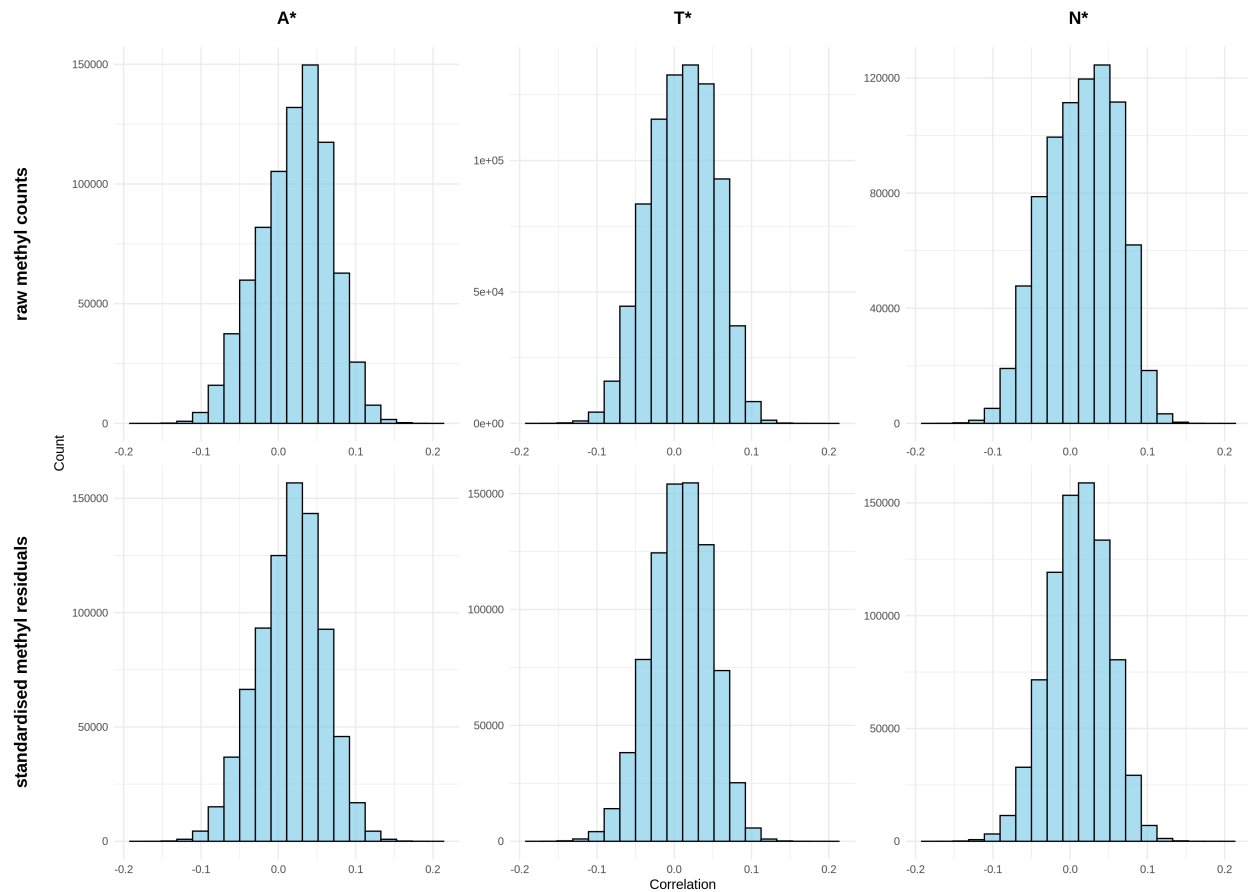
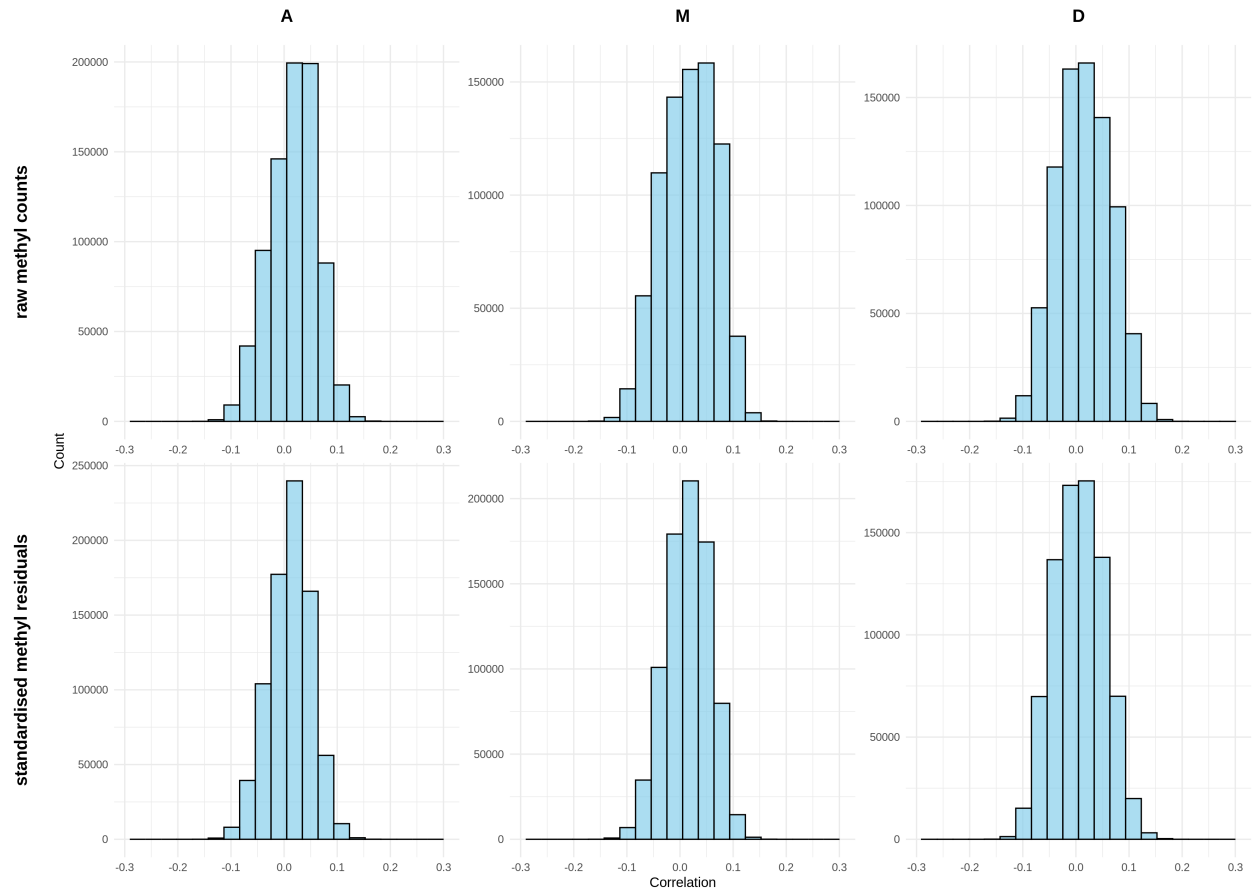
