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Regresjonsmodeller

HEL – 8020 Analyse av registerdata i forskning

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UNIVERSITETET I TROMSØ

Intro

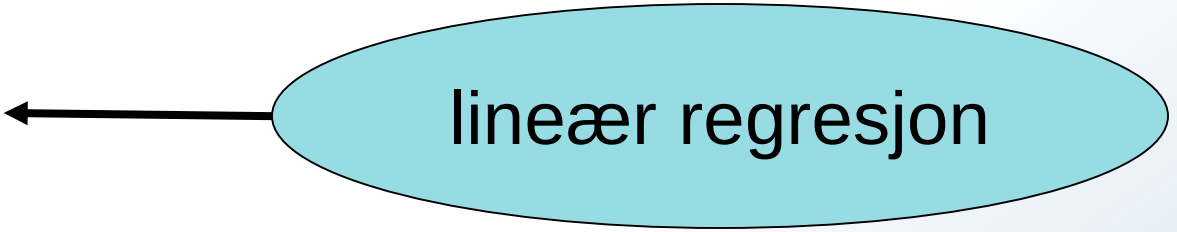
- Mye forskning innen medisin og helsefag dreier seg om å studere
  - assosiasjonen mellom en eller flere eksponeringsvariabler mot en responsvariabel
  - forskjell i respons mellom ulike grupper, justert for kovariater
- Regresjonsmodeller
- For eksempel
  - Er det sammenheng mellom fysisk aktivitet og brystkreft.
  - Finnes det nye biomarkører som kan predikere hjerteinfarkt uavhengig av de kjente kardiovaskulære risikofaktorene
  - Hvilke livsstilsfaktorer er assosiert med ideelle blodtrykksverdier.

Mål

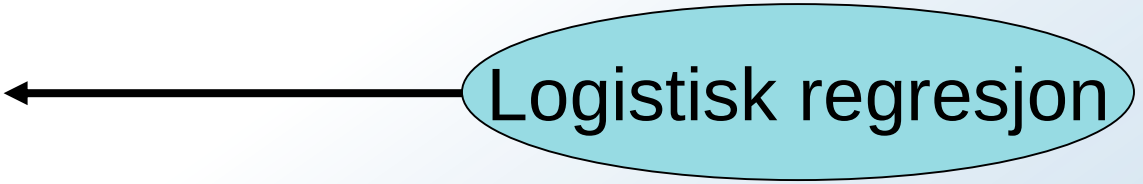
- Introdusere regresjonsanalysemetoder i medisinsk forskning
  - Lineær regresjon
  - Logistisk regresjon
  - Cox regresjon
- Metodevalg avhenger i hovedsak av
  - Type avhengig variabel

Type avhengig variabel

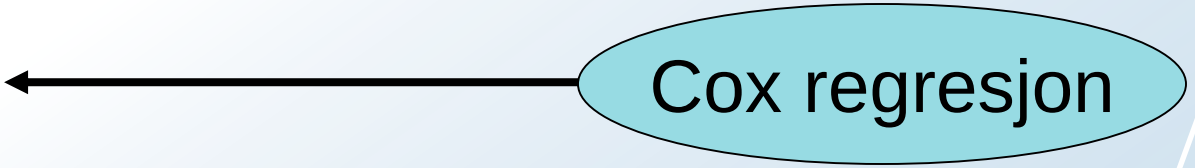
- Måling på en kontinuerlig skala



- Binær respons (syk / ikke syk)



- Tid til hendelse / sykdom



Hva er av interesse

- Oftest er det flere uavhengige variable (prediktorer/kovariater) involvert
- Vi kan da være interessert i
  - Den kombinerte effekten av alle de uavhengige variablene
    - Test av modell, p-verdi
    - «goodnes-of-fit»
    - Forklart varians
  - Den individuelle effekten av hver enkelt uavhengig variabel
    - Mål på effekt
    - Signifikans
    - Rangering
  - Interaksjon og «confounding».

Regresjonsmodeller

Lineær regresjon

$$y = \beta_0 + \beta_1 \cdot x_1 + \beta_2 \cdot x_2 + \beta_3 \cdot x_3 + ... + \beta_m \cdot x_m + \varepsilon$$

Logistisk regresjon

$$P(y) = \frac{1}{1 + e^{-(\beta_0 + \beta_1 \cdot x_1 + \beta_2 \cdot x_2 + \beta_3 \cdot x_3 + ... + \beta_m \cdot x_m)}}$$

Cox regression

$$h(t) = h_0(t) \cdot e^{\beta_1 \cdot x_1 + \beta_2 \cdot x_2 + \beta_3 \cdot x_3 + ... + \beta_m \cdot x_m}$$

Høyre side

- Variablene er
  - Et antall utvalgte variable
  - Eksponeringsvariable, uavhengige variable, kovariater, prediktorer, x-variable
  - Kan være av alle typer
    - Kontinuerlige
    - Nominale – kategoriske
    - Ordinale – kategoriske
  - De kategoriske kan modelleres som indikatorvariable (dummy).

Fra enkel til multivariabel modell

- Når flere x-variabler legges til
  - Modell fit vil bli bedre (R^2 ,verdi av likelihoodfunksjonen)
  - Global test trenger ikke få lavere p-verdi
  - Alle variable er gjensidig justert for hverandre
  - Regresjonskoeffisientene blir ofte mindre (nærmere 0)

Fra enkel til multivariabel modell(2)

Eksempel, y= systolisk BT, n= 31 personer

Modell	x	R^2	Test av modell F (p-verdi)	β (p-verdi)
1	Vekt	0.249	9.64 (.004)	0.633 (.004)
2	Vekt Alder	0.280	5.43 (.010)	0.546 (.018) 0.211 (.288)
3	Vekt Alder Puls	0.385	5.64 (.004)	0.492 (.025) 0.163 (.386) 0.536 (.040)

Utskrift fra statistikkpakker

- Vurder
  - modell-antakelser
  - uvanlige observasjoner
  - Observasjoner med sterk innflytelse på modellen
  - Kolinearitet
  - Modelltilpasning
  - Global modell
  - Blokk av variable
  - Hver x-variabel

