Final

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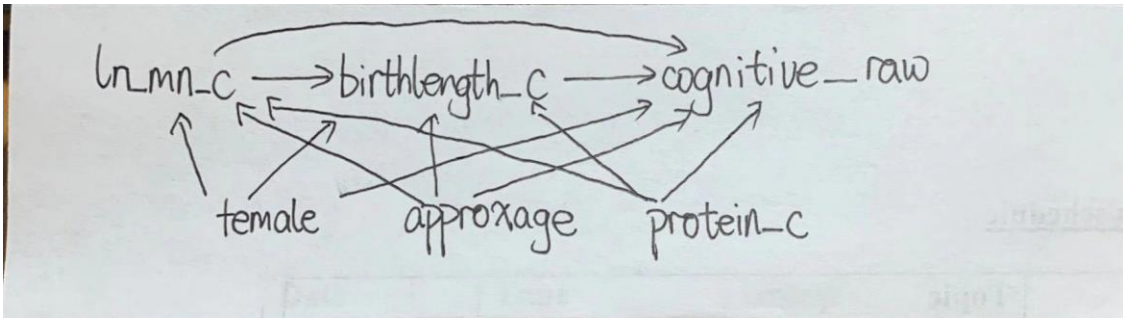
Part 1

Question 1a



Question 1a

Question 1b

```
##        25%        75%
## -0.6099775  0.7058503
```

Regress Y on A and C:

```
##
## Call:
## lm(formula = cognitive_raw ~ ln_mn_c + female + approxage + protein_c,
##     data = data1)
##
## Residuals:
##      Min       1Q   Median       3Q      Max
## -18.1104  -3.5195   0.2701   3.5397  15.4567
##
## Coefficients:
##             Estimate Std. Error t value Pr(>|t|)
## (Intercept) 56.45956    1.43639  39.307  < 2e-16 ***
## ln_mn_c     -0.65445    0.26366  -2.482   0.0134 *
## female1     -0.35578    0.50731  -0.701   0.4834
## approxage    0.11330    0.06094   1.859   0.0636 .
## protein_c    0.23859    0.05482   4.353 1.64e-05 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 5.655 on 495 degrees of freedom
```

```
## Multiple R-squared:  0.05556,    Adjusted R-squared:  0.04793
## F-statistic:  7.28 on 4 and 495 DF,  p-value: 1.057e-05
```

Regress Y on A, M and C:

```
##
## Call:
## lm(formula = cognitive_raw ~ ln_mn_c + birthlength_c + female +
##     approxage + protein_c, data = data1)
##
## Residuals:
##      Min       1Q   Median       3Q      Max
## -17.2818  -3.6632   0.0347   3.5259  14.7940
##
## Coefficients:
##               Estimate Std. Error t value Pr(>|t|)
## (Intercept)   56.13384    1.37348  40.870  < 2e-16 ***
## ln_mn_c       -0.35228    0.25571  -1.378  0.16894
## birthlength_c  0.86369    0.12464   6.929 1.32e-11 ***
## female1       -0.11804    0.48602  -0.243  0.80820
## approxage      0.11898    0.05825   2.043  0.04161 *
## protein_c      0.15369    0.05380   2.857  0.00446 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 5.405 on 494 degrees of freedom
## Multiple R-squared:  0.1392, Adjusted R-squared:  0.1305
## F-statistic: 15.98 on 5 and 494 DF,  p-value: 1.311e-14
```

Regress M on A and C

```
##
## Call:
## lm(formula = birthlength_c ~ ln_mn_c + female + approxage + protein_c,
##     data = data1)
##
## Residuals:
##     Min      1Q  Median      3Q     Max
## -6.1670 -1.2018  0.1061  1.1701  6.6815
##
## Coefficients:
##              Estimate Std. Error t value Pr(>|t|)
## (Intercept)  0.377127   0.495002   0.762 0.446500
## ln_mn_c     -0.349862   0.090862  -3.850 0.000133 ***
## female1     -0.275253   0.174827  -1.574 0.116028
## approxage   -0.006579   0.021002  -0.313 0.754205
## protein_c    0.098298   0.018891   5.203 2.87e-07 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 1.949 on 495 degrees of freedom
```

```
## Multiple R-squared:  0.08192,    Adjusted R-squared:  0.0745
## F-statistic: 11.04 on 4 and 495 DF,  p-value: 1.382e-08
```

The total effect of one unit change in log and centered manganese level is -0.654 and the total effect of a change in log and centered manganese levels from 25th to the 75th percentile is -0.861.

