§ SAS: homework 11:

—. Univariable analysis of age and BMI

(一) Table1:

1. Continuous variables:

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	Robust	Prefrailty	Frailty	ANOVA
Age (years)	Mean : 72.0	Mean : 73.9	Mean : 76.5	p < 0.0001*
Education (years)	Mean : 13.9	Mean : 13.4	Mean : 10.9	p = 0.0023*
cesdsco score	Mean : 1.6	Mean : 3.4	Mean : 9.9	p < 0.0001*

2. Categorial variables:

	Robust	Prefrailty	Frailty	chi-square
Sex Female Male	99 (57.56) 73 (42.44)	115 (51.57) 108 (48.43)	16 (66.67) 8 (33.33)	p = 0.2427
APOE e4 status Carrier Non-carrier	29 (16.86) 143 (83.14)	35 (15.77) 187 (84.23)	4 (17.39) 19 (82.61)	p = 0.9483

3. Descriptions:

- (1) 三個連續變項 age, education year 和 depression symptom score 在 frailty 的 組別的分佈皆呈現顯著的不同。
- (2) 其中, age 在 frailty 和 robust (4.53, 95% CI = 1.75 7.31),以及 prefrailty 與 robust (1.92, 95% CI : 0.63 3.22) 兩組的組間差異皆達顯著, prefrailty 與 frailty (2.61, 95%CI = -0.13 5.34) 兩組未達之差異未達統計顯著。推測 ANOVA 檢定顯著的結果來自於 robust 這組與其他兩組顯著不同的貢獻。
- (3) Education year 在 frailty 和 robust (3.02, 95% CI = 0.95 5.09), prefrailty 與 robust (2.52, 95% CI: 0.48 4.57) 兩組的組間差異皆達上顯著, prefrailty 與 frailty (0.49, 95%CI = -0.47 1.46) 兩組未達之差異未達統計顯著。推測 ANOVA 檢定顯著的結果來自於 robust 這組與其他兩組顯著

不同的貢獻。

- (4) Education year 在 frailty 和 robust (3.02, 95% CI = 0.95 5.09), prefrailty 與 robust (2.52, 95% CI: 0.48 4.57) 兩組的組間 difference 皆達上顯著, prefrailty 與 frailty (0.49, 95% CI = -0.47 1.46) 兩組未達之差異未達統計顯著。推測 ANOVA 檢定顯著的結果來自於 robust 這組與其他兩組顯著不同的貢獻。
- (5) Depression status 在三組之兩兩 difference 皆達統計上顯著。frailty 和 robust (8.23, 95% CI = 5.32 11.14),prefrailty 與 robust (1.71, 95% CI : 0.35 3.01) 和 prefrailty 與 frailty (6.52, 95% CI = 3.65 9.39)。

(二) Distribution between cognitive normal and cognitive impairment:

1. Continuous variables:

	cognitive normal	cognitive impairment	Difference (95% CI)	t-test
Age (years)	Mean : 72.6	Mean : 76.2	3.62 (2.35 - 4.89)	p < 0.001* (pooled)
Education (years)	Mean : 14.1	Mean : 10.6	3.54 (2.32 - 4.78)	p <0.001* (Satterthwaite)
cesdsco score	Mean : 2,6	Mean : 5.0	2.37 (0.52 - 4.22)	p = 0.0125* (Satterthwaite

2. Categorial variables:

	cognitive normal	cognitive impairment	chi-square
Sex Female Male	180 (52.25) 158 (46.75)	51 (62.20) 31 (37.80)	p = 0.1443
APOE e4 status Carrier Non-carrier	56 (16.67) 280 (83.33)	12 (14.63) 70 (85.37)	p = 0.6548

3. Descriptions:

- (1) 三個連續變項 age, education year 和 depression score 在 cognitive normal 和 cognitive impairment 兩組分佈皆呈現顯著不同。
- (2) 其中,education year 和 depression symptom score 兩變項在兩組的變異 數顯著不同(兩組 folded F p-value < 0.001),故使用 Satterthwaite 檢定 兩組是否有顯著差異;age 這個變項在兩組的變異數無顯著差異 (folded F p-value = 0.1660),故使用 pooled t-test。