Enkel lineær regresjon

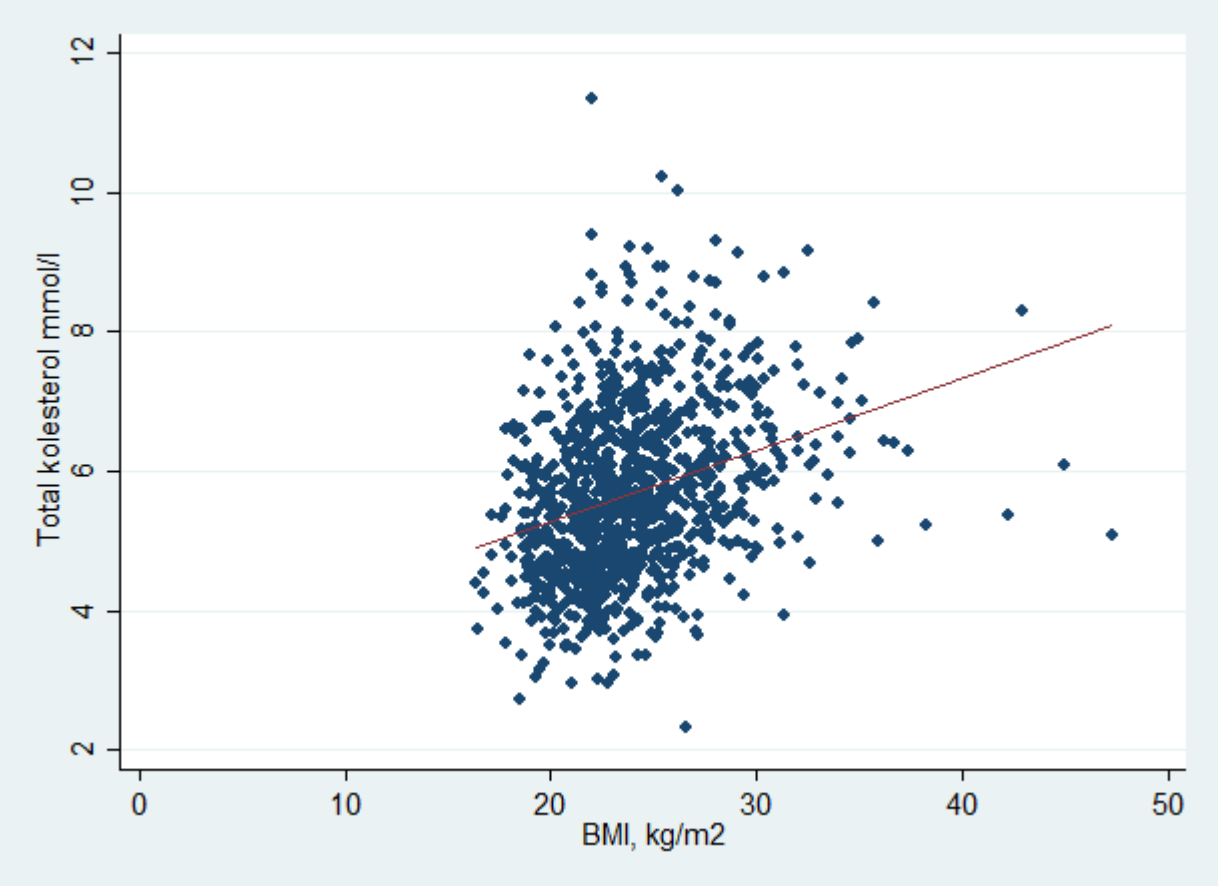
$$y = \beta_0 + \beta_1 \cdot x + \varepsilon$$

Y = response, avhengig variabel
X = uavhengig variabel
β_0 = intercept
β_1 = stigningstall
ε = residual

<u>Modellantakelser</u>
- Uavhengighet
- Linearitet
- Homoskedastisitet
- Normalitet

Enkel lineær regresjon (2)

- Data, kolesterol vs BMI: n=1000 personer, 20-61 år
- Vurder et spredningsplott
- Er det lineær sammenheng



