Supplementary Materials

A. Tables

Part A presents the comparison of the estimated variances and the correlations of the normalized within-stratum imbalances with those derived from the urn model (3.4) for some examples of unequal and equal prevalence minimization.

The results of the simulations of the four scenarios of unequal prevalence minimization with two independent factors (Cases 0-3, Table A1) are presented in Tables A2-A10. For each scenario the normalized within-stratum variances and the correlations of the within-stratum imbalances in treatment assignments were estimated for values of bias 0.9 and 0.8 following 100,000 simulations of minimization. Additionally, for Case 0, the simulations with bias 2/3 were also performed. Each simulation generated a randomization sequence for 12,000 subjects following two-factor minimization.

In the presented simulations both factors had 3 levels; the prevalences of the factor levels were the same for both factors. The simulations where the two factors have different number of levels or different prevalence were also performed. One such example, of the minimization in a multiregional clinical trial is presented in the body of the paper (estimated normalized variances and maximum absolute difference between the theoretical and estimated correlations) and in this document (the detailed correlations examination). Other examples are not presented in this paper.

Table A11 summarizes the results of the simulations of the minimization with 3 independent factors and unequal prevalence of the strata that support relationship (3.4). Tables A12-A14 present the estimates of V for the equal prevalence minimization with 2 to 7 factors.

Table A1: Prevalences of the factor levels in the four presented scenarios.

Scenario	1st factor prevalences	2nd factor prevalences
Case 0	1/3, 4/9, 2/9	1/3, 4/9, 2/9
Case 1	1/3, 3/12, 5/12	1/3, 3/12, 5/12
Case 2	1/3, 4/15, 6/15	1/3, 4/15, 6/15
Case 3	1/3, 8/27, 10/27	1/3, 8/27, 10/27

Table A2: Estimates of V for Cases 0 - 3 of the 2-factor minimization with bias of 0.9

Stratum	V			
	Case 0	Case 1	Case 2	Case 3
11	0.967	0.974	0.971	0.959
12	0.967	0.972	0.975	0.967
13	0.972	0.968	0.976	0.966
21	0.964	0.972	0.967	0.977
22	0.965	0.970	0.975	0.975
23	0.971	0.970	0.976	0.979
31	0.972	0.963	0.965	0.961
32	0.971	0.967	0.965	0.968
33	0.971	0.964	0.968	0.971
Weighted* across strata estimates	0.968	0.968	0.971	0.969

*Weighted proportionally to the strata prevalence.

Table A3: Estimates of V for Cases 0 - 3 of the 2-factor minimization with bias of 0.8

Stratum	V			
	Case 0	Case 1	Case 2	Case 3
11	0.996	0.995	0.992	0.998
12	0.994	0.998	0.996	0.991
13	0.989	0.997	0.992	1.001
21	1.004	0.994	0.998	0.996
22	1.005	0.996	0.996	0.996
23	0.994	0.992	0.999	0.997
31	0.993	0.997	0.990	1.001
32	0.993	0.997	0.993	1.000
33	0.998	0.994	0.990	0.996
Weighted* across strata estimates	0.998	0.995	0.993	0.998

*Weighted proportionally to the strata prevalence.

Table A4: Estimates of V for Case 0 of the 2-factor minimization with bias of 2/3

Stratum	V
11	1.026
12	1.028
13	1.020
21	1.029
22	1.034
23	1.030
31	1.023
32	1.024
33	1.016
Weighted* across strata estimates	1.027

*Weighted proportionally to the strata prevalence.

Table A5: Absolute differences between the estimated correlations of the normalized within-stratum imbalances in treatment assignments and their theoretical values in Case 0 simulations with bias of 0.9, 0.8, and 2/3

Stratum 1	Stratum 2	Theoretical correlation	Absolute difference between the theoretical and the estimated correlation		
			Bias 9/10	Bias 8/10	Bias 2/3
12	11	-0.6325	0.0023	0.0013	0.0000
13	11	-0.3780	0.0014	0.0004	0.0038
13	12	-0.4781	0.0006	0.0032	0.0026
21	11	-0.6325	0.0027	0.0021	0.0001
21	12	0.4000	0.0030	0.0050	0.0023
21	13	0.2391	0.0000	0.0020	0.0039
22	11	0.4000	0.0044	0.0046	0.0010
22	12	-0.6325	0.0018	0.0017	0.0004
22	13	0.3024	0.0016	0.0035	0.0026
22	21	-0.6325	0.0027	0.0029	0.0012
23	11	0.2391	0.0008	0.0022	0.0014
23	12	0.3024	0.0005	0.0024	0.0008
23	13	-0.6325	0.0002	0.0031	0.0000
23	21	-0.3780	0.0008	0.0030	0.0050
23	22	-0.4781	0.0017	0.0023	0.0007
31	11	-0.3780	0.0032	0.0060	0.0039
31	12	0.2391	0.0015	0.0059	0.0035
31	13	0.1429	0.0014	0.0008	0.0002
31	21	-0.4781	0.0007	0.0012	0.0024
31	22	0.3024	0.0006	0.0014	0.0003
31	23	0.1807	0.0011	0.0002	0.0052
32	11	0.2391	0.0026	0.0069	0.0008
32	12	-0.3780	0.0020	0.0073	0.0067
32	13	0.1807	0.0011	0.0015	0.0083
32	21	0.3024	0.0011	0.0017	0.0019
32	22	-0.4781	0.0005	0.0031	0.0004
32	23	0.2286	0.0003	0.0026	0.0029
32	31	-0.6325	0.0004	0.0029	0.0006
33	11	0.1429	0.0008	0.0009	0.0048
33	12	0.1807	0.0001	0.0031	0.0038
33	13	-0.3780	0.0002	0.0018	0.0081
33	21	0.1807	0.0006	0.0017	0.0002
33	22	0.2286	0.0001	0.0016	0.0011
33	23	-0.4781	0.0008	0.0023	0.0004
33	31	-0.3780	0.0005	0.0003	0.0039
33	32	-0.4781	0.0009	0.0002	0.0037