(三) Code (q1):

```
dm "odsresult" clear:
dm "log" clear;
libname data "\\Mac\Home\Desktop\SAS\sas data";
data hw11:
   set data.frailty_cognition_longdata;
run;
/* homework 11 -- cohort study*/
   /*q1 : demostrate distribution of variables */
        data baseline;
            set hw11;
            if fu = 0;
        /* continuous : age, edu_yr, cesdsco */
       title "univarible grouped by frailty groups";
        proc means data = baseline maxdec = 1;
            class frailty gp3;
            var age edu_yr cesdsco;
        run;
        title " age in frailty";
        proc anova data = baseline;
            class frailty_gp3;
           model age = frailty_gp3;
           means frailty_gp3 / bon; /* bonferroni correction */
        run;
        quit;
        title "eduyr in frailty";
        proc anova data = baseline;
           class frailty_gp3;
           model edu_yr = frailty_gp3;
           means frailty_gp3 / bon; /* bonferroni correction */
        run;
        quit;
        title "cesdsco in frailty";
        proc anova data = baseline;
            class frailty_gp3;
           model cesdsco = frailty_gp3;
            means frailty_gp3 / bon; /* bonferroni correction */
        run;
        quit;
       /* category variables sex, apo4car */
       title "sex and apoe in frailty";
        proc freq data = baseline;
            tables frailty_gp3 * sex / nopercent nocol chisq;
            tables frailty_gp3 * apo4car / nopercent nocol chisq;
        run:
   /* q1-2 grouped by mocasco */
        data baseline2;
            set baseline;
            if mocasco = . then mocabi = .;
            else if mocasco >= 24 then mocabi = 0;
```

```
else mocabi = 1;
run;
/* continuous : age, edu_yr, cesdsco */
title "univarible grouped by mocabi";
proc means data = baseline2 maxdec = 1;
   class mocabi;
   var age edu_yr cesdsco;
run;
proc ttest data = baseline2;
   class mocabi;
   var age edu_yr cesdsco;
run;
/* category variables sex, apo4car */
title "sex and apoe in moca";
proc freq data = baseline2;
   tables mocabi * sex / nopercent nocol chisq;
   tables mocabi * apo4car / nopercent nocol chisq;
run;
```

\leq . 10% rule to look for confounder (frailty(E) \rightarrow cognitive impairment(DZ))

(一) Result (odds ratio by GLMM model):

- 1. Crude: 2.11 (95% CI: 1.32 3.39)*
- 2. Age adjusted: 1.51 (95% CI: 0.93 2.47)
- 3. Sex adjusted : $2.12 (95\% \text{ CI} : 1.32 3.40)^*$
- 4. APOE e4 status adjusted : 2.12 (95% CI : 1.32 3.39)*
- 5. Depression symptom score adjusted: 2.14 (95% CI: 1.28 3.55)*
- 6. Alcohol drinking adjusted: 2.11 (95% CI: 1.32 3.39)*
- 7. Gait adjusted: 1.11 (95% CI: 0.66 1.88)
- 8. Hypertension adjusted: 2.08 (95% CI: 1.29 3.34)*
- 9. Diabetes adjusted :2.13 (95% CI: 1.33 3.43)*
- 10. Hyperlipidemia: 2.06 (95% CI: 1.28 3.30)*

(二) 10% rule:

- 1. Age: 28.4% > 10%
- 2. Sex: 0.474% < 10%
- 3. APOE e4 status: 1.42% < 10%
- 4. Depression symptom score: 1.42% < 10%
- 5. Alcohol: 0.00% < 10%
- 6. Gait: 47.4% > 10%
- 7. Hypertension: 1.42% < 10%
- 8. Diabetes: 0.948% < 10%
- 9. Hyperlipidemia: 2.37% < 10%

(三) Descriptions:

- 1. 本題我將 frailty 區分為兩組,robust 的為一組,prefrailty 和 frailty 的為一組。
- 2. 至於校正的變項中, age, gait 和 depression symptom score 是連續變項,其餘為類別變項。此外, hypertension, diabetes 和 hyperlipidemia 在原始資料中有三組(沒病史(0),有病史有吃藥(1)和有病史沒吃藥(2))。由於有病史沒吃藥這組的樣本數非常少,故將沒病史的分為一組,有病史的分為一組。
- 3. 分析結果如上所述, confounder 的變項有 age 和 gait。

