{S \in \mathcal{S}} \left\|\Sigma_{S,Y} - \Sigma_{S,Y}\right\|_2 > (c+1)\tilde{K}_S \left(\sqrt{\frac{r_n}{n}} + \frac{\tilde{r}_n}{n}\right)\right\} \leq 2 \exp(-c\tilde{r}_n),
\]

where the first bound follows from using (A.30) and (A.31), and the second bound follows from substituting $\epsilon$ as: $\epsilon = (c+1)(\tilde{q}_n + \log L_n)/n \equiv (c+1)\tilde{r}_n/n$ for any $c \geq 0$, and noting that $\sqrt{c+1} \leq (c+1)$. This therefore establishes the first claim (i) in (A.14).

Next, similar to arguments used to prove claim (ii) in (A.13), it follows using Lemma B.3, Lemma B.2 (i) and the definition of $\left\|\cdot\right\|_{\psi_2}^*$ in B.2, that

\[
\left\|u^T(Z_S - \nu_S)\right\|_{\psi_2} \leq (4\sigma_{Z,S}/\sqrt{n}) \left\|u\right\|_2, \quad \forall S \in \mathcal{S} \text{ and any } u \in \mathbb{R}^{s+1},
\]
and thus,
\[
\sup_{S \in \mathcal{S}} \| \hat{Z}_S - \nu_S \|_{\psi_2}^* \leq (4 \hat{\sigma}_{Z,S} / \sqrt{n}).
\]

Further, \(\mathbf{E}_{n,S} := \mathbb{E}(\hat{Z}_S - \nu_S)(\hat{Z}_S - \nu_S)^T \equiv \text{Cov}(\hat{Z}_S - \nu_S) = n^{-1} \mathbf{E}_S\), so that \(\|\mathbf{E}_{n,S}\|_2 \equiv n^{-1}\lambda_{\max}(\mathbf{E}_S) \leq n^{-1}\lambda_{\sup,S}.\) Hence, similar to (A.26), applying Lemma B.6 to (a single observation of) \(\hat{Z}_S - \mu_S\) for any \(S \in \mathcal{S}\), we have: for any \(\epsilon \geq 0\) and any \(S \in \mathcal{S}\),
\[
P\left\{ \| \hat{Y}_S \|_2 > \frac{\tilde{\lambda}_{\sup,S}}{n} + 16 \frac{n}{n} K_S (\sqrt{\epsilon} + \epsilon) \right\} \leq 2 \exp(-\epsilon + \tilde{q}_n),
\]
and therefore, for any \(\epsilon \geq 0\),
\[
(A.33) \quad P \left\{ \sup_{S \in \mathcal{S}} \| \hat{Y}_S \|_2 > \frac{\tilde{\lambda}_{\sup,S}}{n} + 16 \frac{n}{n} K_S (\sqrt{\epsilon} + \epsilon) \right\} \leq 2 \exp(-\epsilon + \tilde{q}_n + \log L_n),
\]
where the last bound follows from using the union bound, similar to (A.27). Consequently, for any \(\epsilon \geq 0\),
\[
P \left\{ \sup_{S \in \mathcal{S}} \| \hat{Y}_{S,Y} \|_2 > \frac{\tilde{\lambda}_{\sup,S}}{n} + 16 \frac{n}{n} K_S (\sqrt{\epsilon} + \epsilon) \right\} \leq 2 \exp(-\epsilon + \tilde{q}_n + \log L_n),
\]
and hence, for any \(c \geq 0\),
\[
(A.34) \quad P \left\{ \sup_{S \in \mathcal{S}} \| \hat{Y}_{S,Y} \|_2 > 16(c + 1) K_S (\sqrt{\epsilon} + \epsilon + \tilde{q}_n) \right\} \leq 2 \exp(-c\tilde{q}_n),
\]
where the bounds follow from using (A.30) and (A.33) and the second bound follows from substituting \(\epsilon\) as: \(\epsilon = (c + 1)(\tilde{q}_n + \log L_n) \equiv (c + 1)\tilde{q}_n\) for any \(c \geq 0\), and noting that \(\sqrt{c + 1} \leq (c + 1)\). This therefore establishes the second claim (ii) in (A.14).

The remaining claims at the end of Lemma A.2 are quite straightforward. Using Lemma B.2 (i) and Lemma B.1 (iii), we first note that under Assumption 5.1, for any \(S \in \mathcal{S}\), \(\nu \in \mathbb{R}^s\) and \(u \in \mathbb{R}^{s+1}\), \(\mathbb{E}\{(\nu^T\tilde{X}_S)^2\} \leq 2\tilde{\sigma}_{X,S}^2 \|\nu\|_2^2\) and \(\mathbb{E}\{(u^T\tilde{Z}_S)^2\} \leq 2\tilde{\sigma}_{Z,S}^2\). Further, \(\lambda_{\max}(\Sigma_S) \equiv \sup_{\|\nu\|_2 \leq 1} \mathbb{E}\{(\nu^T\tilde{X}_S)^2\} = \lambda_{\max}(\mathbf{E}_S) \equiv \sup_{\|u\|_2 \leq 1} \mathbb{E}\{(u^T\tilde{Z}_S)^2\}\) for each \(S \in \mathcal{S}\). Hence, we have: \(\sup_{S \in \mathcal{S}} \lambda_{\max}(\Sigma_S) \leq 2\tilde{\sigma}_{X,S}^2\), and \(\sup_{S \in \mathcal{S}} \lambda_{\max}(\Sigma_S) \leq 2\tilde{\sigma}_{Z,S}^2\). This justifies the claimed choices for the constants \(\lambda_{\sup,S}\) and \(\tilde{\lambda}_{\sup,S}\) in Assumption 5.1.

Lastly, owing to the very definition of \(\beta_S\) in (5.1) and the estimating equation satisfied by \(\beta_S\) therein, we have: \(\forall S \in \mathcal{S}, \mathbb{E}\{\tilde{X}_S(Y - \tilde{X}_S^T\beta_S)\} = 0\) and \(\mathbb{E}\{(\tilde{Y} - \tilde{X}_S^T\beta_S)(\tilde{X}_S^T\beta_S)\} = 0\), so that \(\mathbb{E}(\tilde{Y}^2) = \mathbb{E}\{(\tilde{Y} - \tilde{X}_S^T\beta_S)^2\} \equiv \beta_S^T\Sigma_S\beta_S \geq \|\beta_S\|_2^2\lambda_{\min}(\Sigma_S)\). Using (5.4), we therefore have: \(\sup_{S \in \mathcal{S}} \|\beta_S\|_2^2 \leq \lambda_{\inf,S}^{-1} \mathbb{E}(\tilde{Y}^2)\). Further, due to Lemma B.1 (iii), \(\mathbb{E}(\tilde{Y}^2) \leq 2\tilde{\sigma}_{Y}^2\) and thus \(\sup_{S \in \mathcal{S}} \|\beta_S\|_2^2 \leq \lambda_{\inf,S}^{-1} \mathbb{E}(\tilde{Y}^2) \leq 2\lambda_{\inf,S}^{-1}\tilde{\sigma}_{Y}^2\). This establishes the final claim in Lemma A.2. The proof of Lemma A.2 is now complete.
A.8. Proof of Lemma A.3. For any $c > 0$ and any constant $c^* > 0$ satisfying (A.15), let us define the events:

