Ref. Ares(2021)4538810 - 13/07/2021

LifeCycle

Report on approaches to analyse multiple stressor data in the context of longitudinal modelling

Work package 7 - Task 7.3 - Deliverable 7.3

Authors:

Charline Warembourg, Martine Vrijheid, Xavier Basagaña

Organisation Name of Lead Contractor of this Deliverable: UNITO

Version 1.0

Delivery date: 30 June 2021 (Month 54)

Dissemination level:

Public

This project received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 733206 (LifeCycle).

Table of contents

1. Context 3

2. Methods 3

Data simulation 3

Exposome simulation 3

Outcome simulation 4

Statistical Methods to Estimate the Exposome-Health Association 5

3. Results 7

4. Conclusion 8

5. References 9

1. Context

The exposome encompasses all the environmental (i.e., non-genetic) factors that an individual experience from conception onwards. The exposome concept has emerged quite recently and aims at considering all the environmental stressors simultaneously as opposed to the one-by-one approach classically used in epidemiological research. The exposome approach leads to some statistical challenges due to the high number of exposures that need to be considered, which are sometimes highly correlated. The first large epidemiological exposome studies have been published recently, and most of them explore the effects of the exposome at a single time point. In parallel, some methodological papers have reported recommendations on how to analyze exposome data by looking at issues such as false positive or negative associations, statistical power, or how to deal with highly correlated data (Agier et al., 2016; Santos et al., 2020). However, few studies have tried to characterize the longitudinal relationship between repeated measures of the exposome and a health outcome, and there is no clear guidance on what methods to use and their performances. Having repeated measurements of the exposome further increases the dimensionality problem and may also aggravate the problems associated with highly correlated variables, as a variable measured at different time points is expected to have some degree of correlation, although this can vary according by the type of exposure.

Here, we conduct a simulation study is to compare the performance of different statistical approaches to assess exposome-health associations in the context of multiple and repeated exposure variables. We expect that these results start shedding some light on what are the most useful approaches in different scenarios dealing with repeated exposome data and that they can inform future longitudinal exposome analyses.

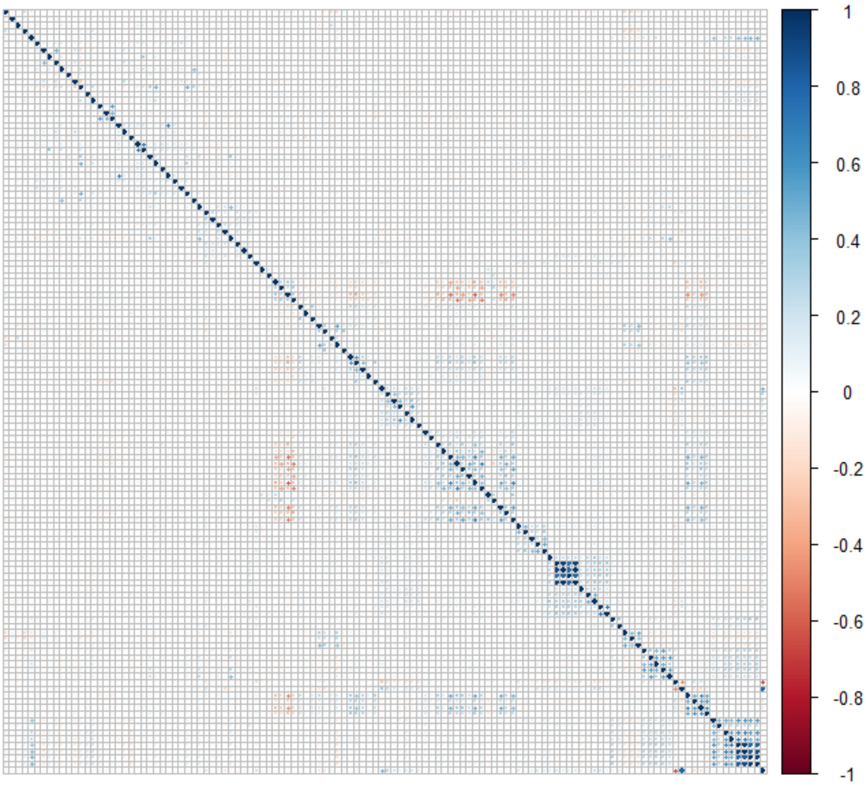
2. Methods

Data simulation

Exposome simulation

We simulated 100 independent datasets, each of them being composed of 500 exposure variables (100 exposures multiplied by 5 time points). The exposure matrix was obtained by summing to components: 1) a subject random effect, that induces correlation between repeated measures from the same subject; and 2) a residual term, that induces correlation between exposures. To generate the random effects, we sampled from a mean zero normal distribution, with a variance according to three values for the intraclass correlation coefficient (ICC): low (0.1), medium (0.5), and high (0.9). Each ICC was used with the same probability, so that simulated dataset approximately had the same number of variables with each ICC. Variables with an ICC of 0.9 are variables that are expected to remain similar over time (e.g., exposures with long half-life), while those with an ICC of 0.1 are expected to vary a lot over time (e.g., compounds with short half-life). The residual component for each time point was generated from a multivariate normal distribution with mean zero and covariance matrix equal to a real correlation matrix from the HELIX project (postnatal exposome, see Figure 1).

Figure 1. Real correlation matrix used to simulate the data at baseline (time point i=1; Postnatal exposome - HELIX project)



Outcome simulation

The health outcome Y was simulated by choosing a reduced subset of exposures that were assumed to be the only ones that were associated with the outcome (hereafter true exposures), according to two scenarios:

- **Scenario 1,** where all the 5 time points of each of the true exposures are truly associated with Y
- **Scenario 2** where only a single time point of each of the true exposures is truly associated with Y

For each scenario, Y was simulated with **k=3, 5, 10, and 25** true exposures. For scenario 1, it means that the total number of terms in the data-generating model (apart from the intercept) was 15, 25, 50, and 125 variables (i.e., k multiplied by 5 time points). For scenario 2, this means that the data-generating model includes k terms (apart from the intercept). Let X_1, … X_{100}, and let l = (l_1,…,l_k) be a set of indices that indicate which are the k true exposures. The mean of Y was calculated as $m = \sum_{j=1}^{k} \beta_j X_{l_j}$. Then, the response variable was generated from a normal distribution with mean m and a variance that resulted in an R2 of the model of 5%.

Statistical Methods to Estimate the Exposome-Health Association

The following methods were applied to the raw data (100 exposures measured at 5 different time points = 500 variables):

1. *Exposome-wide association study (ExWAS)*. ExWAS consists of fitting as many regression models as there are exposure variables in order to evaluate the association between each exposure variable and Y, independently of the other (Patel et al., 2010). The statistical significance is based on the two-sided p-value after applying a correction for multiple testing. For the present study, 500 linear regression models were performed to assess the association between each exposure variable and Y, independently of the other exposure variables and ignoring the dependency between time points. The results are reported with no correction for multiple testing and with correction for multiple testing using the Bonferroni, the Benjamini-Hochberg, and the Benjamini-Yekutieli correction.
2. *ExWAS-multiple linear regression (ExWAS-MLR)*. ExWAS-MLR is an extension of the ExWAS where the statistically significant variables from the ExWAS are introduced simultaneously in a single multi-exposure regression model. Each exposure variable is considered statistically significant if the two-sided p-value obtained in the multi-exposure regression model is below 5%. The candidate variables to be introduced into the multi-exposure model were selected according the ExWAS results, with and without correction for multiple testing.
3. *Elastic Net (ENET)*. ENET is a penalized regression method that performs both regularization and variable selection (Zou & Hastie, 2005). It combines the L1 penalty from LASSO which shrink the coefficient of the uninformative variable to 0, and the L2 penalty from RIDGE which accommodates correlated variables and ensures numerical stability. The tuning parameters were determined in two different ways: 1) by minimizing the prediction root mean squared error (RMSE) using 10-fold cross-validation (ENET.min), and 2) by defining the optimal calibration parameters (in order to prevent over-fitting) as those providing the sparsest model among those yielding an RMSE within 1 standard error of the minimum RMSE (ENET.opt).
4. *Sparse Partial Least Squares regression (sPLS)*. sPLS performs both variable selection and dimension reduction simultaneously (Chun & Keleş, 2010). sPLS is an extension of the partial least squares regression – a supervised dimension reduction technique that builds latent variables as linear combinations of the original set of variables – which additionally imposes sparsity using a L1 penalty in the estimation of the linear combination coefficients. The tuning parameter and the number of components to be included in the regression model were calibrated by minimizing the RMSE using 5-fold cross-validation.
5. *Max-Min Parent Children algorithm (MMPC)*. The MMPC algorithm perform variable selection. MMPC is similar to a forward selection except that, at every step (when searching for the next best variable) it does not use all previously selected variables, but subsets of them and the non-significant variables are removed for further consideration (Tsagris & Tsamardinos, 2019). The number of variables included in the subsets of previously selected variables was set to 3 (default value). Statistical significance is based on the two-sided p-value below 5%.
6. *Deletion-substitution-addition algorithm (DSA)*. DSA is an iterative regression model search algorithm performing variable selection (Sinisi & van der Laan,

2004). It searches for the best model starting with the intercept model and identifying an optimal model for each model size. At each iteration, the following three steps are allowed: *a*) removing a term, *b*) replacing one term with another, and *c*) adding a term to the current model. The final model is selected by minimizing the value of the RMSE using 5-fold cross-validated data. For this simulation study, we did not allow polynomial nor interaction terms, and considered models of size up to 25 variables.

7. *Constrained Distributed Lag Nonlinear Model (DLNM).* Distributed lag models are regression models that assess how an exposure measured at different time points affects the outcome. Constrained distributed lag models allow putting constraints to the regression coefficients at each time point in order to improve in efficiency and to avoid collinearity problems. For example, it is common to constrain regression coefficients to vary smoothly over time, thus assuming that the effects of exposure at two periods that are close in time will be more similar than the effects for two exposure periods that are further apart (Gasparrini et al., 2010). DLNMs describe the bi-dimensional dose-lag-response associations, potentially varying non-linearly in the dimensions of predictor intensity and lag. To do so, we build a cross-basis matrix (one basis for the predictors and one basis for the lags) for each exposure and introduced them in 100 independent linear regression models. To build the basis for the predictors, we assumed a linear effect of the exposures on Y. Regarding the shape in the lag space, we assumed it follows a quadratic B-spline, with two equally-spaced knots. To evaluate the statistical significance of the exposure-outcome association, we first evaluated the significance of the entire cross-basis, applying or not a correction for multiple testing. Then, among the significant cross-bases (with or without p-value correction), we evaluated if a particular lag was statistically significant if the estimated effect for that lag had a confidence interval that excluded 0.
8. *Penalized distributed Lag (Non-)Linear Models (DLNMpen).* This method is an extension of the DLM/DLNM framework to penalized splines within generalized additive models (gam) (Gasparrini et al., 2017). Here, the specification of the dlnm was the same than in the previous method (DLNM), except that we placed knots at all time points, forced the lag structure to follow a cubic regression spline and introduced a penalty term that regulated the degree of smoothing. Significance was assessed as in DLNM.

For methods 1, 2, 7 and 8, results are reported with no correction for multiple testing and with correction for multiple testing using the Bonferroni, the Benjamini-Hochberg (BH), and the Benjamini-Yekutieli (BY) correction.

The dependency between time points was ignored when applying methods 1 to 6 and all variables measured at different time points were considered independently; i.e., only methods 7 and 8 considered the longitudinal character of the exposure variables measure from time i=1 to 5.

In addition, we implemented 2-step approaches: the first step aims to summarize the exposure levels measured at different time points into a single measure (moving from 500 to 100 variables) and to apply an ExWAS analysis on these summarized exposures. At the second step, we applied methods 1 to 6 on the subset of (raw) exposures for which the summarized exposures were significant at 0.05 alpha level in the ExWAS performed at step 1. Step 1 was performed in 2 different ways: 1) by calculating the averaged level of exposure across time points and 2) by building exposure trajectories using latent class mixed model (LCMM).

Statistical Performance Assessment

For all methods, we calculated the sensitivity and the false discovery rate in two different ways: 1) to evaluate the performance to identify the true exposure at the true time point (denominator = 500 variables), and 2) to evaluate the performance to identify the true exposure whatever the time point (denominator=100 variables).

We also compared the performance of the methods to identify the true exposure at the true time point according to the intraclass correlation coefficient of the exposures across time points.

3. Results

Scenario 1. All time points are truly associated with Y

Performance to detect the true exposure whatever the true time point (Table 1): All methods have a good sensitivity when the number of true predictors is low (k=3: min sensitivity = 74% for ENET.opt applied on raw data), but show varying level of FDR. For k=3 and k=5, the methods that show a sensitivity >70% and a FDR <20% include DSA, and ExWAS, DLNM, and penalized DLNM (with p-value correction) applied on the raw data, and some of the 2-step approaches including the ExWAS (with p-value correction) and ENET applied on the exposure trajectories, and the ExWAS (with a Bonferroni correction) applied on the averaged exposure levels. For k=10 and k=25, the sensitivity decreases drastically for all methods (<50% for several of them); the DSA performed on the averaged data shows the best performance with a sensitivity/FDR of 85%/31% when k=10 and 52%/22% when k=25.

Performance to detect the true exposure at the true time point (Table 2): None of the tested methods outperforms the others to detect the true exposure at the true time point. In overall, low FDR are observed for several methods but few of them have a high sensitivity. For k=3 and k=5, only 2 methods, both following a 2-step approach, show a sensitivity >70% and a FDR<20%, that are the ExWAS (with a BY correction) applied on the averaged exposure levels and the ExWAS (with a BH correction) applied on exposure trajectories. ExWAS (with any p-value correction) applied on raw data also shows reasonable performance but with a lower sensitivity. For k=10 and k=25, the sPLS performed on the averaged data shows the best performance with a sensitivity/FDR of 87%/37% when k=10, and 62%/27% when k=25.

Scenario 2. A single time point is truly associated with Y

Performance to detect the true exposure whatever the true time point (Table 3): When only a single time point is truly associated with Y, none of the tested methods perform well to detect the true exposure when k=5, 10, or 25, i.e., none of the methods reach a sensitivity >60% together with a FDR <30%. When k=3, the DSA applied on raw data is the only method which has a sensitivity >80% and a FDR<10%. Other methods including penalized DLNM (with a BH correction), ExWAS and ExWAS-MLM (with a Bonferroni or a BH correction) and sPLS applied on raw data, and also the ExWAS and ExWAS-MLM (with a Bonferroni correction) applied on the averaged exposure levels show a sensitivity >70% and a FDR <20%.

<u>Performance to detect the true exposure at the true time point (Table 4)</u>: Similarly, none of the tested methods perform well when k=5, 10, or 25. When k=3, DSA, sPLS, and ExWAS-MLM (with a Bonferroni or a BH correction) applied on raw data, and ExWAS-MLM (with a Bonferroni correction) applied on averaged exposure levels show a sensitivity >70% and a FDR<20%, followed by ExWAS (with Bonferroni or By correction) applied on raw data and ExWAS-MLM (with a BY correction) with a sensitivity >60% and a FDR <30%.

Comparison of the performances by ICC between time points

Scenario 1. When the ICC is high (>0.6), ExWAS (with any p-value correction) applied on raw data performed well for k=3 and 5 (sensitivity>80% and FDR<10%). sPLS applied on raw data also shows good performance (sensitivity>70% and FDR<20%) up to k=10. Similar performances are observed when these methods are applied on averaged exposure levels with a sensitivity >70% and FDR <20% for ExWAS (with BY correction) up to k=10 and sPLS up to k=25. ExWAS (with p-value correction) applied on exposure trajectories also shows a sensitivity >70 and a FDR<20%, or better, up to k=10.