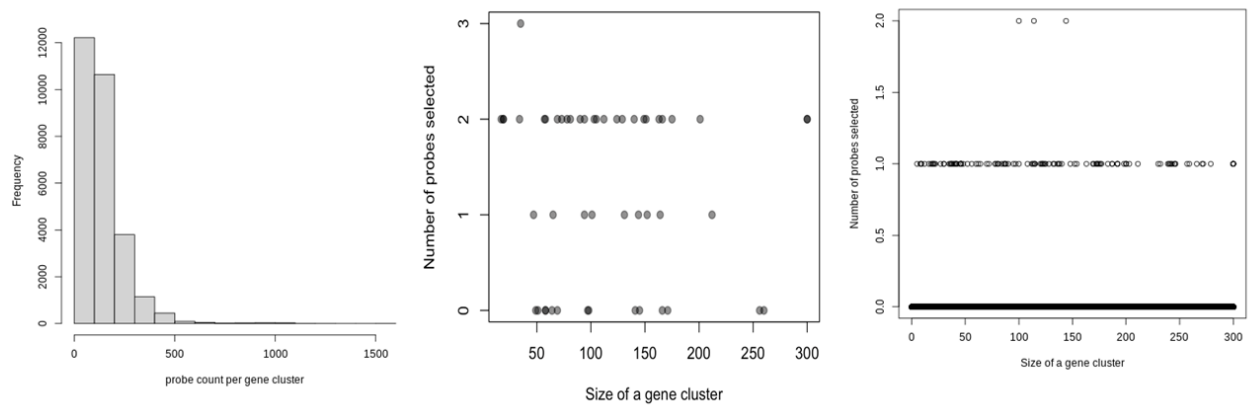