(四) Final model:

- 1. 根據上述分析,最後我將 age 和 gait 放入最終模型。得出 adjusted odds ratio = 0.986 (95% CI: 0.58 1.67)。結果由原本顯著變為不顯著,顯示 age 和 gait 的 confounding effect 很大,且 bias 的方向是 away frow null。
- 2. 此外,查找文獻得知先前研究認為 sex (女性), depression 和 APOE e4 status 都是 cognitive impairment 的危險因子。嘗試再把這三個變項放入模型,得出 adjusted odds ratio = 1.017 (95% CI: 0.561 1.841),未達統計上顯

(五) Figures:

Odds Ratio Estimates					
Comparison	Estimate	ate DF 95% Confidence Limits			
frailtybi 1 vs 0	2.112	916	1.317	3.386	

Odds Ratio Estimates					
Comparison Estimate DF 95% Confidence Limit					
frailtybi 1 vs 0	1.515	915	0.931	2.465	
unit change of age from mean	1.145	915	1.098	1.195	

Odds Ratio Estimates						
Comparison Estimate DF 95% Confidence Limits						
frailtybi 1 vs 0	2.117	916	1.317	3.402		
sex 1 vs 0	0.968	916	0.603	1.553		

Odds Ratio Estimates						
Comparison Estimate DF 95% Confidence Limit						
frailtybi 1 vs 0	2.115	913	1.318	3.394		
apo4car 1 vs 0	1.038	913	0.559	1.929		

Odds Ratio Estimates					
Comparison Estimate DF 95% Confidence Limits					
frailtybi 1 vs 0	2.135	560	1.284	3.553	
unit change of cesdsco from mean	1.061	560	1.023	1.101	

Odds Ratio Estimates						
Comparison Estimate DF 95% Confidence Limits						
frailtybi 1 vs 0	2.114	915	5 1.317 3.			
alcohol 1 vs 0	1.327	915	0.746	2.360		

Odds Ratio Estimates						
Comparison Estimate DF 95% Confidence Limits						
frailtybi 1 vs 0	2.076	915	1.291	3.339		
htnbi 1 vs 0	1.162	915	0.740	1.824		

Odds Ratio Estimates					
Comparison Estimate DF 95% Confidence Limits					
frailtybi 1 vs 0	1.113	915	0.661	1.875	
unit change of gait from mean	1.813	915	1.486	2.213	

Odds Ratio Estimates					
Comparison Estimate DF 95% Confidence Limit					
frailtybi 1 vs 0	2.134	913	1.329	3.426	
dmbi 1 vs 0	0.712	913	0.365	1.388	

Odds Ratio Estimates					
Comparison Estimate DF 95% Confidence Limits					
frailtybi 1 vs 0	2.057	914	1.281	3.303	
cholbi 1 vs 0	0.718	914	0.462	1.116	

Odds Ratio Estimates					
Comparison Estimate DF 95% Confidence Limits					
frailtybi 1 vs 0	0.986	914	0.581	1.673	
unit change of age from mean	1.113	914	1.065	1.163	
unit change of gait from mean	1.560	914	1.268	1.918	

Effects of continuous variables are assessed as one unit offsets from the mean. The AT suboption modifies the reference value and the UNIT suboption modifies the offsets.

Odds Ratio Estimates					
Comparison	Estimate	DF	95% Confidence Limits		
frailtybi 1 vs 0	1.017	557	0.561	1.841	
unit change of age from mean	1.093	557	1.041	1.148	
unit change of gait from mean	1.485	557	1.187	1.858	
unit change of cesdsco from mean	1.067	557	1.027	1.109	
sex 0 vs 1	1.104	557	0.654	1.863	
apo4car 1 vs 0	1.099	557	0.577	2.092	

Effects of continuous variables are assessed as one unit offsets from the mean. The AT suboption modifies the reference value and the UNIT suboption modifies the offsets.

