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Menopause and Cardiometabolic Disease Risk

Charlotte Onland-Moret

Content

- What are cardiometabolic diseases?
- What is menopause?
- Association between menopause and cardiometabolic disease
- Some basic genetics
- Assignment

What are cardiometabolic diseases?

- Combination of different diseases
  - Cardiovascular disease (CVD)
    - Coronary Heart Disease (CHD)
    - Stroke
  - Type 2 diabetes

- Common risk factors
  - Obesity
  - High tiglyceride levels
  - Low HDL cholesterol (good cholesterol)
  - Elevated blood pressure

Cardiovascular diseases

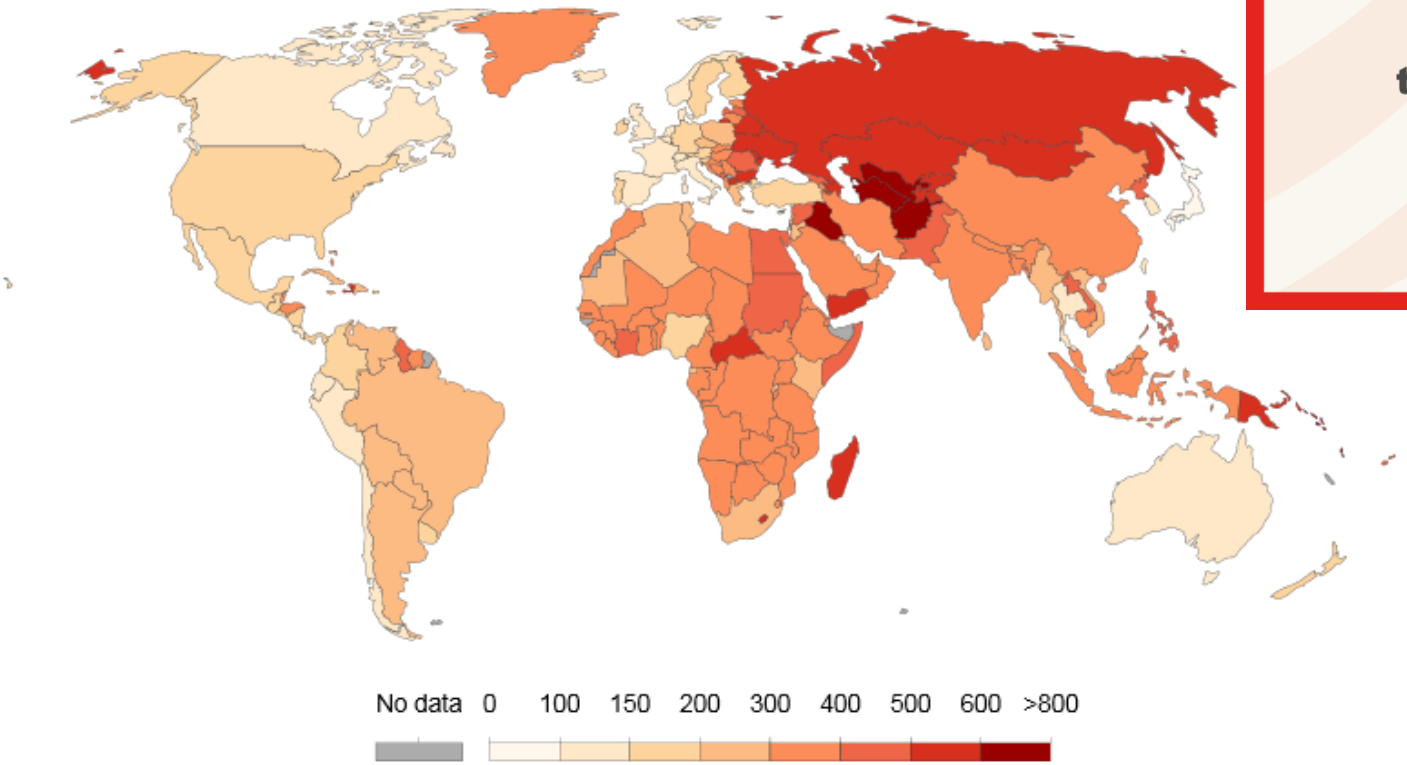
- Class of diseases that involve the heart or blood vessels
- Coronary artery disease (CAD) or coronary heart disease (CHD)
- Stroke
- Heart failure, etc.

- Leading cause of death in the world
- Estimated that 90% is preventable.

- Underlying mechanisms unclear
- For large group: atherosclerosis

Cardiovascular disease death rates (per 100,000), 2016

Age-standardized death rates from cardiovascular disease, measured as the number of deaths per 100,000 individuals across both sexes. Age-standardization assumes a constant population age & structure to allow comparisons between countries and with time without the effects of a changing age distribution within a pop (e.g. aging).



Source: IHME, Global Burden of Disease (GBD)

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17.7 MILLION PEOPLE

die every year from

CARDIOVASCULAR DISEASES

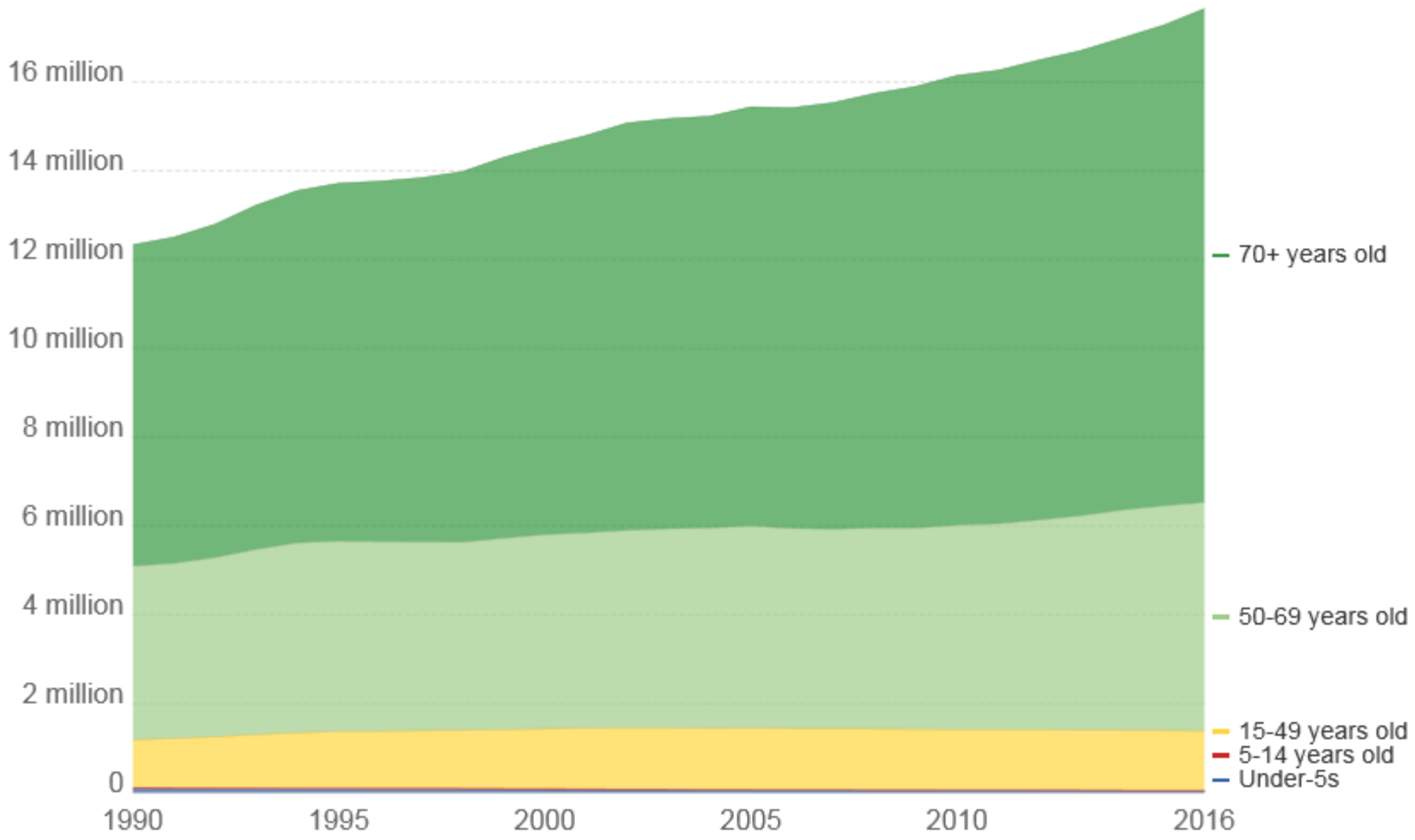
that's 31% of all global deaths

World Health Organization

www.who.int/global_hearts

Cardiovascular disease deaths by age, World

Annual number of deaths from cardiovascular disease, differentiated by age category.