Scenario 2. The results observed with different ICC are similar to the main results; none of the methods perform well for k=5, 10 and 25. In overall, the methods seem to perform slightly better for k=3 when the ICC between time points is low (<0.3) to moderate (>0.3 to <0.6).

4. Conclusion

Some methods, such as ExWAS and DSA applied on raw data, and ExWAS applied on averaged exposure levels show good performance to identify the exposures that are truly associated with Y in both scenarios. However, these methods perform worse to identify the true window of exposure and when the number of true exposures is high (k=10 and k=25). If we are interested in the detection of the true window of exposure and we assumed a low number of true exposures (k=3 or 5), ExWAS applied on averaged exposure levels or on exposure trajectories show the best performance under scenario 1 (all time points truly associated with Y), while DSA, sPLS, and ExWAS-MLM applied on raw data and ExWAS-MLM applied on averaged exposure levels show the best performance under scenario 2 (only a single time point is truly associated with Y). For the scenario 1, the methods seem to perform better when the ICC between time points is high, including when k is high (k=10 and 25).

This simulation study shows that none of the tested methods provided good enough performance to study association between repeated exposome data and health outcome and it is difficult to provide a clear strategy that would fits for all potential scenarios. These results call for the development of new statistical methods or approaches that are able to address both the issue of multiple (and correlated) variables and of repeated exposome data with an improved performance.

5. References

Agier, L., Portengen, L., Chadeau-Hyam, M., Basagaña, X., Giorgis-Allemand, L., Siroux, V., Robinson, O., Vlaanderen, J., González, J. R., Nieuwenhuijsen, M. J., Vineis, P., Vrijheid, M., Slama, R., & Vermeulen, R. (2016). A Systematic Comparison of Linear Regression-Based Statistical Methods to Assess Exposome-Health Associations. *Environmental Health Perspectives*, *124*(12), 1848–1856. https://doi.org/10.1289/EHP172

Chun, H., & Keleş, S. (2010). Sparse partial least squares regression for simultaneous dimension reduction and variable selection. *Journal of the Royal Statistical Society. Series B: Statistical Methodology*, *72*(1), 3–25. https://doi.org/10.1111/j.1467-9868.2009.00723.x

Gasparrini, A., Armstrong, B., & Kenward, M. G. (2010). Distributed lag non-linear models. *Statistics in Medicine*, *29*(21), 2224–2234. https://doi.org/10.1002/sim.3940

Gasparrini, A., Scheipl, F., Armstrong, B., & Kenward, M. (2017). A penalized framework for distributed lag non-linear models. *Biometrics*, *73*(3), 938–948. https://doi.org/10.1111/biom.12645

Patel, C. J., Bhattacharya, J., & Butte, A. J. (2010). An environment-wide association study (EWAS) on type 2 diabetes mellitus. *PLoS ONE*, *5*(5). https://doi.org/10.1371/journal.pone.0010746

Santos, S., Maitre, L., Warembourg, C., Agier, L., Richiardi, L., Basagaña, · Xavier, & Vrijheid, M. (2020). Applying the exposome concept in birth cohort research: a review of statistical approaches. *European Journal of Epidemiology*, *35*, 193–204. https://doi.org/10.1007/s10654-020-00625-4

Sinisi, S. E., & van der Laan, M. J. (2004). Deletion/substitution/addition algorithm in learning with applications in genomics. *Statistical Applications in Genetics and Molecular Biology*, *3*(1), Article18. https://doi.org/10.2202/1544-6115.1069

Tsagris, M., & Tsamardinos, I. (2019). Feature selection with the R package MXM. *F1000Research*, *7*. https://doi.org/10.12688/f1000research.16216.2

Zou, H., & Hastie, T. (2005). Regularization and variable selection via the elastic net. In *J. R. Statist. Soc. B* (Vol. 67, Issue 2).

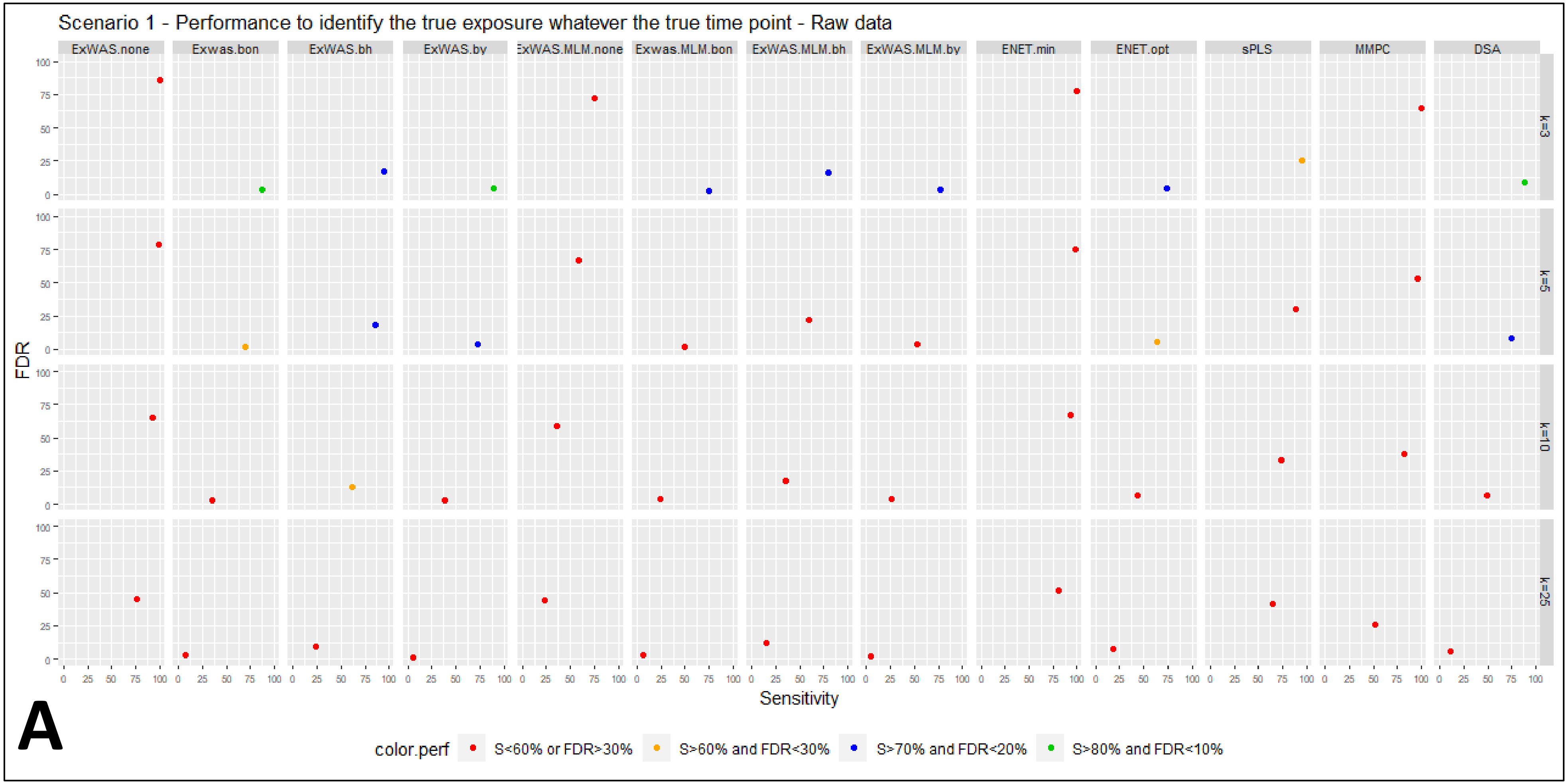
Scenario 1 (all time points are associated with Y)

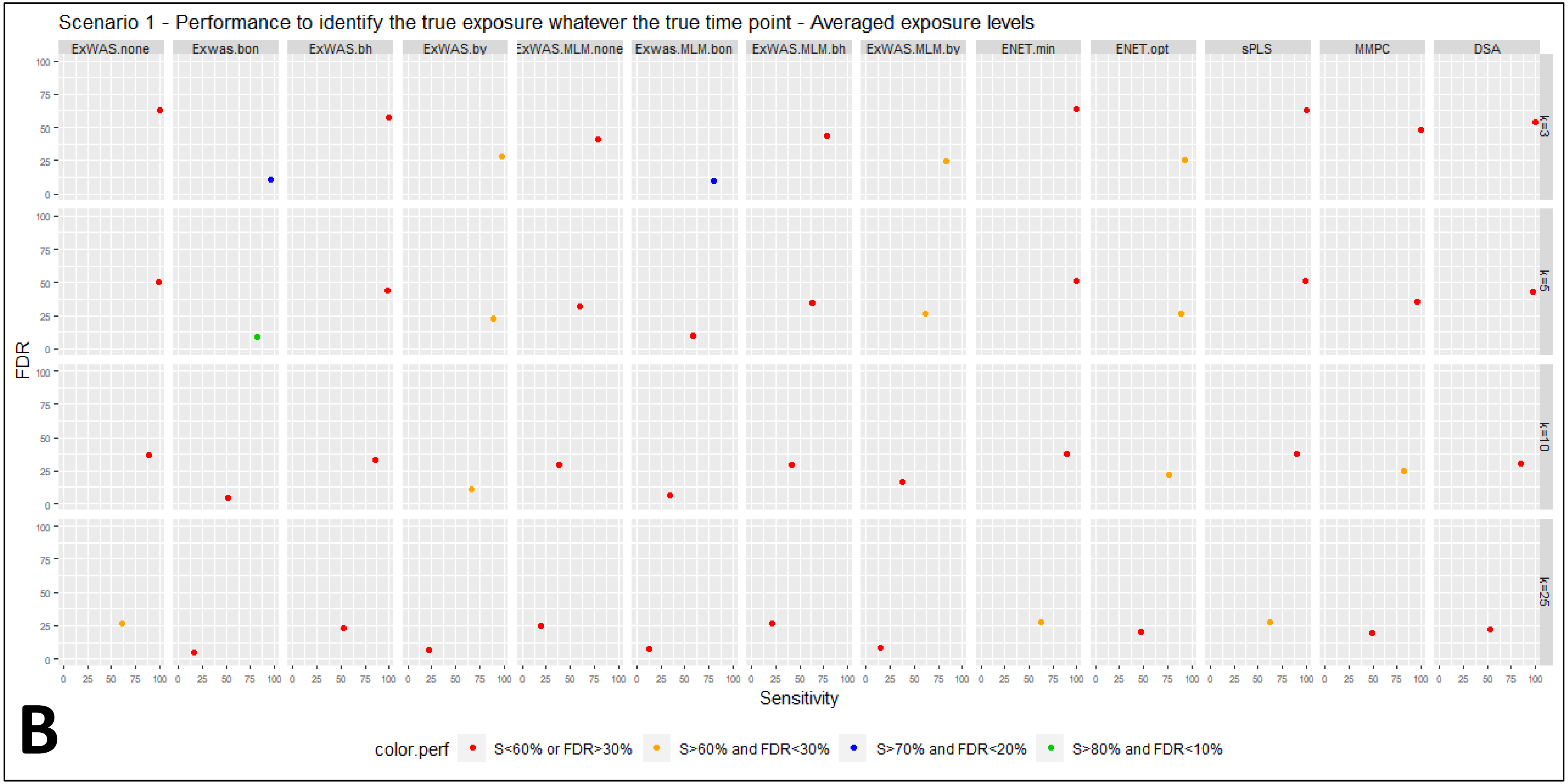
*Table 1. Performance to identify the true exposures **whatever** the true time point(s) – **Scenario 1***

