

# Bangladesh Application

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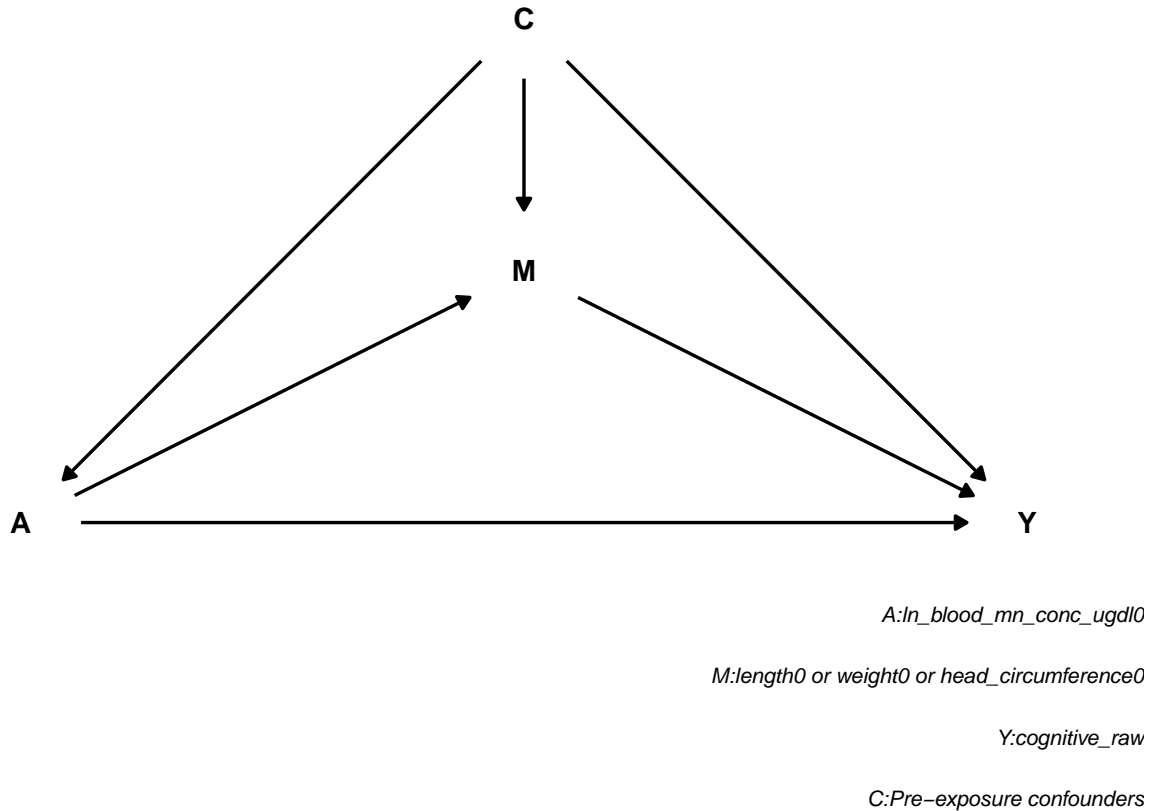
## 1 Variables Used

Table 1: Variables Used

|                               | Name  | Variable Name  | Type   |
|-------------------------------|---|--|--|
| Outcome Y                     | cognitive score   | cognitive_raw  | continuous   |
| Exposure A                    | manganese   | ln_blood_mn_conc_ugdl0   | continuous   |
| Mediator M                    | birth length, birth weight,<br>head circumference   | length0, weight0,<br>head_circumference0   | continuous, continuous,<br>continuous  |
| Pre-exposure<br>Confounder C  | Arsenic,<br>Lead,<br>protein intake, smoking, child age<br>education, mother age,<br>home score, study site | ln_blood_as_conc_ugdl0,<br>ln_blood_pb_conc_ugdl0,<br>allfood, smokenv, agedays<br>educat, approxage,<br>homescore, clinic | continuous,<br>continuous,<br>continuous, binary, continuous<br>categorical, continuous,<br>continuous, binary |
| Post-exposure<br>Confounder L | gestational age,<br>child's haematocrit level   | birthgestationalage,<br>hematocrit2  | continuous<br>continuous   |