Source: IHME, Global Burden of Disease (GBD)

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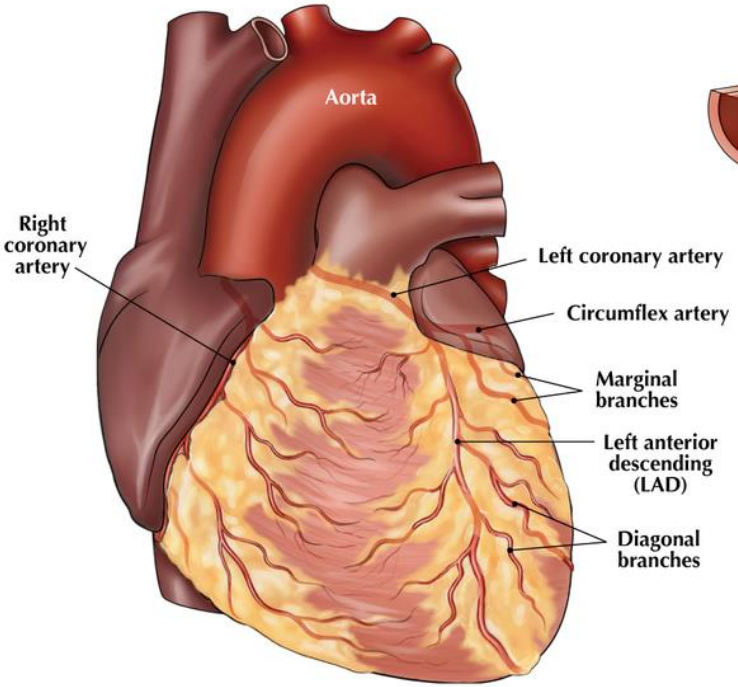
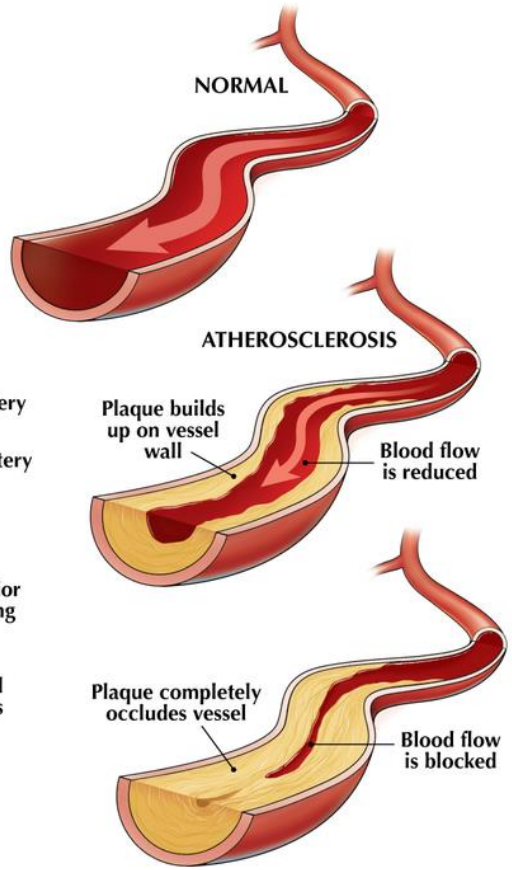
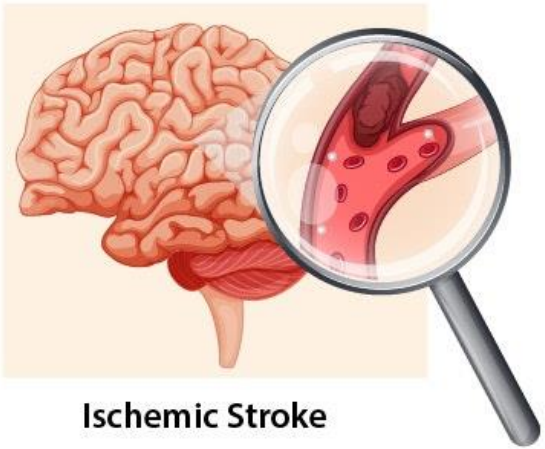
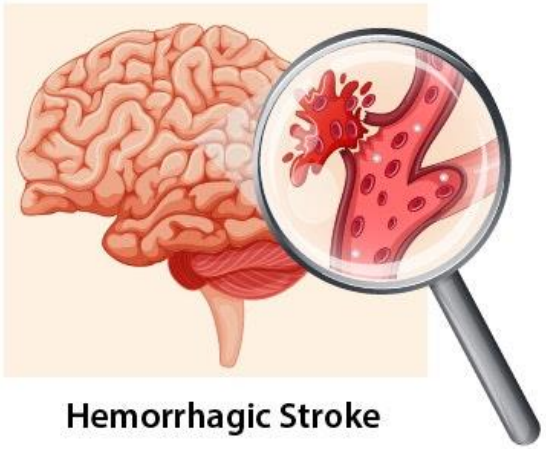
ATHEROSCLEROSIS







Ischemic Stroke



Hemorrhagic Stroke

What is menopause?

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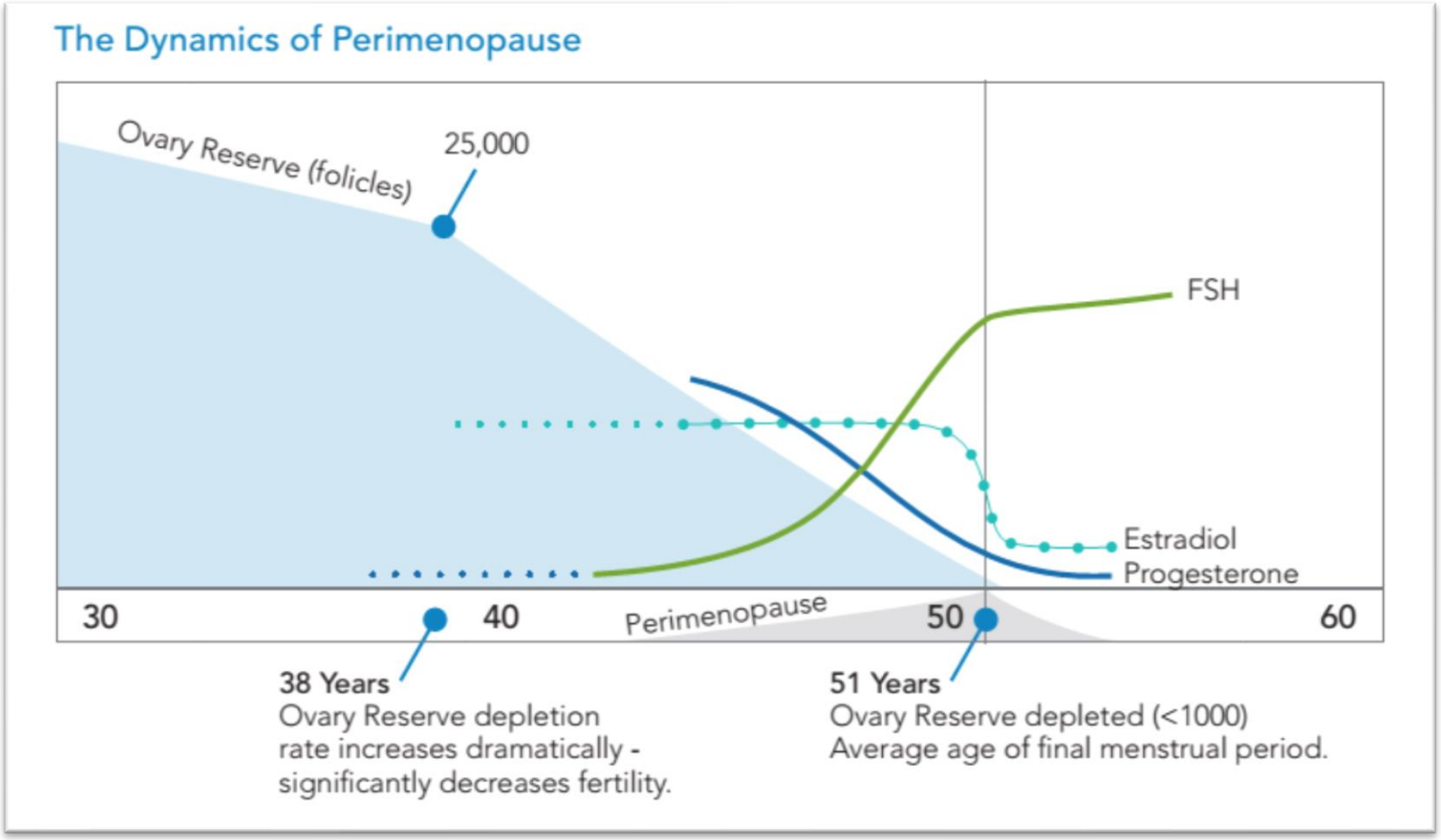
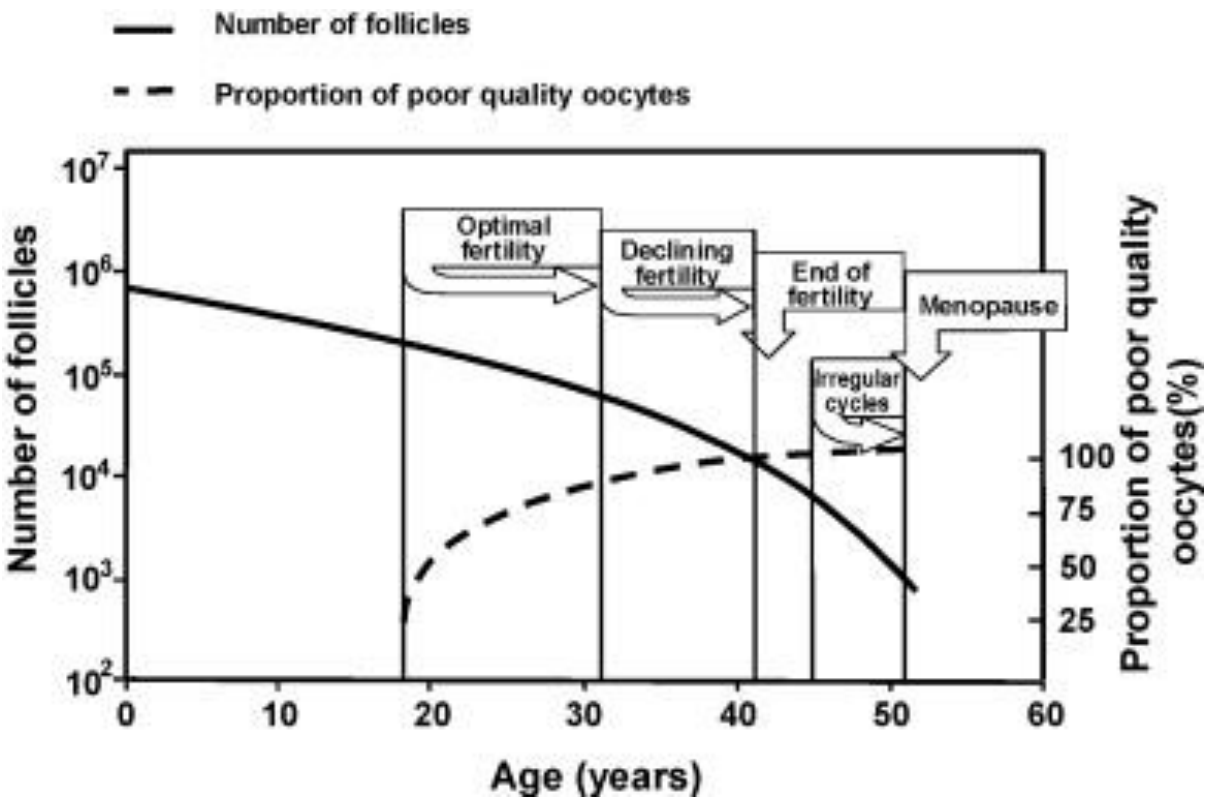
What is menopause