<	Sensitivity				FDR			
N true predictors (x5)	**3**	**5**	**10**	**25**	**3**	**5**	**10**	**25**
Raw data								
ExWAS.none	100 (0)	99 (4.4)	92.5 (8.1)	76.5 (7.9)	85.8 (3.1)	78.6 (4.4)	65.5 (6.2)	45.3 (6.8)
Exwas.bon	86.7 (18.3)	69.4 (17.4)	35.7 (12.4)	8 (5.1)	3.1 (9.8)	1.6 (6)	2.4 (7.9)	2.9 (12.6)
ExWAS.bh	95 (12)	85.4 (15)	61.7 (17.4)	24.1 (14.4)	17.5 (18.7)	18 (15.5)	12.6 (12.4)	9.4 (9.8)
ExWAS.by	88.7 (17.9)	72.6 (18.8)	38.7 (15.5)	5.7 (6)	3.9 (10.5)	3.4 (8.3)	2.9 (7.5)	0.8 (4.1)
ExWAS.MLM.none	74.7 (24.7)	58.4 (23.4)	35.9 (16.8)	23.5 (8.6)	72.5 (12.2)	67.2 (13.1)	58.8 (16.8)	43.9 (15.4)
Exwas.MLM.bon	74.3 (24.6)	49.8 (21)	24.2 (14.5)	6.5 (4.4)	2.6 (9.1)	1.9 (7.1)	4 (14.2)	3.2 (13.3)
ExWAS.MLM.bh	80 (25.1)	59.6 (22.4)	35.6 (16.9)	15.6 (10.1)	16.3 (20.3)	21.7 (19.4)	17.4 (20)	12 (15.8)
ExWAS.MLM.by	76.3 (23.4)	52.4 (23.9)	25.9 (15.7)	4.2 (4.7)	2.9 (9.6)	3.8 (10.7)	3.9 (10.6)	1.7 (10.7)
ENET.min	100 (0)	98.6 (5.1)	92.5 (10.5)	80.6 (13.9)	78 (14.9)	75 (12.3)	66.7 (11.8)	51.8 (10.1)
ENET.opt	74 (27.5)	64 (26.8)	43.4 (29)	18 (21.3)	3.8 (12.9)	5.4 (13.5)	6.4 (11)	7.6 (11.9)
sPLS	95 (12)	89 (13.7)	73.8 (21.7)	65 (35.3)	25.1 (27.4)	30.2 (24.4)	32.7 (24.9)	41.3 (27.6)
MMPC	100 (0)	95.6 (8.8)	82.1 (12.3)	51.9 (8.5)	64.4 (8.2)	53.1 (9.7)	37.6 (10)	25.9 (8.3)
DSA	87.7 (18.1)	74.4 (22.4)	48.9 (21.5)	11.1 (13.1)	8.5 (16.4)	8.4 (13.6)	6.5 (10.1)	5.3 (10.1)
Averaged data								
ExWAS.none	100 (0)	98.6 (5.1)	88.3 (10.7)	61 (8.9)	62.5 (11)	50 (11.3)	36.7 (10.4)	26.7 (8.3)
Exwas.bon	95.7 (11.3)	82.4 (14.3)	51.9 (13.3)	15.9 (7.1)	10.9 (15.3)	8.9 (12.6)	4.2 (8)	5.2 (13.3)
ExWAS.bh	99.7 (3.3)	98 (6)	85.1 (11.5)	53 (11.5)	57 (10.8)	43.9 (13.4)	32.7 (10.4)	23.2 (9.6)
ExWAS.by	97.7 (8.5)	89.8 (12.2)	66.1 (16.4)	21.6 (12.6)	27.7 (19)	22.8 (14)	11.3 (11.3)	6.9 (9.3)
ExWAS.MLM.none	79.3 (25.9)	60 (21.5)	38.8 (18.9)	19.1 (8.2)	40.4 (20.7)	32.3 (20)	29.1 (22.4)	24.9 (17.6)
Exwas.MLM.bon	80.3 (24.7)	58.2 (23.1)	34.2 (16.1)	12.3 (7)	10 (17.3)	10.2 (15.7)	6.1 (14.7)	7.6 (21.3)
ExWAS.MLM.bh	78.7 (23.9)	62.8 (22.7)	41.3 (18.5)	21.8 (8.7)	43.7 (18.6)	34.9 (21.3)	29.4 (20.7)	26.5 (17.3)
ExWAS.MLM.by	83 (23.5)	62.2 (22.2)	37.8 (17.5)	14.4 (9.1)	24.7 (19.3)	26.2 (19.8)	16.5 (21.2)	8.8 (15.7)
ENET.min	100 (0)	99.2 (3.9)	89.8 (10.7)	62.4 (8.7)	63.6 (10.7)	51.4 (10.9)	37.7 (10.1)	27.4 (8.3)
ENET.opt	93.3 (13.4)	89.4 (15.9)	76.6 (19.9)	47.8 (18.8)	25.7 (26.8)	26 (21.7)	22.5 (15)	20 (11)
sPLS	100 (0)	99.2 (3.9)	89.8 (10.7)	62.4 (8.7)	63.3 (11.9)	51.3 (11.1)	37.8 (10.2)	27.6 (8.3)
MMPC	100 (0)	96.2 (7.9)	81.8 (12)	48.8 (8.6)	48 (13.7)	36 (13.9)	24.4 (10.8)	19.4 (9)
DSA	99.3 (6.7)	96.8 (8.9)	84.9 (16.5)	52.4 (17.9)	54.1 (20.6)	42.7 (19.7)	30.7 (12.9)	21.9 (10.6)
Trajectories								
ExWAS.none	99.3 (4.7)	91.2 (11.8)	67.5 (15.9)	32.2 (8.8)	45.1 (14)	34.8 (15.6)	25.7 (12.3)	21.9 (11.6)
Exwas.bon	95.3 (11.6)	80.6 (15.9)	49.6 (13)	15.2 (6.9)	8.3 (13)	6 (10.6)	2.2 (6)	6.3 (11.8)
ExWAS.bh	99.3 (4.7)	90.8 (12.2)	66.3 (15.7)	30 (9.7)	35.7 (15.9)	27 (14.6)	20.7 (11.3)	16.9 (11.8)
ExWAS.by	97.7 (8.5)	86.6 (13.9)	58 (15.9)	19.6 (9.8)	18.2 (17.6)	13.8 (14.4)	6.9 (9.2)	7.4 (10.7)
ExWAS.MLM.none	81.7 (22.9)	57 (21.2)	33.3 (16.9)	11.9 (6.4)	27 (19.8)	25 (23.5)	20.1 (23.8)	22.9 (22.4)
Exwas.MLM.bon	80.3 (24.2)	56.6 (24.1)	31 (16)	11 (6.6)	6.5 (12.6)	7.4 (15.7)	3 (8.5)	8.1 (17.5)
ExWAS.MLM.bh	81.7 (23.4)	57.2 (23.3)	33.3 (16)	12.2 (6.5)	24.3 (20.4)	27.4 (24.6)	20.5 (21.3)	23.3 (20.5)
ExWAS.MLM.by	82.7 (23.4)	58.4 (22.1)	33.1 (15.9)	11.7 (7)	14 (16.3)	16.6 (21.3)	7.9 (13.3)	10.1 (17.4)
ENET.min	99.3 (4.7)	91.4 (11.8)	68.1 (16)	33.3 (8.8)	58.9 (12.7)	50.2 (12.6)	38.4 (11.4)	31.5 (11.4)
ENET.opt	90 (18.6)	81.4 (19.7)	53.6 (26.2)	18.9 (15.1)	13 (19)	12.3 (15.7)	8.5 (10.7)	8.8 (11.8)
sPLS	99.3 (4.7)	91.4 (11.8)	67.7 (16.5)	33.3 (8.8)	49.1 (22.3)	45.7 (17.4)	37.3 (13.1)	31.6 (12.3)
MMPC	99.3 (4.7)	90.4 (11.9)	65.8 (15.4)	29.7 (8.2)	31.1 (15)	24.7 (14.4)	16.3 (11.5)	16.8 (11.5)
DSA	98.3 (7.3)	86.8 (14.3)	6.3 (8.1)	27.7 (12.3)	42.6 (21.4)	30.1 (22.1)	12 (26.9)	17.4 (14)

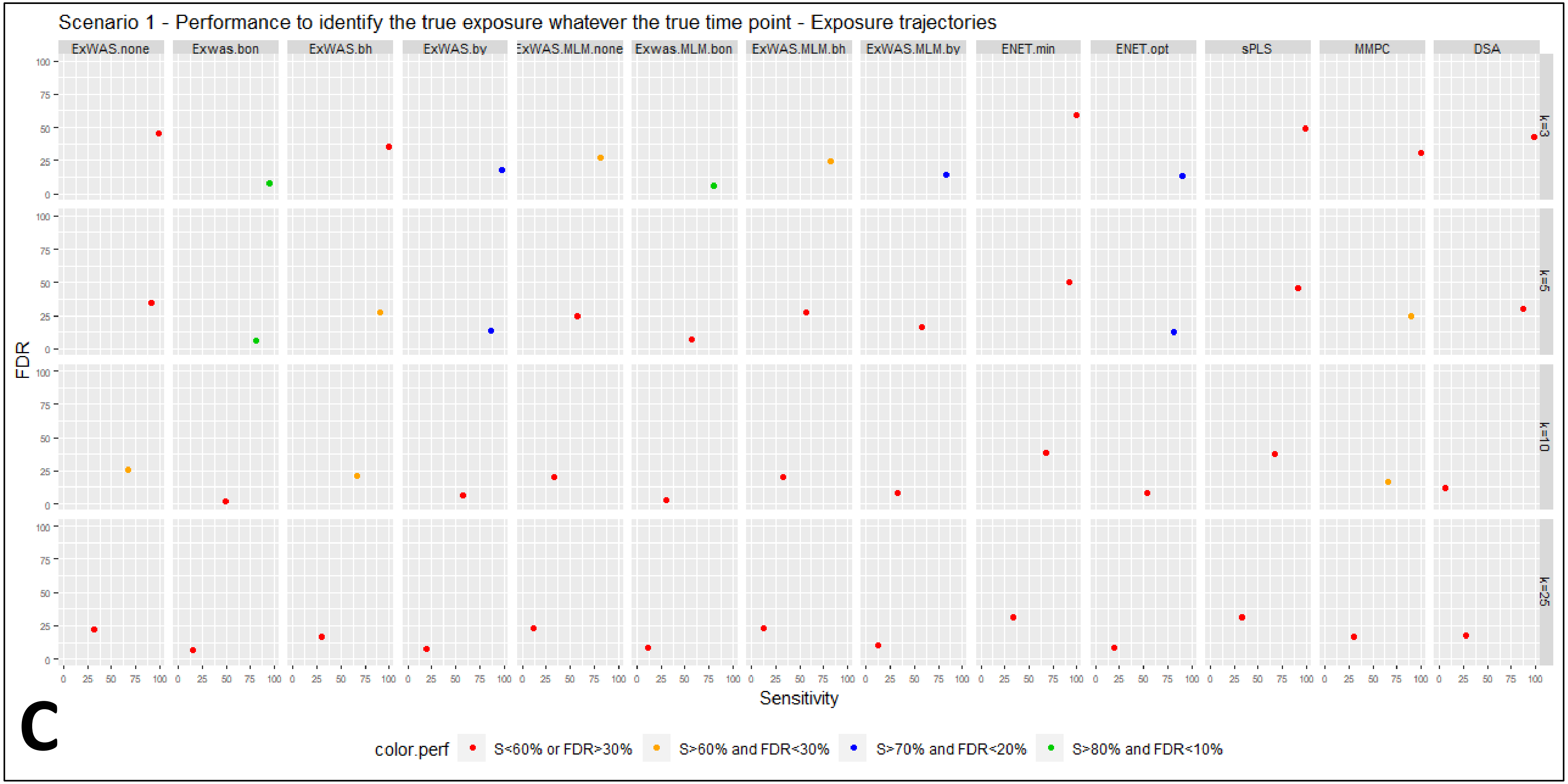
DLNM								
EWAS.none	100 (0)	96 (8)	77.5 (13.1)	43.8 (9.7)	58.5 (16.7)	50.5 (14.1)	35.2 (14.1)	29.2 (11.7)
EWAS.bonf	93.7 (13.1)	71.2 (18.1)	33.6 (13.4)	5.2 (3.8)	2.5 (8.1)	0.8 (4.1)	1.2 (7.1)	4 (12.7)
EWAS.bh	96.3 (10.5)	81 (16.2)	43.8 (14.8)	11.2 (8.9)	7.4 (12.6)	6.8 (12.5)	5.2 (11.1)	6.6 (13)
EWAS.by	92.3 (14.1)	69.4 (19.6)	30.2 (16.2)	2.9 (3.6)	2.1 (7.5)	0.8 (4.1)	0.7 (5.2)	1.2 (7.4)
Penalized DLNM								
EWAS.none	100 (0)	98 (6)	84.9 (13.1)	53.9 (10.3)	68.8 (10.6)	59.7 (12)	43.8 (12)	33.2 (9.6)
EWAS.bonf	99.3 (4.7)	89.4 (12.2)	61.1 (12.9)	23.7 (7.9)	17.1 (18.8)	16.3 (15.6)	12.5 (12.3)	12.1 (13.2)
EWAS.bh	97.7 (8.5)	86.6 (15.1)	57.6 (16.2)	19.6 (11.1)	10.1 (14.9)	10.7 (14.8)	9.6 (12.3)	9.7 (12.8)
EWAS.by	94.7 (12.3)	77.8 (17.7)	35.5 (16)	6.5 (6.1)	1.7 (7)	3.1 (9.2)	2 (7.2)	2.8 (9.9)

Figure 2. Performance to identify the true exposures whatever the true time point(s) – Scenario 1

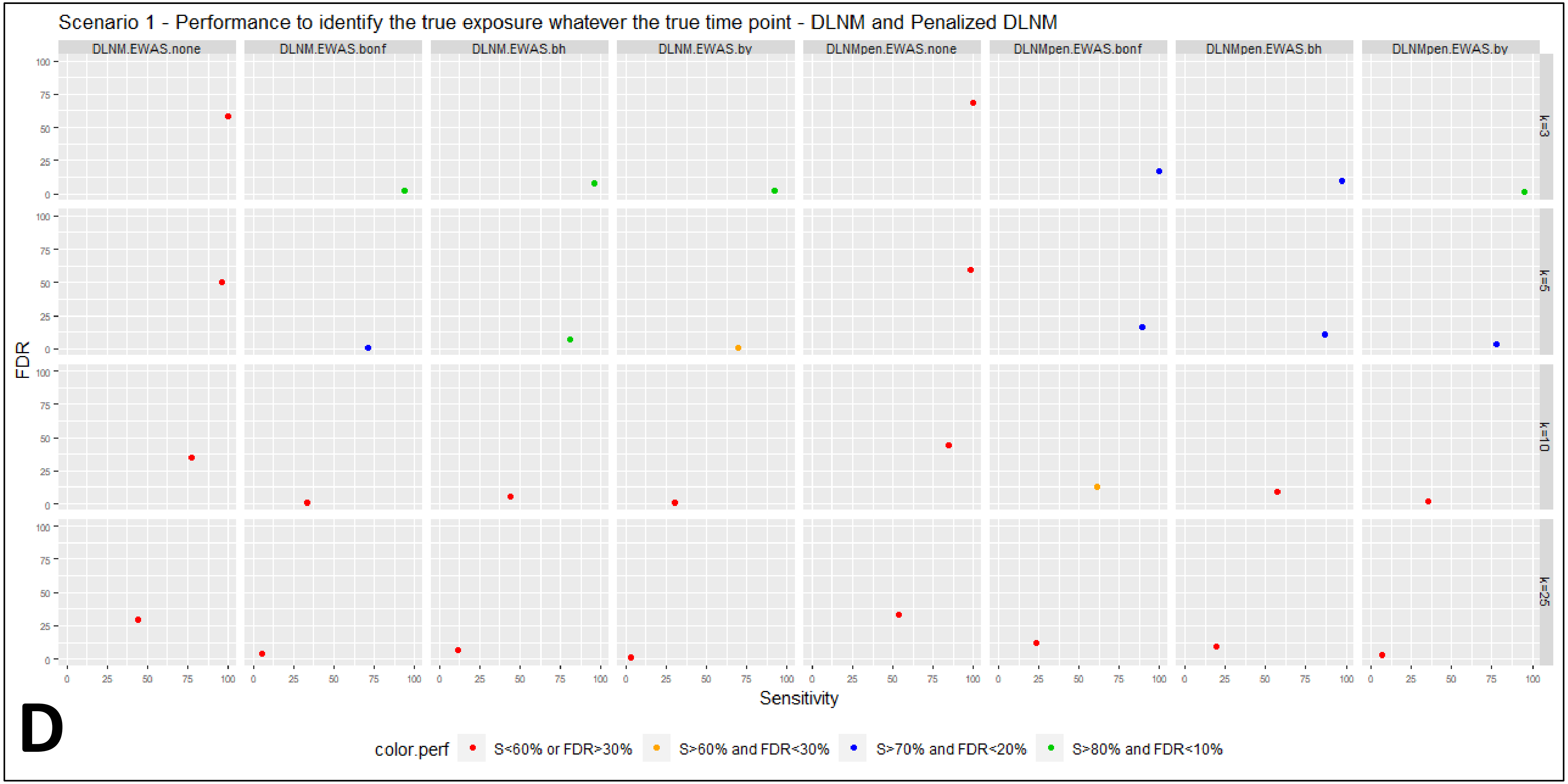




Scenario 1 - Performance to identify the true exposure whatever the true time point - Averaged exposure levels
ExWAS.none
Exwas.bon
ExWAS.bh
ExWAS.by
ExWAS.MLM.none
Exwas.MLM.bon
ExWAS.MLM.bh
ExWAS.MLM.by
ENET.min
ENET.opt
sPLS
MMPC
DSA
k=3
k=5
k=10
k=25
FDR
Sensitivity
B
color.perf
S<60% or FDR>30%
S>60% and FDR<30%
S>70% and FDR<20%
S>80% and FDR<10%



Scenario 1 - Performance to identify the true exposure whatever the true time point - Exposure trajectories
ExWAS.none
Exwas.bon
ExWAS.bh
ExWAS.by
ExWAS.MLM.none
Exwas.MLM.bon
ExWAS.MLM.bh
ExWAS.MLM.by
ENET.min
ENET.opt
sPLS
MMPC
DSA
k=3
k=5
k=10
k=25
FDR
Sensitivity
C
color.perf
S<60% or FDR>30%
S>60% and FDR<30%
S>70% and FDR<20%
S>80% and FDR<10%



