國人生理年齡與五項肥胖指標的關聯性

ASSOCIATIONS OF FIVE OBESITY METRICS WITH EPIGENETIC AGE ACCELERATION

台大公衛學院流預所林菀俞副教授

Wan-Yu Lin, Ph.D

Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University

Web: http://homepage.ntu.edu.tw/~linwy/

實際年齡
CHRONOLOGICAL AGE

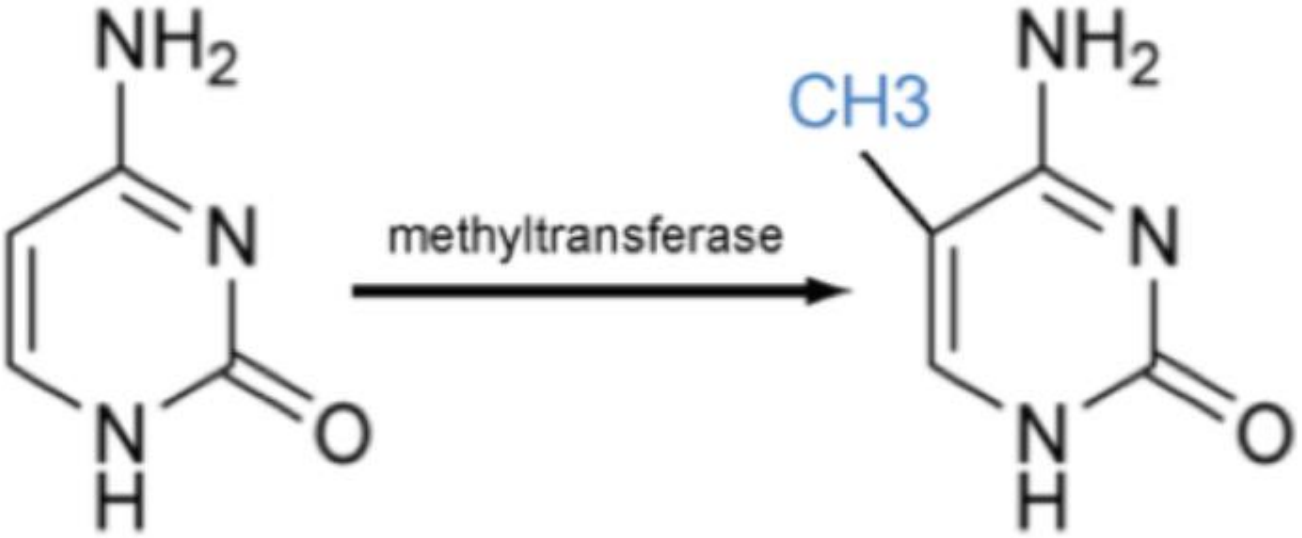
年紀相仿，他/她為何看起來比較年輕？

若有詩書藏於心，歲月從不敗美人　《抱得美人歸》

生理年齡
BIOLOGICAL AGE

- 染色體頂端的「端粒」(telomere)長度 => 抽血進行 DNA 檢測
- Phenotypic age => 抽血驗腎功能指標 (creatinine)、肝功能指標 (albumin) 、代謝功能指標 (fasting glucose) 等
- **Methylation age => 抽血驗特定基因位點的甲基化程度**