(六) Code (q2)

```
dm "odsresult" clear;
dm "log" clear;
libname data "\\Mac\Home\Desktop\SAS\sas data";
data hw11:
   set data.frailty_cognition_longdata;
run;
   /*q2 : generalized model : frailiry status ( e ) --> moca ( dz ) */
       title "q2 unadjusted";
       data frailty;
            set hw11;
            if mocasco = . then mocabi = .;
            else if mocasco >= 24 then mocabi = 0;
            else mocabi = 1;
            if frailty_gp3 = . then frailtybi = .;
            else if frailty_gp3 = 0 then frailtybi = 0;
            else frailtybi = 1;
            if htn = . then htnbi = .;
            else if htn = 0 then htnbi = 0;
            else htnbi = 1;
            if dm = . then dmbi = .;
            else if dm = 0 then dmbi = 0;
            else dmbi = 1;
            if chol = . then cholbi = .;
            else if chol = 0 then cholbi = 0;
            else cholbi = 1;
        run;
        proc freq data = frailty;
            tables frailty_gp3 * frailtybi;
        run;
        proc glimmix data = frailty;
            class new_id frailtybi(ref = "0");
            model mocabi(event = "1") = frailtybi / dist = binary link = logit
solution or(label);
            random intercept / subject = new_id;
        run;
       /*q2 : use 10% rule to decide cf to put in model */
        /* age */
       title "q2 adjust age";
        proc glimmix data = frailty;
            class new_id frailtybi (ref = "0");
            model mocabi(event = "1") = frailtybi age / dist = binary link = logit
solution or(label);
            random intercept / subject = new_id;
        run;
       /* sex */
       title "agjust sex";
```

```
proc glimmix data = frailty;
            class new_id frailtybi (ref = "0") sex(ref = "1");
            model mocabi(event = "1") = frailtybi sex / dist = binary link = logit
solution or(label);
            random intercept / subject = new_id;
        run;
       /*APOE status */
        title "adjust apoe ";
        proc glimmix data = frailty;
            class new_id frailtybi (ref = "0") apo4car(ref = "0");
            model mocabi(event = "1") = frailtybi apo4car / dist = binary link = logit
solution or(label);
            random intercept / subject = new_id;
        run;
       /* cesdsco */
       title "adjust cesdsco";
        proc glimmix data = frailty;
            class new_id frailtybi (ref = "0");
            model mocabi(event = "1") = frailtybi cesdsco / dist = binary link = logit
solution or(label);
            random intercept / subject = new_id;
        run;
        /* alcohol */
        title "adjust alcohol";
        proc glimmix data = frailty;
            class new_id frailtybi (ref = "0") alcohol(ref = "0");
            model mocabi(event = "1") = frailtybi alcohol / dist = binary link = logit
solution or(label);
            random intercept / subject = new_id;
        run;
       /* gait */
        title "adjust gait";
        proc glimmix data = frailty;
            class new id frailtybi (ref = "0");
           model mocabi(event = "1") = frailtybi gait / dist = binary link = logit
solution or(label);
            random intercept / subject = new_id;
        run;
        /* htn */
        title "adjsut htnbi";
        proc glimmix data = frailty;
            class new_id frailtybi (ref = "0") htnbi(ref = "0");
            model mocabi(event = "1") = frailtybi htnbi / dist = binary link = logit
solution or(label);
            random intercept / subject = new_id;
        run;
        /* dm */
       title "adjust dm";
        proc glimmix data = frailty;
           class new_id frailtybi (ref = "0") dmbi(ref = "0");
```

```
model mocabi(event = "1") = frailtybi dmbi/ dist = binary link = logit
solution or(label);
            random intercept / subject = new_id;
        run;
       /* chol */
       title "adjust chol";
       proc glimmix data = frailty;
            class new id frailtybi (ref = "0") cholbi(ref = "0");
            model mocabi(event = "1") = frailtybi cholbi / dist = binary link = logit
solution or(label);
            random intercept / subject = new_id;
       run:
       proc iml;
            crude1 = 2.11;
            age1 = abs(1.51 - crude1) / crude1;
            sex1 = abs(2.12 - crude1) / crude1;
            apo1 = abs(2.12 - crude1) / crude1;
            cesd1 = abs(2.14 - crude1) / crude1;
            alco1 = abs(2.11 - crude1) / crude1;
            gait1 = abs(1.11 - crude1) / crude1;
            htn1 = abs(2.08 - crude1) / crude1;
            dm1 = abs(2.13 - crude1) / crude1;
            chol1 = abs(2.06 - crude1) / crude1;
            print age1 sex1 apo1 cesd1 alco1 gait1 htn1 dm1 chol1;
       /* model 1 moca ~ frailty + age + gait */
       proc glimmix data = frailty;
            class new_id frailtybi (ref = "0");
           model mocabi(event = "1") = frailtybi age gait / dist = binary link =
logit solution or(label);
            random intercept / subject = new_id;
       run;
       /* model 2 moca ~ frailty + age + gait + sex + apo4car + cesdsco */
       proc glimmix data = frailty;
            class new_id frailtybi (ref = "0") sex (ref = "1") apo4car (ref = "0") ;
           model mocabi(event = "1") = frailtybi age gait sex apo4car cesdsco/ dist
= binary link = logit solution or(label);
            random intercept / subject = new_id;
        run;
```