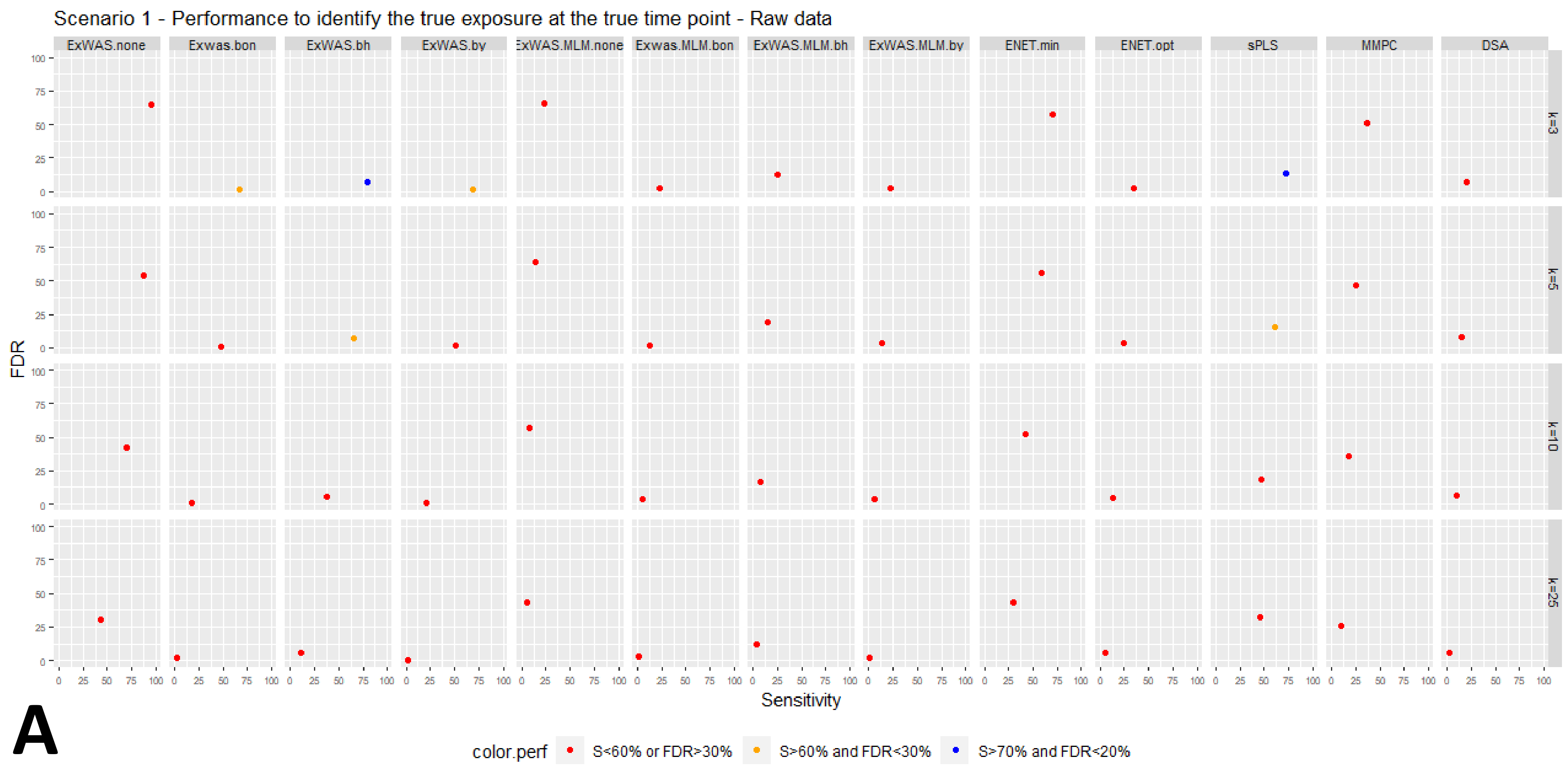
Scenario 1 - Performance to identify the true exposure whatever the true time point - DLNM and Penalized DLNM
DLNM.EWAS.none
DLNM.EWAS.bonf
DLNM.EWAS.bh
DLNM.EWAS.by
DLNMpen.EWAS.none
DLNMpen.EWAS.bonf
DLNMpen.EWAS.bh
DLNMpen.EWAS.by
k=3
k=5
k=10
k=25
FDR
Sensitivity
D
color.perf
S<60% or FDR>30%
S>60% and FDR<30%
S>70% and FDR<20%
S>80% and FDR<10%

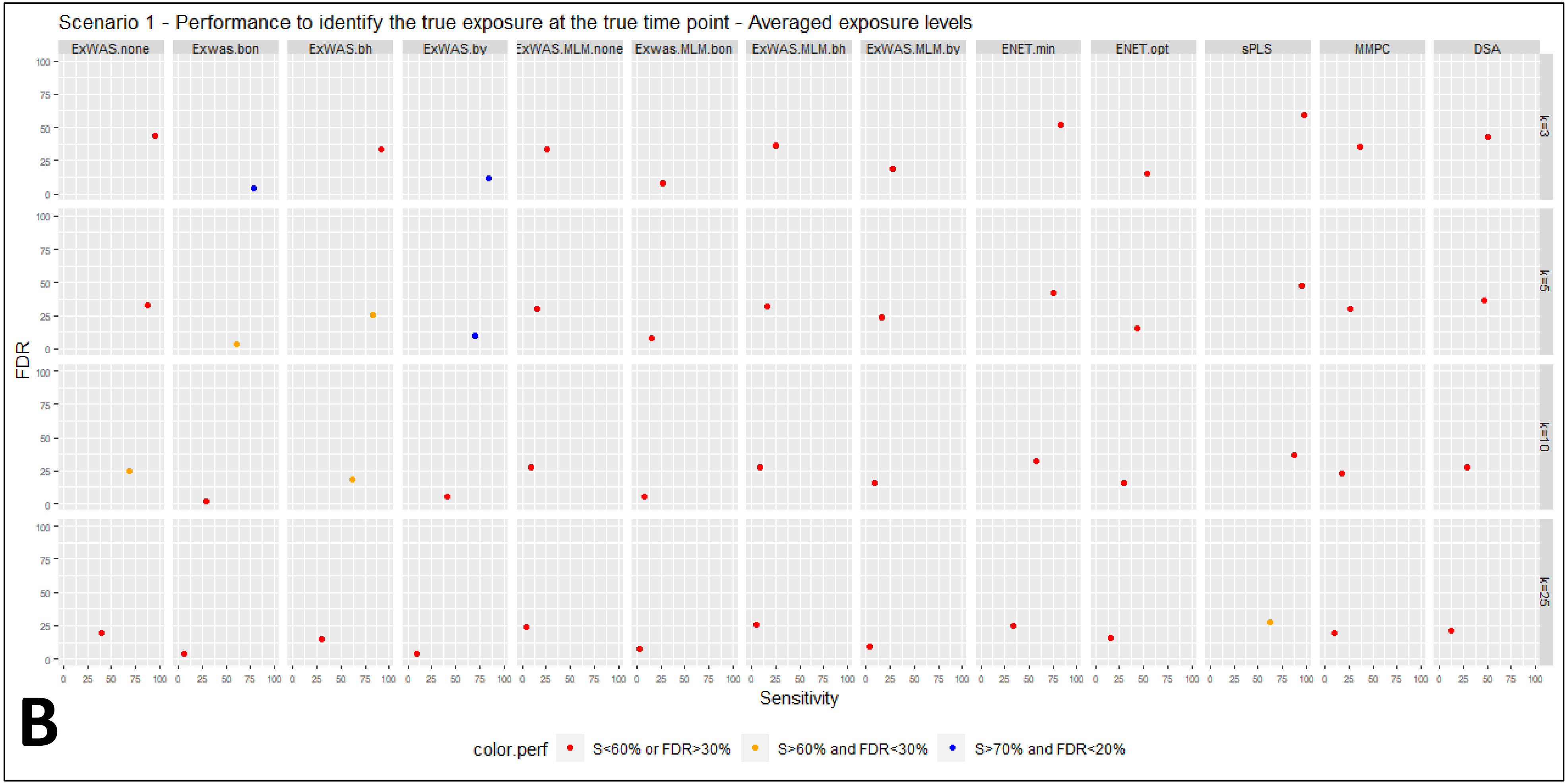
*Table 2. Performance to identify the true exposures **at the true** time point(s) – **Scenario 1***

	Sensitivity				**FDR**			
N true predictors (x5)	**3**	**5**	**10**	**25**	**3**	**5**	**10**	**25**
Raw data								
ExWAS.none	94.9 (6.7)	86.9 (9.3)	69.2 (9.5)	43.1 (7)	64.4 (6.7)	53.8 (7.5)	42.4 (7.6)	30.2 (6.9)
Exwas.bon	66.9 (17.4)	47.4 (13.8)	18.1 (6.8)	2.6 (2)	1.2 (3.7)	0.8 (3)	1.1 (3.7)	2.3 (11.2)
ExWAS.bh	78.9 (14.6)	65.3 (14.6)	37.1 (11.4)	10.3 (6.9)	7 (8.8)	7 (7.6)	5.6 (6.1)	5.5 (6.3)
ExWAS.by	68.6 (17.9)	51.6 (15.7)	20.5 (9.3)	2.1 (2.5)	1.5 (4.2)	1.5 (3.8)	1.2 (3.3)	0.4 (2.2)
ExWAS.MLM.none	22.9 (11.5)	14.3 (6.5)	8 (4)	4.9 (1.9)	65.4 (15.3)	63.8 (14.1)	57.2 (17.5)	43.2 (15.7)
Exwas.MLM.bon	22.6 (11)	12.3 (6)	5.2 (3.1)	1.4 (0.9)	2.1 (7.9)	1.8 (6.8)	4 (14.1)	3.1 (13.2)
ExWAS.MLM.bh	25.8 (12.7)	15.6 (7.5)	7.9 (4.1)	3.3 (2.1)	12.7 (17.3)	18.8 (18.1)	16.6 (19.8)	12 (16)
ExWAS.MLM.by	22.9 (10.8)	13.2 (7.2)	5.5 (3.4)	0.9 (1)	2.5 (8.5)	3.2 (9.7)	3.8 (10.5)	1.6 (10.6)
ENET.min	70.2 (11.9)	59.2 (11.2)	42.8 (9.1)	29.1 (7.5)	57.6 (17.1)	55.8 (14)	51.9 (12.1)	43.1 (9.7)
ENET.opt	34.6 (16.6)	24.2 (13.7)	13.6 (9.9)	5 (6.4)	2.3 (7.8)	3.4 (9.8)	4.6 (8.3)	6.1 (9.7)
sPLS	71.8 (23.5)	61.4 (23.5)	47 (23.4)	45.5 (32.3)	13.2 (16.8)	15.5 (15.5)	18.7 (16.3)	32 (24.6)
MMPC	36.3 (8.7)	25.6 (5.4)	17.7 (3.2)	10.6 (1.8)	51.2 (11.3)	46.7 (10.7)	36.1 (10.6)	25.8 (8.4)
DSA	20.4 (6.9)	15.2 (5)	9.9 (4.5)	2.2 (2.6)	7.2 (14.3)	8.1 (13.3)	6.5 (10.1)	5.4 (10.3)
Averaged data								
ExWAS.none	94.9 (6.7)	86.8 (9.3)	68.2 (10.1)	39.5 (7.5)	43.7 (12.3)	32.8 (10.9)	24.8 (8.9)	19.4 (7.3)
Exwas.bon	78.9 (13.7)	61 (12.5)	28.7 (7.9)	5.8 (2.9)	4.4 (7.1)	3.6 (5.7)	2.2 (4.7)	3.6 (11.5)
ExWAS.bh	92.5 (8.7)	83.3 (10.2)	61.9 (10.7)	29.4 (9.8)	33.7 (12)	25.3 (11)	18.8 (7.7)	15 (7.5)
ExWAS.by	84.7 (12.8)	70.2 (13.6)	40.6 (11)	9 (5.9)	11.4 (10.2)	9.7 (7.5)	5.3 (5.9)	4.3 (6.3)
ExWAS.MLM.none	25.4 (13)	15.3 (6.9)	8.8 (4.7)	4.1 (1.8)	33.8 (20.5)	29.8 (19.9)	27.8 (22.6)	24.5 (17.4)
Exwas.MLM.bon	26.2 (12.5)	15.2 (7.6)	7.5 (3.7)	2.6 (1.5)	8.2 (15.5)	8.4 (13.6)	5.7 (14.2)	7.7 (21.4)
ExWAS.MLM.bh	25.4 (12.3)	16 (7.1)	9.3 (4.4)	4.6 (1.9)	36 (19)	31.6 (20.7)	28 (20.5)	25.9 (17.2)
ExWAS.MLM.by	27.3 (13.1)	16.1 (7.7)	8.2 (4)	3 (1.9)	19.3 (17)	23.3 (19.3)	15.9 (21)	9 (16)
ENET.min	82.6 (9.7)	75.5 (10.1)	57.6 (9.5)	33.1 (6.1)	52.1 (10.5)	41.8 (10.8)	31.7 (9.4)	25.4 (8)
ENET.opt	53.4 (16.6)	43.7 (13.2)	29.9 (11.3)	15.9 (7.5)	14.9 (17)	15.8 (14.7)	15.7 (11.2)	16.2 (9.3)
sPLS	97.1 (10.1)	95 (9.7)	86.9 (13)	62.2 (8.6)	59 (14.5)	47.4 (12.5)	36.8 (10.4)	27.5 (8.3)
MMPC	36.7 (8.5)	26.3 (5.5)	17.7 (3.2)	9.9 (1.8)	35.3 (13)	30.1 (13.3)	23.2 (10.6)	19.3 (8.9)
DSA	50.9 (19.1)	46.2 (21.6)	29.2 (16)	12.3 (4.8)	42.9 (17.5)	36.6 (18.2)	28 (12.6)	21.3 (10.5)
Trajectories								
EWAS.none	94.5 (7.9)	83.6 (12.5)	57.1 (13.3)	23.7 (7.1)	27.3 (12.3)	19.3 (11.7)	14.7 (8.8)	13.9 (9.2)
EWAS.bon	79.1 (13.8)	61 (13.3)	29.1 (7.6)	6.4 (3.2)	3.4 (6.3)	2.4 (4.8)	1.2 (3.5)	4 (8.4)
EWAS.bh	91.3 (9.9)	80.4 (12.3)	53.1 (12.5)	19.7 (7.6)	18.7 (12.3)	13 (9.9)	10.7 (7.8)	10.1 (8.7)
EWAS.by	85.1 (12.5)	69.2 (13.9)	39 (10.9)	9.8 (5.7)	7.5 (8.9)	5.7 (7.1)	3.3 (5.1)	4.4 (7)
EWAS_LM.none	26.5 (11.2)	15.1 (7.2)	7.7 (4.3)	2.6 (1.4)	21.1 (16.8)	22.7 (23)	19.1 (23.6)	22.6 (22.6)
EWAS_LM.bon	25.9 (12.6)	14.8 (7.5)	6.8 (3.6)	2.3 (1.4)	5.1 (10.5)	6.4 (14.5)	2.9 (8.1)	8 (17.3)
EWAS_LM.bh	26.1 (11.4)	15.4 (7.9)	7.6 (3.8)	2.7 (1.4)	19.2 (17.1)	24.6 (24.2)	19.4 (21)	22.3 (20.1)
EWAS_LM.by	27.3 (13)	15.4 (7.6)	7.4 (3.8)	2.5 (1.5)	10.4 (13.1)	14.7 (19.9)	7.5 (12.8)	10 (17.6)
ENET.min	81.5 (10.9)	69.8 (12.2)	44.4 (11.6)	18.4 (5.7)	43.2 (13.5)	36.8 (12.6)	29 (10.7)	26.1 (10.9)
ENET.opt	49.6 (18.5)	38 (14.9)	19.9 (12)	6 (5.5)	6.7 (10.5)	6.9 (9.2)	5.6 (7.6)	7.1 (10.1)
sPLS	91.9 (15.9)	86 (15.9)	63.6 (18.8)	31.5 (9.4)	41.5 (22.7)	38.6 (19.1)	32.4 (14)	28.4 (13.2)
MMPC	37.1 (8.7)	25.3 (5.7)	14.5 (3.9)	6.2 (1.8)	21.5 (12)	20 (12.9)	15.3 (11.2)	16.6 (11.6)
DSA	49.3 (20.8)	33.8 (16.7)	1.4 (1.7)	6.8 (3.7)	31.9 (17.4)	25.4 (19.6)	11.6 (26.4)	17.2 (14.1)
DLNM								
EWAS.none	38.7 (13.7)	24.4 (10.1)	14.9 (6.4)	7.8 (3)	52.7 (19.2)	54.8 (18.8)	45 (18.6)	40 (17.9)
EWAS.bonf	37 (14.6)	19.4 (10.8)	8.4 (5.6)	1.4 (1.3)	2.3 (7.9)	1.2 (6.5)	1.3 (7.7)	5.4 (18.3)