甲基化

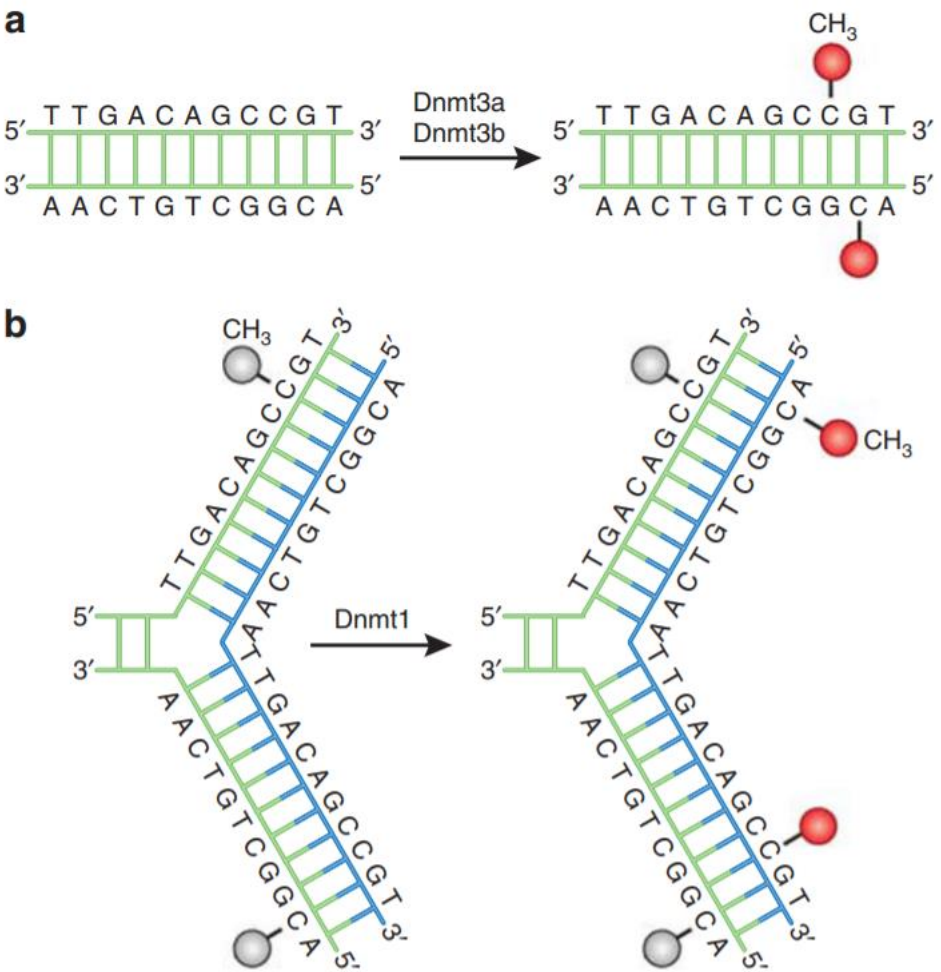


胞嘧啶（cytosine, C），組成DNA的四種基本鹼基之一

http://www.ks.uiuc.edu/Research/methylation/

DNA 甲基化

- 可能弱化基因表現，進而使其失去功能
- 能在不改變 DNA 序列的前提下，改變遺傳表現



DNA Methylation and Its Basic Function

Neuropsychopharmacology REVIEWS (2013) 38, 23–38

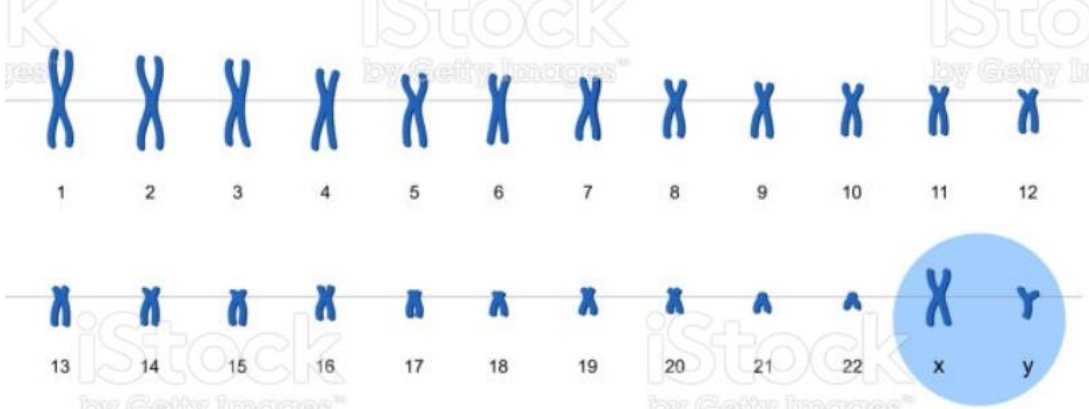
Lisa D Moore[1], Thuc Le[1] and Guoping Fan*,[1]

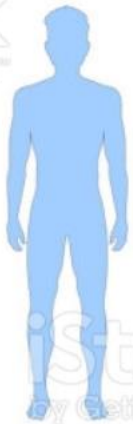
[1]Interdepartmental Program in Neuroscience and Department of Human Genetics, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, CA, USA

Taiwan Biobank (TWB)

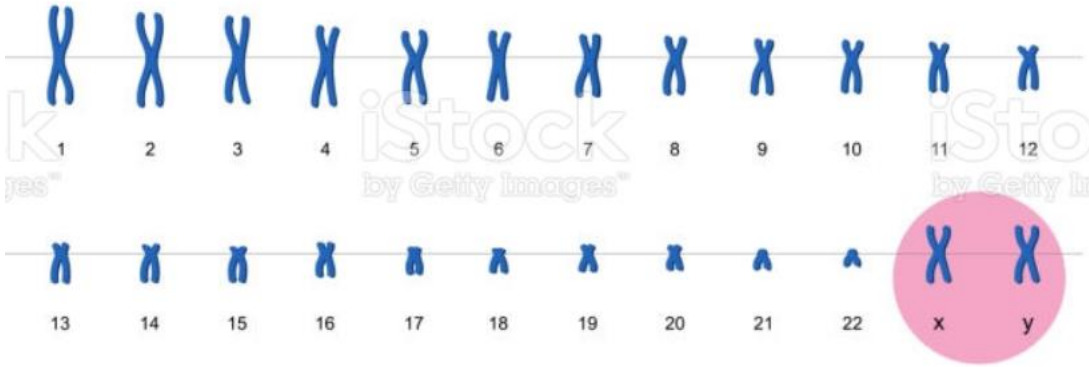
- From 2012 to 2020, TWB has recruited 122,071 community-based volunteers
- Ages: 30-70
- During 2016-2021, TWB researchers randomly selected 2,474 TWB participants and submitted their blood samples for DNAm quantification.
- Illumina Infinium MethylationEPIC BeadChip (Illumina, Inc., San Diego, CA)
- ~860,000 CpG sites

CHROMOSOME





Male



Female

PhenoAge

- The third National Health and Nutrition Examination Survey (NHANES III)

- Levine et al. (*Aging*, 2018) used a Cox regularized regression model to regress the hazard of aging-related mortality on **42 clinical markers** and **chronological age**

Table 1. Phenotypic aging measures and Gompertz coefficients.

Variable		Units	Weight
Albumin	Liver	g/L	-0.0336
Creatinine	Kidney	umol/L	0.0095
Glucose, serum	Metabolic	mmol/L	0.1953
C-reactive protein (log)	Inflammation	mg/dL	0.0954
Lymphocyte percent	Immune	%	-0.0120
Mean (red) cell volume	Immune	fL	0.0268
Red cell distribution width	Immune	%	0.3306
Alkaline phosphatase	Liver	U/L	0.0019
White blood cell count	Immune	1000 cells/uL	0.0554
Age		Years	0.0804

Levine et al. (*Aging*, 2018)

513 CpG sites

磷酸

5'—C—phosphate—G—3'

基因內CpG位點的甲基化會改變此基因的表達

- Among the 513 CpGs, 226 (44.1%) were significantly associated with chronological age in the TWB ($p < 0.05/513 = 9.7\times10^{-5}$).