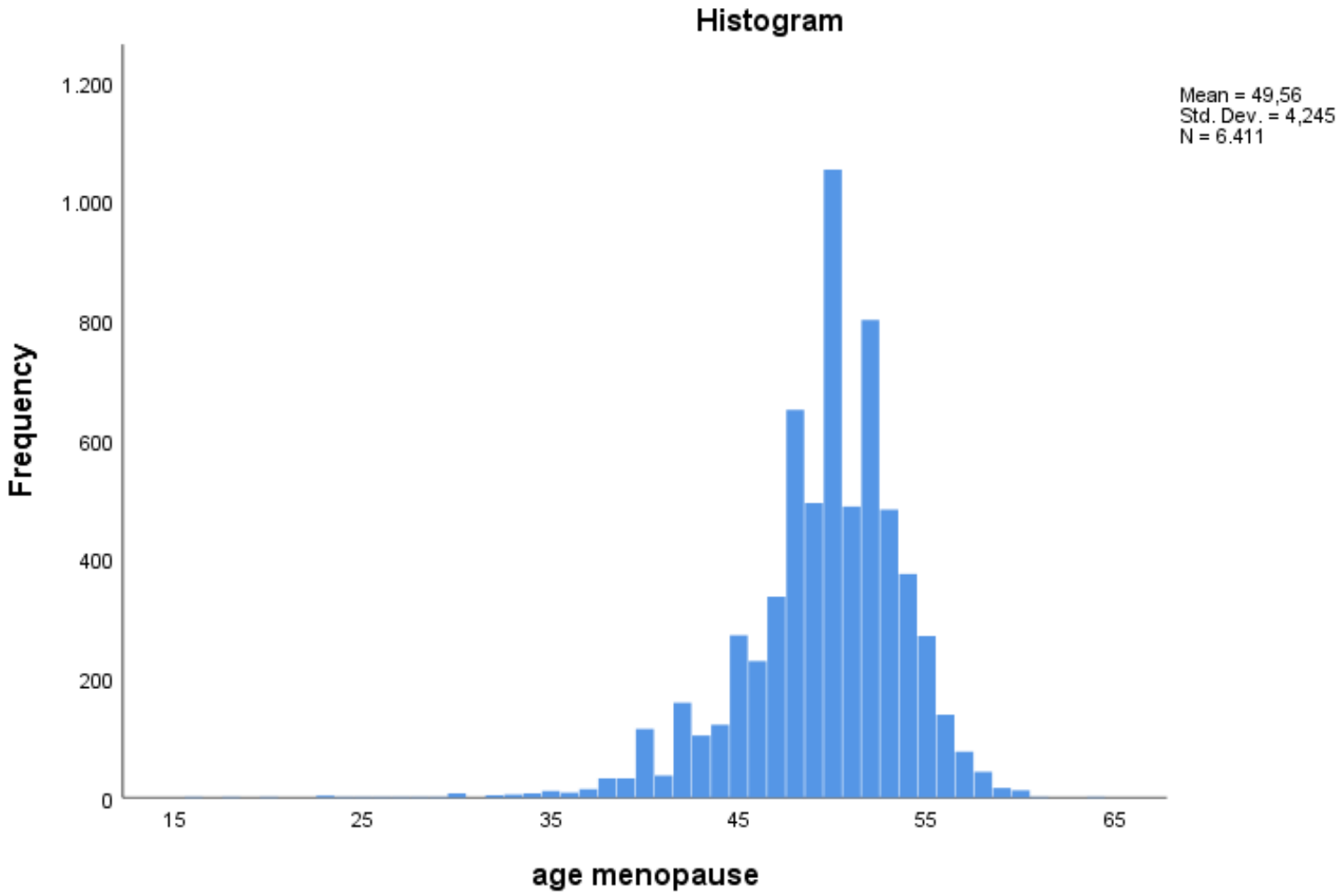


Follicle number and quality with age



Lambalk CB, Maturitas 2009

Distribution in age at menopause



Association between menopause and Cardiometabolic diseases

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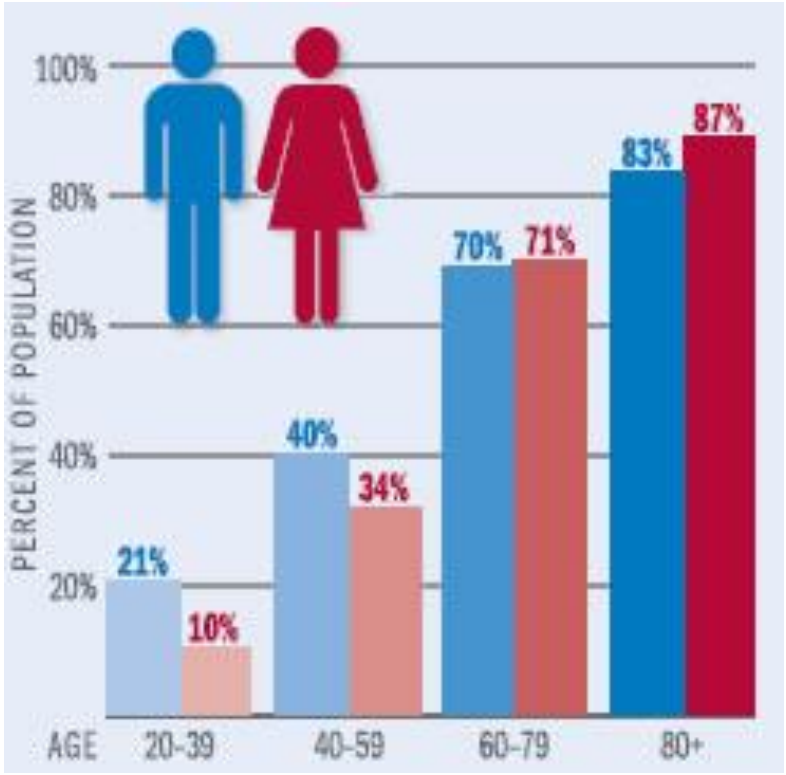
Ratio of male to female death rates in USA of CVD in women by age



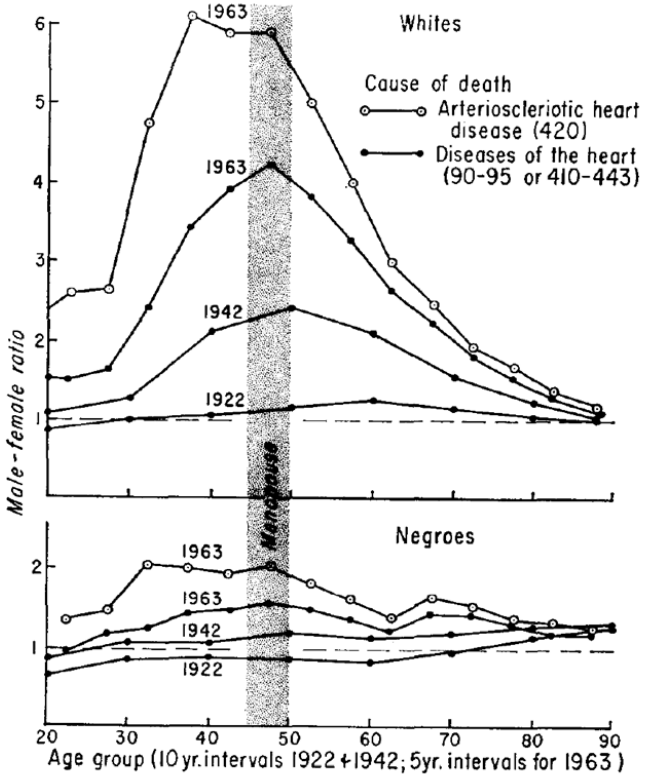


FIG. 1. Ratio of male to female death rates, United States. The dashed line marking a ratio of *one* represents the female death rates, which constitute the baseline to which the males are compared [1, 2].

Tracey RE, J Chron Dis 1966

Early studies quantifying risks

TABLE 2.—*Prevalence of Atherosclerotic Disease in Castrate and Noncastrate (Control) Women*

Group	No.	AP	MI	PVD	Total Definite Atherosclerotic Dis.	QAP	Total
Castrate	102	15	1	3	19	3	22
Control	112	4	1	0	5	3	8
Statistical significance		$0.01<P<0.025$			$P<0.005$		$0.005<P<0.01$

AP indicates angina pectoris; *MI*, myocardial infarction; *PVD*, peripheral vascular disease; *QAP*, questionable angina pectoris.

Robinson et al. 83/909

	D+	D−	
Ca	16	86	102
Co	5	107	112

$OR = \frac{16 \cdot 107}{86 \cdot 5} = 4$

Table 4. Incidence of Coronary Heart Disease by Age, Menopausal Status, and Type of Menopause. Framingham Study: 20-Year Follow-up*

Age at Examination, Menopausal Status	Person-Years at Risk	New CHD† N	New CHD† Rate per 1000 per Year	P‡
Less than 40 *yrs*				
Premenopausal	4718	0	0.0	
Natural menopause	36	0	0.0	
Surgical menopause	406	0	0.0	
40 to 44 *yrs*				
Premenopausal	4922	1	0.2	
Natural menopause	288	0	0.0	1.000
Surgical menopause	1088	5	4.6	0.001
45 to 49 *yrs*				
Premenopausal	4492	5	1.1	
Natural menopause	1726	6	3.5	0.083
Surgical menopause	2026	5	2.5	0.302
50 to 54 *yrs*				
Premenopausal	1382	5	3.6	
Natural menopause	4844	21	4.3	1.000
Surgical menopause	2618	11	4.2	1.000

* Total rates not computed because the age-specific ratios differ more than would be expected by chance. Persons with menopause other than surgical or natural are omitted from this table.