## 2 Singular Mediator Case

### 2.1 Variables and DAG



### 2.2 Mediator: Birth Weight

#### 2.2.1 Causal Effects and Standard Errors Estimated By the Regression-based Approach

##### 2.2.1.1 Closed-form Parameter Function Estimation and Delta Method Inference

```
cmest(data = bangladesh_df, outcome = "cognitive_raw",
      exposure = 'ln_blood_mn_conc_ugdl0',
      exposure.type = "continuous", mediator = 'weight0',
      covariates.pre = c("ln_blood_as_conc_ugdl0",
                        "ln_blood_pb_conc_ugdl0",
                        "sex",
                        "allfood",
                        "smokenv", "educat", "agedays", "approxage",
                        "homescore", "birthgestationalage",
                        "clinic", "hematocrit2"),
      EMint = TRUE,
      yreg = "linear", mreg = "linear",
      a_star = log(5.84), a = log(9.5), mval = list(2.9),
      est.method = "paramfunc", inf.method = "delta", model = "rb")
```

```
##           Estimate Std.error   95% CIL   95% CIU        z    pval
## cde       -0.280876  0.114696 -0.505677 -0.056076 -2.449 0.01455 *
## pnde      -0.291584  0.113848 -0.514722 -0.068447 -2.561 0.01062 *
## tnde      -0.298350  0.113462 -0.520732 -0.075969 -2.630 0.00872 **
## pnle      -0.035761  0.020814 -0.076555  0.005034 -1.718 0.08618 .
## tnle      -0.042527  0.023954 -0.089475  0.004422 -1.775 0.07623 .
## te        -0.334111  0.115341 -0.560176 -0.108046 -2.897 0.00388 **
## pm         0.067967  0.044270 -0.018801  0.154735  1.535 0.12513
## intref     -0.010708  0.008450 -0.027270  0.005854 -1.267 0.20546
## intmed     -0.006766  0.005634 -0.017808  0.004276 -1.201 0.23015
## pie       -0.035761  0.020814 -0.076555  0.005034 -1.718 0.08618 .
## cde_prop   0.840668  0.085177  0.673725  1.007611  9.870 < 2e-16 ***
## intref_prop 0.032049  0.028515 -0.023840  0.087938  1.124 0.26139
## intmed_prop 0.020251  0.017989 -0.015008  0.055509  1.126 0.26064
## pie_prop   0.107032  0.066472 -0.023250  0.237314  1.610 0.10777
## overall_pm 0.127283  0.077629 -0.024867  0.279433  1.640 0.10149
## overall_int 0.052300  0.041724 -0.029477  0.134077  1.253 0.21041
## overall_pe 0.159332  0.085177 -0.007611  0.326275  1.871 0.06178 .
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

### 2.2.1.2 Direct Imputation Estimation and Bootstrap Inference

```
cmest(data = bangladesh_df, outcome = "cognitive_raw",
      exposure = 'ln_blood_mn_conc_ugdl0',
      exposure.type = "continuous", mediator = 'weight0',
      covariates.pre = c("ln_blood_as_conc_ugdl0",
                        "ln_blood_pb_conc_ugdl0",
                        "sex",
                        "allfood",
                        "smokenv", "educat", "agedays", "approxage",
                        "homescore", "birthgestationalage",
                        "clinic", "hematocrit2"),
      EMint = TRUE,
      yreg = "linear", mreg = "linear",
      a_star = log(5.84), a = log(9.5), mval = list(2.9),
      est.method = "imputation", inf.method = "bootstrap", model = "rb")
```

```
##           Estimate Std.error   95% CIL   95% CIU        z    pval
## cde       -0.280876  0.114636 -0.505559 -0.056194 -2.450 0.014501 *
## pnle      -0.293041  0.116556 -0.521487 -0.064595 -2.514 0.012135 *
## tnle      -0.299807  0.117952 -0.530988 -0.068626 -2.542 0.011224 *
## pnle      -0.035761  0.022236 -0.079342  0.007821 -1.608 0.108192
## tnle      -0.042527  0.025783 -0.093061  0.008008 -1.649 0.099476 .
## te        -0.335568  0.118907 -0.568621 -0.102514 -2.822 0.004894 **
## pm         0.067652  0.282874 -0.486772  0.622076  0.239 0.811046
## intref     -0.012165  0.012772 -0.037198  0.012869 -0.952 0.341187
## intmed     -0.006766  0.006885 -0.020261  0.006729 -0.983 0.326082
## pie       -0.035761  0.022236 -0.079342  0.007821 -1.608 0.108192
## cde_prop   0.837019  0.237202  0.372112  1.301926  3.529 0.000442 ***
## intref_prop 0.036251  0.053049 -0.067724  0.140225  0.683 0.494596
## intmed_prop 0.020163  0.025544 -0.029902  0.070228  0.789 0.430154
## pie_prop   0.106568  0.228942 -0.342150  0.555285  0.465 0.641720
## overall_pm 0.126730  0.228865 -0.321836  0.575297  0.554 0.579921
```

```
## overall_int 0.056414 0.070609 -0.081977 0.194804 0.799 0.424560
## overall_pe 0.162981 0.237202 -0.301926 0.627888 0.687 0.492227
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

## 2.2.2 Causal Effects and Standard Errors Estimated By the G-formula Approach

```
cmetest(data = bangladesh_df, outcome = "cognitive_raw",
        exposure = 'ln_blood_mn_conc_ugdl0',
        exposure.type = "continuous", mediator = 'weight0',
        covariates.pre = c("ln_blood_as_conc_ugdl0",
                           "ln_blood_pb_conc_ugdl0",
                           "sex",
                           "allfood",
                           "smokenv", "educat", "agedays", "approxage",
                           "homescore", "birthgestationalage",
                           "clinic", "hematocrit2"),
        EMint = TRUE,
        yreg = "linear", mreg = "linear",
        a_star = log(5.84), a = log(9.5), mval = list(2.9),
        est.method = "imputation", inf.method = "bootstrap", model = "g-formula")
```

```
##          Estimate Std.error  95% CIL  95% CIU      z  pval
## cde      -0.280876  0.132245 -0.540072 -0.021681 -2.124 0.0340 *
## pn      -0.293041  0.134656 -0.556962 -0.029120 -2.176 0.0298 *
## tn      -0.299807  0.135645 -0.565667 -0.033947 -2.210 0.0274 *
## pn      -0.035761  0.021651 -0.078197  0.006675 -1.652 0.0990 .
## tn      -0.042527  0.025198 -0.091914  0.006860 -1.688 0.0919 .
## te      -0.335568  0.135147 -0.600452 -0.070684 -2.483 0.0132 *
## pm       0.067652  1.134795 -2.156505  2.291809  0.060 0.9525
## intref   -0.012165  0.012306 -0.036285  0.011956 -0.988 0.3232
## intmed   -0.006766  0.006327 -0.019167  0.005635 -1.069 0.2852
## pie      -0.035761  0.021651 -0.078197  0.006675 -1.652 0.0990 .
## cde_prop  0.837019  0.342768  0.165205  1.508832  2.442 0.0148 *
## intref_prop 0.036251  0.173563 -0.303927  0.376429  0.209 0.8346
## intmed_prop 0.020163  0.051478 -0.080731  0.121057  0.392 0.6954
## pie_prop  0.106568  0.214349 -0.313548  0.526683  0.497 0.6192
## overall_pm 0.126730  0.229451 -0.322984  0.576445  0.552 0.5809
## overall_int 0.056414  0.221190 -0.377111  0.489938  0.255 0.7988
## overall_pe 0.162981  0.342768 -0.508832  0.834795  0.475 0.6346
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

## 2.3 Mediator: Birth Length

### 2.3.1 Causal Effects and Standard Errors Estimated By the Regression-based Approach

#### 2.3.1.1 Closed-form Parameter Function Estimation and Delta Method Inference