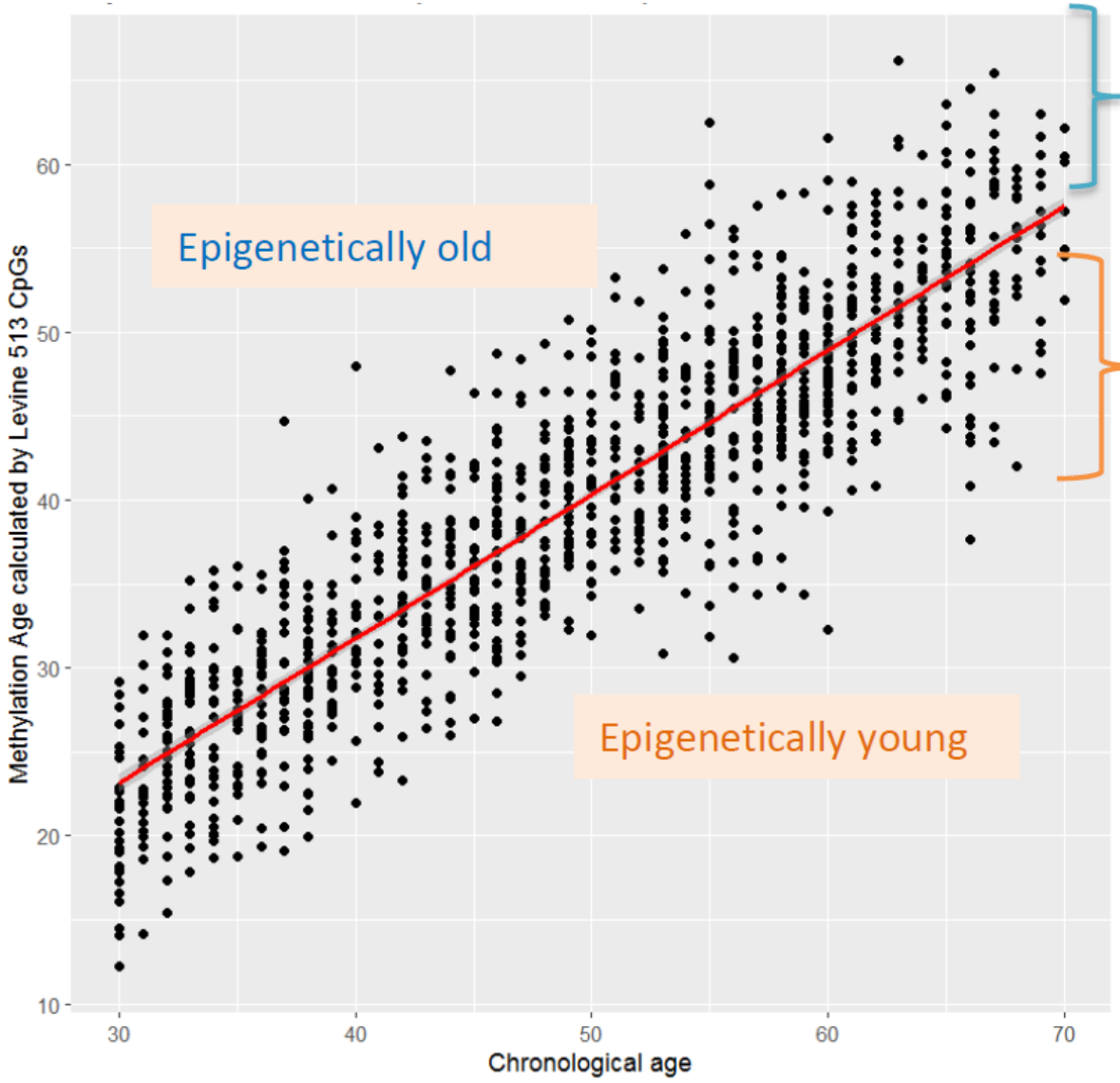
Table S1 - The Levine et al.'s 513 CpGs

	A	B	C	D	E	F	G	H	I
1	CpG	Chrom	Map.Info	Gene.Symbol	Entrez.ID	Weight	Univariate.Age.Correlation.Levine	Regression.Coef.TWB	P.value.TWB
2	Intercept	NA	NA		NA	60.664	NA	NA	NA
3	cg15611364	3	25806427	OXSM	54995	63.12415	0.003807203	1.06E-05	0.39518332
4	cg17605084	12	53177758	HEM1	3071	-44.0094	-0.02916914	-1.64E-05	0.222610451
5	cg26382071	17	6485627	TXNL5	84817	40.42085	0.002996738	6.92E-06	0.510282217
6	cg12743894	11	30301513	C11orf46	120534	36.78818	-0.008386638	-8.94E-07	0.933755645
7	cg19287114	9	107046432	SLC44A1	23446	-36.4938	-0.118250325	1.16E-05	0.448366716
8	cg12985418	18	17574536	MIB1	57534	-35.9001	-0.073728082	6.33E-06	0.591580989
9	cg19398783	4	38460973	TLR10	81793	35.83308	-0.073112025	4.01E-06	0.719761433
10	cg15963417	12	101835430	PAH	5053	-34.6984	0.049223907	2.43E-05	0.188869117
11	cg27187881	22	40796291	NAGA	4668	-33.5456	-0.475052242	-0.00058973	8.64E-34
12	cg09892203	17	62391602	CACNG4	27092	-33.4823	0.130255717	5.35E-05	2.92E-14

CpG = **Age** + sex + BMI + smoking + drinking + …

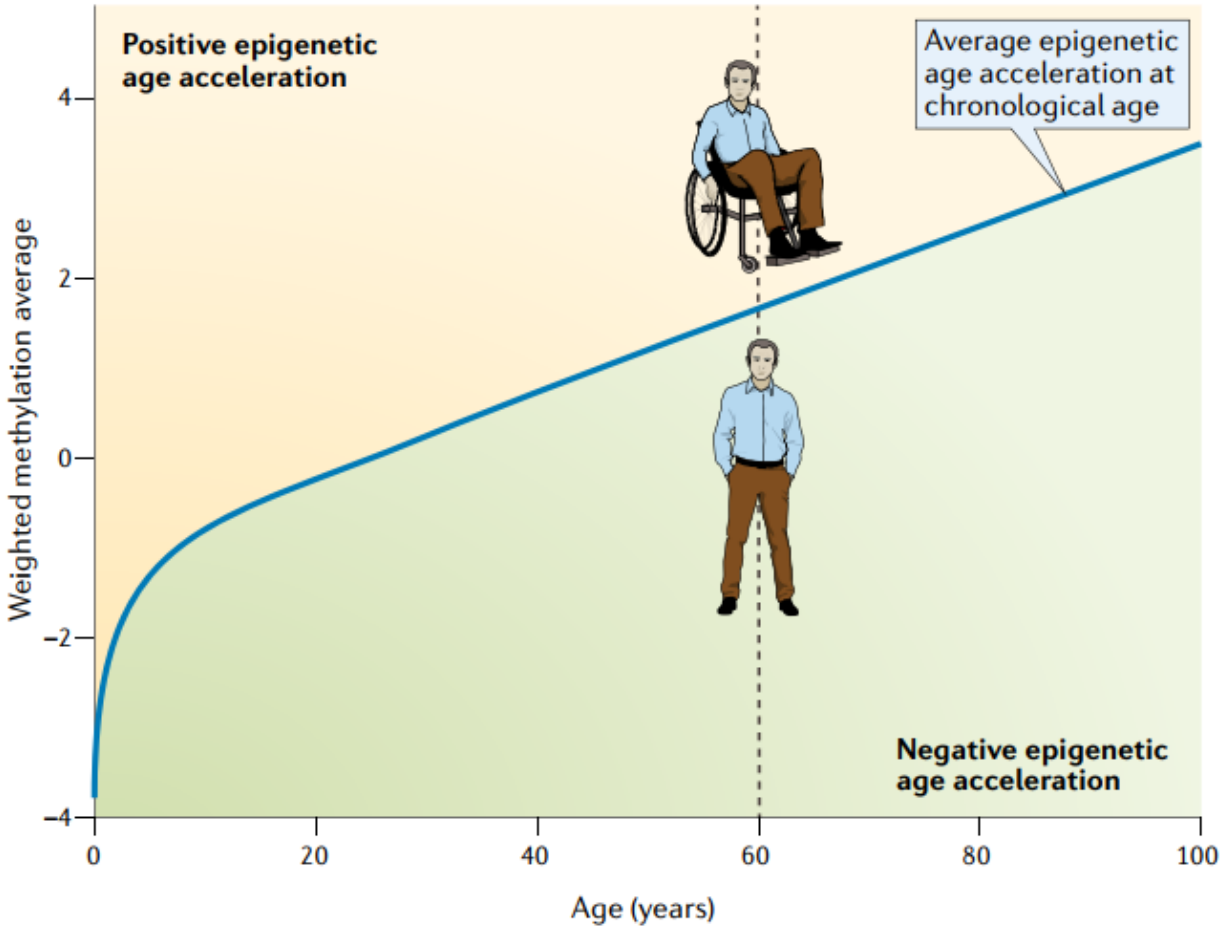
- Among the 513 CpGs, 226 (44.1%) were significantly associated with chronological age in the TWB ($p < 0.05/513 = 9.7 \times 10^{-5}$).
- Among the 226 CpGs, 223 (98.7%) exhibited the same direction of the correlations shown by Levine et al.
- This suggests that many of the 513 aging-related CpGs identified by Levine et al. can be well replicated in the TWB.
- Among the 513 CpGs, 102 (19.9%) showed different directions from the correlations of Levine et al.
- However, 89 of these 102 sites (87.3%) were not significantly associated with chronological age in the TWB ($p > 0.05$).