EWAS.bh	37.7 (14.3)	21.5 (11)	10.3 (6)	2.7 (2.5)	7.1 (12.9)	9.2 (19)	6.1 (13.1)	9.4 (19.3)
EWAS.by	36.5 (14.9)	18.9 (10.5)	7.6 (6)	0.8 (1.2)	2 (7.2)	1.2 (6.5)	0.8 (6)	1.6 (11.2)
Penalized DLNM								
EWAS.none	64.3 (13)	50.4 (11.3)	35.5 (9)	19.4 (5.3)	56.5 (14.3)	51.8 (14.9)	40.7 (13.5)	34.4 (11.8)
EWAS.bonf	61.7 (14.7)	42 (14.1)	18.2 (8)	4.3 (3)	2.6 (8.8)	3.5 (10.1)	2 (7.2)	3.4 (11.5)
EWAS.bh	62.9 (13.6)	45.6 (13.6)	26.1 (9.5)	8.5 (5.2)	8.7 (13.6)	10.6 (16.1)	9.9 (13.6)	11.2 (15.5)
EWAS.by	61.3 (15.2)	41.4 (14.5)	17.2 (9)	3.2 (3.3)	1.6 (7)	3.4 (10.3)	2.3 (8.4)	3 (11.2)

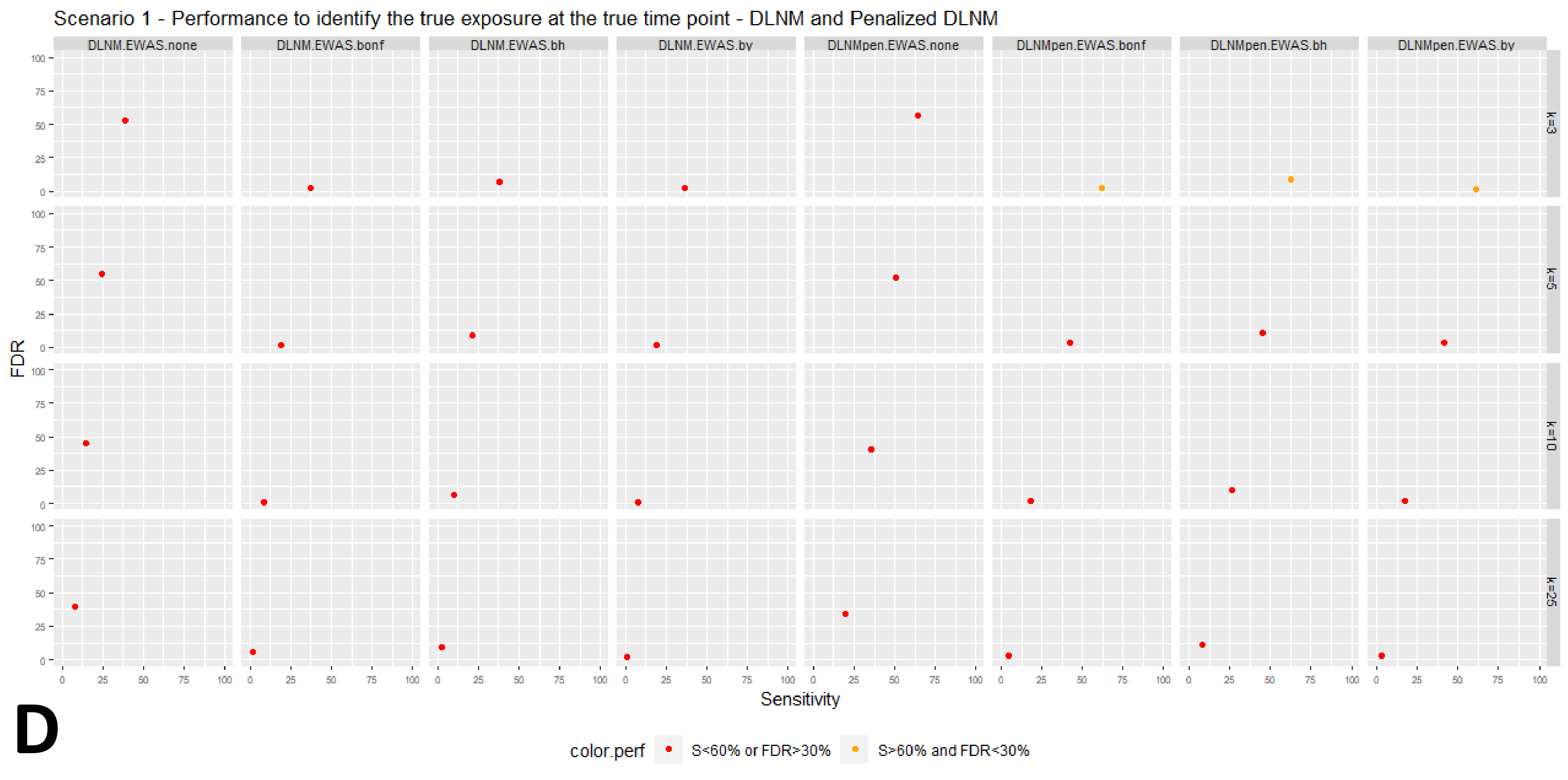
Figure 3. Performance to identify the true exposures at the true time point(s) – Scenario 1





Scenario 1 - Performance to identify the true exposure at the true time point - Averaged exposure levels
ExWAS.none
Exwas.bon
ExWAS.bh
ExWAS.by
ExWAS.MLM.none
Exwas.MLM.bon
ExWAS.MLM.bh
ExWAS.MLM.by
ENET.min
ENET.opt
sPLS
MMPC
DSA
k=3
k=5
k=10
k=25
FDR
Sensitivity
B
color.perf
S<60% or FDR>30%
S>60% and FDR<30%
S>70% and FDR<20%

Scenario 1 - Performance to identify the true exposure at the true time point - Exposure trajectories
ExWAS.none
Exwas.bon
ExWAS.bh
ExWAS.by
ExWAS.MLM.none
Exwas.MLM.bon
ExWAS.MLM.bh
ExWAS.MLM.by
ENET.min
ENET.opt
sPLS
MMPC
DSA
k=3
k=5
k=10
k=25
FDR
Sensitivity
C
color.perf
S<60% or FDR>30%
S>60% and FDR<30%
S>70% and FDR<20%
S>80% and FDR<10%



Scenario 1 - Performance to identify the true exposure at the true time point - DLNM and Penalized DLNM
DLNM.EWAS.none
DLNM.EWAS.bonf
DLNM.EWAS.bh
DLNM.EWAS.by
DLNMpen.EWAS.none
DLNMpen.EWAS.bonf
DLNMpen.EWAS.bh
DLNMpen.EWAS.by
k=3
k=5
k=10
k=25
FDR
Sensitivity
D
color.perf
S<60% or FDR>30%
S>60% and FDR<30%

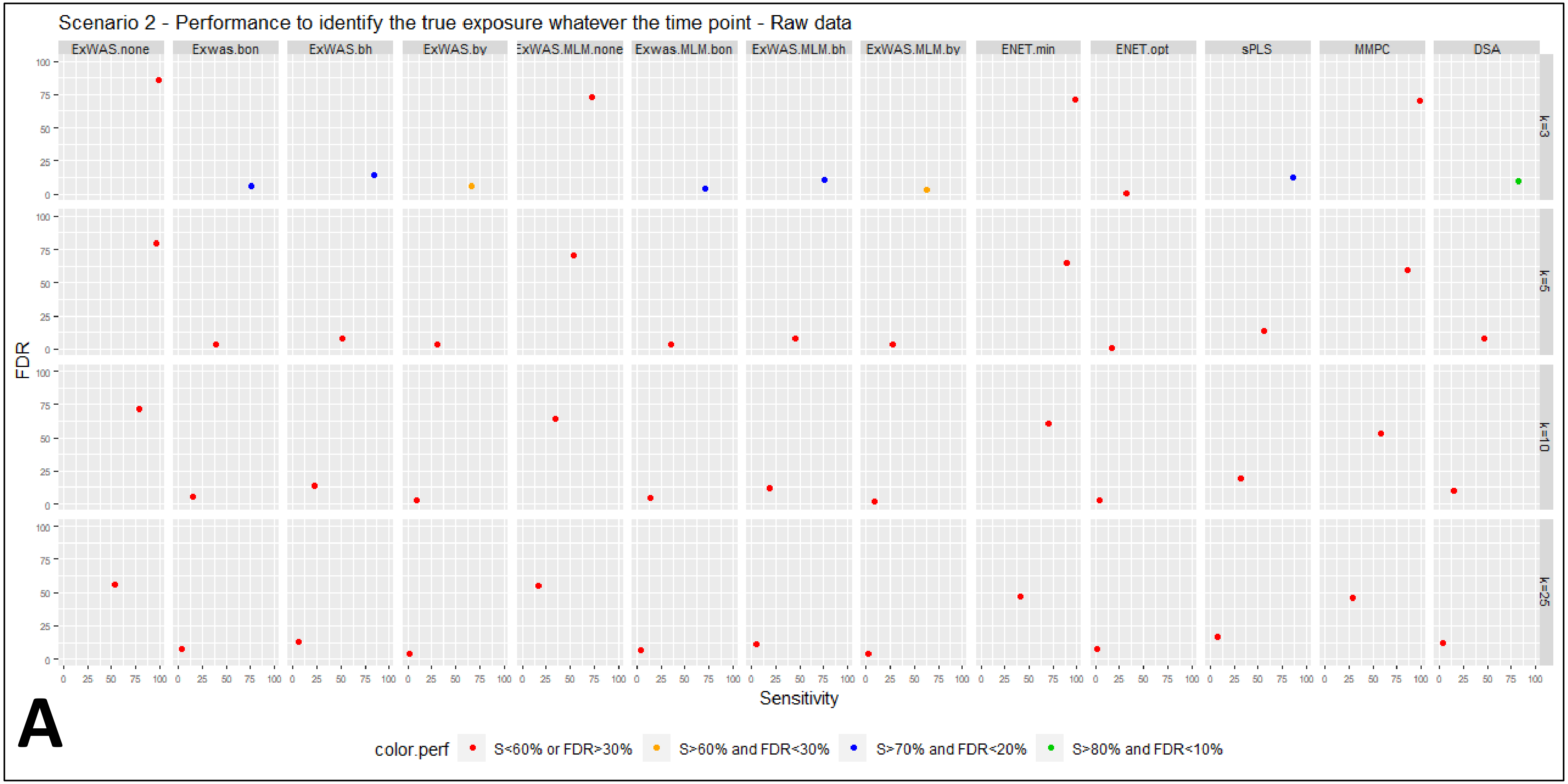
Scenario 2 (a single time point is associated with Y)

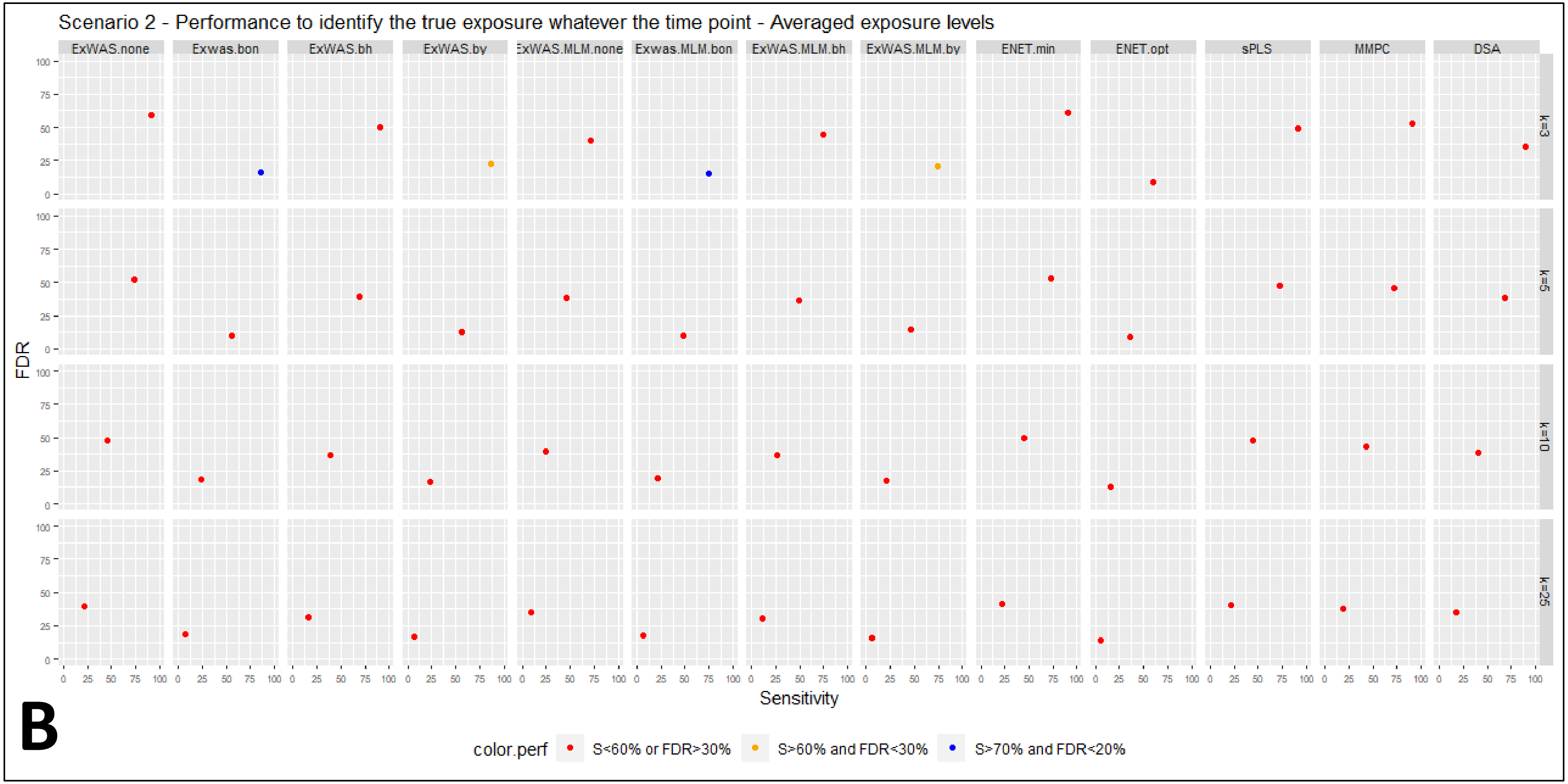
*Table 3. Performance to identify the true exposures **whatever** the true time point – **Scenario 2***