Enkel lineær regresjon, utskrift

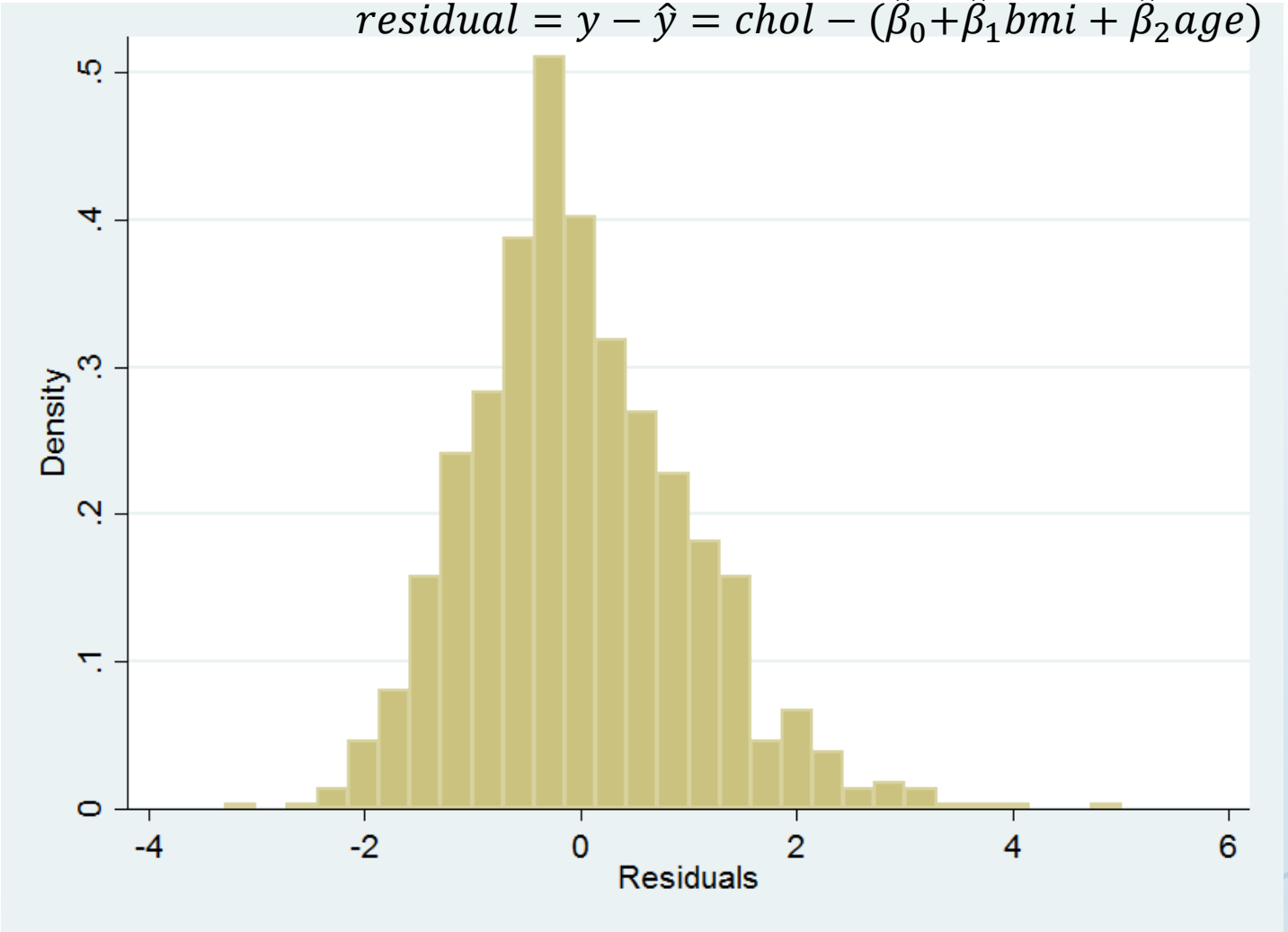
```
regress chol bmi


      Source |       SS           df       MS      Number of obs   =       999
-------------+----------------------------------   F(1, 997)       =    110.80
       Model |   143.73978         1   143.73978   Prob > F        =    0.0000
    Residual |  1293.38325       997  1.29727507   R-squared       =    0.1000
-------------+----------------------------------   Adj R-squared   =    0.0991
       Total |  1437.12303       998  1.44000303   Root MSE        =     1.139

------------------------------------------------------------------------------
        chol |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         bmi |   .1031713   .0098014    10.53   0.000     .0839377     .122405
       _cons |   3.219536   .2370584    13.58   0.000     2.754345    3.684726
------------------------------------------------------------------------------
```

Multivariabel lineær regresjon, utskrift

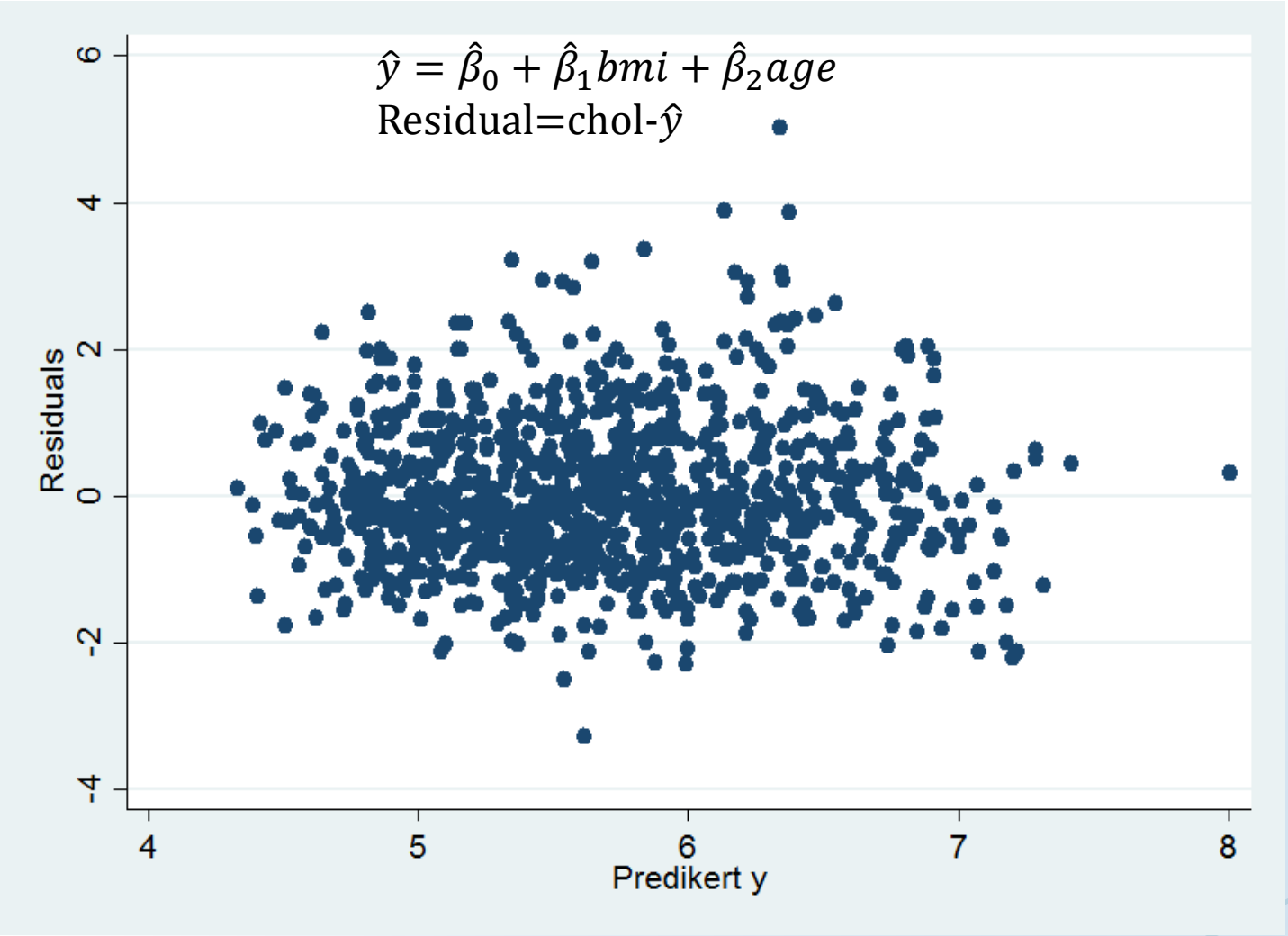
```
regress chol bmi age


      Source |       SS           df       MS      Number of obs   =       999
-------------+----------------------------------   F(2, 996)       =    177.59
       Model |  377.779272         2  188.889636   Prob > F        =    0.0000
    Residual |  1059.34375       996  1.06359815   R-squared       =    0.2629
-------------+----------------------------------   Adj R-squared   =    0.2614
       Total |  1437.12303       998  1.44000303   Root MSE        =    1.0313

------------------------------------------------------------------------------
        chol |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         bmi |   .0611743   .0093155     6.57   0.000     .0428941    .0794545
         age |   .0487547   .0032867    14.83   0.000     .0423051    .0552044
       _cons |   2.417997   .2213453    10.92   0.000      1.98364    2.852353
------------------------------------------------------------------------------
```