The direct effect of one unit change in log and centered manganese level is -0.352 and the direct effect of a change in log and centered manganese levels from 25th to the 75th percentile is -0.464.

The indirect effect of difference method for one unit change in log and centered manganese level is -0.302 and the indirect effect of difference method for a change in log and centered manganese levels from 25th to the 75th percentile is -0.398.

The indirect effect of product method for one unit change in log and centered manganese level is -0.302 and the indirect effect of product method for a change in log and centered manganese levels from 25th to the 75th percentile is -0.39738.

Question 1c

The model including interaction

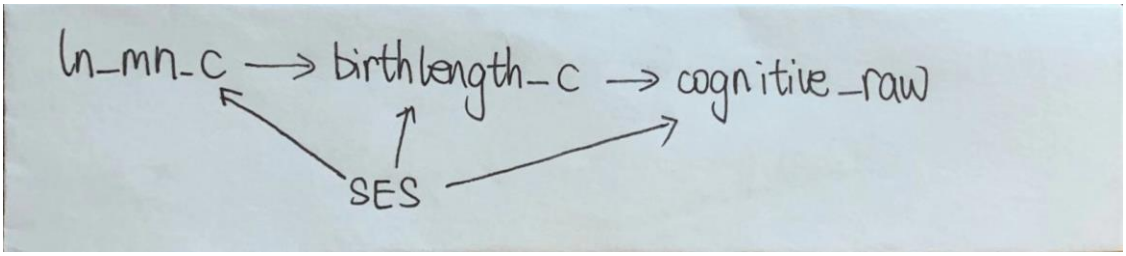
```
##
## Call:
## lm(formula = cognitive_raw ~ ln_mn_c + birthlength_c + ln_mn_c *
##     birthlength_c + female + approxage + protein_c, data = data1)
##
## Residuals:
##     Min      1Q  Median      3Q     Max
## -17.965  -3.333  -0.041   3.528  15.159
##
## Coefficients:
##                       Estimate Std. Error t value Pr(>|t|)
## (Intercept)           56.15984    1.36760  41.064  < 2e-16 ***
## ln_mn_c               -0.37497    0.25480  -1.472  0.14176
## birthlength_c          0.84189    0.12446   6.764 3.81e-11 ***
## female1               -0.08317    0.48416  -0.172  0.86367
## approxage              0.12095    0.05800   2.085  0.03756 *
## protein_c              0.15433    0.05357   2.881  0.00414 **
## ln_mn_c:birthlength_c  0.27738    0.12058   2.300  0.02185 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 5.381 on 493 degrees of freedom
## Multiple R-squared:  0.1484, Adjusted R-squared:  0.138
## F-statistic: 14.32 on 6 and 493 DF,  p-value: 4.545e-15
```

The estimator for the interaction between the manganese exposure and birth length in a linear regression adjusted for the covariates is 0.277. The 95% confidence interval is (0.042, 0.512).

Question 1d

If we believe there is interaction between the manganese exposure and birth length and include interaction term in our model, then the product and difference method estimators are not valid in this context as it is unclear how to handle the interaction coefficient and two methods provide different results. If we believe there is no interaction between the manganese exposure and birth length and there is no need to include interaction term in our model, then two estimators are valid.