Table A6: Absolute differences between the estimated correlations of the normalized within-stratum imbalances in treatment assignments and their theoretical values in Case 1 simulations with bias of 0.9 and 0.8

Stratum 1	Stratum 2	Theoretical correlation	Absolute difference between the theoretical and the estimated correlation	
			Bias 9/10	Bias 8/10
12	11	-0.4082	0.0031	0.0011
13	11	-0.5976	0.0011	0.0020
13	12	-0.4880	0.0031	0.0012
21	11	-0.4082	0.0059	0.0023
21	12	0.1667	0.0043	0.0004
21	13	0.2440	0.0028	0.0034
22	11	0.1667	0.0028	0.0034
22	12	-0.4082	0.0022	0.0003
22	13	0.1992	0.0006	0.0032
22	21	-0.4082	0.0007	0.0006
23	11	0.2440	0.0035	0.0005
23	12	0.1992	0.0022	0.0003
23	13	-0.4082	0.0029	0.0002
23	21	-0.5976	0.0005	0.0021
23	22	-0.4880	0.0017	0.0008
31	11	-0.5976	0.0023	0.0002
31	12	0.2440	0.0006	0.0020
31	13	0.3571	0.0014	0.0006
31	21	-0.4880	0.0044	0.0001
31	22	0.1992	0.0013	0.0032
31	23	0.2916	0.0027	0.0030
32	11	0.2440	0.0012	0.0020
32	12	-0.5976	0.0011	0.0003
32	13	0.2916	0.0019	0.0014
32	21	0.1992	0.0033	0.0004
32	22	-0.4880	0.0024	0.0019
32	23	0.2381	0.0008	0.0007
32	31	-0.4082	0.0005	0.0012
33	11	0.3571	0.0037	0.0013
33	12	0.2916	0.0007	0.0017
33	13	-0.5976	0.0023	0.0003
33	21	0.2916	0.0019	0.0006
33	22	0.2381	0.0001	0.0045
33	23	-0.4880	0.0014	0.0024
33	31	-0.5976	0.0019	0.0013
33	32	-0.4880	0.0004	0.0016

Table A7: Absolute differences between the estimated correlations of the normalized within-stratum imbalances in treatment assignments and their theoretical values in Case 2 simulations with bias of 0.9 and 0.8

Stratum 1	Stratum 2	Theoretical correlation	Absolute difference between the theoretical and the estimated correlation	
			Bias 9/10	Bias 8/10
12	11	-0.4264	0.0025	0.0000
13	11	-0.5774	0.0008	0.0025
13	12	-0.4924	0.0021	0.0007
21	11	-0.4264	0.0023	0.0023
21	12	0.1818	0.0018	0.0013
21	13	0.2462	0.0028	0.0007
22	11	0.1818	0.0011	0.0002
22	12	-0.4264	0.0051	0.0014
22	13	0.2099	0.0035	0.0019
22	21	-0.4264	0.0039	0.0014
23	11	0.2462	0.0010	0.0022
23	12	0.2099	0.0067	0.0003
23	13	-0.4264	0.0045	0.0025
23	21	-0.5774	0.0018	0.0000
23	22	-0.4924	0.0042	0.0010
31	11	-0.5774	0.0001	0.0043
31	12	0.2462	0.0004	0.0017
31	13	0.3333	0.0019	0.0039
31	21	-0.4924	0.0035	0.0003
31	22	0.2099	0.0051	0.0004
31	23	0.2843	0.0009	0.0000
32	11	0.2462	0.0022	0.0004
32	12	-0.5774	0.0024	0.0019
32	13	0.2843	0.0002	0.0009
32	21	0.2099	0.0008	0.0022
32	22	-0.4924	0.0038	0.0017
32	23	0.2424	0.0020	0.0001
32	31	-0.4264	0.0019	0.0003
33	11	0.3333	0.0014	0.0051
33	12	0.2843	0.0029	0.0002
33	13	-0.5774	0.0023	0.0043
33	21	0.2843	0.0032	0.0016
33	22	0.2424	0.0012	0.0012
33	23	-0.4924	0.0031	0.0004
33	31	-0.5774	0.0001	0.0018
33	32	-0.4924	0.0006	0.0003

Table A8: Absolute differences between the estimated correlations of the normalized within-stratum imbalances in treatment assignments and their theoretical values in Case 3 simulations with bias of 0.9 and 0.8