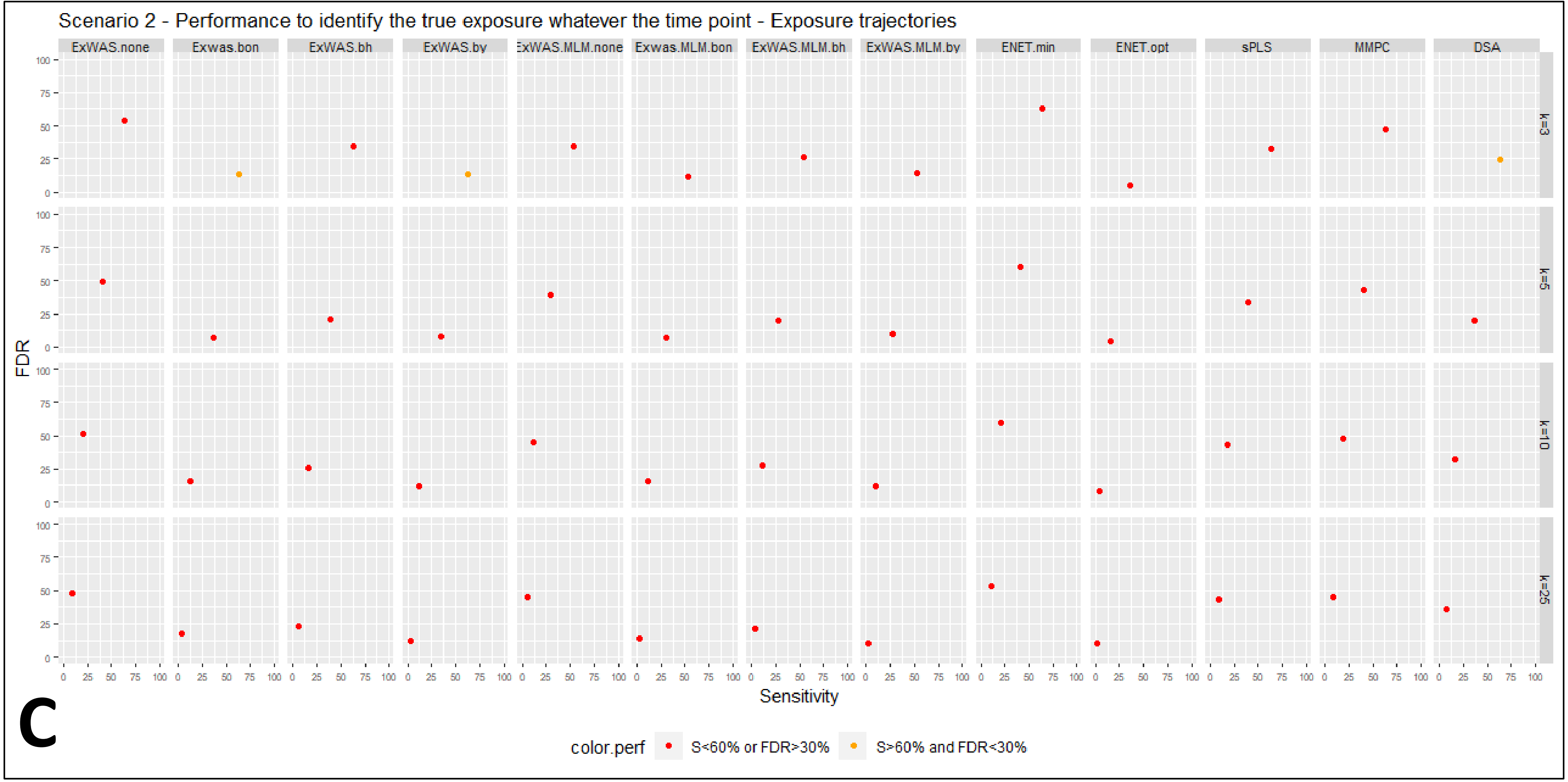
	Sensitivity				FDR			
N true predictors	**3**	**5**	**10**	**25**	**3**	**5**	**10**	**25**
Raw data								
ExWAS.none	99.3 (4.7)	96.2 (8.4)	78 (13.1)	52.8 (11.3)	86.3 (3.4)	79.4 (4.8)	71.1 (6)	56.6 (7.2)
Exwas.bon	75.3 (25.3)	38.4 (23.9)	14.5 (11.8)	3.9 (4.5)	6.3 (15.9)	3.2 (10.6)	5.2 (17.4)	7.6 (23.3)
ExWAS.bh	84.7 (24.3)	51.6 (28.6)	22.4 (17.6)	6.1 (6.5)	13.9 (20.4)	8.2 (13.8)	13.9 (21.9)	12.6 (24.5)
ExWAS.by	66.7 (30.3)	30.8 (25)	9.4 (12.5)	1.9 (3.6)	5.7 (15.7)	3.2 (13.3)	2.5 (9.9)	4 (16)
ExWAS.MLM.none	72 (27.1)	53 (22.6)	34.6 (14.1)	16.8 (7.9)	73.2 (13.3)	70.8 (13.5)	63.9 (15)	55.6 (16.9)
Exwas.MLM.bon	71 (27.1)	35.2 (24.1)	13.7 (11.4)	3.4 (3.6)	4.2 (12.8)	3.2 (11.2)	4.2 (16.5)	6.9 (23.2)
ExWAS.MLM.bh	75.7 (27.6)	44.8 (25.9)	19.3 (15.1)	4.8 (4.9)	10.6 (19.9)	7.7 (16.1)	11.6 (21.4)	11.6 (24.5)
ExWAS.MLM.by	63 (30.7)	28 (23.4)	9.1 (11.7)	1.6 (2.7)	3.6 (12.3)	3.2 (13.7)	1.7 (8.4)	3.7 (16.2)
ENET.min	98.7 (6.6)	88.8 (20.6)	70.4 (19.6)	40.7 (21.8)	70.9 (20.1)	65.3 (22.2)	60.3 (17.7)	47 (20.9)
ENET.opt	32.7 (31.4)	17 (25.6)	4.3 (8.7)	1.9 (5.3)	0.6 (4.1)	1 (5.2)	2.7 (14.9)	7.2 (24.3)
sPLS	86 (21.3)	56.4 (29.7)	31.5 (23.9)	8.2 (12.1)	12.9 (21.1)	13.9 (21.6)	19.3 (23.7)	16.7 (27.4)
MMPC	99 (5.7)	86.2 (15.2)	58 (13.6)	28.4 (7.6)	70.2 (7)	59.8 (9.8)	53 (11.4)	45.7 (12.9)
DSA	82.3 (24.4)	46 (31.2)	14.9 (14.7)	3.5 (5)	9.7 (18.1)	7.9 (18.6)	9.8 (19.8)	12.2 (27.9)
Averaged data								
ExWAS.none	90.7 (15.8)	73 (20.8)	45.1 (17.7)	21.8 (8.3)	59.7 (14.9)	51.7 (15)	47.9 (17.4)	40 (18.5)
Exwas.bon	86.3 (19.6)	55.4 (25.4)	24.1 (13.4)	7.6 (5)	16.6 (20.4)	9.9 (19.4)	18.1 (26.3)	18.5 (28.7)
ExWAS.bh	90.7 (15.8)	69.2 (24)	39 (17)	16.5 (9.1)	50.1 (18.9)	39.5 (19.8)	36.3 (21.7)	31.3 (22.7)
ExWAS.by	86.3 (21.2)	56.4 (27.5)	23.4 (15.8)	6.8 (6.1)	22.2 (21)	12.9 (18.8)	16.7 (23.8)	16.5 (27.4)
ExWAS.MLM.none	71.7 (23.4)	46.4 (23.2)	23.9 (13.9)	9.5 (5.1)	40.3 (22.2)	38.7 (27.9)	39.5 (28.2)	35.3 (25.2)
Exwas.MLM.bon	75.3 (25.3)	47.8 (23.9)	21.8 (12.8)	6.7 (4.5)	14.9 (20.3)	10.1 (21.3)	19 (28.6)	17.5 (27.8)
ExWAS.MLM.bh	74.3 (24.6)	48.6 (24.3)	26.7 (13.1)	11 (6.8)	44.3 (21.8)	36.9 (26.7)	36.5 (26.3)	30.6 (25.2)
ExWAS.MLM.by	74 (26.2)	46.4 (24.4)	20.6 (14.1)	5.9 (5.3)	20.7 (23.1)	14.2 (21.6)	17.1 (26)	16 (27.5)
ENET.min	90.7 (15.8)	73.2 (20.5)	45.2 (17.8)	22.2 (8.3)	60.9 (15.2)	53.1 (14.9)	49.8 (16.7)	41.1 (18.4)
ENET.opt	59.7 (38)	36 (36.5)	16.1 (22.2)	6.1 (9.2)	9 (20.1)	8.8 (18.4)	12.9 (23.9)	14 (25.9)
sPLS	90.7 (15.8)	72.2 (20.7)	44.6 (18.1)	21.9 (8.5)	49.2 (24.3)	47.4 (21.3)	47.6 (18.4)	40.6 (19.2)
MMPC	90.7 (15.8)	71.8 (20.3)	42.9 (16)	19.2 (7.6)	53.2 (16.1)	45.5 (16.8)	42.9 (18.2)	37.8 (19.7)
DSA	89.3 (17.6)	68.2 (24.8)	40.7 (19.2)	17.6 (10.1)	35.2 (28.6)	38.5 (24.7)	38.9 (23.5)	34.8 (23.9)
Trajectories 2-step								
ExWAS.none	63.3 (28.2)	41 (22.8)	20 (13.7)	9.3 (6.4)	53.6 (23.8)	49.5 (26.9)	51.1 (28.7)	47.5 (27.4)
Exwas.bon	62.7 (28.5)	36.4 (24)	13 (11.2)	3.8 (4.1)	13.2 (25)	7.1 (19)	15.7 (28.2)	17.3 (32.5)
ExWAS.bh	63.3 (28.2)	39 (23.5)	16.1 (13.8)	5.9 (5.9)	34.1 (27.3)	20.7 (23.8)	26 (30.3)	23 (31)
ExWAS.by	62 (29.6)	34.2 (25.2)	12.3 (12.5)	3.1 (4.1)	13.4 (21.4)	8.2 (17.6)	11.8 (22.3)	12.5 (27.5)
ExWAS.MLM.none	54 (29.5)	29.2 (21.7)	11.3 (10.8)	4.8 (4)	34.5 (32.1)	39 (33.8)	45.2 (37.6)	45.3 (35.5)
Exwas.MLM.bon	53.3 (28.8)	30.8 (21.7)	11.3 (11.1)	3.2 (3.5)	11.9 (24.7)	7.6 (21)	15.3 (28.7)	14 (29.8)
ExWAS.MLM.bh	53.7 (28.4)	28.2 (21.1)	10.7 (10.8)	3.8 (4.4)	26.2 (29.5)	20 (28.1)	27.8 (34.8)	21.7 (33.2)
ExWAS.MLM.by	52.3 (29.7)	27.6 (21)	10.3 (11.1)	2.6 (3.5)	14.3 (23.9)	9.5 (20.8)	11.7 (24.1)	10.7 (26.6)
ENET.min	63.7 (28.1)	41 (22.8)	20.8 (13.8)	10.3 (6.8)	63.1 (20.4)	60.2 (22.8)	60 (24.6)	53.5 (25.5)
ENET.opt	35.7 (33.3)	16 (25.1)	4.7 (9)	1.5 (4)	4.8 (19.1)	4.6 (18.7)	8 (26.1)	10.6 (30.3)
sPLS	63 (28)	39.6 (22.7)	18.4 (13.8)	9.1 (6.5)	32.8 (32.5)	33.5 (33.3)	43.4 (33.7)	42.9 (28.9)
MMPC	63.3 (28.2)	40.8 (22.9)	19.5 (13.3)	8.5 (5.4)	47.7 (25)	42.8 (29)	48.1 (29.3)	44.7 (29.3)
DSA	63 (28)	36.4 (24.7)	16.7 (13.7)	6.7 (5.8)	23.9 (28.5)	20.4 (26.3)	32 (32.7)	35.8 (32.6)

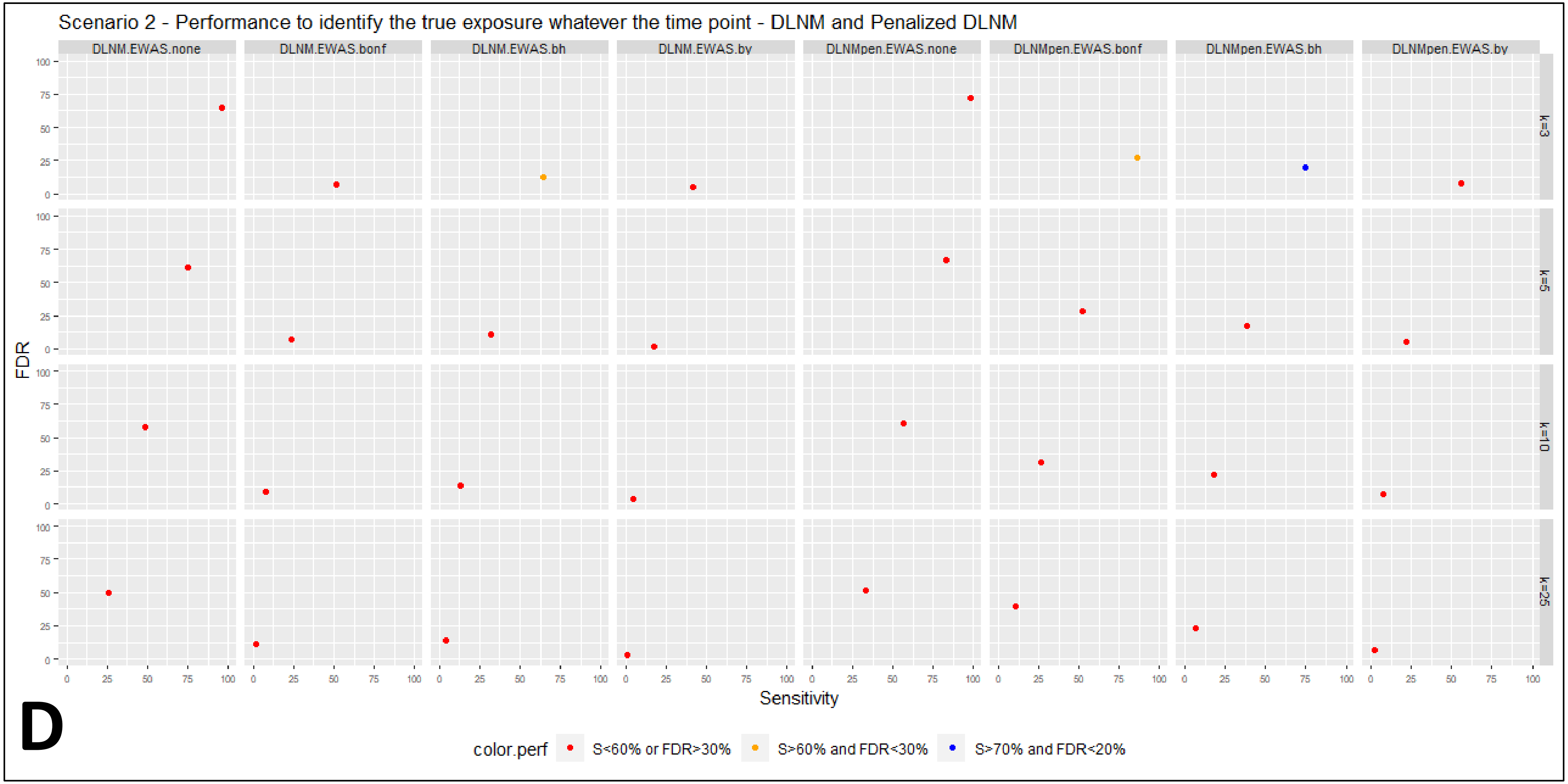
DLNM								
EWAS.none	96 (10.9)	74.6 (20.5)	48.3 (17.1)	25.6 (10)	64.8 (13.8)	61.6 (13.4)	57.9 (15.1)	49.6 (14.3)
EWAS.bonf	51.7 (26.6)	23.6 (19.8)	7.4 (8.5)	2 (3.2)	6.7 (17.8)	6.8 (21)	9.3 (21.9)	11.2 (29)
EWAS.bh	64.7 (30.6)	32 (26.5)	12.7 (14.1)	4.3 (6.5)	12.8 (22.3)	10.8 (23.1)	13.4 (24.7)	14.2 (26.5)
EWAS.by	41.7 (30.1)	17.6 (20.4)	4.6 (7.8)	1 (2.7)	4.8 (15.6)	1.8 (8.2)	3.4 (13.2)	3.4 (16.2)
Penalized DLNM								
EWAS.none	98.3 (7.3)	83 (17.1)	56.4 (16.5)	33 (10.6)	72.5 (12.2)	66.5 (11.7)	61 (11.9)	52 (10.9)
EWAS.bonf	86.3 (21.2)	52.2 (24.8)	26.7 (14.6)	10.8 (7.2)	26.7 (25.7)	27.9 (27.2)	30.8 (26.9)	39.7 (30)
EWAS.bh	75 (28.6)	38.6 (27.3)	18.4 (17.2)	6.9 (8.8)	19.6 (25.2)	17 (26.7)	22 (26.5)	23.1 (31.8)
EWAS.by	56 (31.4)	22.2 (23.8)	7.4 (11.2)	2.2 (4.8)	7.6 (19.4)	5.3 (16.6)	7.6 (21.5)	6.4 (17)