† Coronary heart disease (CHD), is the occurrence of angina pectoris, myocardial infarction, coronary insufficiency, or coronary heart disease death in women free of cardiovascular or rheumatic heart disease.

‡ Probability that the rates for premenopausal and postmenopausal women of the specified type are the same.

Kannel et al. • Menopause and Cardiovascular Disease 449

Robinson RW, Lancet 1959

Kannel WB, Ann Intern Med 1976

Age at menopause and CVD mortality

	Hazard ratio (95% CI)
Crude, adjusted only for biological age	0·982 (0·968–0·996)
Adjusted for all variables simultaneously	0·983 (0·975–0·998)
Adjusted for single variables	
Year of birth	0·982 (0·968–0·996)
Natural menopause	0·981 (0·966–0·996)
Oral contraceptive use	0·983 (0·969–0·998)
Parity/age at first delivery	0·983 (0·969–0·998)
Body-mass index ⩾30 kg/m²	0·982 (0·968–0·997)
Upper-body fat distribution	0·982 (0·969–0·996)
Smoking	0·985 (0·971–0·999)
Hypertension	0·982 (0·968–0·996)
Diabetes	0·982 (0·968–0·996)
Previous cardiovascular disease	0·984 (0·969–0·998)

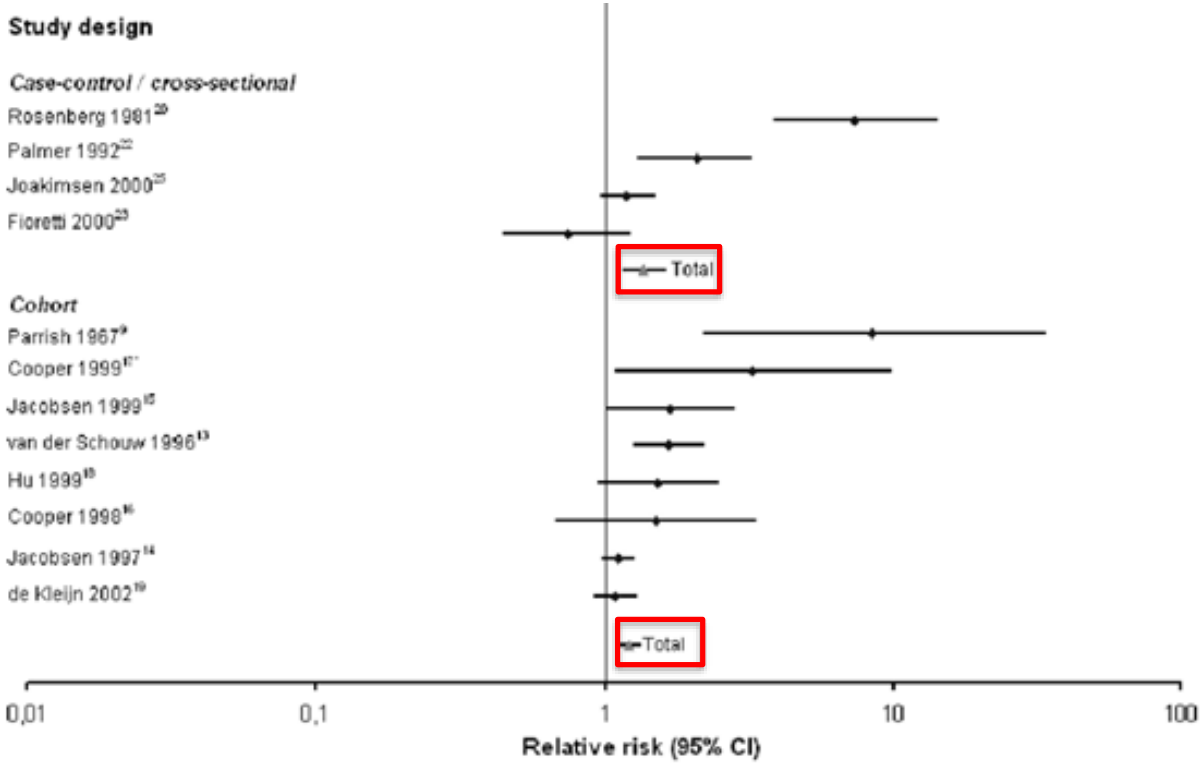
Table 3: **Hazard ratio of age at menopause and cardiovascular mortality adjusted for potential confounders**

Subgroup	n	Hazard ratio (95% CI)
Type of menopause		
Natural	9861	0·985 (0·967–1·003)
Hysterectomy	791	1·010 (0·941–1·084)
Oophorectomy	887	0·940 (0·901–0·981)
Radiation/type of surgery unknown	576	0·979 (0·930–1·031)
Smoking status		
Non-smoker	7220	0·976 (0·957–0·997)
Current smoker	2510	1·007 (0·978–1·037)
Unknown	2385	0·985 (0·957–1·014)

Table 4: **Relation of age at menopause with cardiovascular mortality for subgroups of type of menopause and smoking**

van der Schouw YT, Lancet 1996

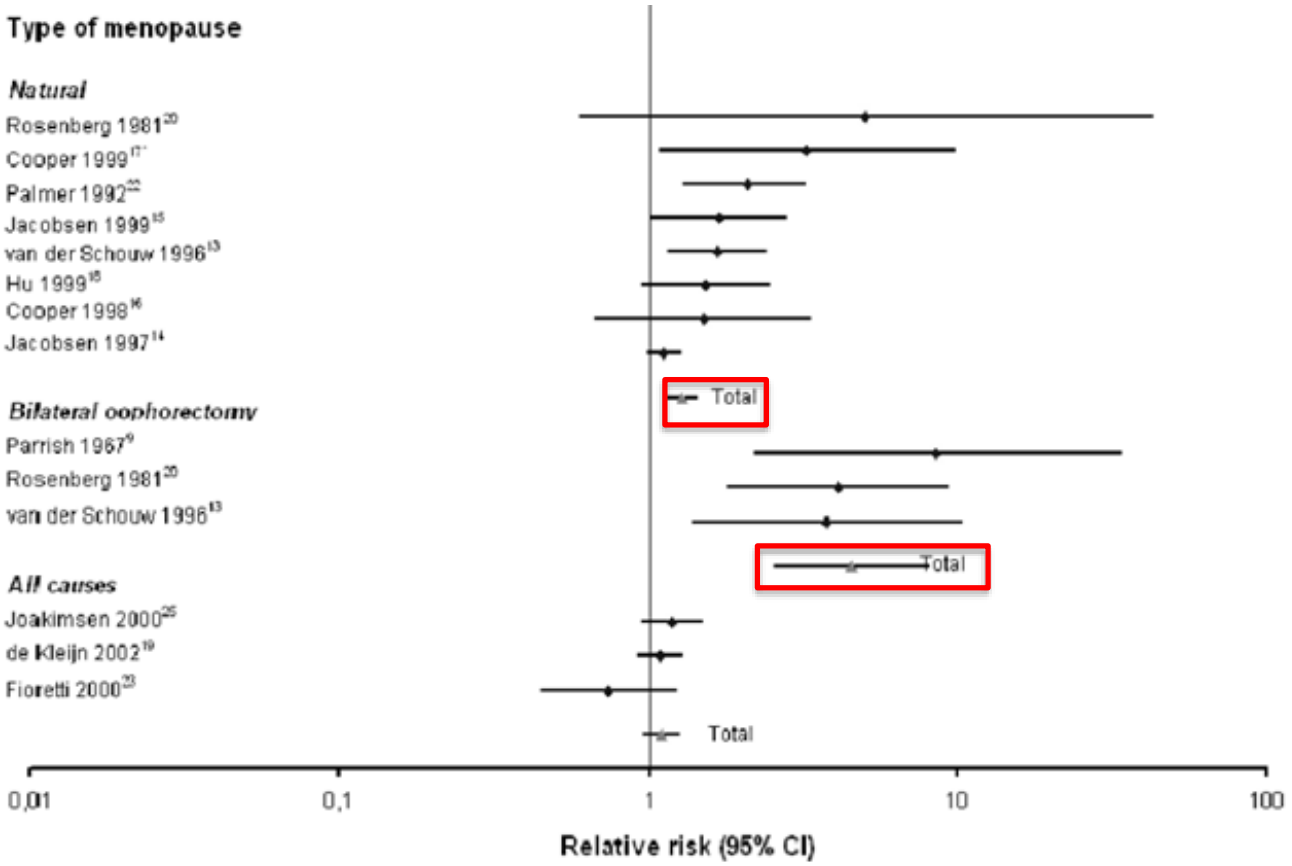
Meta-analyses – Menopause and CVD risk



Early menopause and cardiovascular disease risk, stratification by study design. Menopausal age category including 50 years as the reference.

Atsma F, Menopause 2006

Meta-analyses – Menopause and CVD risk



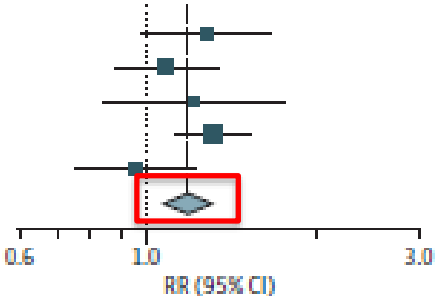
Early menopause and cardiovascular disease risk, stratification on type of menopause. Menopausal age category including 50 years as the reference.