\[(A.35)\quad \mathcal{A}_{n,S}(c) := \left\{ \sup_{S \in \mathcal{S}} \left\| \bar{\Sigma}_S - \Sigma_S \right\|_2 > (c + 1) K_S \left( \sqrt{\frac{r_n}{n}} + \frac{33r_n}{n} \right) + \frac{\lambda_{\sup,S}}{n} \right\},
\]

\[\mathcal{A}_{n,S}(c^*) := \left\{ \sup_{S \in \mathcal{S}} \left| \bar{\Sigma}_S - \Sigma_S \right| > (c^* + 1) K_S^* \left( \sqrt{\frac{r_n}{n}} + \frac{33r_n}{n} \right) + \frac{\lambda_{\sup,S}}{n} \right\},
\]

\[\mathcal{B}_{n,S}(c) := \left\{ \sup_{S \in \mathcal{S}} \left\| \bar{\Sigma}_S^{-1} - \Sigma_S^{-1} \right\|_2 > (c + 1) K_S^* \left( \sqrt{\frac{r_n}{n}} + \frac{33r_n}{n} \right) + \frac{2 \lambda_{\sup,S}}{n} \right\}
\]

and let $\mathcal{A}_{n,S}(c^*)$ denote the complement event of $\mathcal{A}_{n,S}(c)$. Then, for any $c > 0$ and for any $c^* > 0$ satisfying (A.15), we first note that

\[(A.36)\quad \mathbb{P}\{\mathcal{A}_{n,S}(c)\} \leq 4 \exp(-cr_n), \quad \text{and} \quad \mathbb{P}\{\mathcal{A}_{n,S}(c^*)\} \leq 4 \exp(-c^* r_n),
\]

where both bounds are direct consequences of Lemma A.2 (iii), which applies under Assumption 5.1 (i). Further, for the events defined in (A.35), the following inclusions hold:

\[\mathcal{B}_{n,S}(c) \cap \mathcal{A}_{n,S}(c^*) \subseteq (a) \mathcal{B}_{n,S}(c) \cap \left\{ \sup_{S \in \mathcal{S}} \left\| \bar{\Sigma}_S - \Sigma_S \right\|_2 \leq \frac{\lambda_{\inf,S}}{2} \right\}
\]

\[\subseteq (b) \mathcal{A}_{n,S}(c) \cap \left\{ \sup_{S \in \mathcal{S}} \left\| \bar{\Sigma}_S - \Sigma_S \right\|_2 \leq \frac{\lambda_{\inf,S}}{2} \right\} \subseteq \mathcal{A}_{n,S}(c),
\]

and hence, $\mathbb{P}\{\mathcal{B}_{n,S}(c) \cap \mathcal{A}_{n,S}(c^*)\} \leq \mathbb{P}\{\mathcal{A}_{n,S}(c)\}$. The inclusion (a) in (A.37) above follows since $c^*$ satisfies the condition (A.15) in Lemma A.3, while the inclusion (b) follows from an application of Lemma B.5 and from noting the definitions of the constants $K_S^*$ and $\lambda_{\inf,S}$.

Hence, for any $c > 0$ and for any $c^* > 0$ satisfying (A.15), we then have:

\[
\mathbb{P}\left\{ \sup_{S \in \mathcal{S}} \left\| \bar{\Sigma}_S^{-1} - \Sigma_S^{-1} \right\|_2 > (c + 1) K_S^* \left( \sqrt{\frac{r_n}{n}} + \frac{33r_n}{n} \right) + \frac{2 \lambda_{\sup,S}}{n} \right\} \leq \mathbb{P}\{\mathcal{B}_{n,S}(c)\} = \mathbb{P}\{\mathcal{B}_{n,S}(c) \cap \mathcal{A}_{n,S}(c^*)\} + \mathbb{P}\{\mathcal{B}_{n,S}(c) \cap \mathcal{A}_{n,S}(c^*)\}
\]

\[
\leq (a) \mathbb{P}\{\mathcal{A}_{n,S}(c)\} + \mathbb{P}\{\mathcal{A}_{n,S}(c^*)\}
\]

\[
\leq (b) 4 \exp(-cr_n) + 4 \exp(-c^* r_n) = 4a_n(c, c^*, r_n),
\]

where the inequalities (a) and (b) follow from using (A.37) and (A.36), respectively. This establishes the claim in Lemma A.3 and completes the proof.

A.9. Proof of Theorem 6.1.

Proof of the first part of Theorem 6.1. First, note that

\[
\operatorname{aver}(\hat{\Theta}_{jp}(C^*_0)) - \operatorname{aver}(\Theta_{jp}(C^*_0)) = E_{n,jp}(C^*_0) = \operatorname{aver}(\hat{\Theta}_{jp}(C^*_0)) - \operatorname{aver}(\Theta_{jp}(C^*_0)).
\]

Next, let $X_{j_1}, \ldots, X_{j_{\ell_{\text{distinct},j}}} \subseteq \mathcal{A}_{\text{MEC}}(C^*_0)$ be the distinct parent sets of $X_j$ in MEC$(C^*_0)$ with multiplicities $m_{j_1}, \ldots, m_{j_{\ell_{\text{distinct},j}}}$ respectively, so that

\[
\operatorname{aver}(\hat{\Theta}_{jp}(C^*_0)) = \frac{1}{L} \sum_{r=1}^{\ell_{\text{distinct},j}} m_r \beta_{jp}|_{\mathbf{x}_{j_{r_1}^\text{r_1}} \cup \mathbf{x}_{(1, \ldots, r)}} \quad \text{and}
\]

\[
\operatorname{aver}(\Theta_{jp}(C^*_0)) = \frac{1}{L} \sum_{r=1}^{\ell_{\text{distinct},j}} m_r \beta_{jp}|_{\mathbf{x}_{j_{r_1}^\text{r_1}} \cup \mathbf{x}_{(1, \ldots, r)}}, \quad \text{where } L := \sum_{r=1}^{\ell_{\text{distinct},j}} m_r.
\]
These now enable us to apply the results obtained in Section 5.1. To see this, note that the assumptions of Theorem 5.1 for