```
cmetest(data = bangladesh_df, outcome = "cognitive_raw",
        exposure = 'ln_blood_mn_conc_ugdl0',
        exposure.type = "continuous", mediator = 'length0',
```

```

covariates.pre = c("ln_blood_as_conc_ugdl0",
                  "ln_blood_pb_conc_ugdl0",
                  "sex",
                  "allfood",
                  "smokenv", "educat", "agedays", "approxage",
                  "homescore", "birthgestationalage",
                  "clinic", "hematocrit2"),

EMint = TRUE,
yreg = "linear", mreg = "linear",
a_star = log(5.84), a = log(9.5), mval = list(47),
est.method = "paramfunc", inf.method = "delta", model = "rb")

```

```

##           Estimate Std.error   95% CIL   95% CIU        z      pval
## cde      -0.199932  0.112685 -0.420791  0.020927 -1.774 0.076417 .
## pnde     -0.253442  0.112467 -0.473874 -0.033010 -2.253 0.024511 *
## tn timer  -0.288941  0.112666 -0.509763 -0.068119 -2.565 0.010519 *
## pn timer  -0.072365  0.026589 -0.124477 -0.020252 -2.722 0.006643 **
## tn timer  -0.107864  0.036800 -0.179991 -0.035737 -2.931 0.003478 **
## te       -0.361306  0.115238 -0.587169 -0.135442 -3.135 0.001782 **
## pm        0.175461  0.084331  0.010174  0.340747  2.081 0.037800 *
## intref    -0.053510  0.020765 -0.094208 -0.012811 -2.577 0.010153 *
## intmed    -0.035499  0.014543 -0.064004 -0.006995 -2.441 0.014874 *
## pie      -0.072365  0.026589 -0.124477 -0.020252 -2.722 0.006643 **
## cde_prop   0.553360  0.158432  0.242839  0.863880  3.493 0.000505 ***
## intref_prop 0.148101  0.072848  0.005321  0.290881  2.033 0.042395 *
## intmed_prop 0.098253  0.045623  0.008834  0.187672  2.154 0.031582 *
## pie_prop   0.200286  0.086673  0.030410  0.370163  2.311 0.021107 *
## overall_pm 0.298539  0.122068  0.059290  0.537789  2.446 0.014681 *
## overall_int 0.246354  0.102838  0.044794  0.447914  2.396 0.016834 *
## overall_pe 0.446640  0.158432  0.136120  0.757161  2.819 0.004939 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

```

### 2.3.1.2 Direct Imputation Estimation and Bootstrap Inference

```

cmest(data = bangladesh_df, outcome = "cognitive_raw",
      exposure = 'ln_blood_mn_conc_ugdl0',
      exposure.type = "continuous", mediator = 'length0',
      covariates.pre = c("ln_blood_as_conc_ugdl0",
                        "ln_blood_pb_conc_ugdl0",
                        "sex",
                        "allfood",
                        "smokenv", "educat", "agedays", "approxage",
                        "homescore", "birthgestationalage",
                        "clinic", "hematocrit2"),

      EMint = TRUE,
      yreg = "linear", mreg = "linear",
      a_star = log(5.84), a = log(9.5), mval = list(47),
      est.method = "imputation", inf.method = "bootstrap", model = "rb")

```

```

##           Estimate Std.error   95% CIL   95% CIU        z      pval
## cde      -0.199932  0.108189 -0.411978  0.012114 -1.848 0.06499 .
## pn timer  -0.248867  0.108732 -0.461979 -0.035756 -2.289 0.02236 *
## tn timer  -0.284367  0.111821 -0.503532 -0.065201 -2.543 0.01118 *

```