Atsma F, Menopause 2006

Meta-analyses – Menopause and CVD risk

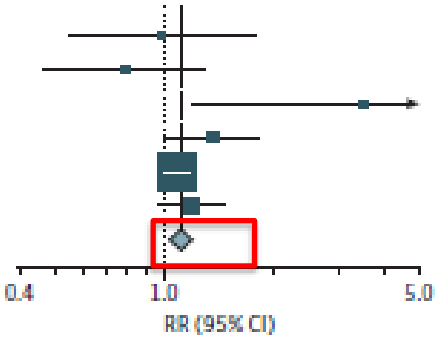
B Cardiovascular disease mortality risk

Source	Reference Comparison Age, y	Participants, No.	RR (95% CI)
Hong et al,[24] 2007	45–49	2658	1.28 (0.98-1.67)
Cui et al,[29] 2006	≥51	37 965	1.08 (0.88-1.34)
Li et al,[25] 2013	50–54	11 212	1.22 (0.84-1.77)
Ossewarde et al,[27] 2005	50–54	12 134	1.32 (1.13-1.54)
Tom et al,[28] 2012	50–54	1684	0.96 (0.75-1.23)
Overall			1.19 (1.08-1.31)



C Coronary heart disease mortality risk

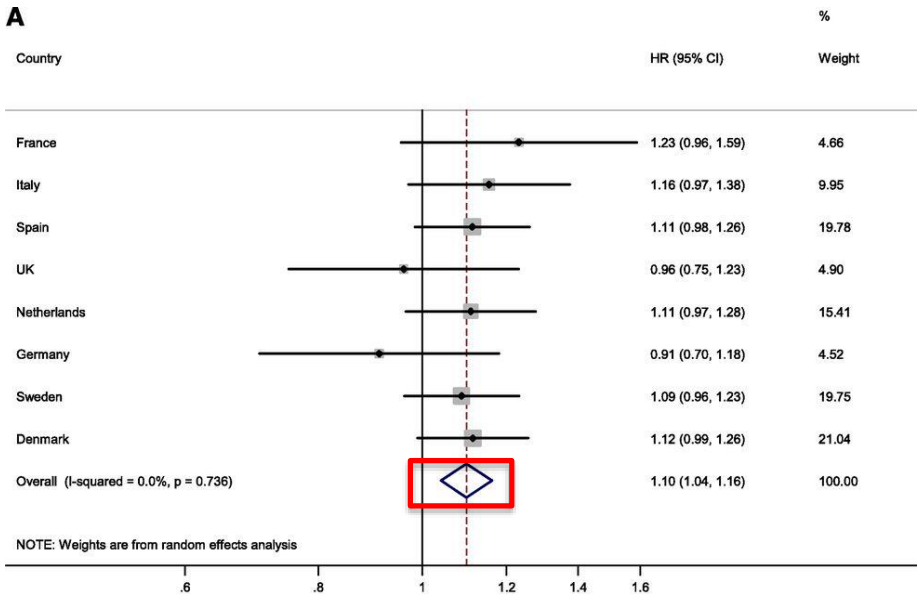
Source	Reference Comparison Age, y	Participants, No.	RR (95% CI)
Cooper et al,[16] 1998	≥50	3191	0.98 (0.55-1.77)
Cui et al,[29] 2006	≥51	37 965	0.78 (0.47-1.29)
Hong et al,[24] 2007	45–49	2658	3.52 (1.19-10.43)
Jacobsen et al,[7] 1999	49–51	6182	1.35 (1.00-1.82)
Mondul et al,[26] 2005	50–54	68 154	1.09 (1.00-1.18)
Ossewarde et al,[27] 2005	50–54	12 134	1.19 (0.97-1.47)
Overall			1.11 (1.03-1.20)



Early menopause and cardiovascular and coronary heart disease mortality.

Muka T, Jama Cardiol 2016

Early menopause and Risk of Type 2 Diabetes



Country-specific HRs of type 2 diabetes per SD decrease in menopausal

Brand JS, Diabetologia 2013

Smoking accelerates menopause

TABLE 3. Age-adjusted Rate Ratios for Occurrence of Menopause According to Duration of Smoking

Duration of Smoking (yrs)	All Smokers RR (95% CI)	Current Smokers RR (95% CI)	Former Smokers RR (95% CI)
0*	1.0	1.0	1.0
1–4	1.14 (0.92–1.40)	1.30 (0.85–2.00)	1.10 (0.87–1.39)
5–10	1.04 (0.89–1.20)	0.93 (0.61–1.43)	1.05 (0.90–1.23)
10–15	1.04 (0.92–1.18)	1.34 (1.01–1.77)	0.99 (0.81–1.13)
15–20	1.09 (0.97–1.23)	1.32 (1.07–1.63)	1.02 (0.89–1.17)
20–25	1.04 (0.93–1.15)	1.29 (1.10–1.52)	0.89 (0.78–1.03)
>25	1.30 (1.22–1.39)	1.48 (1.38–1.59)	0.79 (0.69–0.91)

*Reference category.

Duration of smoking and risk of menopause

van Asselt KM, Epidemiology 2004

Menopause and CVD
Direction of relationship

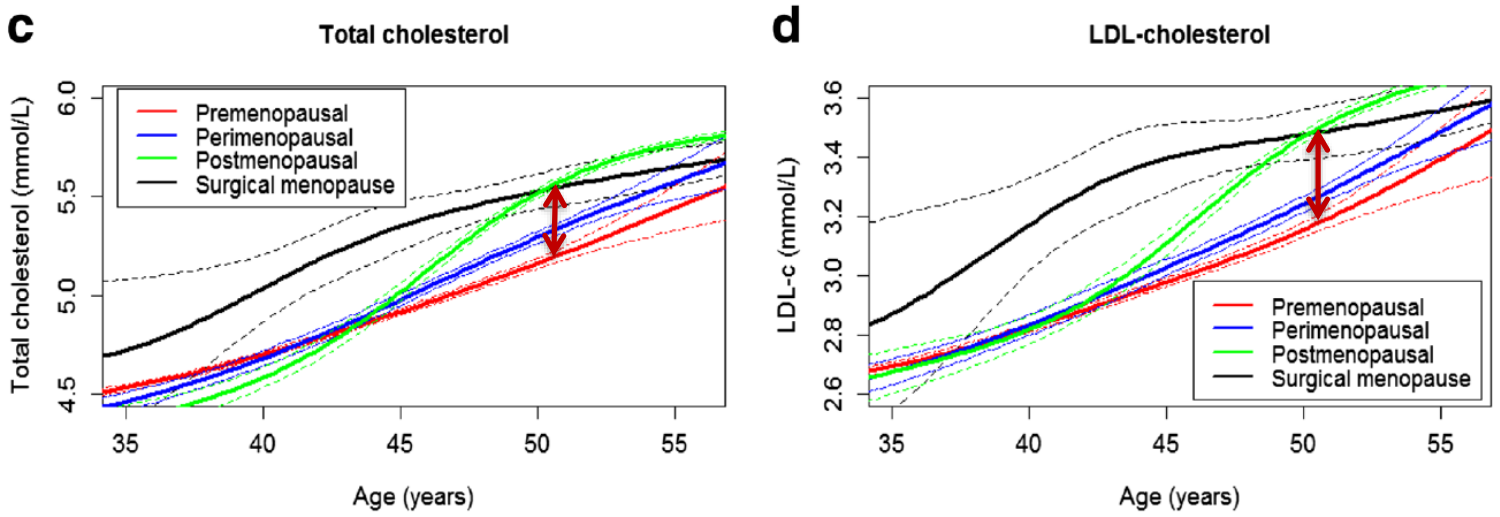
Table 3. Effect of Premenopausal Increasing or Decreasing Cholesterol Level, Relative Weight, and Blood Pressure

Subgroup	n	Crude Change in Age at Menopause (yrs)	95% CI	Adjusted for Smoking Change in Age at Menopause (yrs)	95% CI
Cholesterol					
Increasing cholesterol level	514	−2.48 yrs per 20 mg/dl* increase	−3.88 to −1.08	−2.60 yrs per 20 mg/dl increase	−4.06 to −1.14
Decreasing cholesterol level	94	3.44 yrs per 20 mg/dl* decrease	−0.14 to 7.02	4.16 yrs per 20 mg/dl decrease	0.08 to 8.24
Relative weight					
Increasing relative weight	274	−6.60 yrs per 5% increase	−11.25 to −1.90	−7.15 yrs per 5% decrease	−12.00 to −2.33
Decreasing relative weight	90	−3.36 yrs per 5% decrease	−6.10 to −0.60	−3.54 yrs per 5% increase	−6.20 to −0.88
Systolic blood pressure					
Increase in systolic blood pressure	273	−3.00 yrs per 10 mm Hg increase	−5.06 to −0.96	−3.45 yrs per 10 mm Hg increase	−5.42 to −1.49
Decrease in systolic blood pressure	135	1.74 yrs per 10 mm Hg decrease	0.19 to 3.30	1.53 yrs per 10 mm Hg decrease	−0.00 to 3.06
Diastolic blood pressure					
Increase in diastolic blood pressure	229	−7.01 yrs per 10 mm Hg increase	−10.49 to −3.54	−7.38 yrs per 10 mm Hg increase	−10.78 to −3.98
Decrease in diastolic blood pressure	117	2.98 yrs per 10 mm Hg decrease	−0.11 to 6.06	2.48 yrs per 10 mm Hg decrease	−0.53 to 5.48

*20 mg/dl = 0.5 mmol/l.
CI = confidence interval.