- $PhenoAge = \hat{\alpha}_0 + \sum_{j=1}^{513} \hat{\alpha}_j X_j$
- $\hat{\alpha}_0 = 60.664$, $\hat{\alpha}_1 = 63.124$, etc.
- X_j: β-value according to $\frac{M}{M+U}$, where M is the methylated intensity and U is the unmethylated intensity. Therefore, β-values ranged from 0 to 1.



Positive residuals mean the subjects are epigenetically old.

Negative residuals mean the subjects are epigenetically young.



Steve Horvath[1,2] and Kenneth Raj[3]*

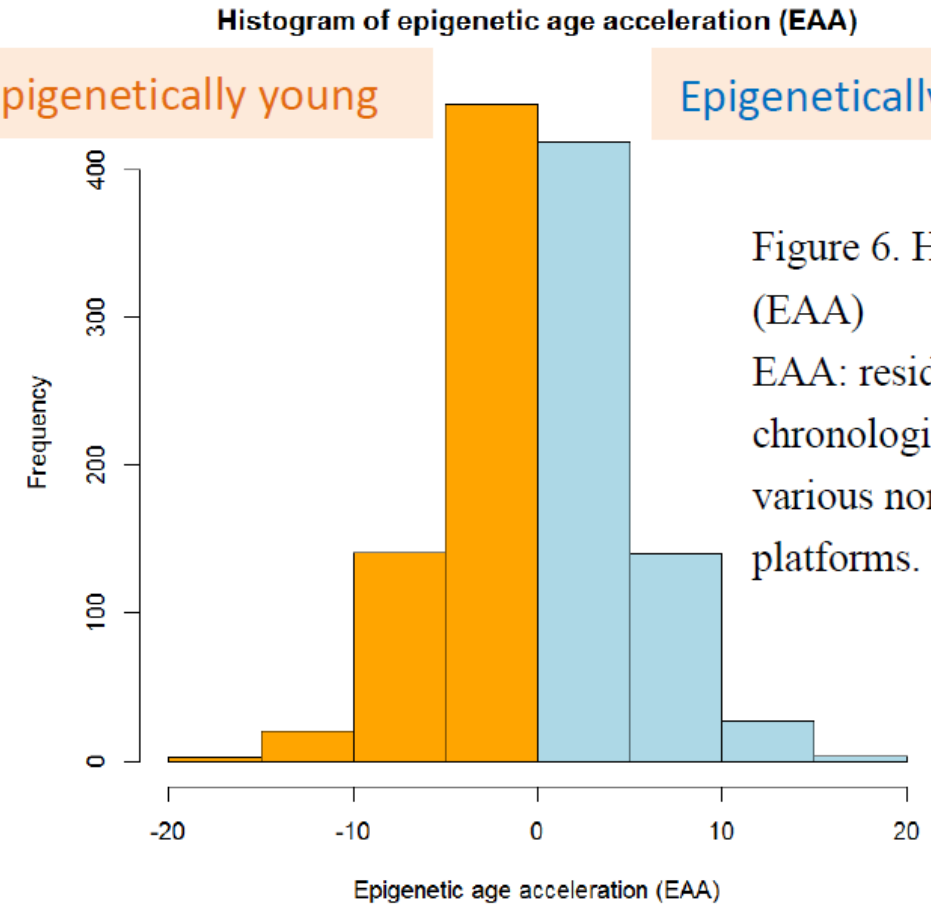
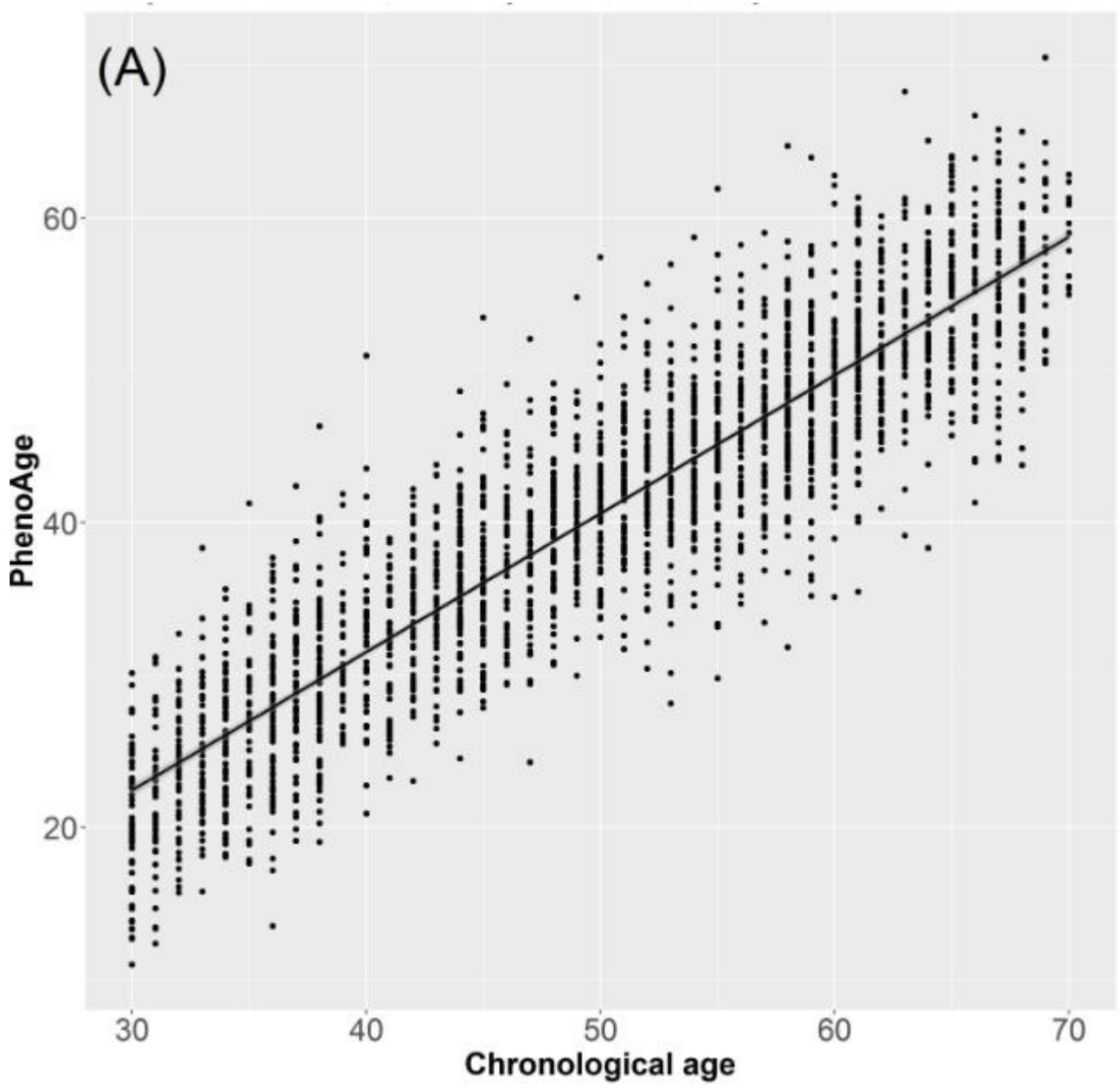