```
## pnle      -0.072365  0.028797 -0.128806 -0.015923 -2.513 0.01218 *
## tnle      -0.107864  0.035280 -0.177011 -0.038717 -3.057 0.00231 **
## te        -0.356731  0.115218 -0.582555 -0.130908 -3.096 0.00203 **
## pm         0.178111  1.515259 -2.791743  3.147965  0.118 0.90646
## intref     -0.048935  0.021035 -0.090163 -0.007708 -2.326 0.02026 *
## intmed     -0.035499  0.015567 -0.066011 -0.004988 -2.280 0.02286 *
## pie        -0.072365  0.028797 -0.128806 -0.015923 -2.513 0.01218 *
## cde_prop   0.560455  0.273573  0.024262  1.096649  2.049 0.04084 *
## intref_prop 0.137177  0.096297 -0.051562  0.325917  1.425 0.15470
## intmed_prop 0.099513  0.067755 -0.033285  0.232310  1.469 0.14232
## pie_prop   0.202855  0.163740 -0.118070  0.523779  1.239 0.21577
## overall_pm 0.302367  0.208140 -0.105580  0.710314  1.453 0.14671
## overall_int 0.236690  0.146575 -0.050592  0.523972  1.615 0.10676
## overall_pe 0.439545  0.273573 -0.096649  0.975738  1.607 0.10853
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

## 2.3.2 Causal Effects and Standard Errors Estimated By the G-formula Approach

```
cmetest(data = bangladesh_df, outcome = "cognitive_raw",
        exposure = 'ln_blood_mn_conc_ugdl0',
        exposure.type = "continuous", mediator = 'length0',
        covariates.pre = c("ln_blood_as_conc_ugdl0",
                           "ln_blood_pb_conc_ugdl0",
                           "sex",
                           "allfood",
                           "smokenv", "educat", "agedays", "approxage",
                           "homescore", "birthgestationalage",
                           "clinic", "hematocrit2"),
        EMint = TRUE,
        yreg = "linear", mreg = "linear",
        a_star = log(5.84), a = log(9.5), mval = list(47),
        est.method = "imputation", inf.method = "bootstrap", model = "g-formula")
```

```
##      Estimate Std.error  95% CIL  95% CIU      z    pval
## cde      -0.199932  0.115292 -0.425901  0.026037 -1.734 0.08330 .
## pnle      -0.248867  0.116780 -0.477753 -0.019982 -2.131 0.03340 *
## tnle      -0.284367  0.119911 -0.519387 -0.049346 -2.371 0.01796 *
## pnle      -0.072365  0.029582 -0.130344 -0.014385 -2.446 0.01466 *
## tnle      -0.107864  0.035663 -0.177762 -0.037966 -3.025 0.00257 **
## te        -0.356731  0.122922 -0.597655 -0.115808 -2.902 0.00381 **
## pm         0.178111  0.498409 -0.798753  1.154975  0.357 0.72092
## intref     -0.048935  0.021359 -0.090799 -0.007072 -2.291 0.02223 *
## intmed     -0.035499  0.014318 -0.063562 -0.007437 -2.479 0.01337 *
## pie        -0.072365  0.029582 -0.130344 -0.014385 -2.446 0.01466 *
## cde_prop   0.560455  0.293077 -0.013965  1.134875  1.912 0.05621 .
## intref_prop 0.137177  0.113158 -0.084609  0.358964  1.212 0.22579
## intmed_prop 0.099513  0.066197 -0.030231  0.229256  1.503 0.13318
## pie_prop   0.202855  0.166089 -0.122673  0.528382  1.221 0.22232
## overall_pm 0.302367  0.215223 -0.119463  0.724198  1.405 0.16045
## overall_int 0.236690  0.156815 -0.070663  0.544043  1.509 0.13162
## overall_pe 0.439545  0.293077 -0.134875  1.013965  1.500 0.13409
## ---
```

```
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

## 2.4 Mediator: Head Circumference

### 2.4.1 Causal Effects and Standard Errors Estimated By the Regression-based Approach

#### 2.4.1.1 Closed-form Parameter Function Estimation and Delta Method Inference

```
cmetest(data = bangladesh_df, outcome = "cognitive_raw",
        exposure = 'ln_blood_mn_conc_ugdl0',
        exposure.type = "continuous", mediator = 'head_circumference0',
        covariates.pre = c("ln_blood_as_conc_ugdl0",
                          "ln_blood_pb_conc_ugdl0",
                          "sex",
                          "allfood",
                          "smokenv", "educat", "agedays", "approxage",
                          "homescore", "birthgestationalage",
                          "clinic", "hematocrit2"),
        EMint = TRUE,
        yreg = "linear", mreg = "linear",
        a_star = log(5.84), a = log(9.5), mval = list(33),
        est.method = "paramfunc", inf.method = "delta", model = "rb")
```

```
##           Estimate Std.error   95% CIL   95% CIU      z    pval
## cde      -0.3390325  0.1169034 -0.5681589 -0.1099060 -2.900 0.00384 **
## pnde     -0.3384610  0.1150130 -0.5638825 -0.1130396 -2.943 0.00335 **
## tnde     -0.3383468  0.1148361 -0.5634214 -0.1132721 -2.946 0.00331 **
## pnle     -0.0135033  0.0119751 -0.0369739  0.0099674 -1.128 0.25983
## tnle     -0.0133890  0.0117278 -0.0363751  0.0095971 -1.142 0.25396
## te       -0.3518500  0.1152877 -0.5778097 -0.1258904 -3.052 0.00235 **
## pm        0.0193956  0.0180345 -0.0159515  0.0547427  1.075 0.28250
## intref    0.0005715  0.0139954 -0.0268591  0.0280020  0.041 0.96744
## intmed    0.0001143  0.0027996 -0.0053728  0.0056013  0.041 0.96746
## pie      -0.0135033  0.0119751 -0.0369739  0.0099674 -1.128 0.25983
## cde_prop  0.9635710  0.0547831  0.8561982  1.0709439 17.589 < 2e-16 ***
## intref_prop -0.0016241  0.0397435 -0.0795200  0.0762717 -0.041 0.96741
## intmed_prop -0.0003247  0.0079498 -0.0159060  0.0152565 -0.041 0.96743
## pie_prop  0.0383779  0.0352110 -0.0306344  0.1073901  1.090 0.27608
## overall_pm 0.0380531  0.0347096 -0.0299765  0.1060827  1.096 0.27328
## overall_int -0.0019489  0.0476892 -0.0954180  0.0915203 -0.041 0.96741
## overall_pe 0.0364290  0.0547831 -0.0709439  0.1438018  0.665 0.50627
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