Normalitetsantakelsen, histogram av residualene

$$residual = y - \hat{y} = chol - (\hat{\beta}_0 + \hat{\beta}_1 bmi + \hat{\beta}_2 age)$$



Homoskedastisitet, plott residualene vs predikert



Logistisk regresjon

$$logit(p) = \ln\left(\frac{p}{1-p}\right) = \beta_0 + \beta_1 x_1 + \beta_2 x_2$$

$$p = \frac{1}{1 + e^{-(\beta_0 + \beta_1 x_1 + \beta_2 x_2)}}$$

p	= P[y=1], sannsynlighet for y = 1
y	= respons, 1=syk; 0=ikke syk
x_i'ene	= uavhengige variabler
β_i'ene	= regresjons-koeffisienter
exp(β_i)	= odds ratio

Logistisk regresjon, utskrift

```
logit status smoke

------------------------------------------------------------------------------
      status |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       smoke |   .6037231   .2056024     2.94   0.003     .2007497    1.006697
       _cons |  -2.397895   .1592796   -15.05   0.000    -2.710077   -2.085713
------------------------------------------------------------------------------
```

```
logit status smoke, or

------------------------------------------------------------------------------
      status | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       smoke |   1.828915   .3760295     2.94   0.003     1.222319    2.736546
       _cons |   .0909091     .01448   -15.05   0.000     .0665317    .1242185
------------------------------------------------------------------------------
```

Logistisk regresjon, fysisk aktivitet

tab phys status

phys	status 0	1	Total
1	217	41	258
2	504	60	564
3	138	11	149
4	29	0	29
Total	888	112	1,000

tab phys status,nofreq row

phys	status 0	1	Total
1	84.11	15.89	100.00
2	89.36	10.64	100.00
3	92.62	7.38	100.00
4	100.00	0.00	100.00
Total	88.80	11.20	100.00

logistic status age phys

status	Odds Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
age	1.132871	.0137844	10.25	0.000	1.106174	1.160213
phys	.5851344	.1034604	-3.03	0.002	.413762	.8274858
_cons	.0018091	.0011352	-10.06	0.000	.0005289	.0061885

Logistisk regresjon, fysisk aktivitet med dummy

```
tab phys status
       phys |      Freq.
------------+-----------
          1 |        258
          2 |        564
          3 |        149
          4 |         29
------------+-----------
      Total |      1,000
```

```
gen phys2 = phys==2
gen phys3 = phys > 2

tab1 phys2
      phys2 |      Freq.     Percent
------------+----------------------------------
          0 |        436       43.60
          1 |        564       56.40
------------+----------------------------------

tab1 phys3
      phys3 |      Freq.     Percent
------------+----------------------------------
          0 |        822       82.20
          1 |        178       17.80
------------+----------------------------------
```

Logistisk regresjon, fysisk aktivitet med dummy(2)

```
logistic status age phys2 phys3
------------------------------------------------------------------------------
      status | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         age |   1.133368   .0138028    10.28   0.000     1.106635    1.160746
       phys2 |   .5365943   .1310052    -2.55   0.011     .3325309    .8658848
       phys3 |   .3785521   .1460737    -2.52   0.012     .1776923      .80646
       _cons |   .0010733   .0006167   -11.90   0.000     .0003481    .0033096
------------------------------------------------------------------------------
```

```
logistic status age phys
------------------------------------------------------------------------------
      status | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         age |   1.132871   .0137844    10.25   0.000     1.106174    1.160213
        phys |   .5851344   .1034604    -3.03   0.002      .413762    .8274858
       _cons |   .0018091   .0011352   -10.06   0.000     .0005289    .0061885
------------------------------------------------------------------------------
```

Haugnes HS et al. Components of the metabolic syndrome in long-term survivors of testicular cancer. Ann Oncol. 2007;18:241-248

Table 5. Logistic regression, with metabolic syndrome (≥2 components present) as the dependent variable