\[ Y := X_p \quad \text{and} \quad S := \{S_{jr} = (j, 1, \ldots, t, S'_{jr}) : r \in \{1, \ldots, L_{\text{distinct},j}\} \}

follow from Assumptions 4.1, 4.2, 4.3 and 4.5 and Lemma A.1. Thus, it follows directly from the first part of Remark 5.2 with \( a^T \alpha_{S_{jr}} = (m_r/L, 0, \ldots, 0) \) that

\[
\text{aver}(\hat{\Theta}_{jp}(C'_0)) - \text{aver}(\Theta_{jp}(C'_0)) = \frac{1}{n} \sum_{r=1}^{n} Z_{jp}^{(r)} + O_P \left( \frac{q_j + \log(L_{\text{distinct},j})}{n} \right),
\]

since

\[
\sum_{r=1}^{L_{\text{distinct},j}} ||a_{S_{jr}}||_2 = \sum_{r=1}^{L_{\text{distinct},j}} \frac{m_r}{L} = 1. \quad \square
\]

**Proof of the second part of Theorem 6.1.** Recall that

\[ \hat{\eta}(\hat{C}'_0) - \eta(C'_0) = \hat{\theta}_{ij} \text{aver}(\hat{\Theta}_{jp}(\hat{C}'_0)) - \theta_{ij} \text{aver}(\Theta_{jp}(C'_0)). \]

Therefore, it is straightforward to obtain the result by applying the identity \( a_n b_n - ab = a(b_n - b) + b(a_n - a) + (a_n - a)(b_n - b) \) with \( a_n = \theta_{ij}, \ b_n = \text{aver}(\hat{\Theta}_{jp}(\hat{C}'_0)), a = \theta_{ij} \), and \( b = \text{aver}(\Theta_{jp}(C'_0)) \), and using the first part of Theorem 6.1 and the following well-known result from the asymptotic theory of multiple linear regression (e.g., see Van der Vaart [1998])

\[
\hat{\theta}_{ij} - \theta_{ij} = \hat{\beta}_{ij} \mathbf{x}_{(1, \ldots, t-1)} - \beta_{ij} \mathbf{x}_{(1, \ldots, t-1)} = \frac{1}{n} \sum_{r=1}^{n} Z_{ij}^{(r)} + O_P \left( \frac{1}{n} \right). \quad \square
\]

**A.10. Proof of Corollary 6.1.** Recall that

\[ \text{aver}(\hat{\Theta}_{jp}(C'_0)) - \text{aver}(\Theta_{jp}(C'_0)) = E_{n,jp}(\hat{C}'_0, C'_0) + \text{aver}(\hat{\Theta}_{jp}(C'_0)) - \text{aver}(\Theta_{jp}(C'_0)). \]

Since from the discussion before Theorem 6.1 (see Section 6) we have

\[ E_{n,jp}(\hat{C}'_0, C'_0) = o_P(1/\sqrt{n}), \]

it is sufficient to show \( \mathbb{E}[Z_{jp}^2] = \Omega(1) \) and

\[
\sqrt{n} \left\{ \text{aver}(\hat{\Theta}_{jp}(C'_0)) - \text{aver}(\Theta_{jp}(C'_0)) \right\} \quad \sim \quad \mathcal{N}(0, 1), \quad (A.38)
\]

As discussed in the proof of Theorem 6.1, \( \text{aver}(\hat{\Theta}_{jp}(C'_0)) - \text{aver}(\Theta_{jp}(C'_0)) \) can be written as \( \sum_{S \in S} a_S^T(\hat{\beta}_S - \beta_S) \), following the notations and setup of Remark 5.2, for some set of vectors \( \{a_S : S \in S\} \) satisfying \( \sum_S ||a_S||_2 = O(1) \), where \( \beta_S \) denotes the vector of regression coefficients in the regression of \( Y := X_p \) on \( X_S \) and \( \hat{\beta}_S \) denotes its sample version (i.e. the corresponding OLS estimator) respectively, and \( S := \{S_{jr} = (j, 1, \ldots, t, S'_{jr}) : r \in \{1, \ldots, L_{\text{distinct},j}\}\} \) is as in the proof of Theorem 6.1.

Therefore, given the stronger sparsity assumption (from Assumption 6.2)

\[ n^{-1/2} \{q_j + \log(L_{\text{distinct},j})\} \rightarrow 0, \]

(A.38) now follows from the second part of Remark 5.2 as long as the second moment of the influence function in the asymptotic linear expansion of \( \text{aver}(\hat{\Theta}_{jp}(C'_0)) - \text{aver}(\Theta_{jp}(C'_0)) \) is bounded below, i.e. \( \mathbb{E}[Z_{jp}^2] = \Omega(1) \). \quad \square
We prove \( \mathbb{E}[Z_{jp}^2] = \Omega(1) \) by verifying the sufficient conditions given in the last paragraph of Appendix C (regarding the two moment conditions required in Remark 5.2), namely: there exist constants \( c_1 > 0 \) and \( c_2 > 0 \) such that

\[
(A.39) \quad \text{Var}(Y | \bigcup_{S \in \mathcal{S}} X_S) > c_1 \quad \text{and} \quad \mathbb{E} \left[ \left( \sum_{S \in \mathcal{S}} a_S^T (\Sigma_{SS})^{-1} (X_S - \mu_S) \right)^2 \right] > c_2.
\]

The first part of Assumption 6.2 and the first part of (A.39) with \( c_1 = v \) are identical, since \( \bigcup_{S \in \mathcal{S}} X_S = P \mathcal{C}^c_j (X_j) \cup \{X_1, \ldots, X_t, X_j\} \). Thus we complete the proof by showing that the second part of (A.39) follows from Assumptions 4.5 and 6.2.

To this end, following the notation in the proof of Theorem 6.1, we write

\[
\sum_{S \in \mathcal{S}} a_S^T (\Sigma_{SS})^{-1} (X_S - \mu_S)
\]

\[
= \sum_{r=1}^{L_{\text{distinct},j}} \frac{m_r}{L} e_{1,|S_{jr}|+t+1}^T \left( \begin{array}{cc}
(\Sigma_0)_{jj} & (\Sigma_0)_{j1,1,...,t,S_{jr}'} \\
(\Sigma_0)_{11,1,...,t,S_{jr}'} & (\Sigma_0)_{11,1,...,t,S_{jr}'}
\end{array} \right)^{-1} \left( X_{j1,1,...,t,S_{jr}'} - \mu_{j1,1,...,t,S_{jr}'} \right),
\]

where \( e_{1,|S_{jr}|+t+1} \) denote the first row of an \((|S_{jr}| + t + 1) \times (|S_{jr}| + t + 1)\) identity matrix.

