Triangulating Instrumental Variable, confounder adjustment and difference-in-difference methods for comparative effectiveness research in observational data

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Appendix 1

Data for the first simulation described in Section 3 was generated under the models listed below. The DAG in Figure 6 visualizes the data structure of the simulation explained in Section 3 as well as the mechanisms with which the simulation scenarios are implemented.

$$
\begin{aligned}
\beta &= 0.1 \\
Z_i &\sim Bern(0.5) \\
W_{0,i} &\sim N(0,1) \\
W_{1,i} &= \gamma_{W_1,W_0} W_{0,i} + \gamma_{W_1,\varepsilon} \varepsilon_{W_1,i} \\
\varepsilon_{W_1,i} &\sim N(0,1) \\
U_i &\sim N(0,1) \\
Y_{0,i} &\sim Bern(\gamma_{Y_0,0} + \gamma_{Y_0,U} U_i + \gamma_{Y_0,W_0} W_{0,i}) \\
X_i &\sim Bern(\gamma_{X,0} + \gamma_{X,Z} Z_i + \gamma_{X,U} U_i + \gamma_{X,W_0} W_{0,i} + \gamma_{X,W_1} W_{1,i} + \gamma_{X,Y_0} Y_{0,i}) \\
Y_{1,i} &\sim Bern(\gamma_{Y_1,0} + \gamma_{Y_1,U} U_i + \beta X_i + \gamma_{Y_1,W_1} W_{1,i} + \gamma_{Y_1,Z} Z_i)
\end{aligned}
$$

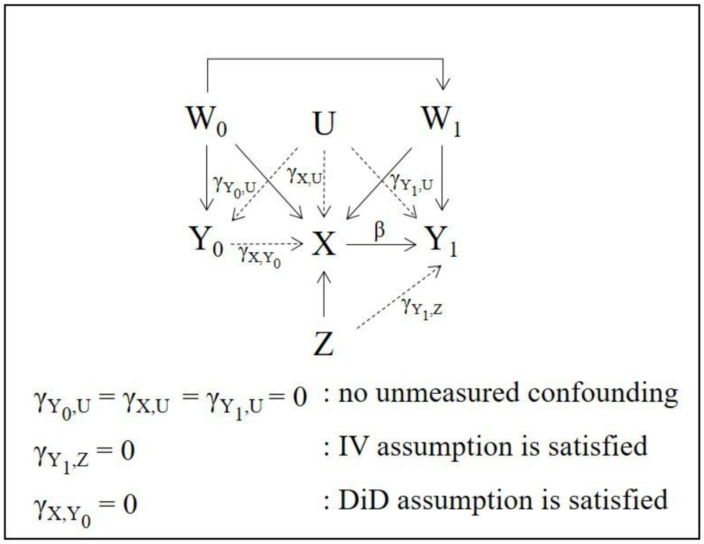

Figure 6: Causal DAG consistent with the data generation of the simulation outlined in Section 3.

Appendix 2

Proof for DiD assumption

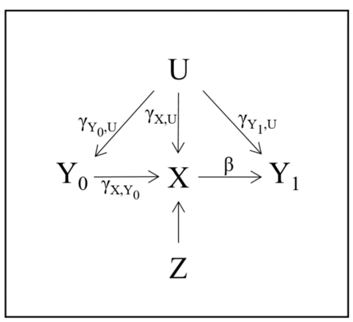

Figure 7: A simplified parameterised causal diagram to accompany the DiD proof argument below.

The parameterised causal diagram in Figure 7 indicates a similar structure to that in Section 1 but without measured confounders W_0 and W_1 for simplification. Removing the individual subscript i for convenience, assume the following models for Y_0, X and Y_1:

$$
\begin{aligned}
Y_0 &= \gamma_{Y_0,U} U + \epsilon_{Y0} && (1)\\
X &= \gamma_{X,U} U + \gamma_{X,Y_0} Y_0 + \epsilon_X && (2)\\
Y_1 &= \beta X + \gamma_{Y_1,U} U + \epsilon_{Y1}, && (3)
\end{aligned}
$$

where β represents the causal effect that DiD is attempting to estimate. The estimand targeted by a regression of Y_1 on X is therefore

$$\frac{Cov(Y_1, X)}{Var(X)} = \frac{\beta Var(X) + \gamma_{Y1,U} Cov(X, U)}{Var(X)}, \tag{4}$$

and the estimand targeted by a regression of Y_0 on X is therefore

$$\frac{Cov(Y_0, X)}{Var(X)} = \frac{Cov(\gamma_{Y_0,U} U + \epsilon_{Y0}, X)}{Var(X)}. \tag{5}$$