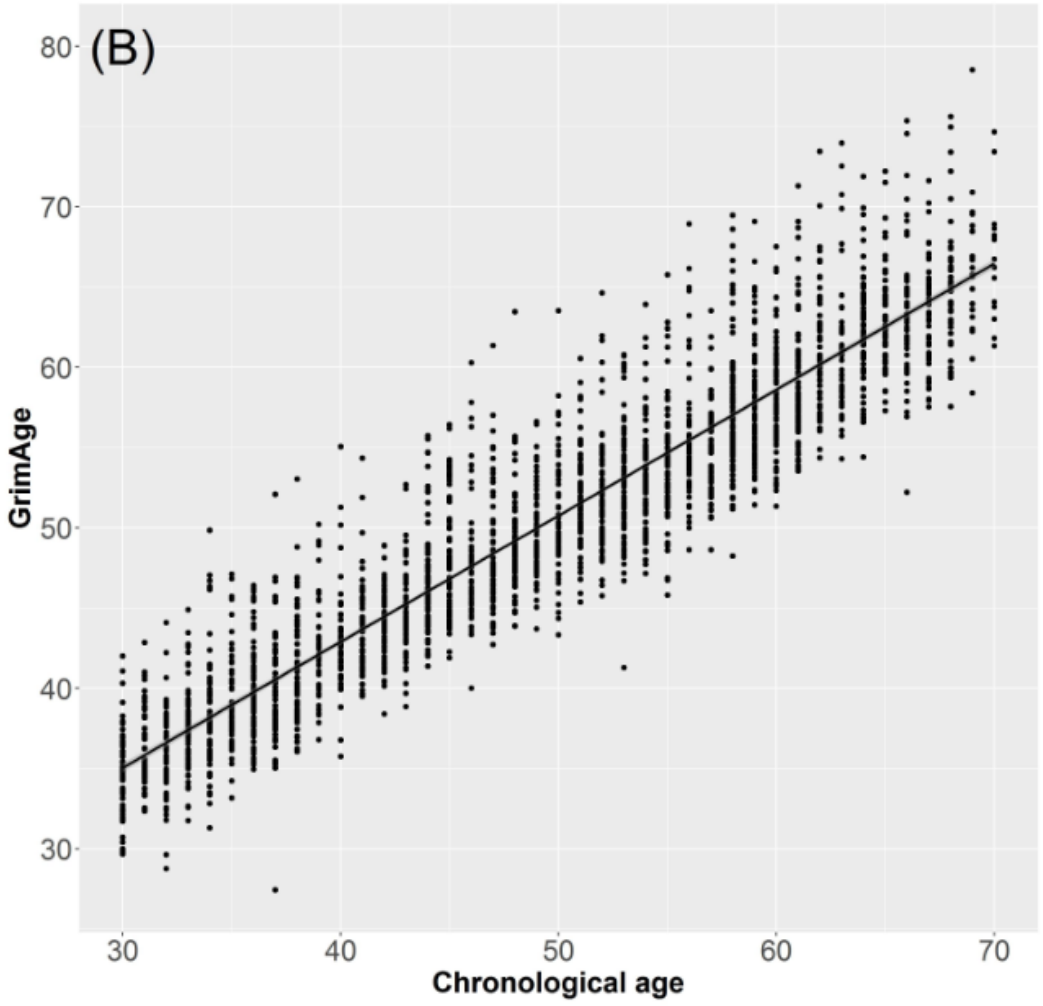
Figure 6. Histogram of epigenetic age acceleration (EAA)