#### 2.4.1.2 Direct Imputation Estimation and Bootstrap Inference

```
cmetest(data = bangladesh_df, outcome = "cognitive_raw",
        exposure = 'ln_blood_mn_conc_ugdl0',
        exposure.type = "continuous", mediator = 'head_circumference0',
        covariates.pre = c("ln_blood_as_conc_ugdl0",
                          "ln_blood_pb_conc_ugdl0",
                          "sex",
                          "allfood",
                          "smokenv", "educat", "agedays", "approxage",
```

```

                                "homescore", "birthgestationalage",
                                "clinic", "hematocrit2"),
    EMint = TRUE,
    yreg = "linear", mreg = "linear",
    a_star = log(5.84), a = log(9.5), mval = list(33),
    est.method = "imputation", inf.method = "bootstrap", model = "rb")

##           Estimate Std.error   95% CIL   95% CIU      z    pval
## cde          -0.3390325  0.1285513 -0.5909885 -0.0870765 -2.637 0.00852 **
## pnde          -0.3385052  0.1282826 -0.5899345 -0.0870760 -2.639 0.00849 **
## tnde          -0.3383910  0.1284430 -0.5901347 -0.0866473 -2.635 0.00859 **
## pnle          -0.0135033  0.0114652 -0.0359746  0.0089681 -1.178 0.23926
## tnle          -0.0133890  0.0117651 -0.0364481  0.0096702 -1.138 0.25546
## te            -0.3518942  0.1285316 -0.6038115 -0.0999769 -2.738 0.00633 **
## pm             0.0193931  0.0270870 -0.0336965  0.0724827  0.716 0.47424
## intref         0.0005272  0.0249557 -0.0483851  0.0494396  0.021 0.98315
## intmed         0.0001143  0.0048370 -0.0093661  0.0095946  0.024 0.98116
## pie           -0.0135033  0.0114652 -0.0359746  0.0089681 -1.178 0.23926
## cde_prop       0.9634499  0.1127316  0.7425000  1.1843999  8.546 < 2e-16 ***
## intref_prop    -0.0014983  0.0973255 -0.1922527  0.1892562 -0.015 0.98772
## intmed_prop    -0.0003247  0.0156409 -0.0309803  0.0303309 -0.021 0.98344
## pie_prop       0.0383730  0.0488064 -0.0572858  0.1340319  0.786 0.43198
## overall_pm     0.0380483  0.0485280 -0.0570649  0.1331616  0.784 0.43325
## overall_int    -0.0018230  0.1091380 -0.2157295  0.2120835 -0.017 0.98668
## overall_pe     0.0365501  0.1127316 -0.1843999  0.2575000  0.324 0.74586
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