Putting (4) and (5) together, DiD estimand can be written as

$$\frac{Cov(Y_1, X)}{Var(X)} - \frac{Cov(Y_0, X)}{Var(X)} = \beta + (\gamma_{Y_1,U} - \gamma_{Y_0,U}) \frac{Cov(U, X)}{Var(X)} - \gamma_{X,Y_0} \frac{Var(\epsilon_{Y_0})}{Var(X)}. \tag{6}$$

From (6) we see that that the DiD estimand is equal to β when $\gamma_{Y_0,U} = \gamma_{Y_1,U}$ (DiD2 assumption) and either γ_{X,Y_0} is zero (DiD1 assumption), or that $Var(\epsilon_{Y_0}) = 0$.

Appendix 3

For the simulation of Section 3 the Monte Carlo standard errors (MCSE) calculated based on Morris et al. [1]. The results are given in the table below for the performance measures: bias, mean squared error, coverage and type 1 error.

		CaT	IV	CF	DiD
Scenario 1	MCSE(bias)	0.0685	0.1207	0.1209	0.0988
	MCSE(MSE)	0.002	0.0064	0.0064	0.0041
	MCSE(coverage)	0.7451	0.676	0.6892	0.7851
	MCSE(T1E)	0.751	0.7332	0.7209	0.6892
Scenario 2	MCSE(bias)	0.0697	0.1251	0.1252	0.0956
	MCSE(MSE)	0.002	0.0071	0.0072	0.1291
	MCSE(coverage)	0.6892	0.676	0.676	0
	MCSE(T1E)	0.7085	0.676	0.676	0
Scenario 3	MCSE(bias)	0.0687	0.1208	0.1209	0.0958
	MCSE(MSE)	0.0021	0.0522	0.0529	0.004
	MCSE(coverage)	0.7392	0.8628	0.8579	0.7332
	MCSE(T1E)	0.6624	0.6957	0.7021	0.7683
Scenario 4	MCSE(bias)	0.0685	0.1346	0.1345	0.1021
	MCSE(MSE)	0.0022	0.0507	0.0518	0.148
	MCSE(coverage)	0.5891	1.094	1.06	0
	MCSE(T1E)	0.6693	1.0164	1.0126	0
Scenario 5	MCSE(bias)	0.0625	0.1336	0.1332	0.0868
	MCSE(MSE)	0.0047	0.0078	0.0078	0.0033
	MCSE(coverage)	1.5775	0.676	0.7085	0.6892
	MCSE(T1E)	1.5744	0.7451	0.7451	0.676
Scenario 6	MCSE(bias)	0.0649	0.1348	0.1349	0.0935
	MCSE(MSE)	0.005	0.0078	0.0078	0.1045
	MCSE(coverage)	1.5719	0.5891	0.6197	0
	MCSE(T1E)	1.5387	0.7271	0.7271	0
Scenario 7	MCSE(bias)	0.0631	0.1397	0.1399	0.0894
	MCSE(MSE)	0.0049	0.0805	0.0835	0.0036
	MCSE(coverage)	1.5715	0.7626	0.7021	0.7147
	MCSE(T1E)	1.5741	0.5812	0.5566	0.6957
Scenario 8	MCSE(bias)	0.0682	0.1412	0.141	0.0958
	MCSE(MSE)	0.0046	0.0768	0.0803	0.1205
	MCSE(coverage)	1.5466	0.8278	0.7796	0
	MCSE(T1E)	1.5452	0.7021	0.6826	0

Table 1: Monte Carlo standard errors (MCSE) of the performance measures of all estimates and all scenarios of the simulation outlined in Section 3. All results are multiplied with 100 and rounded to 3 significant figures.