	Multiple-adjusted results[a,b]			Age-adjusted results[c]			Multiple-adjusted results[b,c]		
	OR	95% CI	*P* value	OR	95% CI	*P* value	OR	95% CI	*P* value
Treatment group[d]			0.002			0.002			0.003
Control group	–	–		1.00	Reference		1.00	Reference	
Surgery	1.00	Reference		0.75	0.54–1.03		0.80	0.57–1.12	
Radiotherapy	1.22	0.84–1.78		0.89	0.71–1.12		0.96	0.75–1.24	
Cis ≤ 850 mg	1.44	0.98–2.12		1.11	0.85–1.43		1.15	0.87–1.52	
Cis >850 mg	3.05	1.72–5.40		2.10	1.31–3.36		2.43	1.46–4.04	
Total testosterone	0.96	0.93–0.98	0.001	0.95	0.93–0.96	<0.001	0.95	0.93–0.96	<0.001
Pack-years[e]			0.273			0.40			0.27
0 (never smoker)	1.00	Reference		1.00	Reference		1.00	Reference	
0.1–9.9	1.05	0.73–1.50		1.09	0.86–1.38		1.16	0.90–1.49	
10–19.9	1.10	0.75–1.60		1.02	0.80–1.31		1.04	0.80–1.35	
≥20	1.48	1.00–2.18		1.23	0.96–1.58		1.29	0.98–1.69	
Physical activity			0.200			0.041			0.12
No activity	1.00	Reference		1.00	Reference		1.00	Reference	
Moderate activity	0.96	0.64–1.44		1.08	0.83–1.41		1.19	0.90–1.58	
Hard activity	0.75	0.50–1.15		0.85	0.65–1.11		0.97	0.73–1.30	
Educational level			0.61			0.018			0.065
Low	1.00	Reference		1.00	Reference		1.00	Reference	
High (college/university)	0.93	0.70–1.23		0.81	0.67–0.96		0.83	0.68–1.01	
Family status			0.57			0.99			0.91
Living alone	1.00	Reference		1.00	Reference		1.00	Reference	
Married/cohabitant	0.91	0.66–1.26		1.00	0.80–1.25		1.01	0.80–1.29	

Odds ratio (OR) and 95% confidence interval (CI) for different predictors of the metabolic syndrome.

[a]For testicular cancer survivors only.

[b]Adjusted for age and all listed variables

[c]For control population and testicular cancer survivors.

[d]There are missing data for 18 patients and nine controls in age-adjusted analyses. There are missing data for 125 patients and 117 controls in the multiple-adjusted analyses.

[e]Number of cigarette packs per day multiplied by number of smoking years.

OR for ≥ 2 metabolic syndrom componts

	OR*	95% CI*	P-value
Control group	1.00	Reference	0.003
Surgery	0.80	0.57-1.12	
Radiotherapy	0.96	0.75-1.24	
Cis ≤ 850 mg	1.15	0.87-1.52	
Cis > 850 mg	2.43	1.46-4.04	

*Adjusted for age and all listed variables

OR for daglig røyking etter utdannelse, kvinner

Utdannelse, nivå	1994-95	2007-08
1	1.00	1.00
2	0.69 (0.63, 0.76)	0.70 (0.62, 0.80)
3	0.36 (0.34, 0.41)	0.39 (0.33, 0.47)
4	0.22 (0.19, 0.25)	0.22 (0.19, 0.27)
P for trend	< 0.001	< 0.001

*Justert for alder

Eggen AE, et al. Trends in CVD risk factors across levels of education. Is the educational gap increasing? The Tromsø Study 1994-2008. JECH 2014

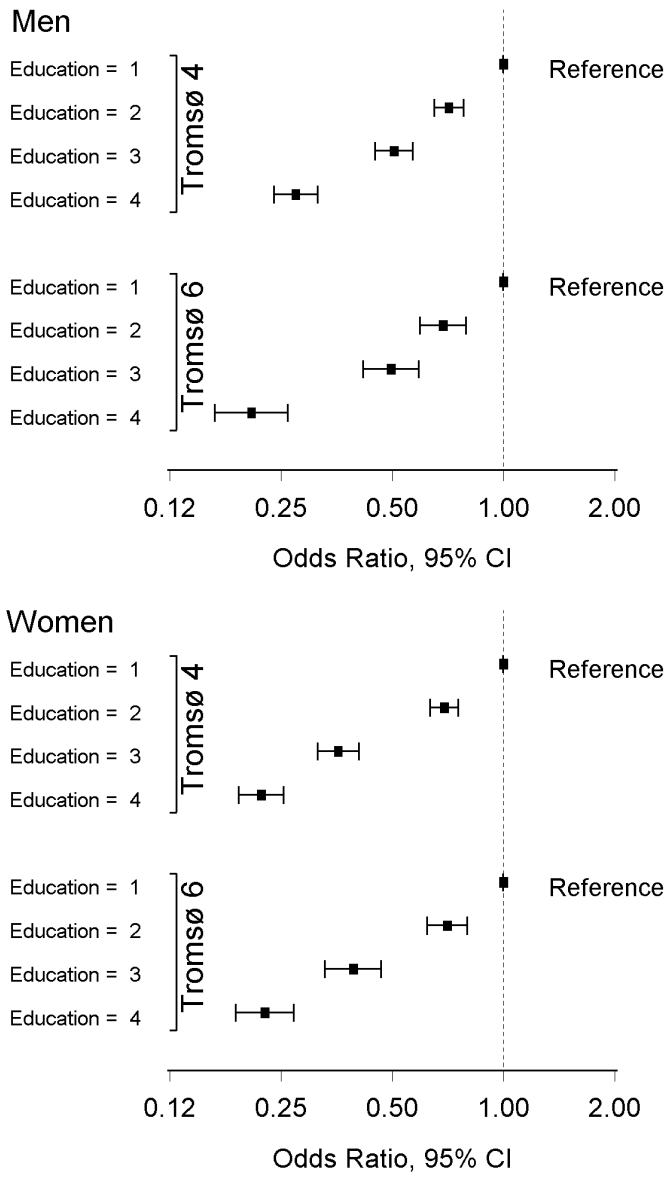
OR for daglig røyking etter utdannelse, kvinner

Utdannelse, nivå	1994-95	2007-08
1	1.00	1.00
2	0.69 (0.63, 0.76)	0.70 (0.62, 0.80)
3	0.36 (0.34, 0.41)	0.39 (0.33, 0.47)
4	0.22 (0.19, 0.25)	0.22 (0.19, 0.27)
P for trend	< 0.001	< 0.001
Pr nivå	0.57 (0.54, 0.59)	0.59 (0.55, 0.64)
P for forskjell i trend	0.67	

*Justert for alder

Eggen AE, et al. Trends in CVD risk factors across levels of education. Is the educational gap increasing? The Tromsø Study 1994-2008. JECH 2014