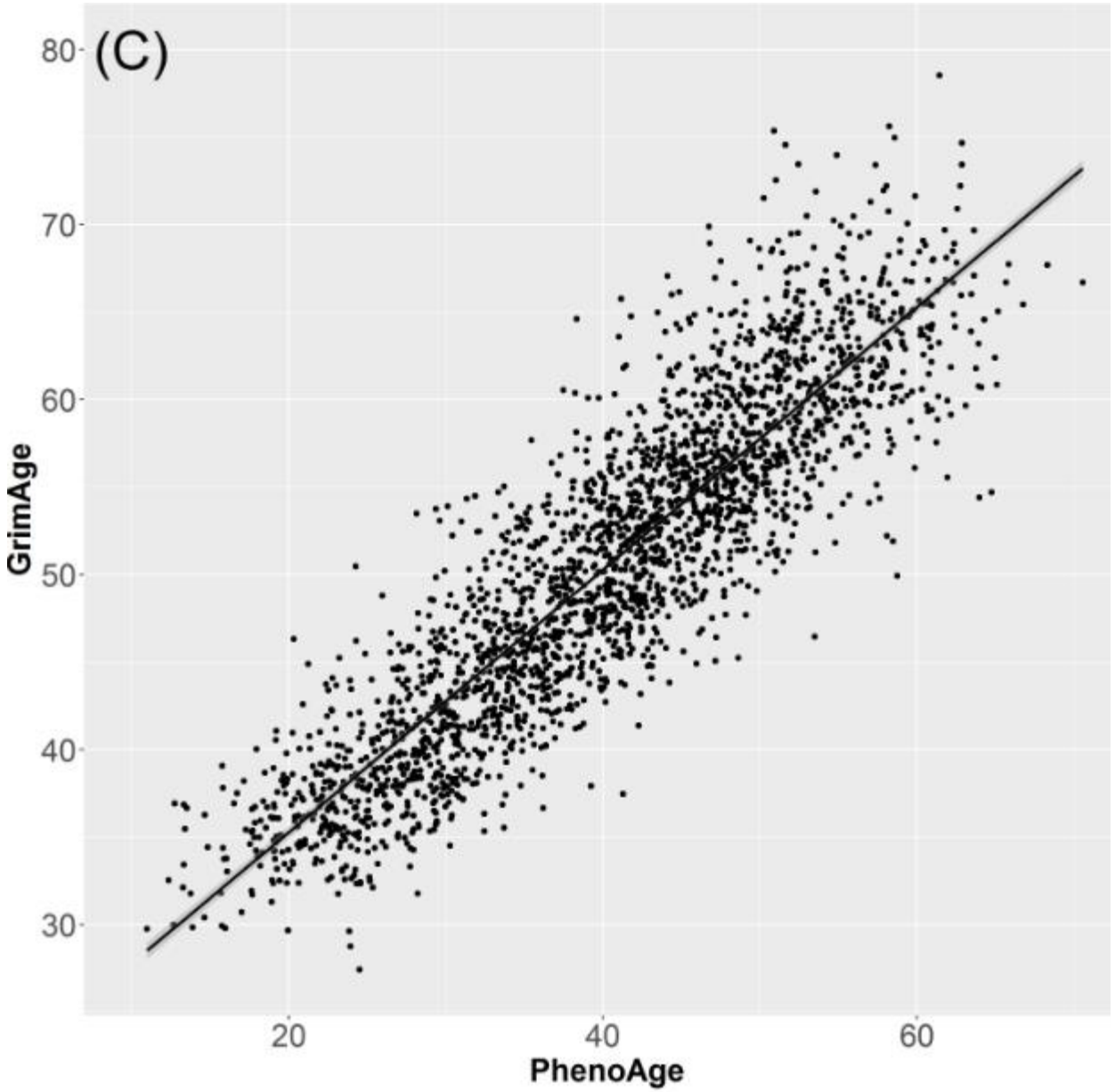
EAA: residuals from regressing methylation age on chronological age. In this way, EAA will be robust to various normalization methods and measurement platforms.


(A)
PhenoAge
60
40
20
30
40
50
60
70
Chronological age

GrimAge is based on 1,030 CpGs that are associated with DNAm-based biomarkers for 7 plasma proteins and smoking pack-years.

Lu AT *et al. Aging (Albany NY)* 2019;**11:** 303-327




(C)
80
70
60
50
40
30
GrimAge
20
40
60
PhenoAge

	Males	Females	*p*-value
Total	1,243 (50.2%)	1,231 (49.8%)	
Age (years)	50.3±11.3	49.3±10.8	0.0246
Drinking	147 (11.8%)	24 (1.9%)	7.7E-22
Smoking	235 (18.9%)	48 (3.9%)	2.0E-31
Regular exercise	595 (47.9%)	497 (40.4%)	2.0E-4
Educational attainment	5.8±0.9	5.4±0.9	1.6E-22
BMI (kg/m^2)	25.2±3.4	23.5±3.7	2.3E-32
Body fat percentage (%)	22.9±5.4	31.8±6.5	4.5E-228
Waist circumference (cm)	87.9±9.3	80.5±9.8	6.8E-76
Hip circumference (cm)	98.2±6.7	95.6±6.9	2.1E-20
Waist-hip ratio	0.89±0.06	0.84±0.07	1.3E-90

Educational attainment ranges from 1 to 7: 1 “illiterate”, 2 “no formal education but literate”, 3 “primary school graduate”, 4 “junior high school graduate”, 5 “senior high school graduate”, 6 “college graduate”, and 7 “Master’s or higher degree”.

衛生福利部
國民健康署

18歲（含）以上的成人 BMI範圍值	體重是否正常
□BMI < 18.5 kg/m2	「體重過輕」，需要多運動，均衡飲食， 以增加體能，維持健康！
□18.5 ≦BMI < 24 kg/m2	恭喜！「健康體重」，要繼續保持！
□24 kg/m2≦BMI < 27 kg/m2	哦！「體重過重」了，要小心囉， 趕快力行「健康體重管理」！
□BMI ≧27 kg/m2	啊～「肥胖」，需要立刻力行「健康體重管理」囉！

Males	Females
-0.23 (p=0.857)	-0.90 (p=0.224)
0.57 (p=0.068)	0.81 (p=0.023)
1.04 (p=0.002)	1.17 (p=0.004)

PhenoEAA ~ underweight + overweight + obesity + smoking + place + drinking + exercise + education

EAA: epigenetic age acceleration

衛生福利部
國民健康署

18歲（含）以上的成人 BMI範圍值	體重是否正常
□BMI < 18.5 kg/m2	「體重過輕」，需要多運動，均衡飲食， 以增加體能，維持健康！
□18.5 ≦BMI < 24 kg/m2	恭喜！「健康體重」，要繼續保持！
□24 kg/m2≦BMI < 27 kg/m2	哦！「體重過重」了，要小心囉， 趕快力行「健康體重管理」！
□BMI ≧27 kg/m2	啊～「肥胖」，需要立刻力行「健康體重管理」囉！

Males	Females
-1.00 (p=0.227)	0.03 (p=0.943)
0.47 (p=0.018)	0.36 (p=0.044)
0.45 (p=0.033)	0.77 (p=0.0002)

GrimEAA ~ underweight + overweight + obesity + smoking + place + drinking + exercise + education

EAA: epigenetic age acceleration

	Males			Females		
	PhenoEAA					
	$\hat{\beta}$	95% C.I.	*P*-value	$\hat{\beta}$	95% C.I.	*P*-value
BMI	0.356	[0.096, 0.616]	0.007	**0.600**	**[0.317, 0.883]**	**3.3E-5**
Body fat percentage	0.313	[0.042, 0.583]	0.024	0.510	[0.225, 0.795]	4.7E-4
Waist circumference	0.427	[0.167, 0.687]	0.001	0.453	[0.170, 0.736]	0.002
Hip circumference	0.111	[-0.150, 0.372]	0.404	0.344	[0.064, 0.624]	0.016
Waist-hip ratio	**0.602**	**[0.341, 0.862]**	**6.3E-6**	0.349	[0.063, 0.634]	0.017

3.7

0.06

PhenoEAA ~ BMI + smoking + place + drinking + exercise + education
PhenoEAA ~ BFP + smoking + place + drinking + exercise + education
PhenoEAA ~ WC + smoking + place + drinking + exercise + education
PhenoEAA ~ HC + smoking + place + drinking + exercise + education
PhenoEAA ~ WHR + smoking + place + drinking + exercise + education