```

## 2.4.2 Causal Effects and Standard Errors Estimated By the G-formula Approach

```

cmest(data = bangladesh_df, outcome = "cognitive_raw",
      exposure = 'ln_blood_mn_conc_ugdl0',
      exposure.type = "continuous", mediator = 'head_circumference0',
      covariates.pre = c("ln_blood_as_conc_ugdl0",
                        "ln_blood_pb_conc_ugdl0",
                        "sex",
                        "allfood",
                        "smokenv", "educat", "agedays", "approxage",
                        "homescore", "birthgestationalage",
                        "clinic", "hematocrit2"),
      EMint = TRUE,
      yreg = "linear", mreg = "linear",
      a_star = log(5.84), a = log(9.5), mval = list(33),
      est.method = "imputation", inf.method = "bootstrap", model = "g-formula")

##           Estimate Std.error   95% CIL   95% CIU      z    pval
## cde          -0.3390325  0.1252085 -0.5844366 -0.0936284 -2.708 0.00692 **
## pnde          -0.3385052  0.1247170 -0.5829461 -0.0940644 -2.714 0.00679 **
## tnde          -0.3383910  0.1246155 -0.5826330 -0.0941490 -2.715 0.00677 **
## pnle          -0.0135033  0.0108393 -0.0347479  0.0077414 -1.246 0.21323
## tnle          -0.0133890  0.0114118 -0.0357557  0.0089777 -1.173 0.24106
## te            -0.3518942  0.1262602 -0.5993597 -0.1044288 -2.787 0.00545 **
## pm             0.0193931  0.0217239 -0.0231850  0.0619712  0.893 0.37229

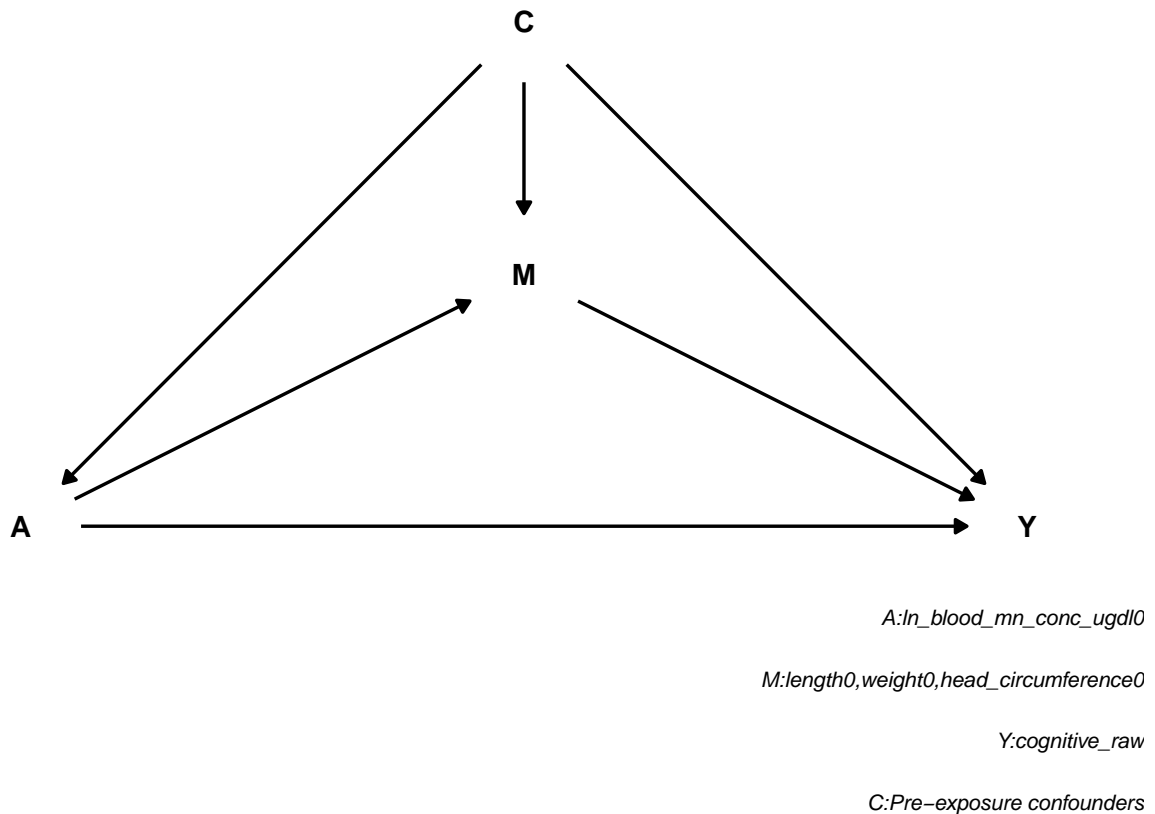
```



```
## intref      0.0005272  0.0226576 -0.0438809  0.0449354  0.023 0.98144
## intmed      0.0001143  0.0056432 -0.0109461  0.0111746  0.020 0.98385
## pie        -0.0135033  0.0108393 -0.0347479  0.0077414 -1.246 0.21323
## cde_prop    0.9634499  0.0864295  0.7940511  1.1328487 11.147 < 2e-16 ***
## intref_prop -0.0014983  0.0795133 -0.1573414  0.1543448 -0.019 0.98497
## intmed_prop -0.0003247  0.0175067 -0.0346372  0.0339878 -0.019 0.98521
## pie_prop    0.0383730  0.0409612 -0.0419094  0.1186554  0.937 0.34915
## overall_pm  0.0380483  0.0398592 -0.0400742  0.1161709  0.955 0.34010
## overall_int -0.0018230  0.0932677 -0.1846244  0.1809784 -0.020 0.98441
## overall_pe  0.0365501  0.0864295 -0.1328487  0.2059489  0.423 0.67249
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

### 3 Multiple Mediator Case

#### 3.1 Variables and DAG



#### 3.2 Methods Can Be Used

##### 3.2.1 Causal Effects and Standard Errors Estimated By the Regression-based Approach

```
cmest(data = bangladesh_df, outcome = "cognitive_raw",
      exposure = 'ln_blood_mn_conc_ugd10',
```

```

exposure.type = "continuous",
mediator = c('weight0', "length0", "head_circumference0"),
covariates.pre = c("ln_blood_as_conc_ugdl0",
                    "ln_blood_pb_conc_ugdl0",
                    "sex",
                    "allfood",
                    "smokenv", "educat", "agedays", "approxage",
                    "homescore", "birthgestationalage",
                    "clinic", "hematocrit2"),

EMint = TRUE,
EMint.terms = c("ln_blood_mn_conc_ugdl0*weight0",
                 "ln_blood_mn_conc_ugdl0*length0",
                 "ln_blood_mn_conc_ugdl0*head_circumference0"),
yreg = "linear", mreg = c("linear", "linear", "linear"),
a_star = log(5.84), a = log(9.5), mval = list(2.9, 47, 33),
est.method = "imputation", inf.method = "bootstrap", model = "rb")

```