By partitioning \((\Sigma_0)_{j1,1,...,t,S_{jr}}(j1,1,...,t,S_{jr})\) as

\[
(\Sigma_0)_{j1,1,...,t,S_{jr}}(j1,1,...,t,S_{jr}) = \left( \begin{array}{cc}
(\Sigma_0)_{jj} & (\Sigma_0)_{j1,1,...,t,S_{jr}} \\
(\Sigma_0)_{11,1,...,t,S_{jr}} & (\Sigma_0)_{11,1,...,t,S_{jr}}
\end{array} \right),
\]

and applying the well-known formula for the inverse of a partitioned matrix, we obtain

\[
e_{1,|S_{jr}|+t+1}^T \left( \begin{array}{cc}
(\Sigma_0)_{jj} & (\Sigma_0)_{j1,1,...,t,S_{jr}} \\
(\Sigma_0)_{11,1,...,t,S_{jr}} & (\Sigma_0)_{11,1,...,t,S_{jr}}
\end{array} \right)^{-1} \left( X_{j1,1,...,t,S_{jr}} - \mu_{j1,1,...,t,S_{jr}} \right)
\]

\[
= \frac{(X_j - \mu_j) - (\Sigma_0)_{j1,1,...,t,S_{jr}} (\Sigma_0)_{j1,1,...,t,S_{jr}}^{-1} (X_{j1,1,...,t,S_{jr}} - \mu_{j1,1,...,t,S_{jr}})}{(\Sigma_0)_{jj} - (\Sigma_0)_{j1,1,...,t,S_{jr}} (\Sigma_0)_{j1,1,...,t,S_{jr}}^{-1} (\Sigma_0)_{j1,1,...,t,S_{jr}} j}.
\]

We define

\[
\beta_{j1,1,...,t,S_{jr}} := (\Sigma_0)_{j1,1,...,t,S_{jr}} (\Sigma_0)_{j1,1,...,t,S_{jr}}^{-1}, \quad \text{and}
\]

\[
\sigma_{j1,1,...,t,S_{jr}}^2 := (\Sigma_0)_{jj} - (\Sigma_0)_{j1,1,...,t,S_{jr}} (\Sigma_0)_{j1,1,...,t,S_{jr}}^{-1} (\Sigma_0)_{j1,1,...,t,S_{jr}} j.
\]

Therefore,

\[
\mathbb{E} \left[ \left( \sum_{S \in \mathcal{S}} a_S^T (\Sigma_{SS})^{-1} (X_S - \mu_S) \right)^2 \right] = \mathbb{E} \left[ \left( \sum_{r=1}^{L_{\text{distinct},j}} \frac{m_r}{L} e_{1,|S_{jr}|+t+1}^T \left( \begin{array}{cc}
(\Sigma_0)_{jj} & (\Sigma_0)_{j1,1,...,t,S_{jr}} \\
(\Sigma_0)_{11,1,...,t,S_{jr}} & (\Sigma_0)_{11,1,...,t,S_{jr}}
\end{array} \right)^{-1} \left( X_{j1,1,...,t,S_{jr}} - \mu_{j1,1,...,t,S_{jr}} \right) \right)^2 \right]
\]

\[
= \mathbb{E} \left[ \sum_{r=1}^{L_{\text{distinct},j}} \frac{m_r}{L} \sigma_{j1,1,...,t,S_{jr}}^2 \left( X_j - \mu_j \right) - \beta_{j1,1,...,t,S_{jr}}^T (X_{j1,1,...,t,S_{jr}} - \mu_{j1,1,...,t,S_{jr}}) \right)^2 \right]
\]
where the second last equality follows from the fact that $X$ implies $\mathcal{S}_{r} \subseteq \mathcal{A}_{1}$. Thus the result follows from the same arguments given in the proof of Corollary 6.1.

Finally, by Assumption 6.2, we have

$$\mathbb{E} \left[ \text{Var} \left( X_{j} \mid \mathcal{A}_{j} \cup X_{\{1,\ldots,t\}} \right) \right] \geq \frac{1}{\xi^{2}}.$$

This therefore establishes (A.39) and completes the proof of Corollary 6.1.

A.11. Proof of Corollary 6.2. It is easy to see that Theorem 6.1, Corollary 6.1 and Assumption 6.1 imply

$$\hat{\eta}(\mathcal{C}_{0}) - \eta(\mathcal{C}_{0}) = \hat{\theta}_{ij} E_{n,jp}(\hat{\mathcal{G}}_{0},\mathcal{C}_{0}) +$$

$$+ \frac{1}{n} \sum_{r=1}^{n} \left\{ \theta_{ij}(\mathcal{C}_{r}) + \text{aver}(\Theta_{jp}(\mathcal{C}_{0}))Z_{ij}(r) \right\} + o_{p} \left( \frac{1}{\sqrt{n}} \right).$$

Thus the result follows from the same arguments given in the proof of Corollary 6.1. This completes the proof of Corollary 6.2.

A.12. Proof of Theorem 6.2. First, consider the case $\theta_{jt} = \text{aver}(\Theta_{jp}(\mathcal{C}_{0})) = 0$. Then $\mathcal{T}_{n,jp}$ can be written as

$$\mathcal{T}_{n,jp} := \frac{W_{n,1j} W_{n,jp}}{\sqrt{W_{n,1j}^{2} + W_{n,jp}^{2} + 2 \rho W_{n,1j} W_{n,jp}}},$$

where $\rho$ is the correlation coefficient between $Z_{jp}$ and $Z_{tj}$, and

$$(W_{n,1j}, W_{n,jp})^{T} := \left( \frac{\sqrt{n} \hat{\theta}_{ij}}{\sqrt{\mathbb{E}[Z_{tj}^{2}]}} , \frac{\sqrt{n} \text{aver}(\hat{\Theta}_{jp}(\mathcal{C}_{0}))}{\sqrt{\mathbb{E}[Z_{jp}^{2}]}} \right)^{T}.$$
By following similar arguments as in Theorem 6.1 and in Corollary 6.2 it can be shown that

\[(W_{n,1j}, W_{n,jp})^T \xrightarrow{d} (W_1, W_2)^T \sim \mathcal{N}\left(0, \begin{pmatrix} 1 & \rho \\ \rho & 1 \end{pmatrix}\right).\]

Therefore, by the continuous mapping theorem, \(\tilde{T}_{n,jp}\) is asymptotically distributed as

\[
W := \frac{W_1 W_2}{\sqrt{W_1^2 + W_2^2 + 2\rho W_1 W_2}}.
\]

(A.40)

Next, suppose at least one of \(\theta_{jt}\) or \(\text{aver}(\Theta_{jp}(C'_0))\) is non-zero. It follows from Theorem 4.1 that the denominator of \(\tilde{T}_{n,jp}\) converges in probability to the denominator of \(T_{n,jp}\). Therefore, \(\tilde{T}_{n,jp} \xrightarrow{d} \mathcal{N}(0, 1)\) follows from Corollary 6.2 and an application of Slutsky’s theorem.