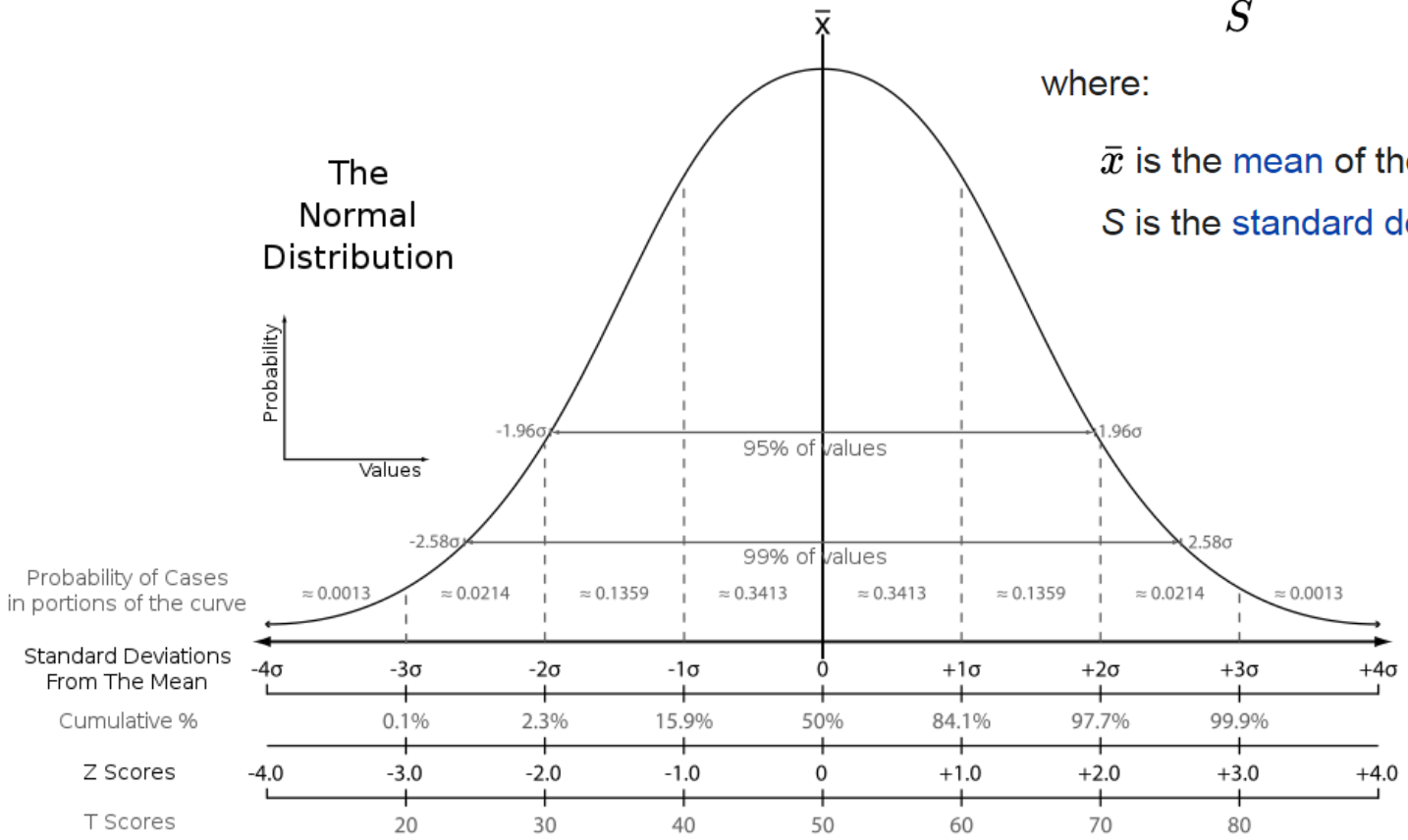
Z-SCORE TRANSFORMATION

$$z = \frac{x - \bar{x}}{S}$$

where:

$\bar{x}$ is the mean of the sample.

S is the standard deviation of the sample.



By Heds 1 at English Wikipedia - Transferred from en.wikipedia to Commons by Abdull., Public Domain, https://commons.wikimedia.org/w/index.php?curid=2799839

	Males			Females		
	GrimEAA					
BMI	0.199	[0.034, 0.365]	0.018	**0.305**	**[0.162, 0.448]**	**3.1E-5**
Body fat percentage	0.213	[0.042, 0.384]	0.015	0.251	[0.107, 0.396]	6.7E-4
Waist circumference	0.277	[0.112, 0.442]	0.001	0.280	[0.137, 0.423]	1.3E-4
Hip circumference	-0.006	[-0.172, 0.160]	0.940	0.159	[0.017, 0.301]	0.028
Waist-hip ratio	**0.481**	**[0.317, 0.645]**	**1.2E-8**	0.271	[0.126, 0.415]	2.4E-4