Question 2a



Question 2a

Identifiability assumptions:

(i) No unmeasured exposure-outcome confounding given C

(ii) No unmeasured mediator-outcome confounding given C

(iii) No unmeasured exposure-mediator confounding given C

(iv) No effect of exposure that confounds the mediator-outcome relationship

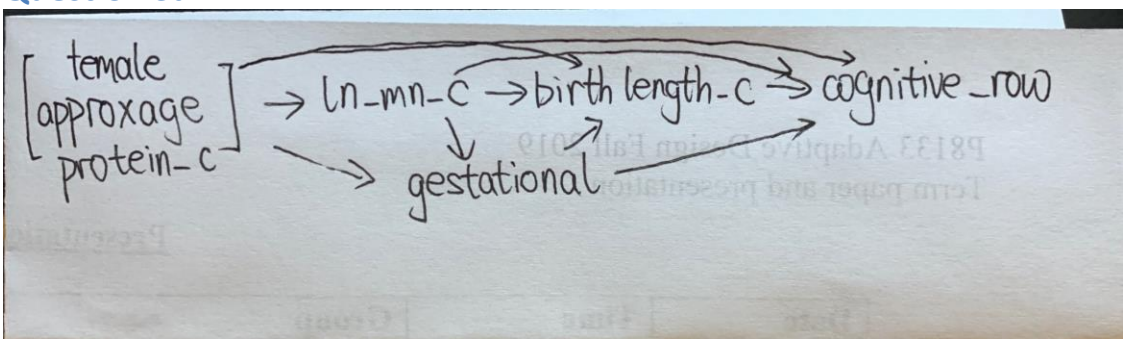
To estimate natural direct and indirect effects, we need above four assumptions. To estimate the controlled direct effect conditional on the covariates, we need assumption 1 and 2. As there are unmeasured confounder SES, assumptions 1,2 and 3 are violated, thus natural direct effect, natural indirect effect and controlled direct effects cannot be identified.

Question 2b

Hypothesize: The direction of SES effect on exposure is negative. The direction of SES effect on mediator is positive. The direction of SES effect on outcome is positive.

As the direction of SES effect on exposure is negative and the direction of SES effect on outcome is positive, the direction of confounding bias for total effects is negative. As the direction of SES effect on mediator is positive, the direction of confounding bias for indirect effects is positive. Thus, the direction of confounding bias for direct effects is negative.

Question 3a



Question 3a

Question 3b

The natural direct and indirect effects are identified in the DAG, becuase following assumptions are not violated.

(i) No unmeasured exposure-outcome confounding given C

(ii) No unmeasured mediator-outcome confounding given C

(iii) No unmeasured exposure-mediator confounding given C

(iv) No effect of exposure that confounds the mediator-outcome relationship

Question 3c

$E[Y|A = a, C = c] = \phi_0 + \phi_1 ln\_mn\_c + \phi_2 female + \phi_3 approxage + \phi_4 protein\_c$
$E[Y|A = a, C = c, M = m_1] = \theta_0 + \theta_1 ln\_mn\_c + \theta_2 birthlenghth\_c + \theta_3 gestational\_age + \theta_4 female + \theta_5 approxage + \theta_6 protein\_c$

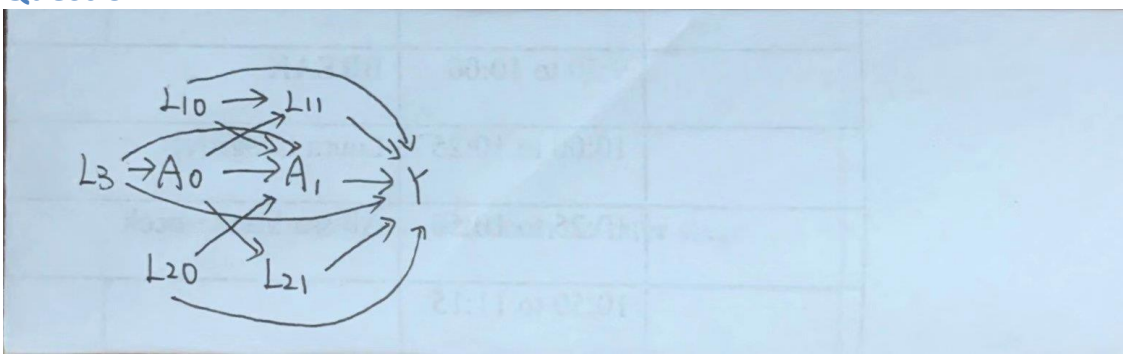
Then, direct effect is θ_1, indirect effect is $\phi_1 - \theta_1$.