```

##           Estimate Std.error  95% CIL  95% CIU      z    pval
## cde      -0.212917  0.113919 -0.436194  0.010361 -1.869 0.06200 .
## pnde     -0.247038  0.113556 -0.469605 -0.024472 -2.175 0.02990 *
## tnde     -0.279741  0.116256 -0.507598 -0.051883 -2.406 0.01635 *
## pnle     -0.084662  0.032244 -0.147858 -0.021465 -2.626 0.00882 **
## tnle     -0.117364  0.038175 -0.192186 -0.042542 -3.074 0.00218 **
## te       -0.364402  0.122007 -0.603532 -0.125273 -2.987 0.00291 **
## pm        0.191947  0.166180 -0.133760  0.517654  1.155 0.24843
## intref    -0.034122  0.024333 -0.081814  0.013570 -1.402 0.16124
## intmed    -0.032702  0.015786 -0.063642 -0.001763 -2.072 0.03863 *
## pie       -0.084662  0.032244 -0.147858 -0.021465 -2.626 0.00882 **
## cde_prop   0.584290  0.225909  0.141517  1.027063  2.586 0.00988 **
## intref_prop 0.093637  0.106920 -0.115921  0.303196  0.876 0.38143
## intmed_prop 0.089742  0.053377 -0.014875  0.194360  1.681 0.09311 .
## pie_prop   0.232330  0.130177 -0.022813  0.487473  1.785 0.07470 .
## overall_pm 0.322073  0.161795  0.004959  0.639186  1.991 0.04688 *
## overall_int 0.183380  0.135988 -0.083152  0.449911  1.349 0.17789
## overall_pe 0.415710  0.225909 -0.027063  0.858483  1.840 0.06613 .
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

```

### 3.2.2 Causal Effects and Standard Errors Estimated By the G-formula Approach

```

cmest(data = bangladesh_df, outcome = "cognitive_raw",
      exposure = 'ln_blood_mn_conc_ugdl0',
      exposure.type = "continuous",
      mediator = c('weight0', "length0", "head_circumference0"),
      covariates.pre = c("ln_blood_as_conc_ugdl0",
                          "ln_blood_pb_conc_ugdl0",
                          "sex",
                          "allfood",
                          "smokenv", "educat", "agedays", "approxage",
                          "homescore", "birthgestationalage",
                          "clinic", "hematocrit2"),

      EMint = TRUE,

```

```

EMint.terms = c("ln_blood_mn_conc_ugdl0*weight0",
                "ln_blood_mn_conc_ugdl0*length0",
                "ln_blood_mn_conc_ugdl0*head_circumference0"),
yreg = "linear", mreg = c("linear", "linear", "linear"), mval = list(2.9,47,33),
a_star = log(5.84), a = log(9.5),
est.method = "imputation", inf.method = "bootstrap", model = "g-formula")

```

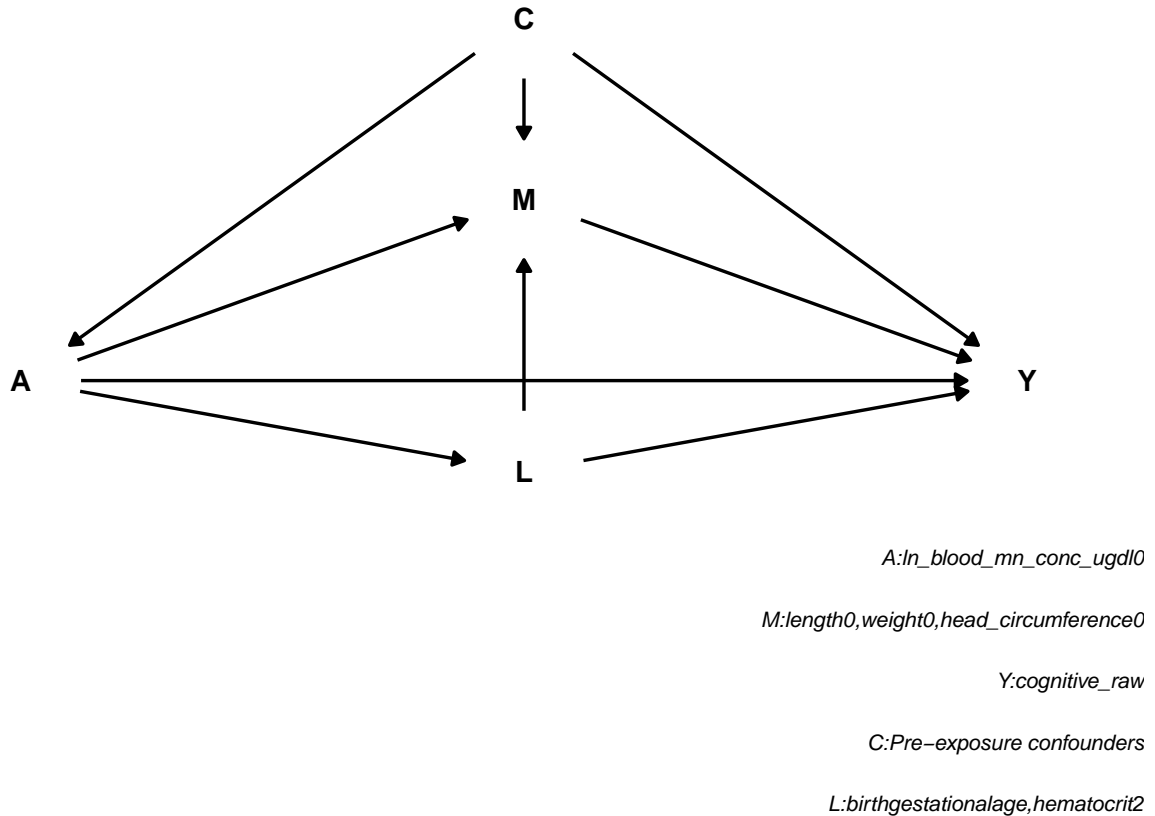
```