Stratum 1	Stratum 2	Theoretical correlation	Absolute difference between the theoretical and the estimated correlation	
			Bias 9/10	Bias 8/10
12	11	-0.4588	0.0025	0.0039
13	11	-0.5423	0.0023	0.0029
13	12	-0.4977	0.0035	0.0012
21	11	-0.4588	0.0029	0.0026
21	12	0.2105	0.0012	0.0076
21	13	0.2488	0.0001	0.0043
22	11	0.2105	0.0010	0.0035
22	12	-0.4588	0.0015	0.0051
22	13	0.2283	0.0011	0.0029
22	21	-0.4588	0.0023	0.0013
23	11	0.2488	0.0013	0.0002
23	12	0.2283	0.0005	0.0024
23	13	-0.4588	0.0000	0.0013
23	21	-0.5423	0.0006	0.0003
23	22	-0.4977	0.0002	0.0005
31	11	-0.5423	0.0082	0.0008
31	12	0.2488	0.0056	0.0024
31	13	0.2941	0.0048	0.0011
31	21	-0.4977	0.0043	0.0003
31	22	0.2283	0.0001	0.0015
31	23	0.2699	0.0038	0.0017
32	11	0.2488	0.0047	0.0025
32	12	-0.5423	0.0042	0.0005
32	13	0.2699	0.0017	0.0005
32	21	0.2283	0.0015	0.0057
32	22	-0.4977	0.0014	0.0034
32	23	0.2477	0.0022	0.0030
32	31	-0.4588	0.0045	0.0018
33	11	0.2941	0.0060	0.0036
33	12	0.2699	0.0017	0.0024
33	13	-0.5423	0.0051	0.0002
33	21	0.2699	0.0033	0.0050
33	22	0.2477	0.0014	0.0020
33	23	-0.4977	0.0041	0.0029
33	31	-0.5423	0.0008	0.0016
33	32	-0.4977	0.0041	0.0020

Table A9: Maximum difference between the estimated correlation and the theoretical correlation of the normalized within-stratum imbalances across all pairs of strata in the Case 0 to Case 3 examples with bias of 0.9, 0.8, and 2/3 (for case 0 only)

Scenario	Maximum absolute difference		
	Bias 9/10	Bias 8/10	Bias 2/3
Case 0	0.0044	0.0073	0.0083
Case 1	0.0059	0.0045	
Case 2	0.0067	0.0051	
Case 3	0.0082	0.0076	

Table A10: Absolute differences between the theoretical and estimated correlations of the normalized within-stratum imbalances (Part 1 of 5).

Stratum 1	Stratum 2	Theoretical correlation	Absolute difference between the theoretical and the estimated correlation		
			Bias 9/10	Bias 8/10	Bias 2/3
12	11	-0.2100	0.0031	0.0037	0.0023
13	11	-0.2750	0.0004	0.0009	0.0016
13	12	-0.3273	0.0019	0.0043	0.0052
14	11	-0.3083	0.0011	0.0026	0.0019
14	12	-0.3669	0.0003	0.0036	0.0043
14	13	-0.4804	0.0018	0.0047	0.0019
21	11	-0.3273	0.0005	0.0057	0.0027
21	12	0.0688	0.0014	0.0019	0.0004
21	13	0.0900	0.0010	0.0041	0.0018
21	14	0.1009	0.0028	0.0012	0.0011
22	11	0.0688	0.0047	0.0024	0.0039
22	12	-0.3273	0.0042	0.0051	0.0099
22	13	0.1071	0.0038	0.0030	0.0066
22	14	0.1201	0.0033	0.0007	0.0054
22	21	-0.2100	0.0046	0.0007	0.0015
23	11	0.0900	0.0039	0.0028	0.0061
23	12	0.1071	0.0006	0.0004	0.0096
23	13	-0.3273	0.0026	0.0031	0.0059
23	14	0.1572	0.0011	0.0057	0.0053
23	21	-0.2750	0.0042	0.0014	0.0014
23	22	-0.3273	0.0006	0.0023	0.0057
24	11	0.1009	0.0007	0.0100	0.0004
24	12	0.1201	0.0026	0.0060	0.0003
24	13	0.1572	0.0003	0.0033	0.0001
24	14	-0.3273	0.0011	0.0054	0.0005
24	21	-0.3083	0.0035	0.0007	0.0003
24	22	-0.3669	0.0049	0.0039	0.0020
24	23	-0.4804	0.0011	0.0019	0.0006
31	11	-0.3273	0.0017	0.0032	0.0002
31	12	0.0688	0.0044	0.0007	0.0005
31	13	0.0900	0.0046	0.0027	0.0021
31	14	0.1009	0.0000	0.0004	0.0008
31	21	-0.2500	0.0024	0.0025	0.0024
31	22	0.0525	0.0003	0.0040	0.0029
31	23	0.0688	0.0005	0.0001	0.0000
31	24	0.0771	0.0016	0.0050	0.0007
32	11	0.0688	0.0004	0.0012	0.0036
32	12	-0.3273	0.0018	0.0013	0.0005
32	13	0.1071	0.0001	0.0049	0.0034
32	14	0.1201	0.0012	0.0041	0.0059
32	21	0.0525	0.0027	0.0048	0.0006
32	22	-0.2500	0.0027	0.0010	0.0007
32	23	0.0818	0.0001	0.0013	0.0028
32	24	0.0917	0.0004	0.0032	0.0031
32	31	-0.2100	0.0054	0.0006	0.0060

Table A10: Absolute differences between the theoretical and estimated correlations of the normalized within-stratum imbalances (Part 2 of 5).