Appendix 4

For the simulation demonstrating the POA-IV and POA-CF estimates the data was generated using the same strategy as for the simulation explained in Section 4.1, except for X and Y_1. The data generation models are shown below and Figure 8 shows the DAG explaining the mechanisms with which the simulation scenarios are implemented.

$$
\begin{aligned}
\beta &= 0.1 \\
Z_i &\sim Bern(0.5) \\
W_{0,i} &\sim N(0,1) \\
W_{1,i} &= \gamma_{W_1,W_0} W_{0,i} + \gamma_{W_1,\varepsilon} \varepsilon_{W_1,i} \\
\varepsilon_{W_1,i} &\sim N(0,1) \\
U_i &\sim N(0,1) \\
Y_{0,i} &\sim Bern(\gamma_{Y_0,0} + \gamma_{Y_0,U} U_i + \gamma_{Y_0,W_0} W_{0,i}) \\
X_i &\sim Bern(\gamma_{X,0} + \gamma_{X,Z} Z_i + \gamma_{X,U} U_i + \gamma_{X,W_0} W_{0,i} + \gamma_{X,W_1} W_{1,i} + \\
&\qquad \gamma_{X,Y_0} Y_{0,i} + \gamma_{X,Y_0 Z} \cdot Z_i \cdot Y_{0,i}) \\
Y_{1,i} &\sim Bern(\gamma_{Y_1,0} + \gamma_{Y_1,U} U_i + \beta X_i + \gamma_{Y_1,W_1} W_{1,i} + \gamma_{Y_1,Z} Z_i + \gamma_{Y_1,Y_0} Y_{0,i})
\end{aligned}
$$

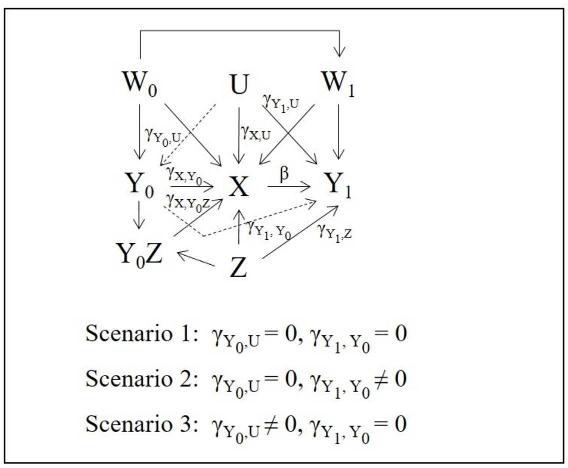

Figure 8: Causal DAG consistent with the data generation of the simulation outlined in Section 4.1

Appendix 5

The Monte Carlo standard errors (MCSE) are calculated based on Morris et al. [1] for the simulation presented in Section 4.1. The results are given in the table below for the performance measures: bias, mean squared error, coverage and type 1 error.

		CaT	IV	CF	DiD	POA-IV	POA-CF
Scenario 1	MCSE(bias)	0.0615	0.1287	0.1288	0.1012	0.1496	0.1356
	MCSE(MSE)	0.0047	0.1095	0.113	0.1809	0.0098	0.0083
	MCSE(coverage)	1.5787	0.1996	0.1996	0	0.7271	0.676
	MCSE(T1E)	1.5712	0.2442	0.2442	0	0.7451	0.7451
Scenario 2	MCSE(bias)	0.0613	0.1353	0.1354	0.0974	0.1505	0.1502
	MCSE(MSE)	0.0047	0.1112	0.1162	0.1559	0.0104	0.0105
	MCSE(coverage)	1.5770	0.2442	0.2230	0	0.6415	0.6486
	MCSE(T1E)	1.5753	0.2636	0.2442	0	0.6197	0.6343
Scenario 3	MCSE(bias)	0.0629	0.1313	0.1314	0.0998	0.1493	0.1306
	MCSE(MSE)	0.005	0.1142	0.1181	0.2327	0.0098	0.0079
	MCSE(coverage)	1.581	0.1729	0.1729	0	0.6556	0.8174
	MCSE(T1E)	1.5808	0.1729	0.1729	0	0.751	0.7626

Table 2: Monte Carlo standard errors (MCSE) of the performance measures of all estimates and all scenarios of the simulation outlined in Section 4.1. All results are multiplied with 100 and rounded to 3 significant figures.

Appendix 6

The propensity score matching procedure matched 100% of the 1966 individuals treated with SGLT2i. Therefore, overall 67.43% of all individuals in the data were matched. No records were discarded for the matching procedure. The love plot in Figure 9 shows that the matched data improved the balance of groups based on the absolute standardize mean difference. The matching process was employed using the baseline characteristics shown in the figure measured at first-line treatment initiation and years of second-line treatment initiation as this covariate has no effect on the treatment effect.