Figure 4. Performance to identify the true exposures whatever the true time point – Scenario 2




Scenario 2 - Performance to identify the true exposure whatever the time point - Averaged exposure levels
ExWAS.none
Exwas.bon
ExWAS.bh
ExWAS.by
ExWAS.MLM.none
Exwas.MLM.bon
ExWAS.MLM.bh
ExWAS.MLM.by
ENET.min
ENET.opt
sPLS
MMPC
DSA
k=3
k=5
k=10
k=25
FDR
Sensitivity
B
color.perf
S<60% or FDR>30%
S>60% and FDR<30%
S>70% and FDR<20%


Scenario 2 - Performance to identify the true exposure whatever the time point - Exposure trajectories
ExWAS.none
Exwas.bon
ExWAS.bh
ExWAS.by
ExWAS.MLM.none
Exwas.MLM.bon
ExWAS.MLM.bh
ExWAS.MLM.by
ENET.min
ENET.opt
sPLS
MMPC
DSA
k=3
k=5
k=10
k=25
FDR
Sensitivity
color.perf
S<60% or FDR>30%
S>60% and FDR<30%
C



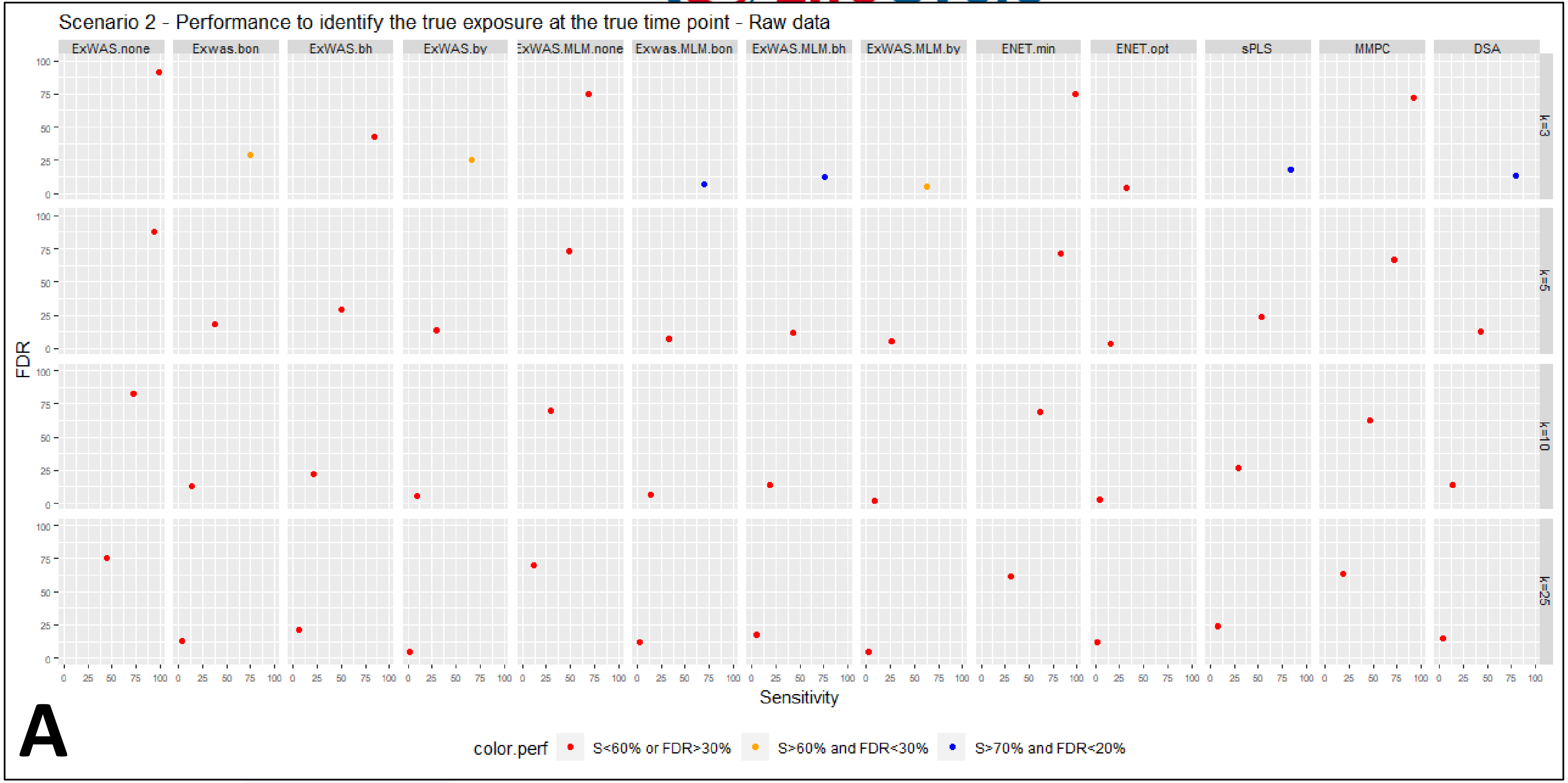
Scenario 2 - Performance to identify the true exposure whatever the time point - DLNM and Penalized DLNM
DLNM.EWAS.none
DLNM.EWAS.bonf
DLNM.EWAS.bh
DLNM.EWAS.by
DLNMpen.EWAS.none
DLNMpen.EWAS.bonf
DLNMpen.EWAS.bh
DLNMpen.EWAS.by
k=3
k=5
k=10
k=25
FDR
Sensitivity
D
color.perf
S<60% or FDR>30%
S>60% and FDR<30%
S>70% and FDR<20%

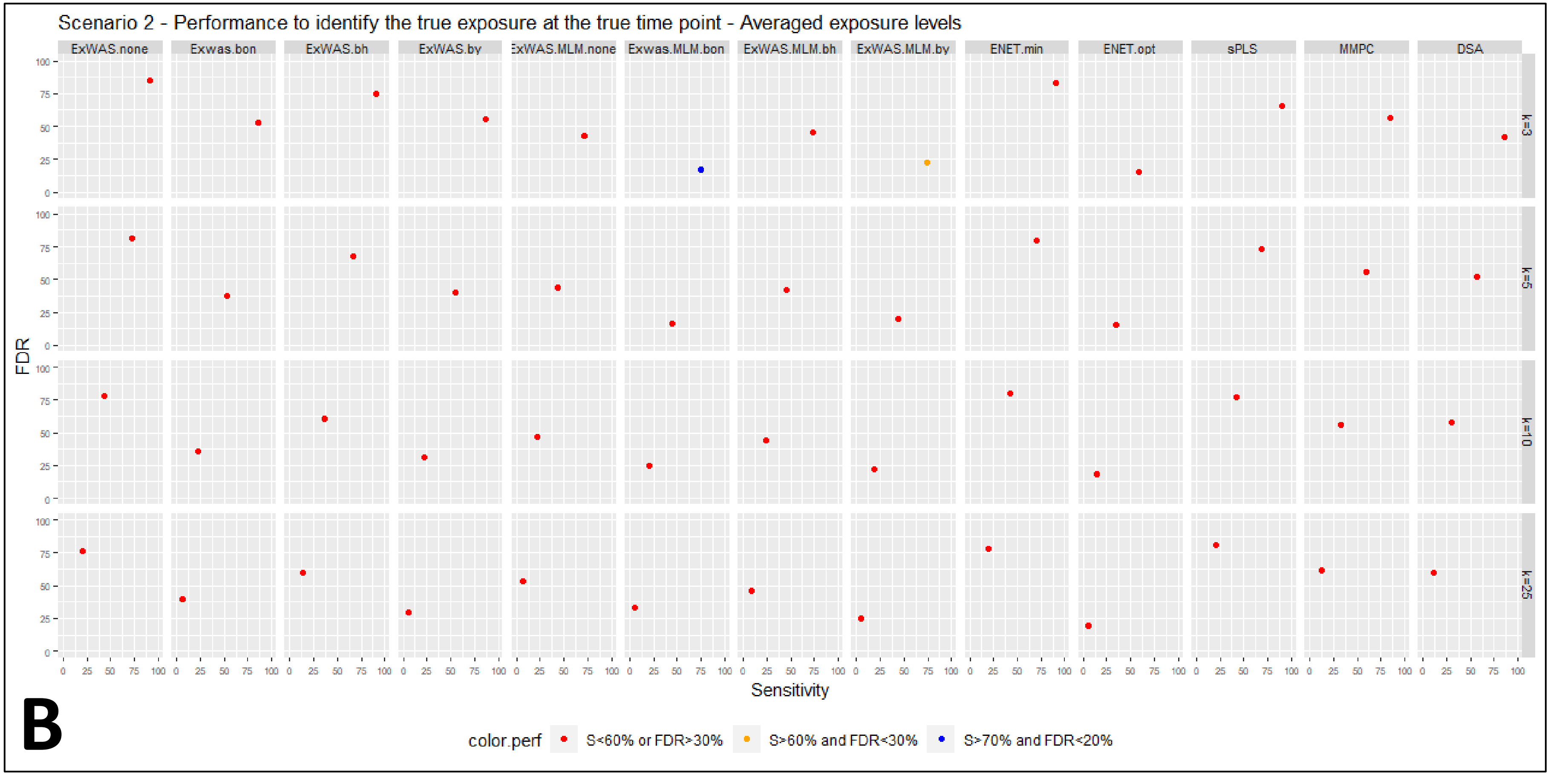
*Table 4. Performance to identify the true exposures **at the true** time point – **Scenario 2***