Stratum 1	Stratum 2	Theoretical correlation	Absolute difference between the theoretical and the estimated correlation		
			Bias 9/10	Bias 8/10	Bias 2/3
33	11	0.0900	0.0051	0.0020	0.0059
33	12	0.1071	0.0034	0.0003	0.0013
33	13	-0.3273	0.0039	0.0027	0.0015
33	14	0.1572	0.0021	0.0015	0.0057
33	21	0.0688	0.0007	0.0033	0.0063
33	22	0.0818	0.0019	0.0036	0.0001
33	23	-0.2500	0.0005	0.0055	0.0028
33	24	0.1201	0.0015	0.0042	0.0013
33	31	-0.2750	0.0034	0.0027	0.0011
33	32	-0.3273	0.0005	0.0029	0.0009
34	11	0.1009	0.0029	0.0035	0.0032
34	12	0.1201	0.0001	0.0018	0.0025
34	13	0.1572	0.0013	0.0004	0.0061
34	14	-0.3273	0.0015	0.0021	0.0009
34	21	0.0771	0.0036	0.0007	0.0039
34	22	0.0917	0.0017	0.0017	0.0028
34	23	0.1201	0.0006	0.0068	0.0063
34	24	-0.2500	0.0016	0.0043	0.0008
34	31	-0.3083	0.0029	0.0015	0.0013
34	32	-0.3669	0.0005	0.0011	0.0001
34	33	-0.4804	0.0010	0.0035	0.0041
41	11	-0.2750	0.0015	0.0031	0.0073
41	12	0.0578	0.0002	0.0002	0.0047
41	13	0.0756	0.0017	0.0008	0.0024
41	14	0.0848	0.0020	0.0028	0.0000
41	21	-0.2100	0.0016	0.0068	0.0005
41	22	0.0441	0.0014	0.0013	0.0035
41	23	0.0578	0.0014	0.0025	0.0062
41	24	0.0648	0.0026	0.0062	0.0028
41	31	-0.2100	0.0004	0.0008	0.0048
41	32	0.0441	0.0033	0.0013	0.0002
41	33	0.0578	0.0015	0.0013	0.0055
41	34	0.0648	0.0044	0.0004	0.0020
42	11	0.0578	0.0019	0.0060	0.0050
42	12	-0.2750	0.0039	0.0011	0.0028
42	13	0.0900	0.0028	0.0061	0.0031
42	14	0.1009	0.0025	0.0011	0.0026
42	21	0.0441	0.0030	0.0008	0.0009
42	22	-0.2100	0.0004	0.0018	0.0047
42	23	0.0688	0.0032	0.0021	0.0013
42	24	0.0771	0.0003	0.0032	0.0034
42	31	0.0441	0.0021	0.0001	0.0024
42	32	-0.2100	0.0021	0.0000	0.0036
42	33	0.0688	0.0027	0.0002	0.0056
42	34	0.0771	0.0020	0.0005	0.0032
42	41	-0.2100	0.0027	0.0017	0.0095

Table A10: Absolute differences between the theoretical and estimated correlations of the normalized within-stratum imbalances (Part 3 of 5).

Stratum 1	Stratum 2	Theoretical correlation	Absolute difference between the theoretical and the estimated correlation		
			Bias 9/10	Bias 8/10	Bias 2/3
43	11	0.0756	0.0048	0.0014	0.0049
43	12	0.0900	0.0035	0.0043	0.0001
43	13	-0.2750	0.0065	0.0033	0.0032
43	14	0.1321	0.0010	0.0002	0.0010
43	21	0.0578	0.0032	0.0037	0.0046
43	22	0.0688	0.0017	0.0057	0.0031
43	23	-0.2100	0.0027	0.0009	0.0019
43	24	0.1009	0.0023	0.0008	0.0053
43	31	0.0578	0.0034	0.0017	0.0067
43	32	0.0688	0.0026	0.0021	0.0006
43	33	-0.2100	0.0001	0.0011	0.0025
43	34	0.1009	0.0008	0.0013	0.0029
43	41	-0.2750	0.0006	0.0028	0.0046
43	42	-0.3273	0.0022	0.0028	0.0026
44	11	0.0848	0.0032	0.0041	0.0028
44	12	0.1009	0.0002	0.0046	0.0060
44	13	0.1321	0.0031	0.0021	0.0058
44	14	-0.2750	0.0012	0.0029	0.0009
44	21	0.0648	0.0023	0.0007	0.0046
44	22	0.0771	0.0026	0.0063	0.0044
44	23	0.1009	0.0009	0.0034	0.0024
44	24	-0.2100	0.0009	0.0082	0.0025
44	31	0.0648	0.0012	0.0011	0.0012
44	32	0.0771	0.0011	0.0005	0.0022
44	33	0.1009	0.0033	0.0003	0.0018
44	34	-0.2100	0.0045	0.0017	0.0006
44	41	-0.3083	0.0011	0.0005	0.0028
44	42	-0.3669	0.0036	0.0014	0.0075
44	43	-0.4804	0.0028	0.0009	0.0107
51	11	-0.2750	0.0024	0.0046	0.0018
51	12	0.0578	0.0001	0.0027	0.0001
51	13	0.0756	0.0049	0.0010	0.0024
51	14	0.0848	0.0023	0.0041	0.0043
51	21	-0.2100	0.0000	0.0016	0.0046
51	22	0.0441	0.0026	0.0016	0.0001
51	23	0.0578	0.0011	0.0018	0.0011
51	24	0.0648	0.0021	0.0018	0.0027
51	31	-0.2100	0.0038	0.0016	0.0072
51	32	0.0441	0.0026	0.0034	0.0010
51	33	0.0578	0.0001	0.0087	0.0047
51	34	0.0648	0.0005	0.0061	0.0002
51	41	-0.1765	0.0027	0.0025	0.0033
51	42	0.0371	0.0054	0.0049	0.0007
51	43	0.0485	0.0049	0.0010	0.0026
51	44	0.0544	0.0027	0.0043	0.0002

Table A10: Absolute differences between the theoretical and estimated correlations of the normalized within-stratum imbalances (Part 4 of 5).