B. Technical Tools - Definitions and Supporting Lemmas. In this section, we collect some definitions referred in the main paper and some key technical lemmas that will be useful in the proofs of all our main results.

B.1. Sub-Gaussians and Sub-Exponentials. Here, we formally define sub-Gaussian and sub-exponential random variables (and vectors), used in some of our assumptions, based on the concept of (exponential) Orlicz norms.

**Definition B.1 (The \(\psi_\alpha\)-Orlicz norm, and sub-Gaussian and sub-exponential variables).** For any \(\alpha > 0\), define the function \(\psi_\alpha(u) := \exp(u^\alpha) - 1 \forall u \geq 0\). For any random variable \(X\) and any \(\alpha > 0\), the \(\psi_\alpha\)-Orlicz norm (the exponential Orlicz norm of order \(\alpha > 0\)) of \(X\) is then defined as:

\[
\|X\|_{\psi_\alpha} := \inf\{c > 0 : \mathbb{E}\{\psi_\alpha(|X|/c)\} \leq 1\},
\]

where \(\|X\|_{\psi_\alpha}\) is understood to be \(\infty\) if the infimum above is over an empty set. The special cases of \(\alpha = 2\) and \(\alpha = 1\) correspond to the sub-Gaussian and sub-exponential random variables, respectively. \(X\) is said to be sub-Gaussian if \(\|X\|_{\psi_2} < \infty\) (and \(\|X\|_{\psi_2}\) is called the ‘sub-Gaussian norm’ of \(X\)), and \(X\) is sub-exponential if \(\|X\|_{\psi_1} < \infty\) (and \(\|X\|_{\psi_1}\) is its ‘sub-exponential norm’).

**Definition B.2 (Sub-Gaussian norm(s) for random vectors).** A random vector \(X = (X_j)_{j=1}^d \in \mathbb{R}^d\) (\(d \geq 1\)) is defined to be sub-Gaussian if and only if for all \(v \in \mathbb{R}^d\), \(v^T X\) is sub-Gaussian, as in Definition B.1. For such random vectors, we define two-sub-Gaussian norms as follows:

\[
\|X\|_{\psi_2} := \max_{1 \leq j \leq d} \|X_j\|_{\psi_2} \quad \text{and} \quad \|X\|^*_{\psi_2} := \sup_{\|v\|_2 \leq 1} \|v^T X\|_{\psi_2}.
\]

For a general \(\alpha > 0\), we also define, analogous to \(\|X\|_{\psi_2}\), the \(\psi_\alpha\)-Orlicz norm of a random vector \(X \in \mathbb{R}^d\) as: \(\|X\|_{\psi_\alpha} := \max_{1 \leq j \leq d} \|X_j\|_{\psi_\alpha}\).

For most of our analyses, we use \(\|\cdot\|^*_{\psi_2}\) as the vector sub-Gaussian norm which has usually been the accepted definition [Vershynin, 2012, 2018, e.g.]. The corresponding extension of the \(\|X\|^*_{\psi_2}\) norm to a \(\|\cdot\|^*_{\psi_\alpha}\) norm for a general \(\alpha > 0\) is however not immediate, and certainly not standard in the literature.
B.2. Properties of Orlicz Norms and Concentration Bounds. We next enlist, through a sequence of lemmas, some useful general properties of Orlicz norms, as well as a few specific ones for sub-Gaussians and sub-exponentials. These are all quite well known and routinely used. Their statements (possibly with slightly different constants) and proofs can be found in several relevant references, including Van der Vaart and Wellner [1996]; Pollard [2015]; Vershynin [2012, 2018]; Wainwright [2019] and Rigollet and Hütter [2017], among others. The proofs are therefore skipped here for brevity.

**Lemma B.1** (General properties of Orlicz norms, sub-Gaussians and sub-exponentials). In the following, $X, Y \in \mathbb{R}$ denote generic random variables and $\mu$ denotes $\mathbb{E}(X) \in \mathbb{R}$.

(i) (Basic properties). For $\alpha \geq 1$, $\|\cdot\|_{\psi, \alpha}$ is a norm (and a quasinorm if $\alpha < 1$) satisfying:
(a) $\|X\|_{\psi, \alpha} \geq 0$ and $\|X\|_{\psi, \alpha} = 0 \iff X = 0$ almost surely (a.s.), (b) $\|cX\|_{\psi, \alpha} = |c| \|X\|_{\psi, \alpha}$ for all $c \in \mathbb{R}$ and (c) $\|X + Y\|_{\psi, \alpha} \leq \|X\|_{\psi, \alpha} + \|Y\|_{\psi, \alpha}$.

(ii) (Tail bounds and equivalences). (a) If $\|X\|_{\psi, \alpha} \leq \sigma$ for some $(\sigma, \alpha) > 0$, then $\forall \epsilon \geq 0$, $\mathbb{P}(|X| > \epsilon) \leq 2 \exp(-\epsilon^{\alpha}/\sigma^{\alpha})$. (b) Conversely, if $\mathbb{P}(|X| > \epsilon) \leq C \exp(-\epsilon^{\alpha}/\sigma^{\alpha})$ for some $(C, \sigma, \alpha) > 0$, then $\|X\|_{\psi, \alpha} \leq \sigma(1 + C/2)^{1/\alpha}$.

(iii) (Moment bounds). If $\|X\|_{\psi, \alpha} \leq \sigma$ for some $(\sigma, \alpha) > 0$, then $\mathbb{E}(|X|^m) \leq C^m \sigma^{m \alpha} m^{m/\alpha}$ for all $m \geq 1$, for some constant $C_{\alpha}$ depending only on $\alpha$. (A converse of this result also holds, although not explicitly presented here). For $\alpha = 1$ and $2$ in particular, we have:
(a) If $\|X\|_{\psi, 1} \leq \sigma$, then for each $m \geq 1$, $\mathbb{E}(|X|^m) \leq \sigma^m m! \leq \sigma^m m^m$. (b) If $\|X\|_{\psi, 2} \leq \sigma$, then $\mathbb{E}(|X|^m) \leq 2\sigma^m \Gamma(m/2 + 1)$ for each $m \geq 1$, where $\Gamma(a) := \int_0^\infty x^{a-1} \exp(-x) dx \forall a > 0$ denotes the Gamma function. Hence, $\mathbb{E}(|X|) \leq \sigma \sqrt{\pi}$ and $\mathbb{E}(|X|^m) \leq 2\sigma^m (m/2)^{m/2}$ for any $m \geq 2$.