≡. Frailty status(E) → cognitive impairment(DZ), stratified analysis by GLMN model

(一) Sex

1. Stratum specific odds ratio:

(1) Female:

(a) Prefrailty vs. robust : 2.34 (95% CI : 1.14 – 4.80)

(b) Frailty vs. robust : 6.61(95% CI : 2.10 – 20.82)

Odds Ratio Estimates				
Comparison Estimate DF 95% Confidence Limit				dence Limits
frailty_gp3 1 vs 0	2.335	227	1.136	4.799
frailty_gp3 2 vs 0	6.615	227	2.102	20.820

(2) Male:

(a) Prefrailty vs. robust : 1.34 (95% CI : 0.58 – 3.10)

(b) Frailty vs. robust : 2.10 (95% CI : 0.37 – 12.02)

Odds Ratio Estimates					
Comparison Estimate DF 95% Confidence Limit				dence Limits	
frailty_gp3 1 vs 0	1.345	186	0.583	3.104	
frailty_gp3 2 vs 0	2.100	186	0.367	12.026	

2. Description:

(1) Female 與 male 兩組差異甚大,可能 sex 與 frailty status 之間具有 interaction。

(二) Age group:

1. Stratum specific odds ratio:

(1) Under and equal to 74:

(a) Prefrailty vs. robust : 1.50 (95% CI : 0.68 – 3.31)

(b) Frailty vs. robust : 3.03 (95% CI: 0.54 – 16.84)

Odds Ratio Estimates				
Comparison Estimate DF 95% Confidence Limit				dence Limits
frailty_gp3 1 vs 0	1.499	246	0.680	3.305
frailty_gp3 2 vs 0	3.028	246	0.544	16.844

(2) Over and equal to 75:

(a) Prefrailty vs. robust: 1.64 (95% CI: 0.74 – 3.62)

(b) Frailty vs. robust: 3.63 (95% CI: 1.10 – 12.00)

Odds Ratio Estimates					
Comparison Estimate DF 95% Confidence Limit				dence Limits	
frailty_gp3 1 vs 0	1.639	167	0.742	3.621	
frailty_gp3 2 vs 0	3.636	167	1.102	12.004	

2. Descriptions:

(1) 兩組差異並不大,比較 age 與 frailty status 比較不可能有 interaction。

(三) APOE e4 status:

1. Stratum specific odds ratio:

(1) Non-carrier:

(a) Prefrailty vs. robust : 1.89 (95% CI : 1.04 – 3.43)

(b) Frailty vs. robust : 5.87 (95% CI : 2.11 – 16.38)

Odds Ratio Estimates				
Comparison Estimate DF 95% Confidence Limit				dence Limits
frailty_gp3 1 vs 0	1.890	346	1.043	3,426
frailty_gp3 2 vs 0	5.874	346	2.107	16.377

(2) Carrier:

(a) Prefrailty vs. robust: 1.56 (95% CI: 0.40 – 6.13)

(b) Frailty vs. robust : 2.08 (95% CI : 0.16 – 26.53)

Odds Ratio Estimates				
Comparison Estimate DF 95% Confidence Limits				
frailty_gp3 1 vs 0	1.562	65	0.398	6.131
frailty_gp3 2 vs 0	2.083	65	0.164	26.537

2. Descriptions:

(1) 兩組差異甚大,尤其是 frailty vs. robust 的 odds ratio。APOE e4 status 與 frailty status 可能具有 interactions。