OR for daglig røyking



Cox proporsjonale hasard regresjon

$$h(t) = h_0(t) \cdot e^{\beta_1 x_1 + \beta_2 x_2}$$

t	= tid til hendelse
h(t)	= hasard som funksjon av tid
$h_0(t)$	= baseline hasard, dvs. hasard når alle x=0
x_i'ene	= uavhengige variabler
β_i'ene	= regresjons-koeffisienter
$\exp(\beta_i)$	= hasard-ratio (HR)

Modellantakelser
- Uavhengighet
- Linearitet, logskala
- Konstant HR over tid (proporsjonale hasardantakelsen)

Cox regresjon, utskrift

```
stset obstime,failure(status)
stcox age smoke
```

```
------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         age |   1.123149   .0116965    11.15   0.000     1.100456    1.146309
       smoke |   1.965788   .3824019     3.47   0.001     1.342622    2.878191
------------------------------------------------------------------------------
```

```
stcox age smoke, nohr
```

```
------------------------------------------------------------------------------
          _t |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         age |   .1161362    .010414    11.15   0.000     .0957251    .1365473
       smoke |   .6758931   .1945286     3.47   0.001     .2946241    1.057162
------------------------------------------------------------------------------
```

Cox regresjon, kjønnsspesifikk

```
stcox age smoke if sex==0

------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         age |   1.123518   .0230406     5.68   0.000     1.079255    1.169597
       smoke |   2.169104   .7722115     2.18   0.030     1.079564    4.358251
------------------------------------------------------------------------------
```

```
stcox age smoke if sex==1

------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         age |   1.113783   .0136012     8.82   0.000     1.087442    1.140762
       smoke |   1.840968   .4286248     2.62   0.009     1.166446    2.905547
------------------------------------------------------------------------------
```

Cox regresjon, test av kjønnsforskjell

- Interaksjon mellom kjønn og røyk
- Inkluder kryssprodukt mellom kjønn og røyk i modellen

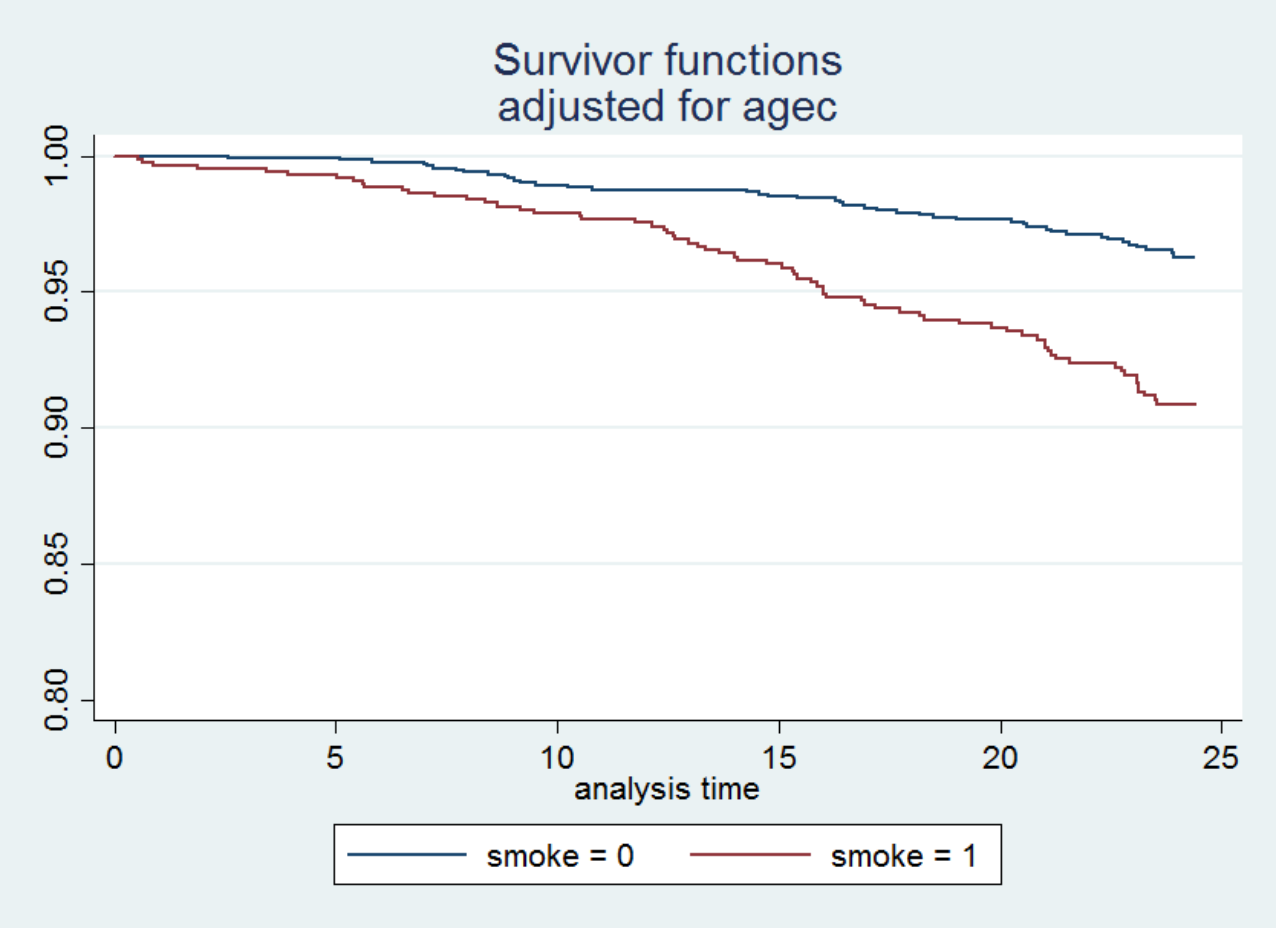
```
generate int_sex_smoke= sex*smoke
stcox age smoke sex int_sex_smoke

------------------------------------------------------------------------------
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         age |    1.11637   .0117325    10.47   0.000      1.09361    1.139604
         sex |   1.785369   .5965232     1.73   0.083     .9275272    3.436603
       smoke |   2.146293   .7592013     2.16   0.031     1.072991    4.293206
int_sex_smoke |   .8547785   .3618855    -0.37   0.711     .3728057    1.959859
------------------------------------------------------------------------------
```