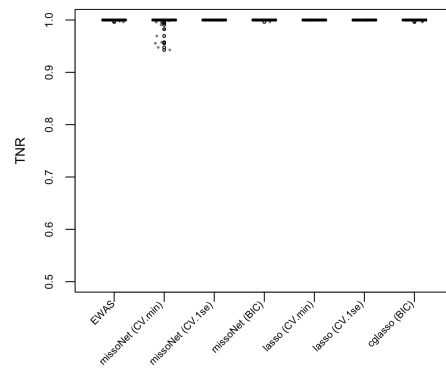
Supplementary Figure 1: Correlations between individual DNA methylation probes and the 3 original CSF biomarkers (A*,T*,N*). For each CSF biomarker, correlations were estimated for both the raw methylation measurements (row 'Raw methylation counts') and the standardized methylation residuals obtained from stage 1 (row 'Standardised methylation residuals'). Most of the methylation probes had small correlations with the CSF biomarkers. Some probes showed correlations as large as 0.2.



Supplementary Figure 2: Correlations between individual DNA methylation probes and the transformed CSF biomarkers (A/M/D). For each CSF biomarker, correlations were estimated for both the raw methylation measurements (top row) and the standardised methylation residuals obtained from stage 1 (bottom row). Most of the methylation probes had small correlations with the CSF biomarkers. The highest correlations from both raw methylation and standardized residuals are around ± 0.3

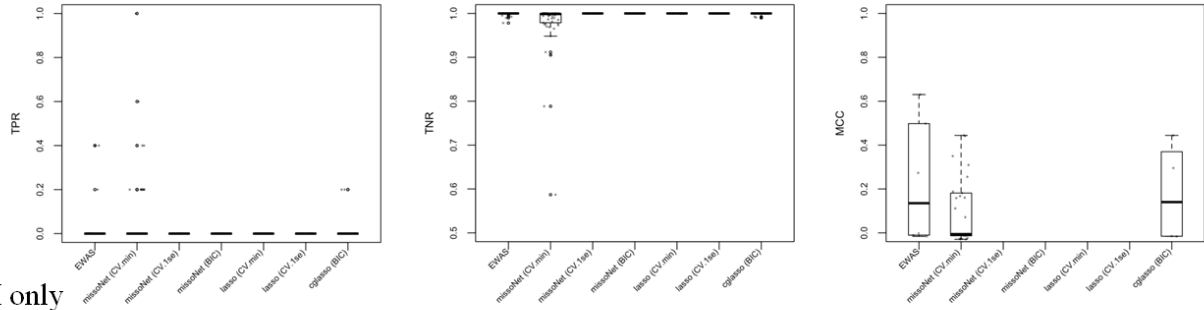


Supplementary Figure 3: **Left:** Distribution of number of probes per gene cluster across the genome, before dividing gene clusters larger than 300 probes into smaller sets. **Middle:** Number of probes selected by *missoNet*-BIC in a gene cluster with respect to cluster size calculated from simulated dataset. **Right:** Number of probes selected by *missoNet*-BIC in a gene cluster with respect to cluster size calculated from the ADNI data. There is no association shown here between the size of a gene cluster and how many probes are selected in a gene cluster both in simulated data and in the ADNI data.