(iv) (Hölder-type inequality for the Orlicz norm of products). For any $\alpha, \beta > 0$, let $\gamma := (\alpha + 1 + \beta^{-1})^{-1}$. Then, for any two random variables $X$ and $Y$ with $\|X\|_{\psi, \alpha} < \infty$ and $\|Y\|_{\psi, \beta} < \infty$, $\|XY\|_{\psi, \gamma} \leq \|X\|_{\psi, \alpha} \|Y\|_{\psi, \beta}$. In particular, for any two sub-Gaussians $X$ and $Y$, $XY$ is sub-exponential and $\|XY\|_{\psi, \gamma} \leq \|X\|_{\psi, \alpha} \|Y\|_{\psi, \beta}$. Moreover, if $Y \leq M$ a.s. and $\|X\|_{\psi, \gamma} < \infty$, then $\|XY\|_{\psi, \gamma} \leq M \|X\|_{\psi, \gamma}$.

(v) (MGF related properties of sub-Gaussians). Let $\mathbb{E}(\exp\{t(X - \mu)\})$ denote the moment generating function (MGF) of $X - \mu$ at $t \in \mathbb{R}$. Then:
(a) If $\|X - \mu\|_{\psi, 2} < \sigma$ for some $\sigma > 0$, then $\mathbb{E}(\exp\{t(X - \mu)\}) \leq \exp(2\sigma^2 t^2) \forall t \in \mathbb{R}$. (b) Conversely, if $\mathbb{E}(\exp\{t(X - \mu)\}) \leq \exp(2\sigma^2 t^2) \forall t \in \mathbb{R}$ for some $\sigma \geq 0$, then for any $\epsilon \geq 0$, $\mathbb{P}(\|X - \mu\| > \epsilon) \leq 2 \exp(-\epsilon^{2}/4\sigma^{2})$ and hence, $\|X - \mu\|_{\psi, 2} \leq 2\sqrt{2}\sigma$.

**Lemma B.2** (Properties of sub-Gaussian random vectors). Let $X = (X_j)_{j=1}^d \in \mathbb{R}^d$ be any random vector, and let $\nu \in \mathbb{R}^d$ and $M \in \mathbb{R}^{d \times d}$ denote any generic (fixed) vectors and matrices, for any $d \geq 1$. Then,

(i) For any $\nu \in \mathbb{R}^d$, $\|\nu^T \cdot X\|_{\psi, 2} \leq \|\nu\|_2 \|X\|_{\psi, 2}$ and $\|\nu^T \cdot X\|_{\psi, 2} \leq \|\nu\|_1 \|X\|_{\psi, 2} \leq \sqrt{d} \|\nu\|_2 \|X\|_{\psi, 2}$. Hence, $\|X\|_{\psi, 2} \leq \sqrt{d} \|X\|_{\psi, 2}$. Further, for any matrix $M \in \mathbb{R}^{d \times d}$, $\|M \cdot X\|_{\psi, 2} \leq \|M\|_\infty \|X\|_{\psi, 2} \leq \sqrt{d} \|M\|_2 \|X\|_{\psi, 2}$ and $\|M \cdot X\|_{\psi, 2} \leq \|M\|_2 \|X\|_{\psi, 2} \leq \sqrt{d} \|M\|_2 \|X\|_{\psi, 2}$.

(ii) Suppose $\mathbb{E}(X) = 0$. $\|X\|_{\psi, 2} \leq \sigma$ and assume further that the coordinates $\{X_j\}_{j=1}^d$ of $X$ are independent. Then for any $\nu \in \mathbb{R}^d$, $\|\nu^T \cdot X\|_{\psi, 2} \leq 2\sqrt{2}\sigma \|\nu\|_2$. Thus, under these additional assumptions on $X$, it holds that $\|X\|_{\psi, 2} \leq \|X\|_{\psi, 2} \leq 2\sqrt{2}\sigma \|\nu\|_2$. Further, for any $M \in \mathbb{R}^{d \times d}$, $\|M \cdot X\|_{\psi, 2} \leq \|M\|_2 \|X\|_{\psi, 2} \leq \|M\|_2 \|X\|_{\psi, 2} \leq 2\sqrt{2}\sigma \|\nu\|_2$. 

\[ \]
Lemma B.3 (Concentration bounds for sums of independent sub-Gaussian variables). For any $n \geq 1$, let $\{X_i\}_{i=1}^n$ be independent (not necessarily i.i.d.) random variables with means $\{\mu_i\}_{i=1}^n$ and $\max_{1 \leq i \leq n} \|X_i - \mu_i\|_{\psi_2} \leq \sigma$ for some constant $\sigma \geq 0$. Then, for any collection of real numbers $\{a_i\}_{i=1}^n$ and letting $a = (a_1, \ldots, a_n) \in \mathbb{R}^n$, we have:

$$
\mathbb{E} \left[ \exp \left\{ t \sum_{i=1}^n a_i (X_i - \mu_i) \right\} \right] \leq \exp \left( 2\sigma^2 t^2 \|a\|_2^2 \right) \quad \forall t \in \mathbb{R}, \text{ and}
$$

$$
\mathbb{P} \left\{ \sum_{i=1}^n a_i (X_i - \mu_i) > \epsilon \right\} \leq 2 \exp \left\{ -\epsilon^2 / \left( 8\sigma^2 \|a\|_2^2 \right) \right\} \quad \forall \epsilon > 0.
$$

In particular, when $a_i = 1/n$, we have: $\| \frac{1}{n} \sum_{i=1}^n (X_i - \mu_i) \|_{\psi_2} \leq \left( 4\sigma \right) / \sqrt{n}$, and for any $\epsilon \geq 0$, $\mathbb{P} \left\{ \frac{1}{n} \sum_{i=1}^n (X_i - \mu_i) > \epsilon \right\} \leq 2 \exp \left\{ -n \epsilon^2 / \left( 8\sigma^2 \right) \right\}$.

B.3. Basic Matrix Inequalities and Deviation Bounds for Random Matrices under the Spectral Norm. We provide here a sequence of lemmas collecting some useful and fairly well known inequalities regarding matrix norms and spectral properties of matrices and their submatrices and inverses. The lemmas also include some important results such as deterministic inequalities relating spectral distance between inverses of two p.d. matrices to that between the original matrices, as well as exact concentration bounds for deviations (under the spectral norm) of covariance-type random matrices defined by sub-gaussian random vectors.

Lemma B.4 (Basic inequalities on matrix norms and spectral properties of submatrices). Let $M \in \mathbb{R}^{d \times d}$ ($d \geq 1$) denote any generic square matrix. Then, $\|M\|_{\infty} \leq \sqrt{d} \|M\|_2 \leq d \|M\|_{\max}$ and $\|M\|_{\max} \leq \|M\|_2 \leq d \|M\|_{\max}$. Further, the following results hold.