Stratum 1	Stratum 2	Theoretical correlation	Absolute difference between the theoretical and the estimated correlation		
			Bias 9/10	Bias 8/10	Bias 2/3
52	11	0.0578	0.0005	0.0028	0.0010
52	12	-0.2750	0.0007	0.0003	0.0029
52	13	0.0900	0.0014	0.0022	0.0002
52	14	0.1009	0.0028	0.0009	0.0016
52	21	0.0441	0.0003	0.0025	0.0016
52	22	-0.2100	0.0035	0.0030	0.0040
52	23	0.0688	0.0013	0.0011	0.0023
52	24	0.0771	0.0043	0.0018	0.0056
52	31	0.0441	0.0026	0.0064	0.0017
52	32	-0.2100	0.0014	0.0030	0.0007
52	33	0.0688	0.0006	0.0081	0.0031
52	34	0.0771	0.0006	0.0053	0.0032
52	41	0.0371	0.0021	0.0011	0.0011
52	42	-0.1765	0.0004	0.0015	0.0049
52	43	0.0578	0.0004	0.0020	0.0048
52	44	0.0648	0.0022	0.0003	0.0002
52	51	-0.2100	0.0007	0.0008	0.0002
53	11	0.0756	0.0053	0.0007	0.0004
53	12	0.0900	0.0033	0.0010	0.0001
53	13	-0.2750	0.0001	0.0006	0.0016
53	14	0.1321	0.0018	0.0006	0.0040
53	21	0.0578	0.0004	0.0043	0.0027
53	22	0.0688	0.0005	0.0046	0.0013
53	23	-0.2100	0.0009	0.0003	0.0053
53	24	0.1009	0.0005	0.0006	0.0032
53	31	0.0578	0.0029	0.0008	0.0022
53	32	0.0688	0.0015	0.0042	0.0011
53	33	-0.2100	0.0002	0.0029	0.0016
53	34	0.1009	0.0001	0.0002	0.0006
53	41	0.0485	0.0001	0.0032	0.0053
53	42	0.0578	0.0007	0.0016	0.0010
53	43	-0.1765	0.0005	0.0013	0.0050
53	44	0.0848	0.0013	0.0014	0.0034
53	51	-0.2750	0.0021	0.0075	0.0035
53	52	-0.3273	0.0014	0.0028	0.0010

Table A10: Absolute differences between the theoretical and estimated correlations of the normalized within-stratum imbalances (Part 5 of 5).

Stratum 1	Stratum 2	Theoretical correlation	Absolute difference between the theoretical and the estimated correlation		
			Bias 9/10	Bias 8/10	Bias 2/3
54	11	0.0848	0.0020	0.0051	0.0030
54	12	0.1009	0.0037	0.0030	0.0016
54	13	0.1321	0.0034	0.0027	0.0037
54	14	-0.2750	0.0010	0.0032	0.0048
54	21	0.0648	0.0013	0.0003	0.0020
54	22	0.0771	0.0016	0.0009	0.0028
54	23	0.1009	0.0015	0.0012	0.0013
54	24	-0.2100	0.0013	0.0009	0.0009
54	31	0.0648	0.0011	0.0056	0.0017
54	32	0.0771	0.0018	0.0012	0.0012
54	33	0.1009	0.0001	0.0031	0.0003
54	34	-0.2100	0.0009	0.0006	0.0012
54	41	0.0544	0.0040	0.0036	0.0019
54	42	0.0648	0.0042	0.0010	0.0044
54	43	0.0848	0.0022	0.0020	0.0004
54	44	-0.1765	0.0029	0.0045	0.0014
54	51	-0.3083	0.0009	0.0036	0.0009
54	52	-0.3669	0.0010	0.0054	0.0061
54	53	-0.4804	0.0043	0.0006	0.0033

Table A11: Comparison of the observed correlations and variances of the normalized within-stratum imbalances with the theoretical correlations and model variances in 12 examples of the 3-factor minimization with independent factors, unequal strata prevalence, and bias of 0.9

Example	Prevalences 1st factor	Prevalences 2nd factor	Prevalences 3rd factor	Mean[1] difference	Median[2] absolute difference	Estimated[3] V
1	$\frac{1}{3}, \frac{4}{9}, \frac{2}{9}$	$\frac{1}{3}, \frac{1}{3}, \frac{1}{3}$	$\frac{1}{3}, \frac{1}{3}, \frac{1}{3}$	0.0000	0.0059	0.993
2	$\frac{1}{3}, \frac{4}{9}, \frac{2}{9}$	$\frac{1}{3}, \frac{4}{9}, \frac{2}{9}$	$\frac{1}{3}, \frac{1}{3}, \frac{1}{3}$	0.0000	0.0065	0.982
3	$\frac{1}{3}, \frac{3}{12}, \frac{5}{12}$	$\frac{1}{3}, \frac{1}{3}, \frac{1}{3}$	$\frac{1}{3}, \frac{1}{3}, \frac{1}{3}$	0.0000	0.0064	0.986
4	$\frac{1}{3}, \frac{3}{12}, \frac{5}{12}$	$\frac{1}{3}, \frac{3}{12}, \frac{5}{12}$	$\frac{1}{3}, \frac{1}{3}, \frac{1}{3}$	0.0000	0.0061	0.985
5	$\frac{1}{3}, \frac{4}{15}, \frac{6}{15}$	$\frac{1}{3}, \frac{1}{3}, \frac{1}{3}$	$\frac{1}{3}, \frac{1}{3}, \frac{1}{3}$	0.0000	0.0054	0.986
6	$\frac{1}{3}, \frac{4}{15}, \frac{6}{15}$	$\frac{1}{3}, \frac{4}{15}, \frac{6}{15}$	$\frac{1}{3}, \frac{1}{3}, \frac{1}{3}$	0.0000	0.0054	0.993
7	$\frac{1}{3}, \frac{8}{27}, \frac{10}{27}$	$\frac{1}{3}, \frac{1}{3}, \frac{1}{3}$	$\frac{1}{3}, \frac{1}{3}, \frac{1}{3}$	0.0000	0.0058	0.987
8	$\frac{1}{3}, \frac{8}{27}, \frac{10}{27}$	$\frac{1}{3}, \frac{8}{27}, \frac{10}{27}$	$\frac{1}{3}, \frac{1}{3}, \frac{1}{3}$	0.0000	0.0059	0.988
9	$\frac{1}{3}, \frac{4}{9}, \frac{2}{9}$	$\frac{1}{3}, \frac{4}{9}, \frac{2}{9}$	$\frac{1}{3}, \frac{4}{9}, \frac{2}{9}$	0.0000	0.0062	0.990
10	$\frac{1}{3}, \frac{3}{12}, \frac{5}{12}$	$\frac{1}{3}, \frac{3}{12}, \frac{5}{12}$	$\frac{1}{3}, \frac{3}{12}, \frac{5}{12}$	0.0000	0.0058	0.981
11	$\frac{1}{3}, \frac{4}{15}, \frac{6}{15}$	$\frac{1}{3}, \frac{4}{15}, \frac{6}{15}$	$\frac{1}{3}, \frac{4}{15}, \frac{6}{15}$	0.0000	0.0062	0.995
12	$\frac{1}{3}, \frac{8}{27}, \frac{10}{27}$	$\frac{1}{3}, \frac{8}{27}, \frac{10}{27}$	$\frac{1}{3}, \frac{8}{27}, \frac{10}{27}$	0.0000	0.0059	0.985