Part 2

Question 1

1. Time point 0: L1, L2, L3, A
2. Time point 1: L1, L2, A
3. Time point 2: Y

Question 2



Part 2 Question 2

Question 3

The causal contrast $E[Y_{11} - Y_{00}]$ means the causal effect comparing $A_0 = A_1 = 1$ to $A_0 = A_1 = 0$.

Question 4

In order to identify the causal contrast of interest, we need to know direct effect and indirect effec, thus following no unmeasured confounding assumptions need to hold:

1) exchangability, positivity, consistency and SUTVA.
2) At baseline: $Y \perp A_0|L_3$. At time point 1: $Y \perp A_0|[L_{10}, L_{20}, L_3, A_0]$
3) No unmeasured exposure-outcome confounding given C
4) No unmeasured mediator-outcome confounding given C
5) No unmeasured exposure-mediator confounding given C
6) No effect of exposure that confounds the mediator-outcome relationship

Question 5

As we are interested in the treatment effect of overall treatment process influenced by both treatmengt at baseline and time point 1, I choose following marginal model:

$$E[Y_{a0a1}] = \beta + \beta_0 A_0 + \beta_1 A_1$$

Then causal contrast $E[Y_{11} - Y_{00}]$ equals to $\beta_0 + \beta_1$. Using bootstrap, we can get estimates and 95% confidence interval as following:

name	Estimate	CIL	CIU
beta	-4.1961	-4.3905	-3.9959
beta0	0.0339	-0.1163	0.1777
beta1	-0.3157	-0.4656	-0.1641
Causal Contrast	-0.2818	-0.5522	-0.0266

So the estimate of causal contrast $E[Y_{11} - Y_{00}]$ is -0.2818, the 95% confidence interval is (-0.5522, -0.0266).

Question 6

The causal contrast $E[Y_{11} - Y_{00}]$ means the causal effect comparing $A_0 = 1, A_1 = 0$ to $A_0 = 0, A_1 = 0$.

Question 7

In order to identify the causal contrast of interest, we need to know direct effect and indirect effec, thus following no unmeasured confounding assumptions need to hold:

1) exchangability, positivity, consistency and SUTVA.
2) At baseline: $Y \perp A_0|L_3$. At time point 1: $Y \perp A_0|[L_{10}, L_{20}, L_3, A_0]$
3) No unmeasured exposure-outcome confounding given C
4) No unmeasured mediator-outcome confounding given C
5) No unmeasured exposure-mediator confounding given C
6) No effect of exposure that confounds the mediator-outcome relationship

Question 8

As we are interested in the treatment effect of overall treatment process influenced by both treatmengt at baseline and time point 1, I still choose following marginal model:

$$E[Y_{a0a1}] = \beta + \beta_0 A_0 + \beta_1 A_1$$

Then causal contrast $E[Y_{10} - Y_{00}]$ equals to β_0. According to bootstrap results, we can get the estimate of causal contrast $E[Y_{10} - Y_{00}]$ is 0.0339, the 95% confidence interval is (-0.1163, 0.1777).

Question 9

If we treat A_1 as mediator, than M_0 means the value of mediator given exposure is control which means $A_0 = 0$. And M_1 means the value of mediator given exposure is treatment which means $A_0 = 1$. The natural direct effect is $E[Y_{1M_0} - Y_{0M_0}]$ and the natural indirect effect is $E[Y_{1M_1} - Y_{1M_0}]$.

As we already have the information of L_1, L_2, L_3. If we assume following assumptions hold, which means the DAG in question 1 is valid, then these causal effects are identified.