(i) $\|Mv\|_2 \leq \|M\|_2 \|v\|_2$ and $\|Mv\|_{\infty} \leq \|M\|_{\infty} \|v\|_{\infty}$ for any $v \in \mathbb{R}^d$. Further, for any $M_1, M_2 \in \mathbb{R}^{d \times d}$, $\|M_1 M_2\|_2 \leq \|M_1\|_2 \|M_2\|_2$ and $\|M_1 M_2\|_{\infty} \leq \|M_1\|_{\infty} \|M_2\|_{\infty}$.

(ii) Let $M$ be symmetric and let $M_k$ denote any principal submatrix of $M$ of order $k \leq d$. Let $\lambda_1 \geq \ldots \geq \lambda_d$ and $\mu_1 \geq \ldots \geq \mu_k$ respectively denote the ordered eigenvalues of $M$ and $M_k$. Then, these are 'interlaced' as: $\lambda_i \leq \mu_i \leq \lambda_i \forall 1 \leq i \leq k$.

(iii) For any $M \in \mathbb{R}^{d \times d}$ (not necessarily symmetric) and any square submatrix (not necessarily principal) $M_k$ of $M$ of order $k \leq d$, let $\lambda_1 \geq \ldots \geq \lambda_d$ and $\mu_1 \geq \ldots \geq \mu_k$ respectively denote the ordered singular values of $M$ and $M_k$. Then, we have the 'upper' and 'lower' interlacing(s): $\mu_i \leq \lambda_i \forall 1 \leq i \leq k$, and $\mu_i \geq \lambda_{2d-2k+i} \forall 1 \leq i \leq (2k - d)$.

A few remarks regarding Lemma B.4 (ii)–(iii) are in order. The interlacing inequalities in (ii) are special cases of the well known Poincare Separation Theorem (and more generally, the Courant-Fisher Min-Max Theorem). The particular case of $k = d - 1$ is also known as the Cauchy Interlacing Theorem (see Thompson [1972] for further details). Note that these inequalities are only for the eigenvalues (not singular values) of symmetric matrices and their principal submatrices (for n.n.d. matrices however, these two coincide). The inequalities in (iii) are adopted from Thompson [1972] (they also apply more generally to non-square matrices). Notably, they apply directly to singular values (not eigenvalues) of matrices and submatrices of arbitrary nature and order. Among other implications, they also establish that $\|M^*\|_2 \leq \|M\|_2$ for arbitrary matrices $M$ and submatrices $M^*$ of $M$.

Lemma B.5 (Inequalities relating spectral deviations of p.d. matrices and their inverses). Let $M_0 \in \mathbb{R}^{d \times d}$ be any symmetric positive definite matrix with inverse $M_0^{-1}$
and minimal eigenvalue (also singular value) \( \lambda_{\min}(M_0) \equiv \|M_0^{-1}\|_2^{-1} > 0 \). Let \( M \in \mathbb{R}^{d \times d} \) be any matrix such that \( \|M - M_0\|_2 \leq \lambda_{\min}(M_0) \). Then, \( \| (M - M_0)M_0^{-1} \|_2 < 1 \), and \( \{I + (M - M_0)M_0^{-1}\} \) and \( M \) are both invertible. Further,

\[
\|M^{-1} - M_0^{-1}\|_2 \leq \frac{2\lambda_{\min}^2(M_0)}{1 - \|M - M_0\|_2 \lambda_{\min}^{-1}(M_0)} \|M - M_0\|_2
\]

\[
\leq 2\lambda_{\min}^2(M_0) \|M - M_0\|_2 \quad \text{if} \quad \|M - M_0\|_2 \leq \frac{1}{2} \lambda_{\min}(M_0).
\]

**Lemma B.6** (Deviation bounds under the spectral norm for covariance-type matrices). Let \( X \in \mathbb{R}^d \) be any random vector with \( \mathbb{E}(X) = 0 \) and \( \|X\|_{\psi_2}^* \leq \sigma_* \) for some \( \sigma_* \geq 0 \). Let \( \Sigma := \mathbb{E}(XX^T) \) which is assumed to be positive definite with minimum and maximum eigenvalues \( \lambda_{\min}(\Sigma) > 0 \) and \( \lambda_{\max}(\Sigma) \equiv \|\Sigma\|_2 \geq \lambda_{\min}(\Sigma) > 0 \) respectively. Consider a collection \( \{X_i\}_{i=1}^n \) of \( n \geq 1 \) independent realizations of \( X \). Then, for any \( \epsilon \geq 0 \), we have:

\[
\mathbb{P} \left\{ \left\| \frac{1}{n} \sum_{i=1}^n X_iX_i^T - \Sigma \right\|_2 > C_1 K_X^2 \left( \sqrt{\frac{d + \epsilon}{n} + \frac{d + \epsilon}{n}} \right) \right\} \leq 2 \exp(-\epsilon)
\]

and

\[
\mathbb{E} \left( \left\| \frac{1}{n} \sum_{i=1}^n X_iX_i^T - \Sigma \right\|_2 \right) \leq C_2 K_X^2 \left( \sqrt{\frac{d}{n} + \frac{d}{n}} \right), \quad \text{where}
\]

\[
K_X^2 = \frac{\sigma_{\max}^2(\Sigma)}{\lambda_{\min}(\Sigma)} \quad \text{and} \quad C_1, C_2 > 0 \quad \text{are absolute constants that do not depend on any other quantities introduced above. Specifically, choosing \( \epsilon = cd \) for any \( c > 0 \) and noting that \( \sqrt{c + 1} \leq c + 1 \), we have: for any \( c > 0 \),}
\]

\[
\mathbb{P} \left\{ \left\| \frac{1}{n} \sum_{i=1}^n X_iX_i^T - \Sigma \right\|_2 > C_1 K_X^2 (c + 1) \left( \sqrt{\frac{d}{n} + \frac{d}{n}} \right) \right\} \leq 2 \exp(-cd).
\]

Lemma B.5 is adopted from (the proof of) Lemma 5 in Harris and Drton [2013]. Lemma B.6 is obtained using Theorem 4.7.1 (more fundamentally, Theorem 4.6.1) of Vershynin [2018], in conjunction with Exercise 4.7.3 therein, along with appropriate modifications of his notations and assumptions to adapt to our setting. Similar results, though slightly more involved and with less explicit constants, may also be obtained using Theorem 5.39 of Vershynin [2012], along with equation (5.26) in Remark 5.40 therein.