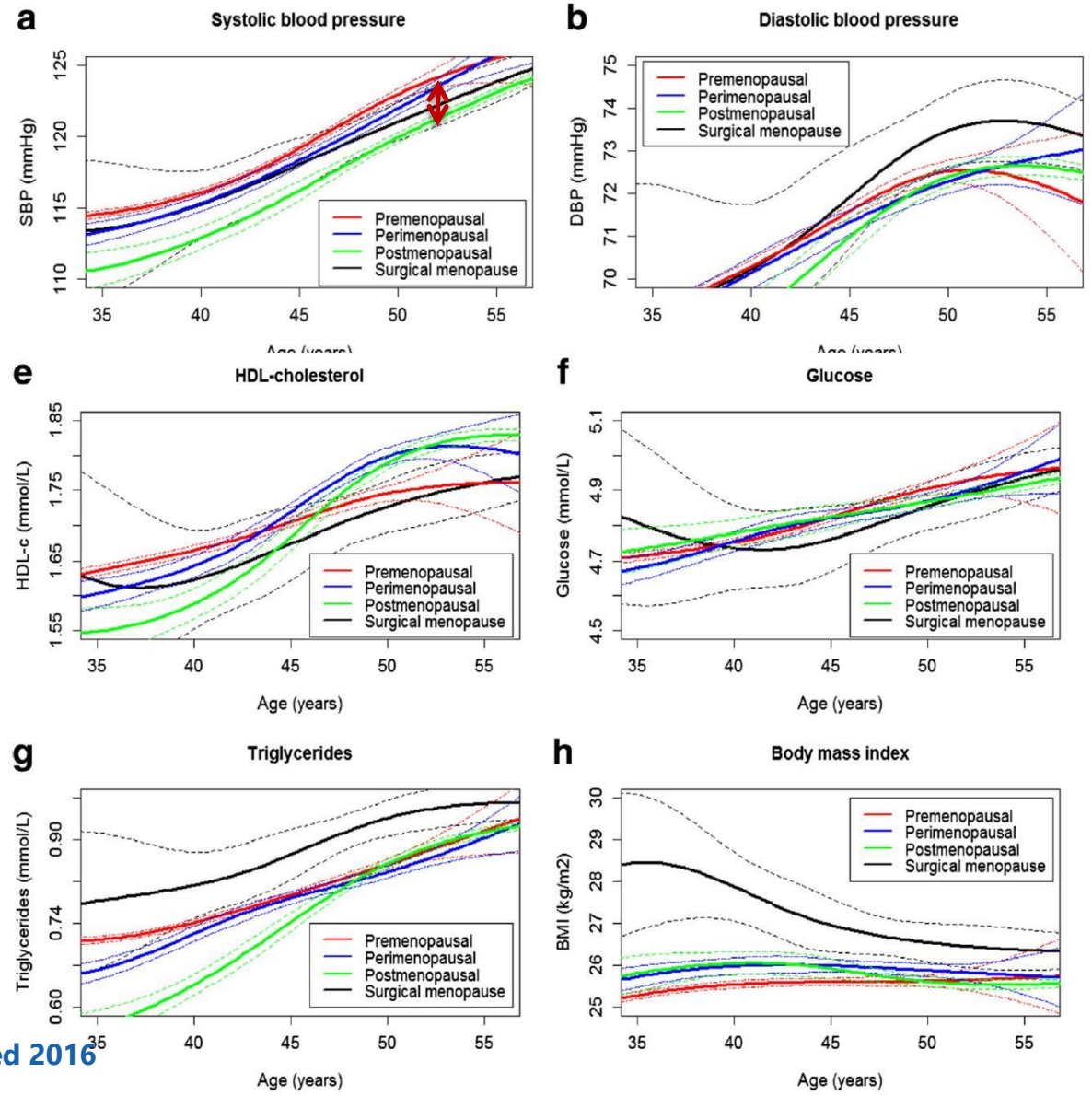
Kok HS, J Am Coll Cardiol 2006

Mechanisms – classical risk factors



De Kat AC, BMC Med 2016

Mechanisms – classical risk factors



De Kat AC, BMC Med 2016

Mechanisms – Estrogens?
Incident Cardiovascular events

TABLE V Age adjusted mean hormone concentrations by 19 year mortality and relative risk (95% confidence interval) for ischaemic heart disease in women from Rancho Bernardo

	Died from ischaemic heart disease(n=93)	Alive or died from causes other than ischaemic heart (n=558)disease	P value *	Relative risk (95% confidence interval)
Androstenedione (nmol/l)	2.08	2.12	0.76	1.00 (0.99 to 1.01)
Testosterone (nmol/l)	9.26	9.29	0.98	1.01 (0.99 to 1.03)
Oestrone (pmol/l)	135.4	144.5	0.73	0.32 (0.03 to 2.97)
Oestradiol (pmol/l)	54.3	57.0	0.69	1.06 (0.89 to 1.19)
Bioavailable oestradiol (pmol/l)	28.1	33.6	0.44	0.94 (0.84 to 1.06)
Bioavailable testosterone (nmol/l)	39.8	39.0	0.89	1.34 (0.58 to 1.83)

↵*For comparison of hormone concentrations.

TABLE IV Age adjusted mean hormone concentration by 19 year mortality and relative risk (95% confidence interval) for cardiovascular disease in women from Rancho Bernardo

Hormone	Died from cardiovascular disease(n=176)	Alive, or died from causes other than cardiovascular disease(n=475)	P value *	Relative risk (95% confidence interval)
Androstenedione (nmol/l)	2.14	2.11	0.74	1.00 (0.99 to 1.01)
Testosterone (nmol/l)	8.81	9.43	0.53	1.00 (0.99 to 1.03)
Oestrone (pmol/l)	154.4	139.8	0.49	1.70 (0.37 to 2.98)
Oestradiol (pmol/l)	56.2	56.8	0.92	1.27 (0.79 to 2.03)
Bioavailable oestradiol (pmol/l)	32.0	33.1	0.85	0.98 (0.94 to 1.02)
Bioavailable testosterone (nmol/l)	37.8	39.5	0.72	0.98 (0.95 to 1.02)

↵*For comparison of hormone concentrations.

Urinary E2 excretion and risk of ischaemic mortality, Rancho Bernardo

Urinary E2 excretion and risk of cardiovascular mortality, Rancho Bernardo

Barret-Connor E, BMJ 1995

Mechanisms – estrogens
Incident Cardiovascular events

TABLE 4. Multivariate OR of Cardiovascular Events by Quartile of Hormone Level in HT Nonusers and Current Users

Quartiles (Q) of Hormone	HT Nonusers			Quartiles (Q) of Hormone	Current HT Users		
	Model 1*	Model 2†	Model 3‡		Model 1*	Model 2†	Model 3‡
SHBG, nmol/L							
Q1 (<32.4)	2.45 (1.14–5.23)	2.25 (1.03–4.91)	1.18 (0.46–2.99)	Q1 (<64.5)	0.89 (0.37–2.11)	0.99 (0.40–2.44)	0.66 (0.23–1.90)
Q2 (32.4–<48.5)	1.17 (0.52–2.64)	1.12 (0.48–2.61)	0.73 (0.27–1.96)	Q2 (64.5–<120)	1.23 (0.52–2.91)	1.40 (0.56–3.49)	0.99 (0.36–2.73)
Q3 (48.5–<69.5)	1.42 (0.64–3.17)	1.27 (0.56–2.91)	1.42 (0.57–3.54)	Q3 (120–<171)	0.71 (0.30–1.72)	0.73 (0.29–1.80)	0.56 (0.21–1.49)
Q4 (≥69.5)	1.00 referent	1.00	1.00	Q4 (≥171)	1.00	1.00	1.00
P for trend	0.03	0.05	0.94		0.90	0.70	0.69
Testosterone, ng/dL							
Q1 (<14)	1.00 referent	1.00	1.00	Q1 (<13)	1.00	1.00	1.00
Q2 (14–<18)	1.33 (0.62–2.83)	1.22 (0.56–2.66)	1.40 (0.58–3.36)	Q2 (13–<18)	0.41 (0.16–1.07)	0.38 (0.14–1.01)	0.23 (0.08–0.71)
Q3 (18–<26)	1.22 (0.57–2.63)	1.15 (0.52–2.52)	0.99 (0.40–2.42)	Q3 (18–<24)	0.65 (0.27–1.55)	0.61 (0.25–1.49)	0.48 (0.18–1.28)
Q4 (≥26)	1.58 (0.75–3.34)	1.39 (0.64–3.00)	1.16 (0.48–2.78)	Q4 (≥24)	1.24 (0.55–2.80)	1.05 (0.44–2.47)	0.74 (0.30–1.87)
P for trend	0.28	0.46	0.92		0.44	0.73	0.87
FAI							
Q1 (<0.008)	1.00 referent	1.00	1.00	Q1 (<0.003)	1.00 referent	1.00	1.00
Q2 (0.008–<0.013)	0.68 (0.29–1.59)	0.59 (0.25–1.44)	0.58 (0.22–1.54)	Q2 (0.003–<0.005)	0.69 (0.29–1.65)	0.68 (0.28–1.69)	0.65 (0.25–1.71)
Q3 (0.01–<0.026)	1.82 (0.86–3.82)	1.68 (0.78–3.63)	1.34 (0.53–3.41)	Q3 (0.005–<0.009)	0.77 (0.32–1.88)	0.75 (0.29–1.93)	0.66 (0.24–1.83)
Q4 (≥0.026)	1.94 (0.91–4.14)	1.80 (0.82–3.93)	0.99 (0.37–2.62)	Q4 (≥0.009)	0.97 (0.42–2.26)	0.94 (0.39–2.26)	0.59 (0.21–1.68)
P for trend	0.02	0.03	0.69		0.95	1.00	0.37
Estradiol, pg/mL							
Q1 (<8)	1.09 (0.50–2.35)	1.10 (0.49–2.44)	1.95 (0.72–5.28)	Q1 (<14)	0.83 (0.33–2.10)	0.96 (0.36–2.56)	0.95 (0.32–2.80)
Q2 (8–<10)	0.56 (0.26–1.22)	0.63 (0.28–1.40)	0.95 (0.36–2.54)	Q2 (14–<25)	1.56 (0.66–3.71)	1.63 (0.67–3.94)	2.01 (0.78–5.19)
Q3 (10–<14)	0.81 (0.39–1.67)	0.85 (0.40–1.79)	0.73 (0.31–1.76)	Q3 (25–<45)	1.54 (0.66–3.60)	1.66 (0.69–3.98)	2.13 (0.81–5.61)
Q4 (≥14)	1.00 referent	1.00	1.00	Q4 (≥45)	1.00 referent	1.00	1.00
P for trend	0.89	0.96	0.15		0.81	0.94	0.89

Rexrode KM, Circulation 2003

Mechanisms – estrogens
Incident schemic Arterial Disease

	Ischemic Arterial Disease*						
		Age Adjusted			Adjusted‡		
SSH Level	No. of Events	HR	95% CI	P†	HR	95% CI	P†
Total estradiol, pg/mL							
For 1 SD log	106	1.39	(1.13–1.72)	<0.01	1.42	(1.12–1.79)	<0.01
Q1 <3.51	19	1	[reference]	0.02	1	[reference]	<0.05
Q2 [3.51–5.27]	20	1.33	(0.66–2.66)		1.46	(0.70–3.09)	
Q3 [5.27–7.83]	31	1.71	(0.91–3.23)		1.84	(0.90–3.76)	
Q4 ≥7.83	36	1.99	(1.06–3.73)		1.99	(0.96–4.10)	
Bioavailable estradiol, pg/mL							
For 1 SD log	106	1.38	(1.12–1.70)	<0.01	1.42	(1.12–1.78)	<0.01
Q1 <2.32	18	1	[reference]	0.02	1	[reference]	0.05
Q2 [2.32–3.56]	25	1.83	(0.92–3.63)		2.03	(0.96–4.26)	
Q3 [3.56–5.49]	26	1.73	(0.89–3.35)		1.90	(0.90–3.98)	
Q4 ≥5.49	37	2.22	(1.18–4.20)		2.19	(1.05–4.56)	
Total testosterone, ng/mL							
For 1 SD log	106	0.93	(0.76–1.14)	0.49	0.91	(0.72–1.15)	0.42
Q1 <0.23	34	1	[reference]	0.76	1	[reference]	0.33
Q2 [0.23–0.33]	21	0.71	(0.39–1.30)		0.67	(0.36–1.26)	
Q3 [0.33–0.45]	25	1.03	(0.56–1.87)		0.95	(0.49–1.85)	
Q4 ≥0.45	26	0.83	(0.47–1.47)		0.70	(0.37–1.32)	