[1] Mean difference between the observed and model correlation

[2] Median absolute difference between the observed and model correlation

[3] Estimated as the weighted average of the stratum-specific ratios of the observed variance to the model variance with weights proportional to the strata prevalence

Table A12: Comparison of the estimated variances for the normalized within-stratum imbalances with the model variances in the simulations of 2-factor minimization with independent factors, equal strata prevalence, and bias of 0.9 and 0.8

n_1	n_2	Model variance	Estimated variance $p = 0.9$	Estimated variance $p = 0.8$	Estimated[1] V $p = 0.9$	Estimated[1] V $p = 0.8$
2	2	0.2500	0.2351	0.2520	0.940	1.008
2	3	0.3333	0.3218	0.3330	0.965	0.999
2	4	0.3750	0.3671	0.3738	0.979	0.997
2	5	0.4000	0.3895	0.3952	0.974	0.988
2	6	0.4167	0.4078	0.4124	0.979	0.990
2	7	0.4286	0.4174	0.4236	0.974	0.988
2	8	0.4375	0.4306	0.4367	0.984	0.998
3	3	0.4444	0.4307	0.4418	0.969	0.994
3	4	0.5000	0.4828	0.4988	0.966	0.998
3	5	0.5333	0.5188	0.5317	0.973	0.997
3	6	0.5556	0.5406	0.5463	0.973	0.983
3	7	0.5714	0.5615	0.5725	0.983	1.002
3	8	0.5833	0.5738	0.5841	0.984	1.001
4	4	0.5625	0.5480	0.5621	0.974	0.999
4	5	0.6000	0.5913	0.5954	0.985	0.992
4	6	0.6250	0.6109	0.6234	0.977	0.997
4	7	0.6429	0.6269	0.6398	0.975	0.995
4	8	0.6563	0.6469	0.6544	0.986	0.997
5	5	0.6400	0.6305	0.6376	0.985	0.996
5	6	0.6667	0.6553	0.6633	0.983	0.995
5	7	0.6857	0.6748	0.6823	0.984	0.995
5	8	0.7000	0.6890	0.6993	0.984	0.999
6	6	0.6944	0.6852	0.6909	0.987	0.995
6	7	0.7143	0.7030	0.7103	0.984	0.994
6	8	0.7292	0.7186	0.7281	0.985	0.999
7	7	0.7347	0.7265	0.7318	0.989	0.996
7	8	0.7500	0.7411	0.7472	0.988	0.996
8	8	0.7656	0.7554	0.7624	0.987	0.996

[1]Estimated as the ratio of the estimated within-stratum variance and the model variance.

Table A13: Comparison of the estimated variances for the normalized within-stratum imbalances with the model variances in the simulations of 3-factor minimization with independent factors, equal strata prevalence, and bias of 0.9 and 0.8

n_1	n_2	n_3	Model variance	Estimated variance $p = 0.9$	Estimated variance $p = 0.8$	Estimated[1] V $p = 0.9$	Estimated[1] V $p = 0.8$
2	2	2	0.5000	0.4887	0.4936	0.977	0.987
2	2	3	0.5833	0.5703	0.5776	0.978	0.990
2	2	4	0.6250	0.6135	0.6219	0.982	0.995
2	2	5	0.6500	0.6437	0.6470	0.990	0.995
2	2	6	0.6667	0.6591	0.6638	0.989	0.996
2	2	7	0.6786	0.6718	0.6776	0.990	0.999
2	2	8	0.6875	0.6845	0.6882	0.996	1.001
2	2	9	0.6944	0.6881	0.6926	0.991	0.997
2	3	3	0.6667	0.6550	0.6687	0.983	1.003
2	3	4	0.7083	0.7018	0.7091	0.991	1.001
2	3	5	0.7333	0.7276	0.7332	0.992	1.000
2	3	6	0.7500	0.7421	0.7440	0.989	0.992
2	3	7	0.7619	0.7558	0.7613	0.992	0.999
2	3	8	0.7708	0.7653	0.7692	0.993	0.998
2	3	9	0.7778	0.7716	0.7735	0.992	0.994
2	4	4	0.7500	0.7383	0.7538	0.984	1.005
2	4	5	0.7750	0.7668	0.7728	0.989	0.997
2	4	6	0.7917	0.7850	0.7895	0.992	0.997
2	4	7	0.8036	0.7965	0.8015	0.991	0.997
2	4	8	0.8125	0.8064	0.8094	0.992	0.996
2	4	9	0.8194	0.8111	0.8183	0.990	0.999
2	5	5	0.8000	0.7949	0.7953	0.994	0.994
2	5	6	0.8167	0.8148	0.8134	0.998	0.996
2	5	7	0.8286	0.8258	0.8274	0.997	0.999
3	3	3	0.7407	0.7325	0.7396	0.989	0.998
3	3	4	0.7778	0.7746	0.7815	0.996	1.005
3	3	5	0.8000	0.7943	0.7976	0.993	0.997
3	3	6	0.8148	0.8081	0.8152	0.992	1.001
3	4	4	0.8125	0.8032	0.8113	0.989	0.998
3	4	5	0.8333	0.8247	0.8319	0.990	0.998
3	4	6	0.8472	0.8412	0.8496	0.993	1.003
3	5	5	0.8533	0.8462	0.8529	0.992	0.999
3	5	6	0.8667	0.8613	0.8638	0.994	0.997
3	6	6	0.8796	0.8767	0.8801	0.997	1.001
4	4	4	0.8438	0.8384	0.8445	0.994	1.001
5	5	5	0.8960	0.8928	0.8780	0.996	0.980