	Sensitivity				**FDR**			
N true predictors	**3**	**5**	**10**	**25**	**3**	**5**	**10**	**25**
Raw data								
ExWAS.none	99.3 (4.7)	93.6 (10.6)	72.1 (13.7)	44.4 (11.3)	91.5 (2)	87.5 (2.9)	82.2 (4.3)	75.6 (5.3)
Exwas.bon	74.7 (25.6)	37.2 (23.6)	14.2 (11.6)	3.7 (4.4)	29.2 (27.6)	18.1 (23.6)	12.7 (26)	13.2 (29.7)
ExWAS.bh	84.3 (24.4)	50.2 (28.1)	21.6 (17.1)	5.8 (6.5)	42.7 (27.4)	28.9 (25.7)	22.3 (27.2)	21.1 (30.5)
ExWAS.by	66.3 (30.2)	30 (23.9)	9.3 (12.2)	1.8 (3.4)	24.9 (28.3)	14 (22.8)	5.3 (15.2)	5.2 (19)
ExWAS.MLM.none	69 (27.7)	48.6 (23)	29.6 (13.9)	11.4 (6.3)	74.8 (13.7)	73.6 (13.4)	69.4 (14.9)	70.2 (15.9)
Exwas.MLM.bon	70 (27)	33.4 (22.9)	13.4 (11.4)	3.2 (3.6)	6.5 (15.1)	7.5 (17.5)	6.6 (21.6)	11.9 (29.9)
ExWAS.MLM.bh	75.3 (27.5)	42.4 (25)	18.5 (14.5)	4.5 (4.9)	12.5 (20.4)	11.9 (19.7)	14.1 (22.9)	17.3 (31.2)
ExWAS.MLM.by	62.3 (30.2)	26.8 (21.7)	9 (11.4)	1.5 (2.7)	5.5 (14.1)	5.6 (15.8)	1.9 (8.6)	4.7 (18.8)
ENET.min	97.7 (8.5)	83 (21.3)	61.8 (18.7)	30.7 (16.4)	74.8 (18.5)	71.2 (20.9)	69.1 (15.5)	61.7 (23.3)
ENET.opt	31.7 (31.6)	16.2 (24.6)	4.3 (8.7)	1.5 (3.8)	4.1 (16.3)	3.4 (13.2)	2.8 (15.2)	11.8 (30.9)
sPLS	84 (21.4)	52.8 (28.4)	29.5 (22.9)	7.4 (10.8)	17.9 (24.7)	24 (27.4)	26.5 (28.4)	24.2 (32.3)
MMPC	92.3 (14.9)	72.6 (20.2)	46.7 (14)	19.2 (6.4)	72.3 (7.8)	66.3 (11.2)	62.3 (11.6)	63.5 (11.2)
DSA	79.3 (25.4)	42.4 (28.9)	13.3 (12.4)	3.1 (4.4)	13 (20.8)	12.5 (23)	13.9 (23.2)	15 (30.9)
Averaged data								
ExWAS.none	90.7 (15.7)	71.6 (20.9)	42.8 (17)	19.8 (7.6)	84.7 (5.6)	81.4 (7.4)	78.2 (11)	76.8 (7.5)
Exwas.bon	86.3 (19.5)	53 (25.1)	22.3 (12.9)	6.5 (5.1)	52.7 (19.9)	37.6 (26.5)	36 (29.8)	39.9 (34.3)
ExWAS.bh	90.7 (15.7)	67.2 (24)	36.3 (16)	14 (8.3)	75.2 (14.6)	67.8 (22.4)	60.2 (22.9)	59.9 (22.1)
ExWAS.by	86.3 (21.2)	54.6 (27.3)	22.1 (15.2)	6 (5.7)	55.9 (22.9)	39.9 (27.8)	30.9 (30.3)	29.9 (33.2)
ExWAS.MLM.none	71 (23.9)	43.6 (22.6)	21.3 (12.9)	7.1 (4.9)	42.5 (22.6)	44.2 (27.4)	46.5 (28.4)	53 (27.7)
Exwas.MLM.bon	75 (25.2)	44.6 (23.2)	20 (12.4)	5.4 (4.4)	17.1 (20.3)	16.2 (23.8)	25.1 (31.2)	33.1 (36.7)
ExWAS.MLM.bh	73.3 (24.1)	45.8 (23.1)	23.4 (12.1)	8.4 (5.6)	45.8 (22.1)	42 (26.9)	43.7 (27.3)	45.8 (26.5)
ExWAS.MLM.by	73.7 (26)	43.4 (22.7)	18.9 (13.1)	5 (4.8)	22.6 (22.9)	19.9 (22.9)	22.2 (28.8)	25 (33.6)
ENET.min	90 (16)	70 (20.7)	42.1 (17)	19 (8.1)	82.9 (8.2)	79.9 (8.8)	79.4 (8.7)	78.4 (8.1)
ENET.opt	58 (38)	34.2 (35.1)	14 (18.9)	5 (7.4)	15.6 (26.4)	15.2 (24.3)	18.4 (29.1)	19.2 (31.1)
sPLS	90.3 (15.9)	69 (20.7)	42.4 (17)	20.4 (8.9)	65.4 (31.5)	73 (24.9)	77.4 (19.2)	81.3 (12)
MMPC	84.3 (18.6)	59.6 (21.4)	33 (14.2)	12 (5.9)	56.9 (15.7)	55.8 (15.7)	56.2 (16.9)	61.4 (16.3)
DSA	85.7 (19)	56.2 (22.6)	30.2 (15.7)	11.3 (6.9)	41.5 (30.9)	52.5 (28.2)	57.8 (26.8)	60.1 (27.4)
Trajectories								
EWAS.none	63.3 (28.2)	40.4 (23.1)	18.9 (13.6)	8.3 (6.1)	84.4 (7.1)	80.9 (13.1)	79.6 (16.7)	78.3 (16)
EWAS.bon	62.7 (28.5)	35 (24)	11.5 (10.4)	3.1 (3.8)	55.2 (26.3)	38.5 (30.7)	36 (34)	36.5 (39.2)
EWAS.bh	63.3 (28.2)	38.6 (23.3)	15.1 (13.2)	5.1 (5.4)	71.6 (22.3)	57.8 (29.4)	50.7 (35)	47.5 (37.9)
EWAS.by	62 (29.6)	33.4 (25.4)	11.4 (11.8)	2.8 (3.8)	51.4 (30.9)	37.8 (33)	28.7 (32.6)	24.9 (34.8)
EWAS_LM.none	52.7 (28.9)	26.4 (20.7)	9.9 (10.1)	3.4 (3.4)	39.3 (32.3)	46.8 (34.4)	51.1 (37.4)	61.3 (36.1)
EWAS_LM.bon	53 (28.5)	29.2 (21.5)	9.7 (10.1)	2.5 (3.1)	14.2 (25.5)	13.2 (25.4)	22.8 (32.5)	26 (39.2)
EWAS_LM.bh	52.7 (28.1)	26.4 (19.9)	9.6 (10)	3 (3.7)	29.4 (30.5)	26.7 (30.5)	32.9 (36.5)	31.5 (39)
EWAS_LM.by	52 (29.3)	26 (20.4)	9.1 (10.2)	2.2 (3)	16.4 (24.9)	16 (26.1)	16.6 (28.6)	16.8 (32.8)
ENET.min	63 (28)	39.4 (23.2)	18.6 (13.7)	8.6 (5.9)	80.3 (15.5)	78.2 (18.7)	79.1 (20.1)	79.2 (19.2)
ENET.opt	34.3 (32.6)	15 (24.7)	4.1 (8.3)	1.2 (2.7)	8.9 (24.3)	11 (27.7)	11.9 (31.3)	15.6 (35.5)
sPLS	62 (27.6)	37 (22.3)	16.9 (13.3)	7.8 (6.8)	43.7 (36.1)	50.9 (36.7)	59.9 (37.2)	70.2 (30.4)
MMPC	59 (27.6)	34 (24.5)	15 (11.5)	5.2 (4.4)	52.8 (23.8)	55 (31.4)	60.3 (29.6)	67.5 (27)
DSA	59.7 (28.6)	30.2 (22.3)	13.2 (11.4)	4.5 (4.4)	30.8 (32.3)	35.9 (35)	44.2 (38.1)	55.6 (37.3)
DLNM								
EWAS.none	81.3 (22.9)	58.2 (23.6)	36.9 (15.6)	18 (9.6)	81.5 (10.5)	81.4 (9.5)	80.3 (8.6)	78.7 (9.5)
EWAS.bonf	45.7 (27.1)	21.6 (19.6)	6.7 (8.3)	1.8 (3.2)	46.3 (26.1)	41.7 (30.6)	32.1 (33.8)	31.4 (38.1)

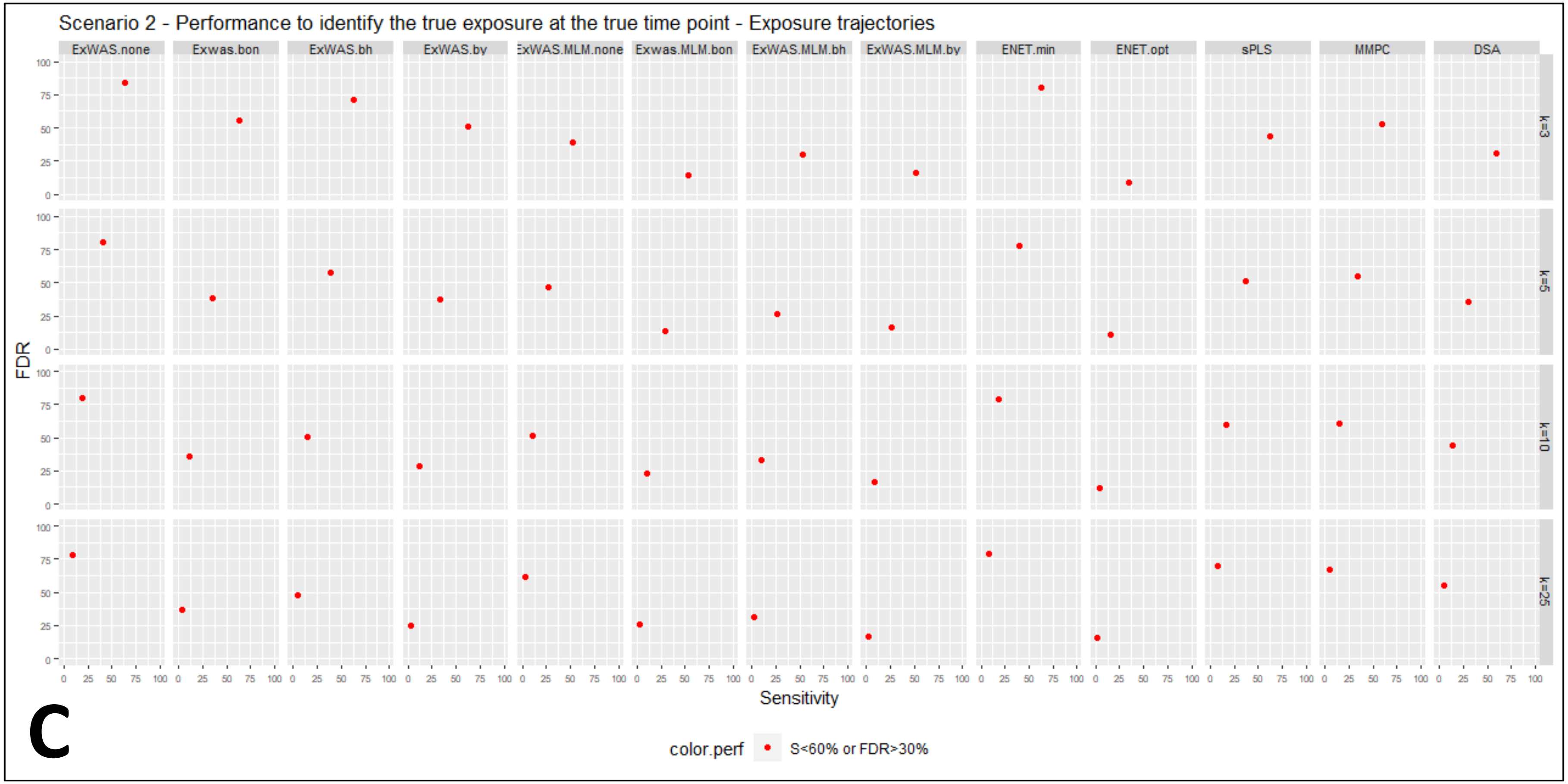
EWAS.bh	57.3 (32.5)	28.2 (25)	11.4 (13.5)	3.9 (6.1)	50.1 (26.4)	45.3 (31.3)	38.6 (34.9)	33.1 (37.9)
EWAS.by	38.3 (29.4)	17 (20)	4.5 (7.8)	1 (2.7)	40.1 (28.2)	28.9 (29.8)	18.5 (29.6)	13.8 (29.8)
Penalized DLNM								
EWAS.none	85.3 (21.3)	67.2 (21)	43.6 (15.6)	23.9 (10.4)	84.8 (11)	83.8 (6.4)	80.8 (8.6)	79.5 (7.3)
EWAS.bonf	58.7 (30.8)	26.8 (22.1)	10.7 (10.9)	3.3 (4.4)	36.6 (30.1)	37.3 (34.4)	30.5 (34.2)	34.1 (38.2)
EWAS.bh	67.3 (30.3)	35.8 (25.8)	16.9 (16.2)	6.6 (8.7)	47.8 (29.9)	41.7 (33.2)	41.1 (35.3)	42.5 (38.5)
EWAS.by	51.7 (31.2)	21.2 (23.2)	7 (10.8)	2.2 (4.7)	33 (30.5)	24.9 (30.5)	19.1 (31.5)	14.2 (27.6)

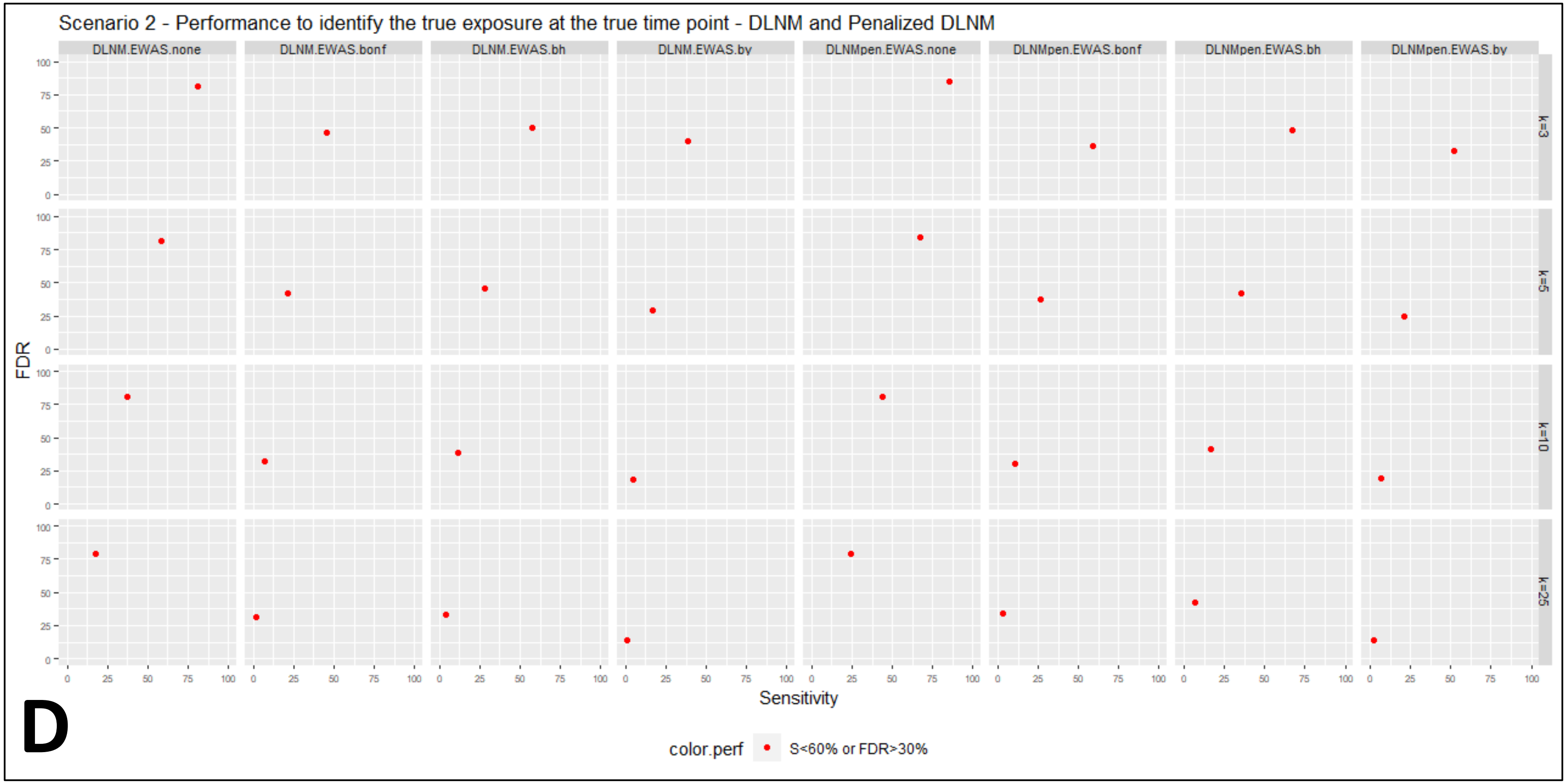
Figure 5. Performance to identify the true exposures at the true time point – Scenario 2




Scenario 2 - Performance to identify the true exposure at the true time point - Averaged exposure levels
ExWAS.none
Exwas.bon
ExWAS.bh
ExWAS.by
ExWAS.MLM.none
Exwas.MLM.bon
ExWAS.MLM.bh
ExWAS.MLM.by
ENET.min
ENET.opt
sPLS
MMPC
DSA
k=3
k=5
k=10
k=25
FDR
Sensitivity
B
color.perf
S<60% or FDR>30%
S>60% and FDR<30%
S>70% and FDR<20%

1


Scenario 2 - Performance to identify the true exposure at the true time point - Exposure trajectories
ExWAS.none
Exwas.bon
ExWAS.bh
ExWAS.by
ExWAS.MLM.none
Exwas.MLM.bon
ExWAS.MLM.bh
ExWAS.MLM.by
ENET.min
ENET.opt
sPLS
MMPC
DSA
k=3
k=5
k=10
k=25
FDR
Sensitivity
C
color.perf
S<60% or FDR>30%


Scenario 2 - Performance to identify the true exposure at the true time point - DLNM and Penalized DLNM
DLNM.EWAS.none
DLNM.EWAS.bonf
DLNM.EWAS.bh
DLNM.EWAS.by
DLNMpen.EWAS.none
DLNMpen.EWAS.bonf
DLNMpen.EWAS.bh
DLNMpen.EWAS.by
k=3
k=5
k=10
k=25
FDR
Sensitivity
D
color.perf
S<60% or FDR>30%