Scarabin-Carre V, J Am Heart Assoc 2012

Mechanisms – estrogens
Incident Stroke

Table 4. OR Estimates for Stroke in Bivariate Logistic Regression Models According to Quartiles of FEI in Postmenopausal Women in a Prospective Case-Control Study of Incident Stroke From the Study of Osteoporotic Fractures[a]

	OR Estimate (95% CI)			
Covariate	Quartile 1	Quartile 2	Quartile 3	Quartile 4 (Highest)
Age only	1 [Reference]	1.46 (0.80-2.68)	1.52 (0.83-2.78)	2.31 (1.28-4.17)
Age + hypertension	1 [Reference]	1.36 (0.73-2.53)	1.51 (0.81-2.79)	2.04 (1.12-3.73)
Age + current smoking	1 [Reference]	1.43 (0.78-2.63)	1.47 (0.80-2.69)	2.29 (1.27-4.13)
Age + alcohol intake	1 [Reference]	1.44 (0.79-2.64)	1.51 (0.83-2.77)	2.28 (1.26-4.11)
Age + weight	1 [Reference]	1.48 (0.81-2.72)	1.56 (0.84-2.90)	2.41 (1.26-4.59)
Age + BMI	1 [Reference]	1.47 (0.80-2.70)	1.53 (0.82-2.86)	2.34 (1.22-4.49)
Age + waist circumference	1 [Reference]	1.39 (0.76-2.57)	1.36 (0.73-2.55)	1.90 (0.99-3.66)
Age + TG level	1 [Reference]	1.46 (0.79-2.70)	1.41 (0.76-2.63)	1.79 (0.95-3.39)
Age + TC:HDL-C ratio	1 [Reference]	1.39 (0.75-2.58)	1.33 (0.71-2.49)	1.81 (0.96-3.40)
Age + HDL-C level	1 [Reference]	1.46 (0.79-2.69)	1.43 (0.76-2.67)	2.06 (1.10-3.85)
Age + LDL-C level	1 [Reference]	1.48 (0.80-2.74)	1.53 (0.83-2.82)	2.06 (1.13-3.77)
Age + TC level	1 [Reference]	1.49 (0.81-2.75)	1.52 (0.82-2.80)	2.24 (1.23-4.08)
Age + diabetes mellitus	1 [Reference]	1.34 (0.72-2.47)	1.40 (0.76-2.59)	1.91 (1.05-3.50)
Age + CRP level	1 [Reference]	1.34 (0.73-2.48)	1.37 (0.75-2.53)	1.94 (1.05-3.59)

Abbreviations: BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; FEI, free estradiol index; HDL-C, high-density lipoprotein level; LDL-C, low-density lipoprotein cholesterol; OR, odds ratio; TC, total cholesterol; TG, triglyceride.

[a]The FEI was calculated by dividing total estradiol level (in picomoles per liter) by SHBG level (in nanomoles per liter) (to convert estradiol to picomoles per liter, multiply by 3.671; SHBG to nanomoles per liter, multiply by 8.896).

Lee JS, Arch Neurol 2010

AMH level and decline rate and Cardiovascular Risk

Table 3. Hazard Ratios for the Association of Fully Adjusted AMH Levels and AMH Decline Trajectories With the Risk of Total CVD, CHD, and Stroke

Variable	↓AMH Level HR (95% CI)	*P* Value	AMH Decline Rate HR (95% CI)	*P* Value
Total cardiovascular disease				
Only time-varying AMH level	1.21 (1.07–1.37)	<0.01		
Only time-varying decline rate			1.46 (1.14–1.87)	<0.01
Time-varying AMH level and decline rate	1.12 (0.98–1.28)	0.09	1.42 (1.09–1.86)	0.01
Coronary heart disease				
Only time-varying AMH level	1.26 (1.08–1.46)	<0.01		
Only time-varying decline rate			1.56 (1.15–2.12)	<0.01
Time-varying AMH level and decline rate	1.16 (0.98–1.37)	0.09	1.49 (1.07–2.07)	0.02
Stroke				
Only time-varying AMH level	1.03 (0.82–1.30)	0.78		
Only time-varying decline rate			1.17 (0.94–1.45)	0.16
Time-varying AMH level and decline rate	1.00 (0.78–1.25)	0.93	1.14 (0.94–1.37)	0.17

Models are adjusted for age, OC use, smoking, BMI, menopausal status, TC, DBP, $_{log}$HDL-C, HT, glucose, lipid-lowering medication, and blood pressure-lowering medication.

AMH indicates anti-Müllerian hormone; BMI, body mass index; CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; HT, hormone replacement therapy; OC, oral contraceptive; and TC, total cholesterol.

De Kat AC, Circulation 2017

Concluding

- Menopause is associated with higher cardiometabolic disease risk
- Causality is unclear
- Mechanism is unclear
  - Estrogens -> not very likely
  - Traditional risk factors: only total and LDL cholesterol are higher in postmenopausal women
- AMH may consitute a new possible mechanism

Any questions so far?

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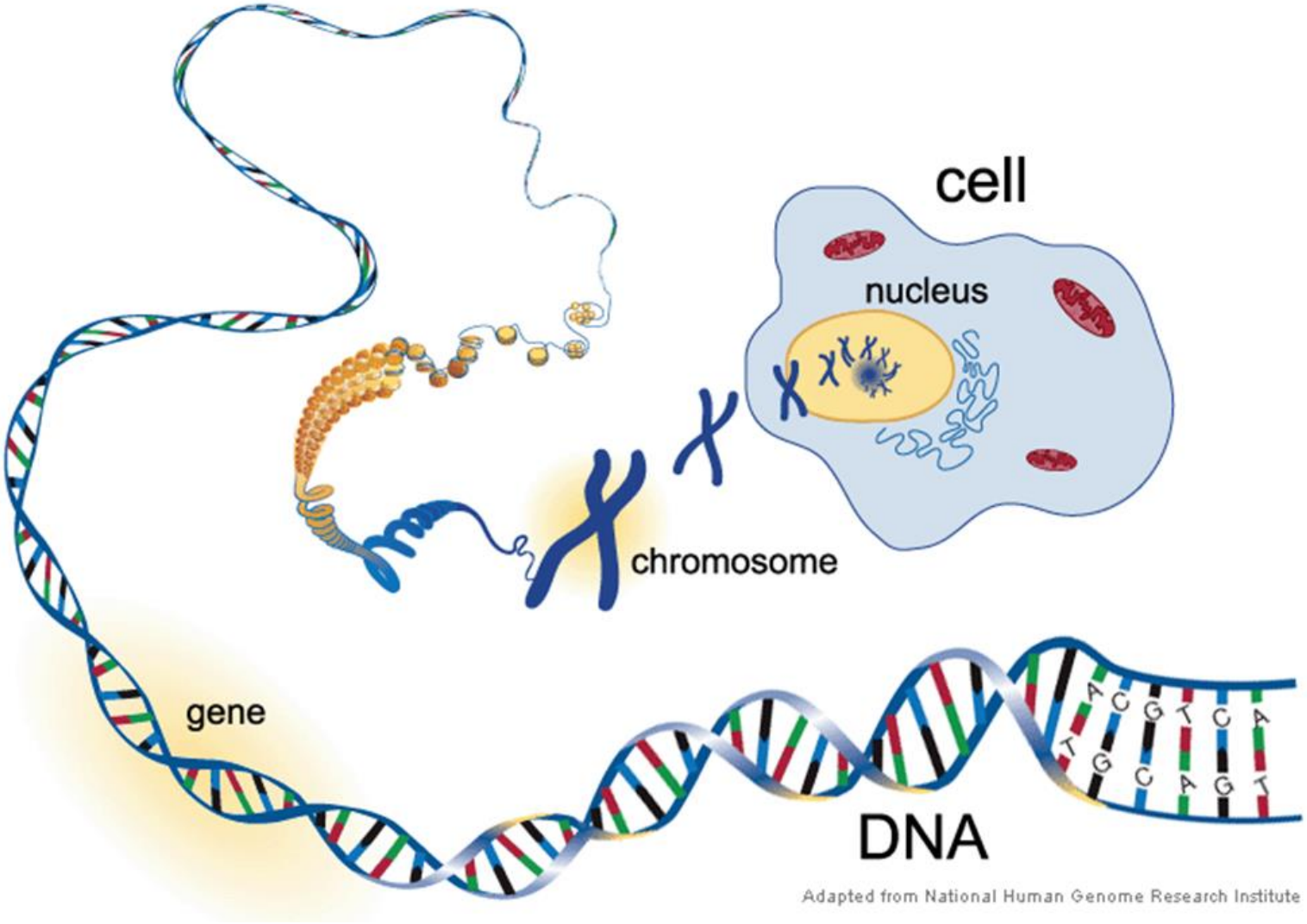
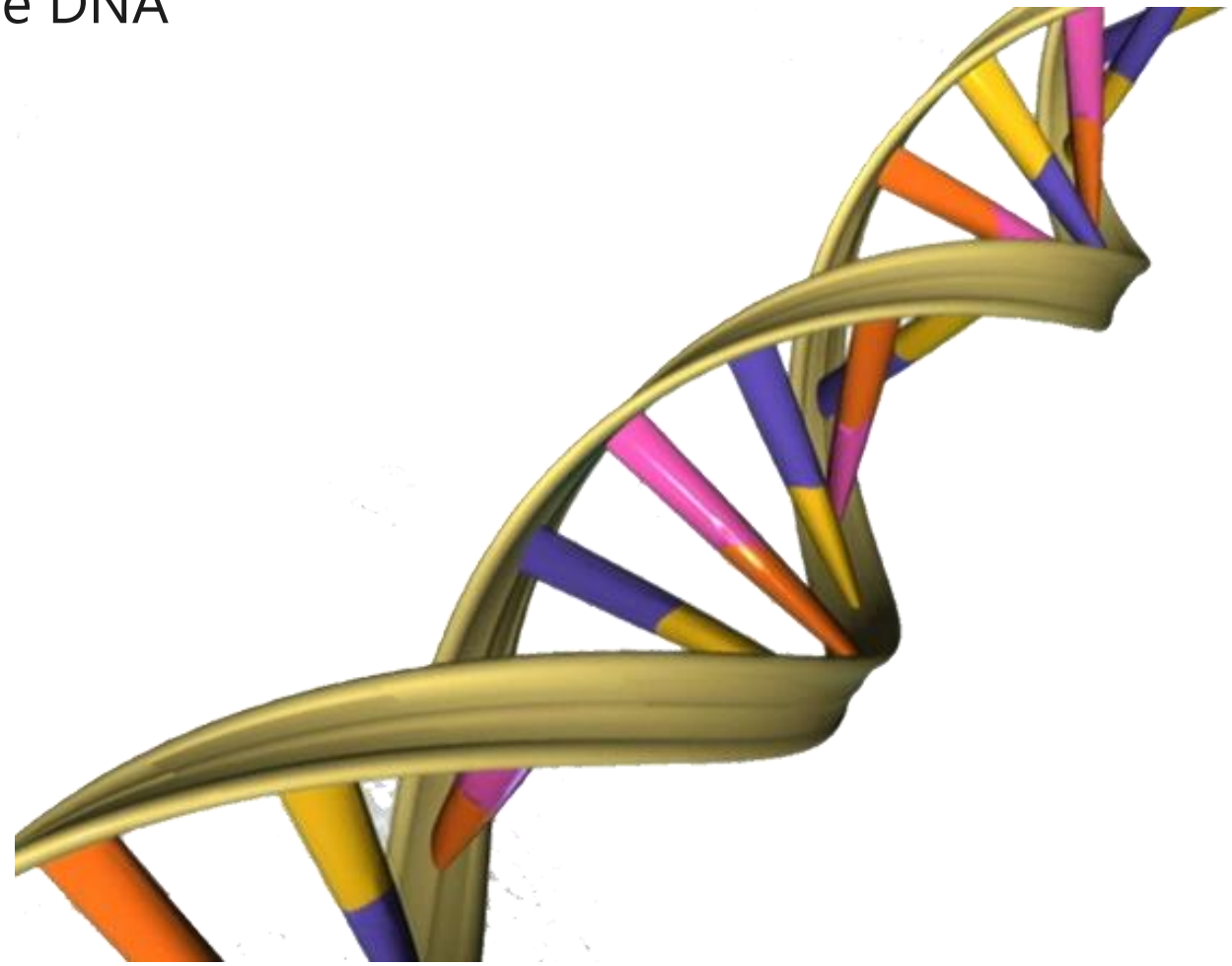
Intermezzo: some basic genetics