[1]Estimated as the ratio of the estimated within-stratum variance and the model variance.

Table A14: Comparison of the estimated variances for the normalized within-stratum imbalances with the model variances in the simulations of minimization with independent factors, equal strata prevalence, 4 to 7 factors and bias of 0.9 and 0.8

M	n_1	n_2	n_3	n_4	n_5	n_6	n_7	Model variance	Estimated variance $p = 0.9$	Estimated variance $p = 0.8$	Estimated[1] V $p = 0.9$	Estimated[1] V $p = 0.8$
4	2	2	2	2	.	.	.	0.6875	0.6776	0.6835	0.986	0.994
4	2	2	2	3	.	.	.	0.7500	0.7446	0.7478	0.993	0.997
4	2	2	2	4	.	.	.	0.7813	0.7729	0.7840	0.989	1.004
4	2	2	2	5	.	.	.	0.8000	0.7951	0.8001	0.994	1.000
4	2	2	2	6	.	.	.	0.8125	0.8125	0.8108	1.000	0.998
4	2	2	3	3	.	.	.	0.8056	0.7989	0.8007	0.992	0.994
4	2	2	3	4	.	.	.	0.8333	0.8272	0.8295	0.993	0.995
4	2	2	3	5	.	.	.	0.8500	0.8461	0.8454	0.995	0.995
4	2	2	3	6	.	.	.	0.8611	0.8560	0.8606	0.994	0.999
4	2	2	4	4	.	.	.	0.8594	0.8550	0.8613	0.995	1.002
4	2	2	4	5	.	.	.	0.8750	0.8690	0.8749	0.993	1.000
4	2	2	4	6	.	.	.	0.8854	0.8805	0.8833	0.994	0.998
5	2	2	2	2	2	.	.	0.8125	0.8117	0.8094	0.999	0.996
5	2	2	2	2	3	.	.	0.8542	0.8499	0.8488	0.995	0.994
6	2	2	2	2	2	2	.	0.8906	0.8891	0.8881	0.998	0.997
7	2	2	2	2	2	2	2	0.9375	0.9364	0.9360	0.999	0.998

[1]Estimated as the ratio of the estimated within-stratum variance and the model variance.

B1. Derivation of (3.5), the conditional covariance $\mathrm{Cov}(Y_{z_1}, Y_{z_2}|A)$

The constraints in Condition A span the same subspace as the orthonormal family of constraints below. First is the constraint on the difference in the treatment totals:

$$\sum_z u_0(z) Y_z = 0, \quad \text{where } u_0(z) := \sqrt{w_z}.$$

For each factor k, let us choose an orthonormal basis of contrasts $\{\psi_{k,a}(i_k)\}_{a=1}^{n_k-1}$ on its levels $\{1, \ldots, n_k\}$ such that

$$\sum_{i_k} w_{k,i_k} \psi_{k,a}(i_k) \psi_{k,b}(i_k) = \delta_{ab}, \quad \sum_{i_k} w_{k,i_k} \psi_{k,a}(i_k) = 0.$$

Let us define $u_{k,a}(z) := \sqrt{w_z}\psi_{k,a}(i_k)$. Because w_z factorizes, these vectors are orthonormal in $\mathbb{R}^{M_s}$ with the usual dot product:

$$\langle u_{k,a}, u_{l,b} \rangle = \sum_z w_z \psi_{k,a}(i_k) \psi_{l,b}(i_l) = \begin{cases} \delta_{ab}, & k = l \\ 0, & k \neq l \end{cases}$$

and similarly, $\langle u_0, u_{k,a} \rangle = 0$. Thus, the subspace in Condition A is the same as the space spanned by $\mathcal{U} := \{u_0\} \cup \{u_{k,a} : k = 1, \ldots, M, a = 1, \ldots, n_k - 1\}$, and $\mathcal{U}$ is orthonormal. So conditioning on Condition A is equivalent to the conditioning on

$$\langle u_0, Y \rangle = 0, \quad \langle u_{k,a}, Y \rangle = 0, \quad \text{for all } k, a.$$

Let P be the orthogonal projector onto the span of $\mathcal{U}$: $P = \sum_{u \in \mathcal{U}} u u^T$. Its orthogonal complement projector is $I_{M_s} - P$. Then $\mathrm{Cov}(Y_z|A) = I_{M_s} - P$, so

$$\mathrm{Cov}(Y_{z_1}, Y_{z_2}|A) = \mathbb{I}\{z_1 = z_2\} - \sum_{u \in \mathcal{U}} u(z_1) u(z_2).$$