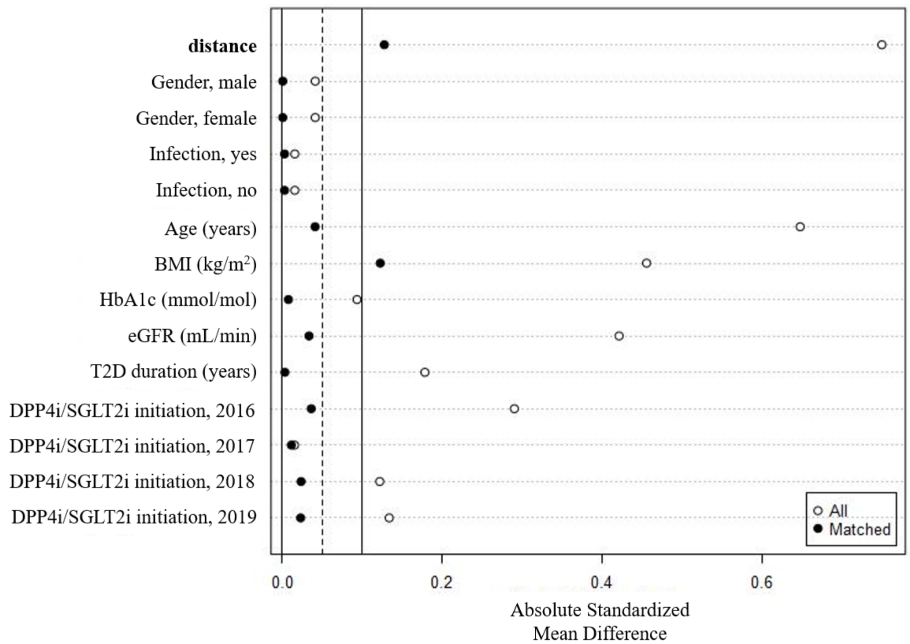

Figure 9: Love plot of the original and propensity score matched data.

Appendix 7

Correlation plot shows the pairwise correlation of all estimates using 500 bootstrap samples as explained in Section 5. Estimates of the CaT and PSM as well as the estimates of the POA-IV and POA-CF are highly correlated.

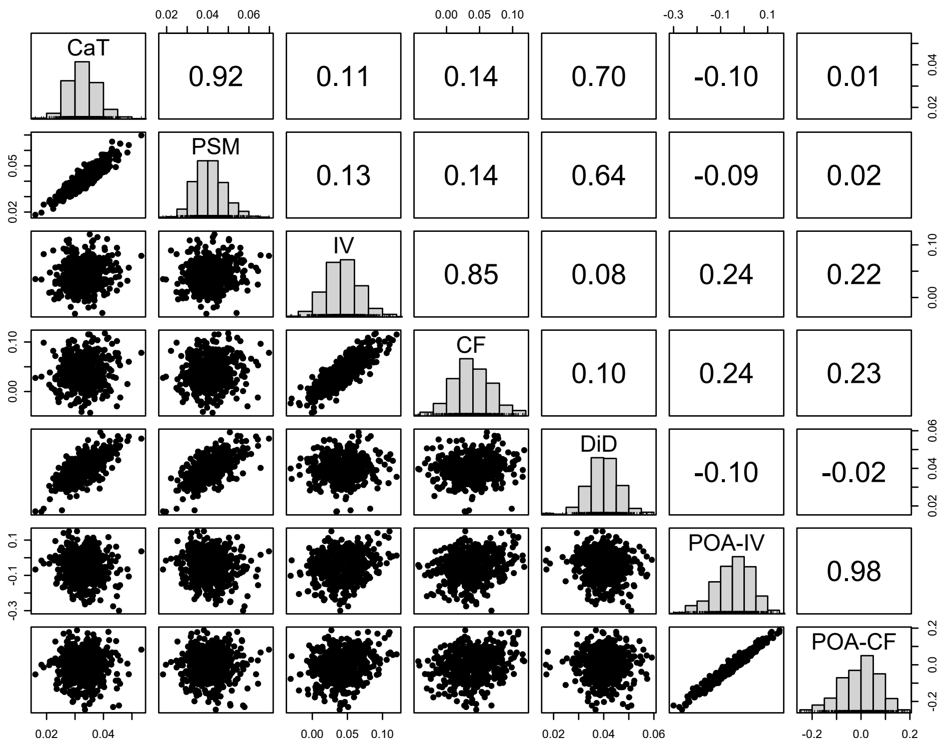

Figure 10: Correlation plot of all bootstrapped estimates of the application study.

References

[1] T. P. Morris, I. R. White, and M. J. Crowther, "Using simulation studies to evaluate statistical methods," *Statistics in Medicine*, vol. 38, pp. 2074–2102, 5 2019.