Ikke signifikant

Overleveseskurver

gen agec=age-37.03

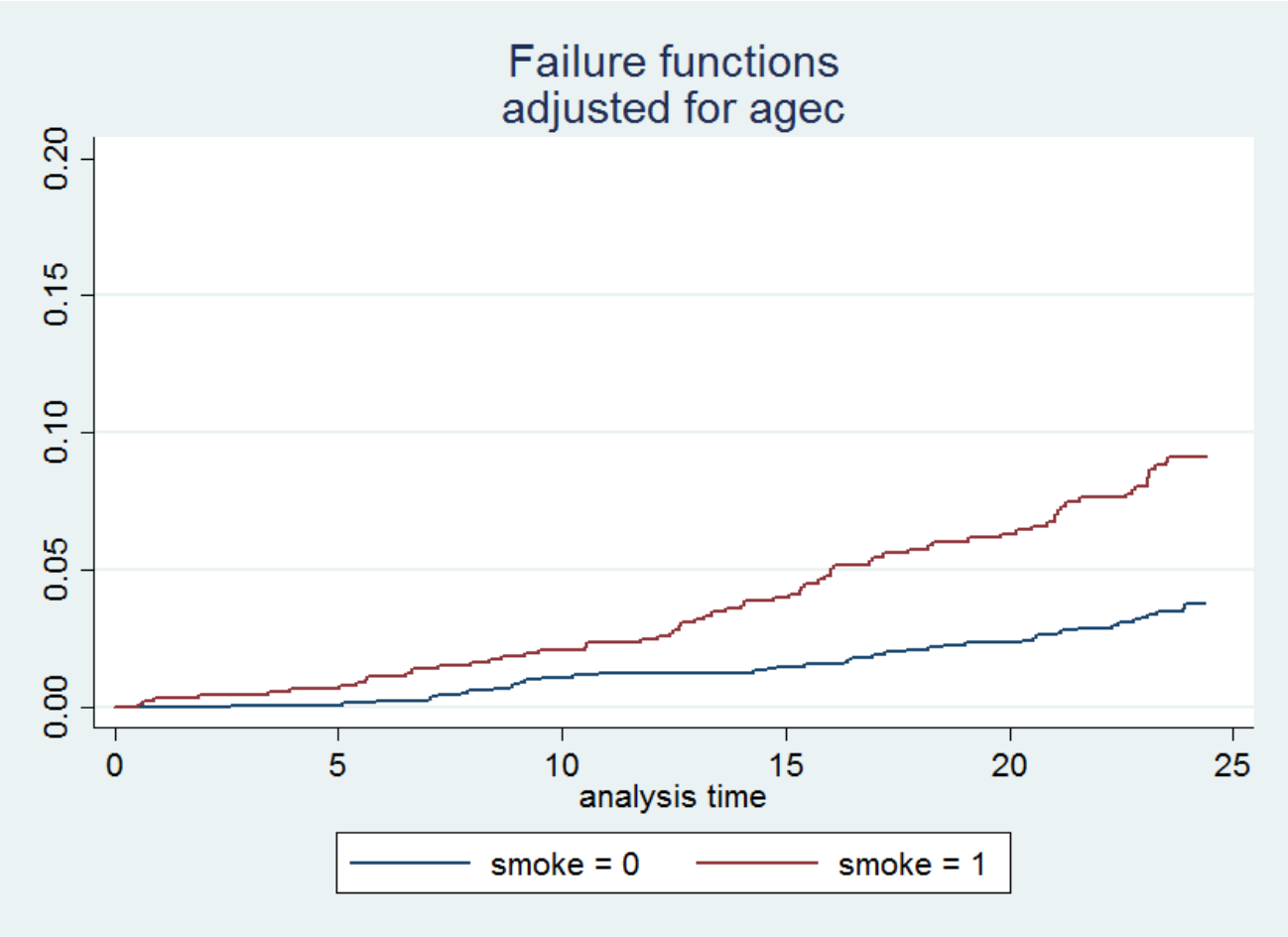
sts graph, by(smoke) adjustfor(agec) ylabel(0.80(0.05)1.0)