(四) Code (q3):

```
dm "odsresult" clear;
dm "log" clear;
/*q3 : use GLMM to perform stratified analysis by sex, age, group, and APOE status at
baseline */
       /* sex */
       title "q3 stratified by sex";
        proc sort data = baseline2;
            by sex;
        run;
        proc glimmix data = baseline2 order = data;
            by sex;
            class new_id frailty_gp3(ref = "0");
            model mocabi(event = "1") = frailty_gp3 / dist = binary link = logit
solution or(label);
        run;
        /* age */
        title "q3 stratified by age";
        data baseline3;
            set baseline2;
            if age = . then agebi = .;
            else if age <= 74 then agebi = 0;
            else agebi = 1;
        run;
        proc sort data = baseline3;
            by agebi;
        run;
        proc glimmix data = baseline3 order = data;
            by agebi;
            class new_id frailty_gp3(ref = "0");
            model mocabi(event = "1") = frailty_gp3 / dist = binary link = logit
solution or(label);
        run;
        /* APOE status */
        title "q3 stratified by APOE status";
        proc sort data = baseline3;
            by apo4car;
        run;
        proc glimmix data = baseline3 order = data;
            by apo4car;
            class new_id frailty_gp3(ref = "0");
            model mocabi(event = "1") = frailty_gp3 / dist = binary link = logit
solution or(label);
        run;
```

四. Propensity score:

(一) Result:

1. 首先,用GLMM model 計算結果模型不會收斂。(如下圖)

Odds Ratio Estimates					
Comparison Estimate DF 95% Confidence Limits					
frailtybi 1 vs 0	0,435	915	0.238	0.793	
unit change of drs from mean	>999.999	915	>999.999	>999.999	

Effects of continuous variables are assessed as one unit offsets from the mean. The AT suboption modifies the reference value and the UNIT suboption modifies the offsets.

2. 改用 logistic model 並只取 baseline 的資料,模型依然收斂不了。

Odds Ratio Estimates				
Effect	95% Wald Point Estimate Confidence Lim			
frailtybi 1 vs 0	1.164	0.649	2.089	
drs	>999,999	>999.999	>999.999	

(二) Descriptions:

- 我嘗試只放一個 age 或只放一個 gait 進入模型,也都無法收斂。此外,我尚嘗試將 age 及 gait 變為類別變項放入模型也無法收斂,不論是用 long data 的 GLMM model 或是只用 baseline data 的 logistic model。
- 2. 我不太清楚為什麼模型會收斂不了 QQ

(三) 與 Q2 的比較:

- 1. 若先不論 DRS 收斂不了的問題,本題若以 GLMM model 計算的結果, frailty 變為 cognition impairment 顯著的保護因子 (Q2 的結果 frailty 與 outcome 的關係不顯著)
- 2. 我想這樣的結果不太合理,也沒有先前文獻支持這樣的結果。我想這個結果 與模型無法收斂有關,而模型無法收斂可能跟資料分布或是 propensity score 的計算方式有關。

(四) Code (q4)

```
data drs2;
           set drs;
            drs = exp(pred_value) / (1 + exp(pred_value));
        proc glimmix data = drs2;
            class new_id frailtybi (ref = "0");
            model mocabi(event = "1") = frailtybi drs / dist = binary link = logit
solution or(label);
            random intercept / subject = new_id;
        run;
        data baseline2;
           set baseline;
           if mocasco = . then mocabi = .;
            else if mocasco >= 24 then mocabi = 0;
            else mocabi = 1;
            if frailty_gp3 = . then frailtybi = .;
            else if frailty_gp3 = 0 then frailtybi = 0;
            else frailtybi = 1;
           if htn = . then htnbi = .;
            else if htn = 0 then htnbi = 0;
            else htnbi = 1;
            if dm = . then dmbi = .;
            else if dm = 0 then dmbi = 0;
           else dmbi = 1;
           if chol = . then cholbi = .;
            else if chol = 0 then cholbi = 0;
           else cholbi = 1;
        run;
        proc logistic data = baseline2;
           class new_id ;
           model mocabi(event = "1") = age gait ;
            output out = drs predicted = pred_value;
        run;
        data drs2;
            set drs;
            drs = exp(pred_value) / (1 + exp(pred_value));
        run;
        proc logistic data = drs2;
           class frailtybi (ref = "0");
            model mocabi(event = "1") = frailtybi drs ;
        run;
```