(i) No unmeasured exposure-outcome confounding given C

(ii) No unmeasured mediator-outcome confounding given C

(iii) No unmeasured exposure-mediator confounding given C

(iv) No effect of exposure that confounds the mediator-outcome relationship

Appendix

```
knitr::opts_chunk$set(echo = FALSE)
library(tidyverse)
library(survey)
# Part 1
data1 = read.csv("./data1_final.csv") %>%
  mutate(female = as.factor(female))
# Question 1b
exp_q = quantile(data1$ln_mn_c, c(0.25, 0.75))
exp_q
exp.model = lm(cognitive_raw~ln_mn_c+female+approxage+protein_c, data =
data1)
summary(exp.model)
med.model =
lm(cognitive_raw~ln_mn_c+birthlength_c+female+approxage+protein_c, data =
data1)
summary(med.model)
MA.model = lm(birthlength_c~ln_mn_c+female+approxage+protein_c, data = data1)
summary(MA.model)
phi1 = -0.65445
theta1 = -0.35228
theta2 = 0.86369
beta1 = -0.349862
dif_ind = phi1-theta1
prd_ind = theta2*beta1
exp_chg = exp_q[2]-exp_q[1]
# Question 1c
int.model =
lm(cognitive_raw~ln_mn_c+birthlength_c+ln_mn_c*birthlength_c+female+approxage
+protein_c, data = data1)
summary(int.model)
CIL = 0.277-1.96*0.12
CIU = 0.277+1.96*0.12
# Part 2
data2 = read.csv("./data2_final.csv")
# create wide data
AC_data = data2 %>%
 gather(key = "Lt", value = "value", c(L1,L2,A)) %>%
 arrange(id) %>%
 mutate(Lt = str_c(Lt, t0)) %>%
 select(id, Lt, value) %>%
 spread(key = Lt, value = value)
Y_data = data2 %>%
 select(id, Y) %>%
 na.omit()
L3_data = data2 %>%
  select(id,L3) %>%
  na.omit()
wide_data = merge(merge(AC_data, Y_data),L3_data) %>%
```

```r
  select(-c(A2,L12,L22))
set.seed(123)
nboots = 1000
n_sample = nrow(wide_data)
beta = rep(NA, nboots)
beta0 = rep(NA, nboots)
beta1 = rep(NA, nboots)
CauEff = rep(NA, nboots)
for (i in 1:nboots) {
  S.b <- sample(1:n_sample, size = n_sample, replace = TRUE)
  data.b <- wide_data[S.b, ]
  # Time point 0
  glm.model0 = glm(A0~L3, data = data.b, family = binomial)
  p0 = predict(glm.model0, type = "response")
  w0 = ifelse(data.b$A0==1, 1/p0, 1/(1-p0))
  # Time point 1
  glm.model1 = glm(A1~L3+A0+L10+L20, data = data.b, family = binomial)
  p1 = predict(glm.model1, type = "response")
  w1 = ifelse(data.b$A1==1, 1/p1, 1/(1-p1))
  w = w0*w1

  data.b$w = w
  design = svydesign(ids = ~id, weights = ~w, data = data.b)
  msm = svyglm(Y ~ A0 + A1, family = gaussian(link = "identity"), design =
design)
  beta[i] = msm$coef[1]
  beta0[i] = msm$coef[2]
  beta1[i] = msm$coef[3]
  CauEff[i] = msm$coef[2] + msm$coef[3]
}
Estimate = c(mean(beta), mean(beta0), mean(beta1), mean(CauEff)) %>% round(4)
CI = rbind(quantile(beta, probs = c(0.025, 0.975)),
           quantile(beta0, probs = c(0.025, 0.975)),
           quantile(beta1, probs = c(0.025, 0.975)),
           quantile(CauEff, probs = c(0.025, 0.975))) %>% round(4)
name = c("beta", "beta0", "beta1", "Causal Contrast")
cbind(name, Estimate, CI) %>%
  as.data.frame() %>%
  mutate(CIL = `2.5%`,
         CIU = `97.5%`) %>%
  select(name, Estimate, CIL, CIU) %>%
  knitr::kable()
```