##           Estimate Std.error  95% CIL  95% CIU      z    pval
## cde      -0.212917  0.105407 -0.419511 -0.006322 -2.020 0.04374 *
## pnde     -0.247038  0.106077 -0.454945 -0.039131 -2.329 0.02012 *
## tn timer  -0.279741  0.106630 -0.488732 -0.070749 -2.623 0.00888 **
## pn timer  -0.084662  0.033598 -0.150512 -0.018811 -2.520 0.01194 *
## tn timer  -0.117364  0.040652 -0.197040 -0.037688 -2.887 0.00400 **
## te       -0.364402  0.113465 -0.586790 -0.142014 -3.212 0.00138 **
## pm        0.191947  0.452757 -0.695441  1.079335  0.424 0.67172
## intref    -0.034122  0.024033 -0.081225  0.012982 -1.420 0.15608
## intmed    -0.032702  0.015103 -0.062304 -0.003101 -2.165 0.03067 *
## pie      -0.084662  0.033598 -0.150512 -0.018811 -2.520 0.01194 *
## cde_prop   0.584290  0.226956  0.139465  1.029115  2.574 0.01023 *
## intref_prop 0.093637  0.082607 -0.068269  0.255543  1.134 0.25734
## intmed_prop 0.089742  0.063670 -0.035049  0.214534  1.409 0.15909
## pie_prop   0.232330  0.158184 -0.077704  0.542364  1.469 0.14231
## overall_pm 0.322073  0.195934 -0.061951  0.706097  1.644 0.10063
## overall_int 0.183380  0.121233 -0.054233  0.420992  1.513 0.13079
## overall_pe 0.415710  0.226956 -0.029115  0.860535  1.832 0.06739 .
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

```

## 4 Multiple Mediator with Time-dependent Confounding Case

### 4.1 Variables and DAG



### 4.2 Methods Can Be Used

#### 4.2.1 G-formula approach

```
cmest(data = bangladesh_df, outcome = "cognitive_raw",
      exposure = 'ln_blood_mn_conc_ugdl0',
      exposure.type = "continuous",
      mediator = c('weight0', "length0", "head_circumference0"),
      covariates.pre = c("ln_blood_as_conc_ugdl0",
                        "ln_blood_pb_conc_ugdl0",
                        "sex",
                        "allfood",
                        "smokenv", "educat", "agedays", "approxage",
                        "homescore", "birthgestationalage",
                        "clinic", "hematocrit2"),
      covariates.post = c("birthgestationalage", "hematocrit2"),
      covariates.post.type = c("continuous", "continuous"),
      EMint = TRUE,
      EMint.terms = c("ln_blood_mn_conc_ugdl0*weight0",
                     "ln_blood_mn_conc_ugdl0*length0",
```

```

                                "ln_blood_mn_conc_ugdl0*head_circumference0"),
yreg = "linear", mreg = c("linear", "linear", "linear"),
mval = list(2.9,47,33),
a_star = log(5.84), a = log(9.5),
est.method = "imputation", inf.method = "bootstrap", model = "g-formula")

```

```

##           Estimate Std.error   95% CIL   95% CIU      z    pval
## cde      -0.2129166  0.1127904 -0.4339817  0.0081484 -1.888 0.05944 .
## pnde     -0.2470382  0.1096205 -0.4618905 -0.0321859 -2.254 0.02450 *
## tnde     -0.2797405  0.1140884 -0.5033497 -0.0561314 -2.452 0.01443 *
## pnle     -0.0846616  0.0349755 -0.1532123 -0.0161109 -2.421 0.01573 *
## tnle     -0.1173639  0.0409885 -0.1976999 -0.0370279 -2.863 0.00431 **
## te       -0.3644021  0.1194247 -0.5984703 -0.1303340 -3.051 0.00236 **
## pm        0.1919466  0.1251462 -0.0533355  0.4372288  1.534 0.12550
## intref    -0.0341216  0.0232503 -0.0796914  0.0114482 -1.468 0.14263
## intmed    -0.0327023  0.0153023 -0.0626942 -0.0027104 -2.137 0.03291 *
## pie       -0.0846616  0.0349755 -0.1532123 -0.0161109 -2.421 0.01573 *
## cde_prop   0.5842902  0.1929606  0.2060945  0.9624860  3.028 0.00254 **
## intref_prop 0.0936372  0.0964074 -0.0953178  0.2825923  0.971 0.33172
## intmed_prop 0.0897424  0.0453947  0.0007703  0.1787145  1.977 0.04841 *
## pie_prop   0.2323301  0.1270897 -0.0167611  0.4814214  1.828 0.06792 .
## overall_pm 0.3220725  0.1448221  0.0382264  0.6059187  2.224 0.02644 *
## overall_int 0.1833796  0.1219041 -0.0555480  0.4223073  1.504 0.13292
## overall_pe 0.4157098  0.1929606  0.0375140  0.7939055  2.154 0.03152 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

```