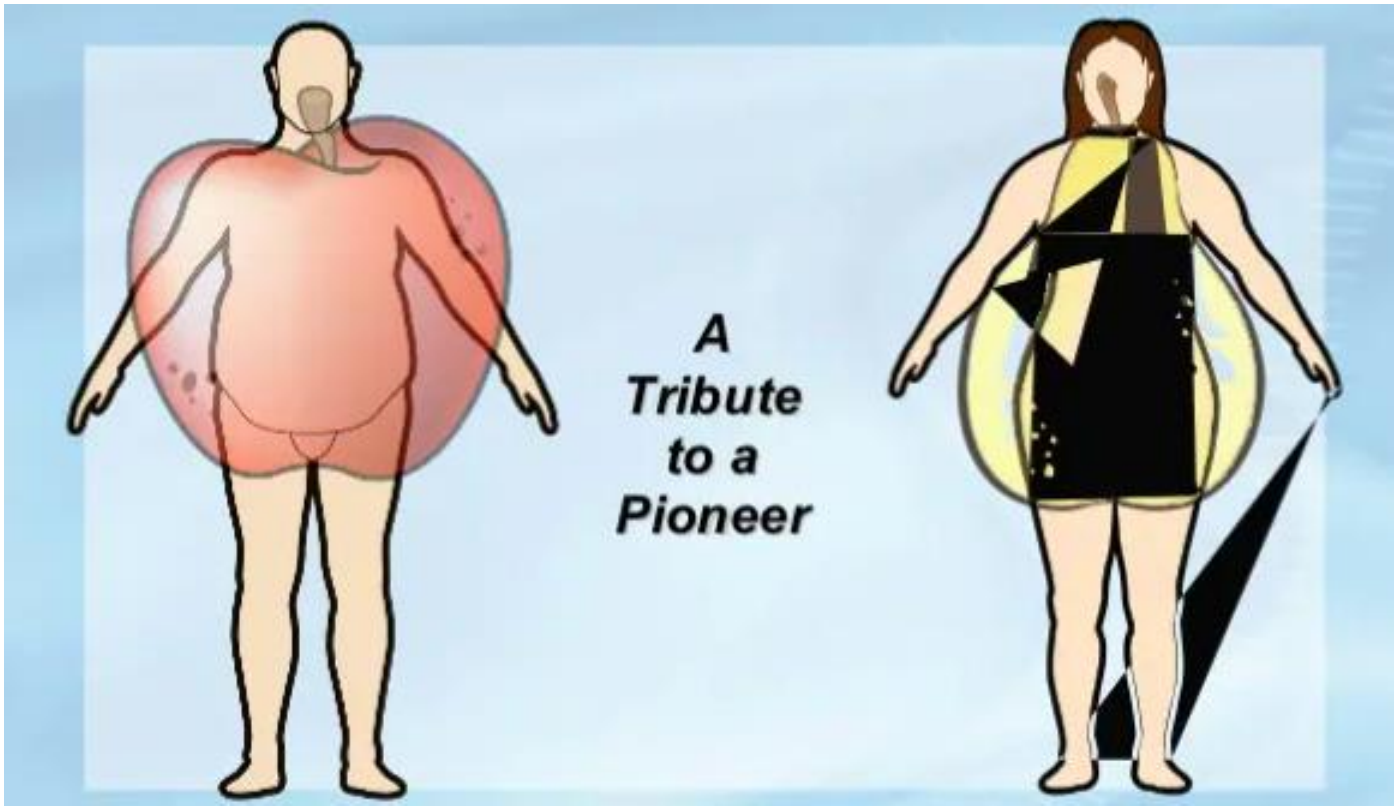
3.7

0.06

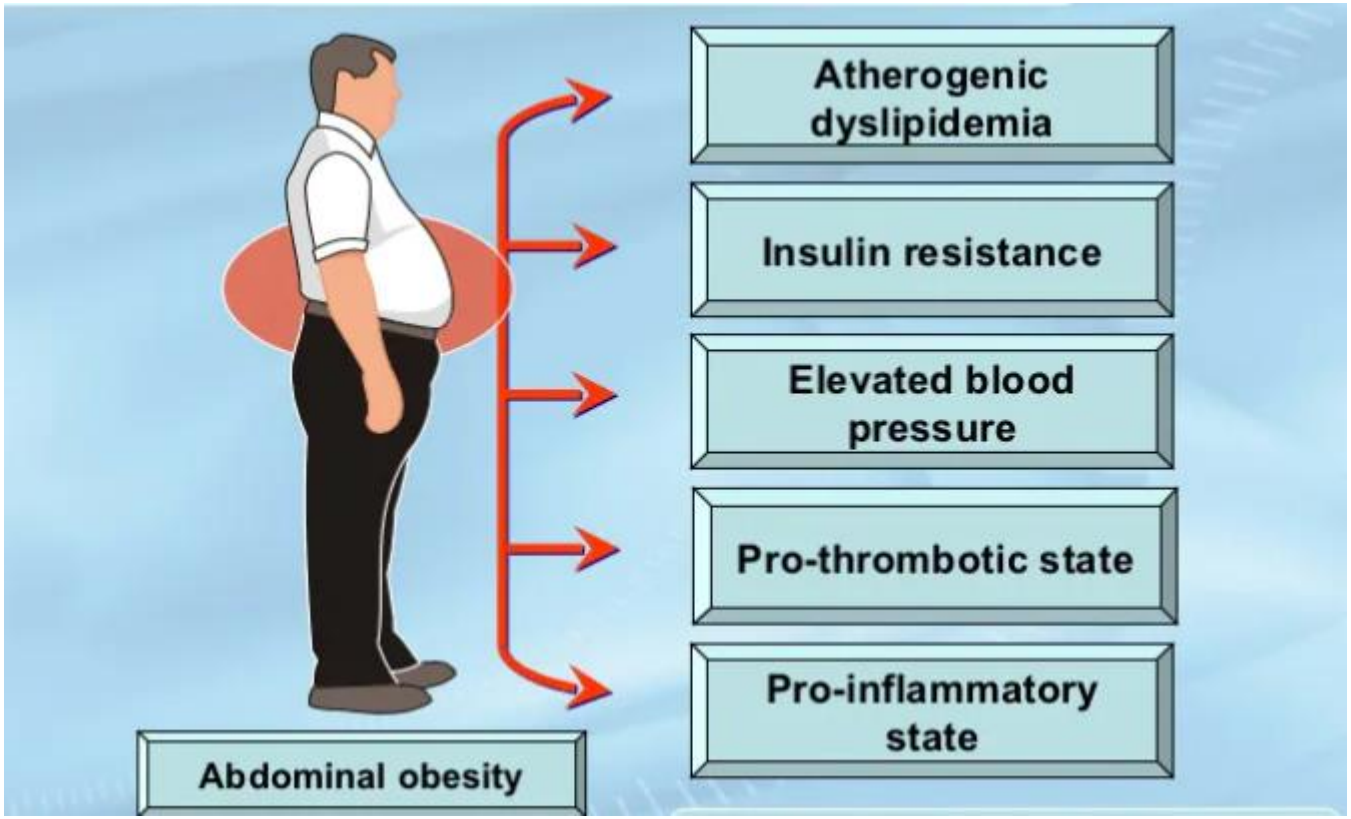
GrimEAA ~ BMI + smoking + place + drinking + exercise + education
GrimEAA ~ BFP + smoking + place + drinking + exercise + education
GrimEAA ~ WC + smoking + place + drinking + exercise + education
GrimEAA ~ HC + smoking + place + drinking + exercise + education
GrimEAA ~ WHR + smoking + place + drinking + exercise + education

Summary

- Prevention of abdominal obesity is associated with a lower risk of EAA in men
- Prevention of general obesity is associated with a lower risk of EAA in women



Jean-Pierre Després, PhD, FAHA



致動脈粥樣化的血脂肪異常

胰島素阻抗

血壓上升

前血栓狀態

前發炎狀態

Jean-Pierre Després, PhD, FAHA

Received: 30 March 2021 | Revised: 16 June 2021 | Accepted: 18 June 2021

DOI: 10.1002/oby.23255

Obesity A Research Journal | THE OBESITY SOCIETY | WILEY

ORIGINAL ARTICLE

Epidemiology/Genetics

Associations of five obesity metrics with epigenetic age acceleration: Evidence from 2,474 Taiwan biobank participants

Wan-Yu Lin[1,2,3] | Yu-Cyuan Wang[1] | I-Hsuan Teng[1] | Chi Liu[4] | Xiang-Yang Lou[5]

- http://homepage.ntu.edu.tw/~linwy/