**C. Verifying the Moment Conditions in Remark 5.2.** We provide here some discussions regarding verification of the moment conditions: \( \rho_{\xi_{A_S}} = O(1) \) and \( \sigma_{\xi_{A_S}} = \Omega(1) \) required in the last part of Remark 5.2. The first condition (and more) can indeed be verified generally under our basic assumptions in Section 5.1. To this end, note that under Assumption 5.1 (i), and through multiple uses of Lemma B.2 (i), Lemma B.1 (i) and Lemma B.1 (iv), as well as the last claim in Lemma A.2, we have: for each \( S \in \mathcal{S} \),

\[
\|a_S^T \Psi_S(Z)\|_{\psi_1} \leq \left\| a_S^T \Sigma_S^{-1} \bar{X}_S \right\|_{\psi_2} \left\| \bar{Y} - \bar{X}_S^T \beta_S \right\|_{\psi_2}
\]

\[
\leq \|a_S\|_2 \left\{ \lambda_{\min}^{-1}(\Sigma_S) \right\}^{-1} \|X_S\|_{\psi_2} (\sigma_Y + \|X_S\|_{\psi_2}^* \|\beta_S\|_2)
\]

\[
\leq \|a_S\|_2 \left\{ \lambda_{\inf,S}^{-1} \sigma_{X,S} \sigma_Y + \sqrt{2} \sigma_{X,S} \lambda_{\inf,S}^{-1/2} \right\} \equiv \|a_S\|_2 D_S \quad \text{(say),}
\]

where \( D_S := \lambda_{\inf,S}^{-1} \sigma_{X,S} \sigma_Y (1 + \sqrt{2} \sigma_{X,S} \lambda_{\inf,S}^{-1/2}) \) depends only on the constants in Assumption 5.1 (i). Thus, as long as \( D_S = O(1) \) and \( \sum_{S \in \mathcal{S}} \|a_S\|_2 = O(1) \), as assumed before, we
have:

\[ \| \xi_{AS}(Z) \|_{\psi_1} \equiv \left\| \sum_{S \in S} a_s^T \Psi_S(Z) \right\|_{\psi_1} \leq D_S \left( \sum_{S \in S} \| a_S \|_2 \right) = O(1). \]

Consequently, using Lemma B.1 (iii), we have \( 0 \leq \sigma_{\xi_{AS}} \leq \rho_{\xi_{AS}} \leq O(1) \). Among other implications, this verifies the first condition: \( \rho_{\xi_{AS}} = O(1) \). \( \square \)

Next, we provide some sufficient conditions for verifying the other moment condition:

\[ \sigma_{\xi_{AS}}^2 \equiv \text{Var} \{ \xi_{AS}(Z) \} \geq \mathbb{E} [ \text{Var} \{ \xi_{AS}(Z) | \cup_{S \in S} X_S \} ] \]
\[ \equiv \mathbb{E} \left[ \text{Var} \left\{ \sum_{S \in S} a_s^T \Sigma_S^{-1} \bar{X}_S (\bar{Y} - \bar{X}_S \beta_S) | \cup_{S \in S} X_S \right\} \right] \]
\[ = \mathbb{E} \left\{ \text{Var} \left( Y | \cup_{S \in S} X_S \right) \left( \sum_{S \in S} a_s^T \Sigma_S^{-1} \bar{X}_S \right)^2 \right\} \geq \eta_S \mathbb{E} \left( \sum_{S \in S} a_s^T \Sigma_S^{-1} \bar{X}_S \right)^2. \]

Hence, as long as \( \mathbb{E} \left\{ (\sum_{S \in S} a_s^T \Sigma_S^{-1} \bar{X}_S)^2 \right\} = \Omega(1) \), and \( \eta_S = \Omega(1) \) as assumed, we have \( \sigma_{\xi_{AS}}^2 = \Omega(1) \), thereby verifying the second condition. \( \square \)

D. False Discovery Rate (FDR) Control for MIDA. As an additional validation to our asymptotic results on the theoretical properties and inferential tools for MIDA, we discuss here some numerical results on FDR control for MIDA, based on the setting used for our simulation studies in Section 7, for estimating the set of significant mediators: \( \cup_{r=1}^{m} S^{(r)} := \cup_{r=1}^{m} \{ X_j^{(r)} : \eta_j^{(r)} \neq 0, j = 2, \ldots, p - 1 \} \) (Target) and \( \cup_{r=1}^{m} S^{s(r)} := \cup_{r=1}^{m} \{ X_j^{(r)} : \theta_j^{(r)} \text{aver}(\Theta_j^{(r)}) \neq 0, j = 2, \ldots, p - 1 \} \) (Target_CPDAG), when the true CPDAG is known as well as when the CPDAG is estimated. The BH procedure at a level \( \alpha \) (asymptotically) guarantees to control the FDR at level \( \alpha m_0/M \) for estimating Target_CPDAG, where for each simulation setting, \( m_0 \) denotes the total number of true hypotheses \( | \cup_{r=1}^{m} S^{s(r)} | \) among the \( M = m \times (p - 2) = 5000 \) hypotheses. Since \( \cup_{r=1}^{m} S^{s(r)} \subseteq \cup_{r=1}^{m} S^{(r)} \), it is expected that the empirical FDR level would be higher when it is measured with respect to Target.

Figure A shows that the BH procedure becomes quite conservative for estimating \( \cup_{r=1}^{m} S^{s(r)} \), though we ignore the additional adjustment suggested by Benjamini and Yekutieli [2001] in order to correct for possible dependencies among the hypotheses here. The conservativeness of the BH procedure can be attributed to the fact (a consequence of Theorem 6.2, as was discussed in Section 6.3) that the \( p \)-value corresponding to the test: \( \theta_{ij}^{(r)} \text{aver}(\Theta_{2p}^{(r)}) = 0 \) has a stochastically larger distribution than Uniform[0,1] when both \( \text{aver}(\Theta_{2p}^{(r)}) \) and \( \theta_{ij}^{(r)} \) are zero. In order to mitigate this issue, we apply a heuristic screening, whereby we first select the potential mediators for which the total effect of the treatment \( \bar{X}_1 \) on the mediator is non-zero, by testing \( \theta_{ij}^{(r)} = 0 \) at the significance level 0.01. Then, we apply the BH procedure on this selected set. Figure B shows the empirical FDR of the estimated sets based on the BH procedure after this screening, and demonstrates that the heuristic screening method above is indeed effective in reducing the conservativeness of the BH procedure in controlling the FDR level for multiple testing using MIDA.
Fig A: Empirical FDR of the estimated sets based on the BH procedure without any $p$-value screening for estimating Target and Target_CPDAG when the true CPDAG is known as well as when the CPDAG is estimated.

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Fig B: Empirical FDR of the estimated sets based on the BH procedure with $p$-value screening for estimating Target and Target_CPDAG when the true CPDAG is known as well as when the CPDAG is estimated.

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