Failure-kurver

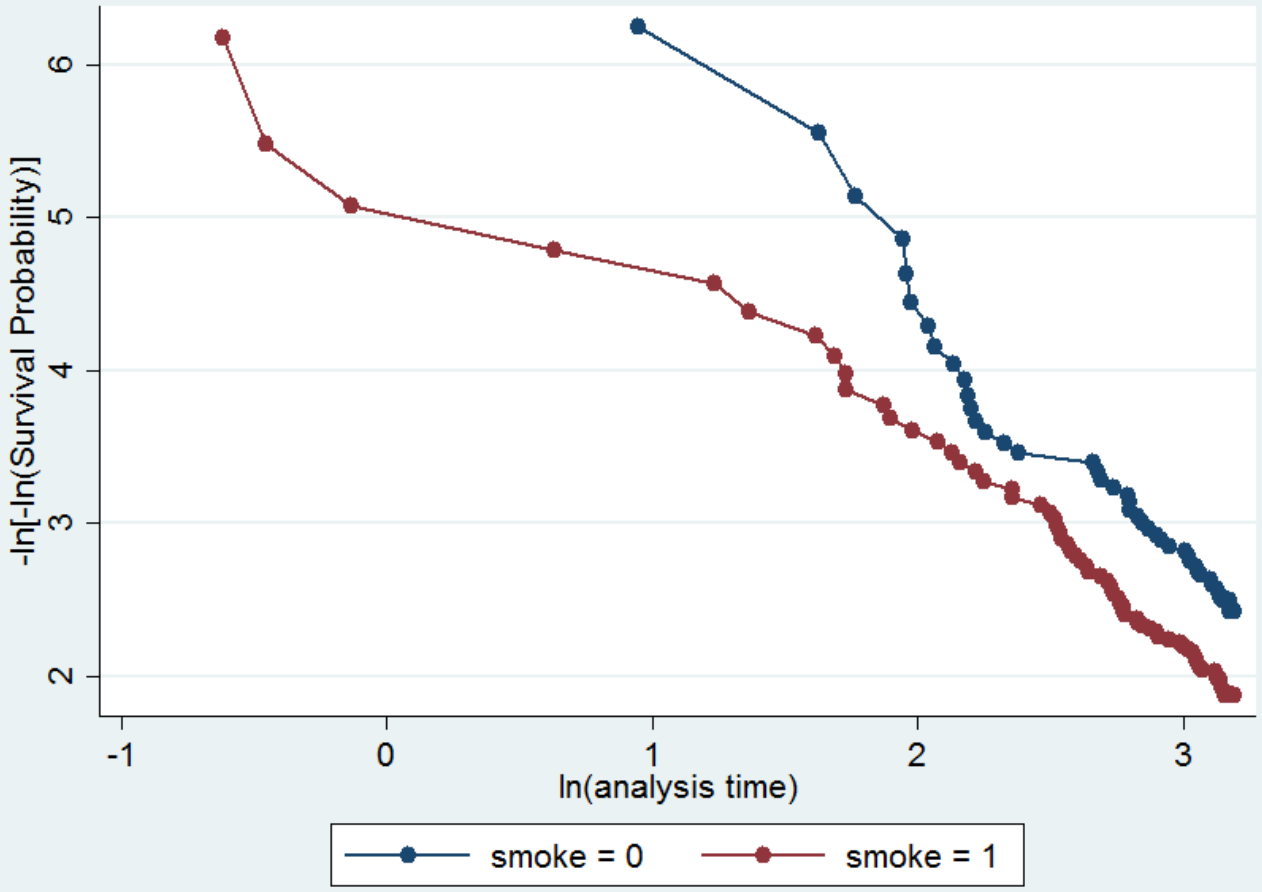
gen agec=age-37.03

sts graph failure, by(smoke) adjustfor(agec) ylabel(0.80(0.05)1.0)



Proporsjonal hasard-antakelse

stphplot,by(smoke)



Hazard ratios for mortality by BMI change in n=4881 men

10 yr BMI change	Person-years	Deaths	MR*	HR†	95% CI†
< -1	1,928	45	7.8	1.94	1.35, 2.80
-1 to 0	7,046	77	4.3	1.25	0.93, 1.68
0 to 1	16,187	101	3.2	1.00	ref
1 to 2	14,916	67	3.0	0.92	0.67, 1.25
2 to 3	7,841	31	3.1	0.91	0.61, 1.36
3 +	3,881	20	4.9	1.22	0.75, 1.99
P value difference					0.0027

*Age adjusted mortality rate per 1,000 person-years using poisson regression models.
†Adjusted for initial BMI, age, smoking status, and leisure time physical activity using Cox proportional hazard regression models.

Wilsgaard et al. Weight loss and mortality. A gender specific analysis. The Tromsø Study. Gender Medicine 2009

Fractional polynomials

- Anta en uavhengig variabel x
- Cox model, lineær sammenheng (på log skala)

$$h(t) = h_0(t) \cdot e^{\beta_1 x}$$

- Cox model ikke –lineær sammenheng

$$h(t) = h_0(t) \cdot e^{\beta_1 x^p + \beta_2 x^q},$$
$$\text{hvor p og q} = (-2, -1, -0.5, 0, 0.5, 1, 2, 3)$$

- Dersom p=0 blir transformasjonen ln(x) (ikke x^0)
- Dersom p = q, f.eks.= 2

$$h(t) = h_0(t) \cdot e^{\beta_1 x^2 + \beta_2 \ln(x) \cdot x^2}$$

Eksempel «BMI change»

- Eksponeringsvariabel, ΔBMI
- I frac pol kan ikke variabelen ≤ 0
- Sentrerte variabelen på -11
  - ΔBMIc = ΔBMI +11
- Beste powers ble estimert til p = 2 og q = 3
- Cox modell:

$$h(t) = h_0(t)\exp\left(\beta_1 \Delta BMIc^2 + \beta_2 \Delta BMIc^3 + \beta_3 x\right)$$

Beregning av HR

$$h(t) = h_0(t)\exp\left(\beta_1 \Delta BMIc^2 + \beta_2 \Delta BMIc^3 + \beta_3 x\right)$$

- Anta vi ønsker å beregne HR mellom ΔBMI = -2 mot ΔBMI =1
- ΔBMI = -2
  - ΔBMIc = ΔBMI +11 = -2 + 11 = 9
- ΔBMI =1
  - ΔBMIc = ΔBMI +11 = 1 + 11 = 12

- HR = h(t gitt ΔBMIc =9) / h(t gitt ΔBMIc =11)
- $HR = \frac{e^{(\beta_1 \cdot 9^2 + \beta_2 \cdot 9^3)}}{e^{(\beta_1 \cdot 12^2 + \beta_2 \cdot 12^3)}} = 2.09$

Hazard ratios* for mortality by levels of BMI change in n=4881 men

Modell: $h(t) = h_0(t)\exp\left(\beta_1 \Delta BMIc^2 + \beta_2 \Delta BMIc^3 + \beta_3 x\right)$

10 yr BMI change	Men		Women	
-2	2.09	1.56, 2.81	1.19	0.81, 1.75
-1	1.53	1.28, 1.83	1.11	0.88, 1.41
0	1.19	1.10, 1.29	1.05	0.94, 1.17
1	1.00	ref	1.00	ref
2	0.92	0.85, 0.99	0.97	0.88, 1.07
3	0.95	0.79, 1.13	0.96	0.80, 1.15
4	1.10	0.80, 1.52	0.97	0.74, 1.29
P value BMI change†		<0.0001		0.63

*Adjusted for initial BMI, age, smoking status, and leisure time physical activity.
†The joint effect of two fractional polynomial terms of BMI change.

Takk