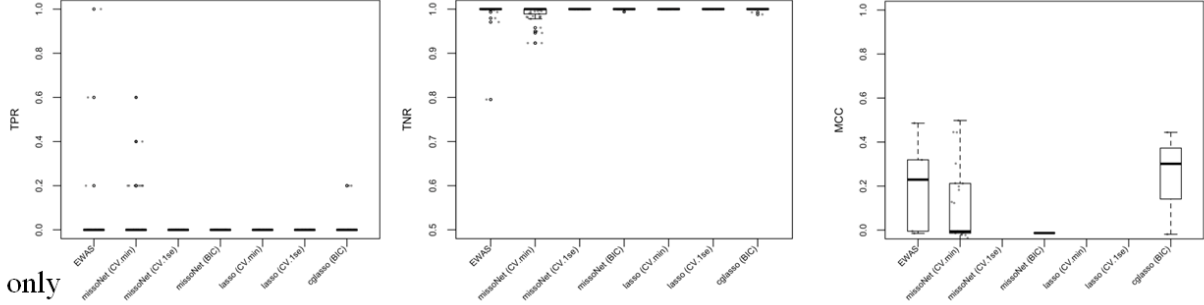


Supplementary Figure 4: True negative rate (TNR) for each method in simulation when no true associations are present. The results for each simulated dataset (grey dots) are overlaid with boxplots.

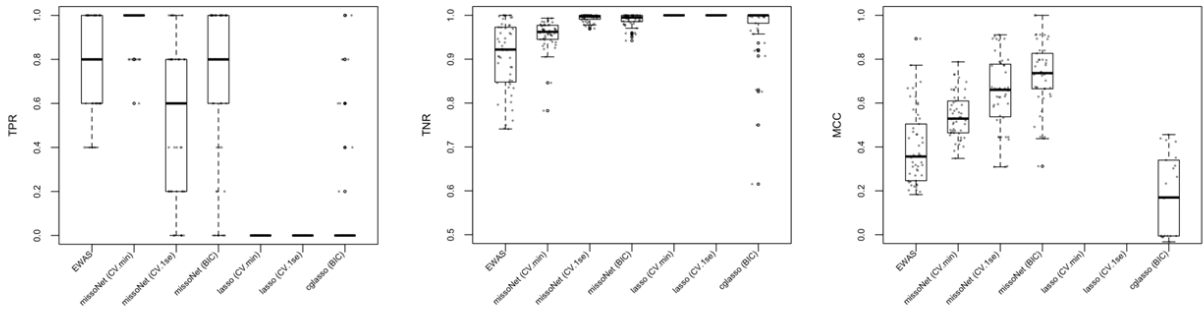
A only



M only



D only



TPR

TNR

MCC

Supplementary Figure 5: Performance of different methods in simulations when the true associations (effect size = 0.04) affect only one phenotype. Top row shows results when associations are solely with *A*, middle row shows associations solely with *M*, and bottom row shows associations solely with *D*. The results for each simulated dataset (grey dots) are overlaid with boxplots. *TPR* True positive rate; *TNR* True negative rate; *MCC* Matthews correlation coefficient.