The sum over $\mathcal{U}$ can be expanded as

$$\sum_{u \in \mathcal{U}} u(z_1) u(z_2) = u_0(z_1) u_0(z_2) + \sum_{k=1}^{M} \sum_{a=1}^{n_k-1} u_{k,a}(z_1) u_{k,a}(z_2).$$

Using definitions,

$$\begin{aligned} u_0(z_1) u_0(z_2) &= \sqrt{w_{z_1}}\sqrt{w_{z_2}} \\ u_{k,a}(z_1) u_{k,a}(z_2) &= \sqrt{w_{z_1}}\sqrt{w_{z_2}} \psi_{k,a}(i_k) \psi_{k,a}(j_k), \end{aligned}$$

and so

$$\sum_{u \in \mathcal{U}} u(z_1) u(z_2) = \sqrt{w_{z_1}}\sqrt{w_{z_2}} \left(1 + \sum_{k=1}^{M} \sum_{a=1}^{n_k-1} \psi_{k,a}(i_k) \psi_{k,a}(j_k) \right).$$

For a factor k, the set including the constant function $\psi_{k,0}(i) \equiv 1$ and the $n_k - 1$ contrasts $\psi_{k,a}$ is an orthonormal basis in $\mathbb{R}^{n_k}$ with respect to weights $w_{k,i}$:

$$\sum_{i=1}^{n_k} w_{k,i}\psi_{k,a}(i)\psi_{k,b}(i) = \delta_{ab}, \quad a, b = 0, \dots, n_k - 1.$$

Let $\mathbf{F}_k$ be the $n_k \times n_k$ matrix with entries $[\mathbf{F}_k]_{i,a} = \sqrt{w_{k,i}}\psi_{k,a}(i)$. Then the orthonormality says $\mathbf{F}_k^T\mathbf{F}_k = I$, and since $\mathbf{F}_k$ is square, also $\mathbf{F}_k\mathbf{F}_k^T = I$. The entry (i, j) of $\mathbf{F}_k\mathbf{F}_k^T$ is

$$\delta_{ij} = (\mathbf{F}_k\mathbf{F}_k^T)_{ij} = \sum_{a=0}^{n_k-1} \left(\sqrt{w_{k,i}}\psi_{k,a}(i)\right)\left(\sqrt{w_{k,j}}\psi_{k,a}(j)\right).$$

Therefore,

$$\sum_{a=0}^{n_k-1} \psi_{k,a}(i)\psi_{k,a}(j) = \frac{\delta_{ij}}{\sqrt{w_{k,i}w_{k,j}}}.$$

Since $\psi_{k,0} \equiv 1$,

$$\sum_{a=1}^{n_k-1} \psi_{k,a}(i)\psi_{k,a}(j) = \frac{\delta_{ij}}{\sqrt{w_{k,i}w_{k,j}}} - 1.$$

Thus,

$$\sum_{a=1}^{n_k-1} \psi_{k,a}(i_k)\psi_{k,a}(j_k) = \frac{\delta_{i_k,j_k}}{\sqrt{w_{k,i_k}w_{k,j_k}}} - 1$$

and

$$\mathrm{Cov}(Y_{z_1}, Y_{z_2}|A) = \mathbb{I}\{z_1 = z_2\} - \sqrt{w_{z_1}w_{z_2}}\left(1 + \sum_{k=1}^{M}\left(\frac{\delta_{i_k,j_k}}{\sqrt{w_{k,i_k}w_{k,j_k}}} - 1\right)\right),$$

which is formula (3.1).

B2. Proof of Theorem 1

The M_s-component vector of normalized within-stratum imbalances from the urn model

$$Y_z = \frac{N_1(z) - N_0(z)}{\sqrt{Nw_z}}$$

is asymptotically distributed as the normal vector with 0 mean and $M_s \times M_s$ identity covariance matrix I_{M_s}.

The set of $q = n_1 + \cdots + n_k - M + 1$ equations in Condition A can be written as $AY = 0$, where A is the $q \times M_s$ matrix $A_{(k,i_k),z} := \sqrt{Nw_z}\mathbb{I}(z_k = i_k)$. Then the conditional covariance is the standard linear-Gaussian formula:

$$\mathrm{Cov}(Y \mid AY = 0) = I_{M_s} - A^T(AA^T)^{-1}A$$

Matrix $P := A^T(AA^T)^{-1}A$ is an orthogonal projection matrix onto the row space of A (i.e., onto $\mathrm{col}(A^T)$). Indeed, P is symmetric ($P^T = P$) and P is idempotent ($P^2 = P$), thus P is an orthogonal projector.

The image of P is exactly the column space of A^T, i.e., the span of the constraint vectors. Therefore, $\mathrm{Cov}(Y \mid AY = 0) = I_{M_s} - P$ is also a symmetric matrix. Additionally,

$$(\mathrm{Cov}(Y \mid AY = 0))^2 = (I_{M_s} - P)^2 = I_{M_s} - P = \mathrm{Cov}(Y \mid AY = 0),$$

so $\mathrm{Cov}(Y \mid AY = 0)$ is also idempotent. As an idempotent and symmetric matrix, $\mathrm{Cov}(Y \mid AY = 0)$ has eigenvalues of only 1 and 0.

Since P is a projection onto a q-dimensional subspace, it has eigenvalue 1 with multiplicity q, and eigenvalue 0 with multiplicity $M_s - q$. Therefore, $\mathrm{Cov}(Y \mid AY = 0)$ has eigenvalue 0 with multiplicity q, and eigenvalue 1 with multiplicity $M_s - q$.