Supplementary Section 1: Replication study using data from the Canadian Longitudinal Study on Aging

We used data from the Canadian Longitudinal Study on Aging (CLSA) (project #2104015) to replicate our findings in ADNI. We obtained their demographic data as well as methylation data on 1478 individuals. In the CLSA dataset, there is information on self-reported AD status, but no clinical diagnosis. We also analyzed a cognitive test, REYII, as a second phenotype related to AD. We are lacking the genotypes for the *APOE4*, and there were no CSF biomarkers measured in CLSA. Therefore, we tested associations for the 34 probes in Table 2 using the formula below:

$$g(AD/REYII) = \beta_{0j} + \beta_{1j} * yoe_i + \beta_{2j} * age_i + \beta_{3j} * eaa_i + \beta_{4j} * sex_i + \beta_{5j} * PC1_i + \beta_{6j} * PC2_i + \beta_{7j} * PC3_i + \beta_{8j} * probe + \epsilon_{ij},$$

where "AD/REYII" implies that we fit models for each of these phenotypes separately. The two phenotypes were modelled using generalized linear models with different link functions. For reported AD, we used the *logit* function, and for the cognitive test REYII, we used a *quasi-poisson* function since this is count data. We summarized the replication results in Supplementary Tables 5 and 6.

Supplementary Section 2: Simulation Results

As mentioned in the Methods section, we conducted simulations for several different scenarios. This section shows additional scenarios that were not in the Results section. First, we present here the performance of each of the methods when no true association exists (i.e. a null model). Since there are no true associations, the true positive rates will all be zero, and MCC is not computable. Thus, we are only showing the true negative rate results in Supplementary Figure 4. All methods perform similarly.

In Supplementary Figure 5 we show three simulation scenarios where all true signals lie in just one phenotype: A , M , or D . These scenarios represent different detection powers given the same fixed true effect size: A and M both have low detection power, and the performances of all methods are more vulnerable to 2-3 dataset that select the true associated probes by random. On the other hand, D has a higher detection power, and that most of the methods can reliably and robustly identify true signals (see TPR performance from Supplementary Figure 5). In this case, *missoNet*-BIC achieves the most balanced performance (the highest MCC), reflecting its superior ability to differentiate true associations from noises.

The difference we see in detection power among these phenotypes is due to their variance differences. Given a fixed sample size, phenotypes with larger variances result in a lower detection power for a given effect size. Since both A and M have higher variance, all methods have very low detection power when true signals lie on these two phenotypes. On the other hand, D is inherently less variable than A and M , and thus the same effect size yields a higher signal-to-noise ratio, resulting in a substantial increase of the detection power and MCC for most methods.

Supplementary Section 3: Interaction models

We are also interested in understanding whether an interaction may exist between DNA methylation probes and our AD-specific covariates (namely, AD diagnosis and *APOE4* count). We were not able to use a similar multivariate approach as in our main analyses to answer this question for the following reasons. Firstly, the number of covariates in the second stage model could be very large, since the interactions would need to include all probes in an extended gene region. Secondly, *missoNet*, as implemented, cannot guarantee an appropriate inclusion of a hierarchy of terms in an interaction (i.e. to keep the two main effects when an interaction is retained). Such hierarchies are crucial to interpretability. Instead, we have conducted single-phenotype analyses on the three phenotypes separately for the 34 probes identified by *missoNet* in Table 2, and investigated two-way interactions with AD diagnosis and *APOE4*. Namely, we fit

$$Y = \beta_0 + \beta_1 * \text{probe} + \beta_2 * \text{AD} + \beta_3 * \text{APOE4} + \beta_{12} * \text{probe} * \text{AD} + \beta_{13} * \text{probe} * \text{APOE4}$$

where *probe* refers to the methylation residuals obtained from stage 1.

The summary statistics for the two interaction terms are summarized in Supplementary Tables 7-9.

Supplementary Section 4: ADNI authors' list

The investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data are provided here, but they do not participate in analysis or writing of this report. The full list can also be found using the following link: <https://adni.loni.usc.edu/wp-content/themes/freshnews-dev-v2/documents/policy/ADNI%20Groups%20Acknowledgements%20Journal%20Format.pdf>

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