Watson and Crick

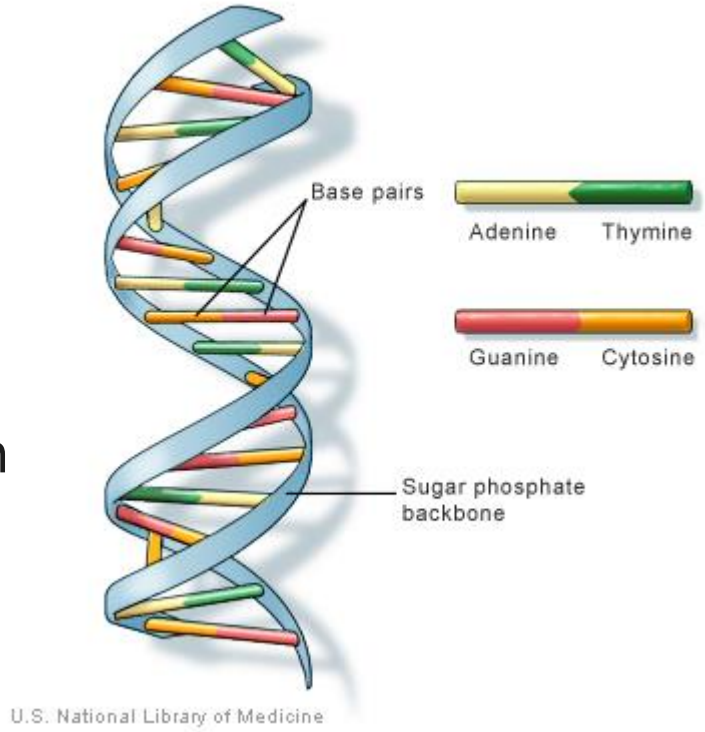
1953: Watson and Crick described double helix structure of the DNA



DNA

- All living things have DNA

- Sugar phosphate backbone
- 4 bases
  - Adenine, Thymine
  - Guanine, Cytosine
- 2 strands joined together through complementary basepairs
  - A-T
  - C-G

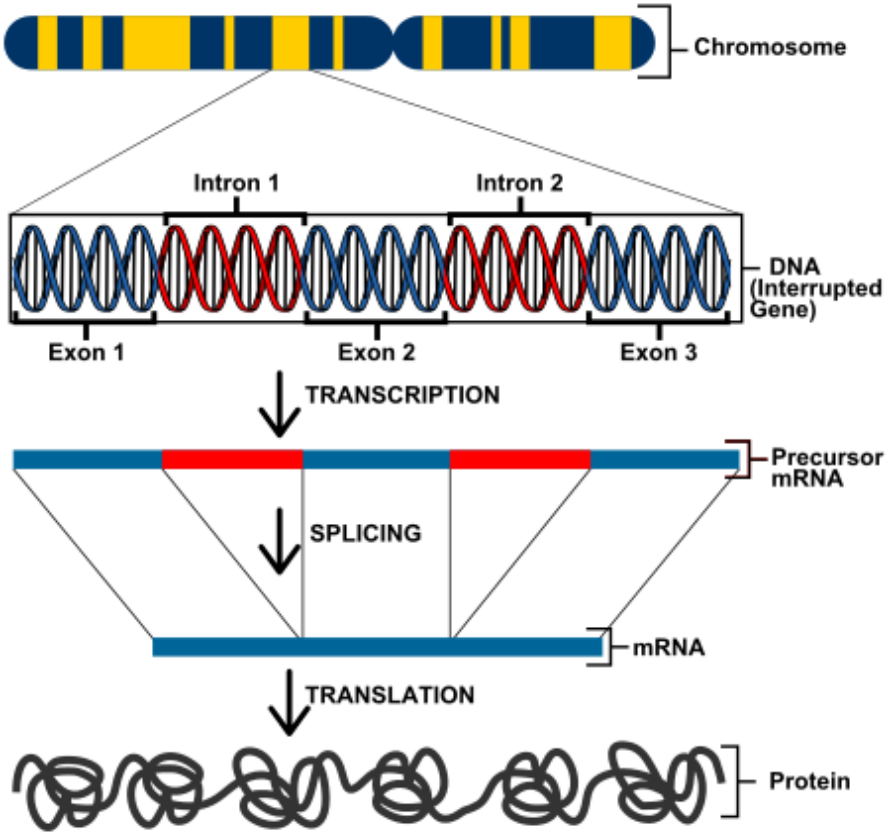


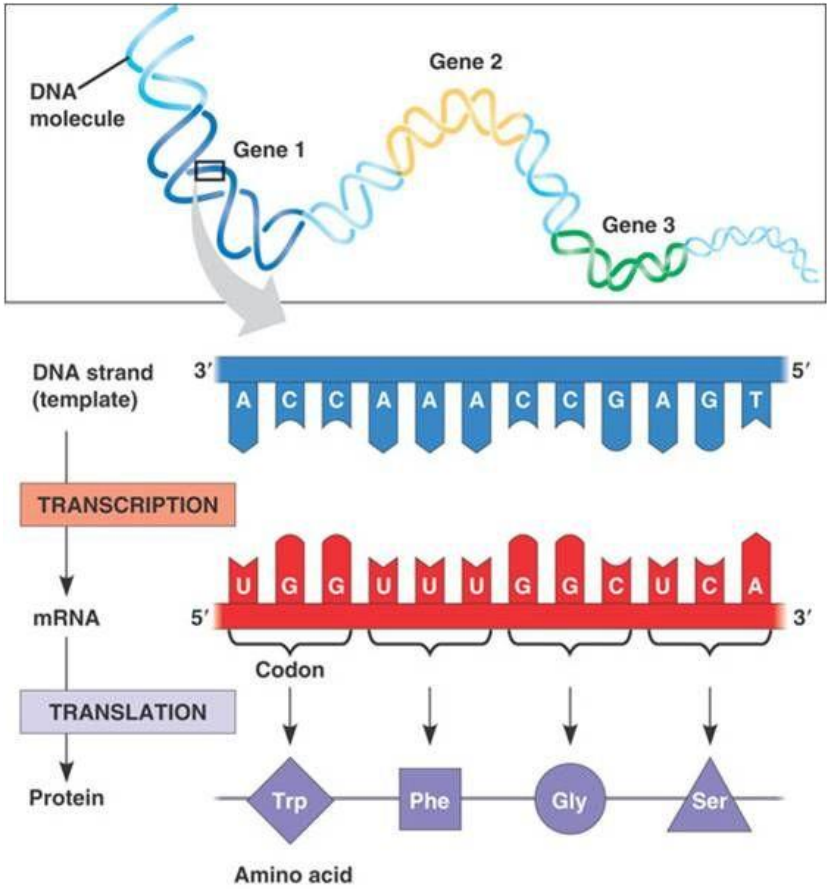
Sequence

- Order of bases make up a sequence
- Human genome:
  - 3 billion letters
  - Fill 1,000 200 page books
- >99.9% of our DNA is the same
  - 1.4M differences

  -> makes us unique

Transcription and Translation





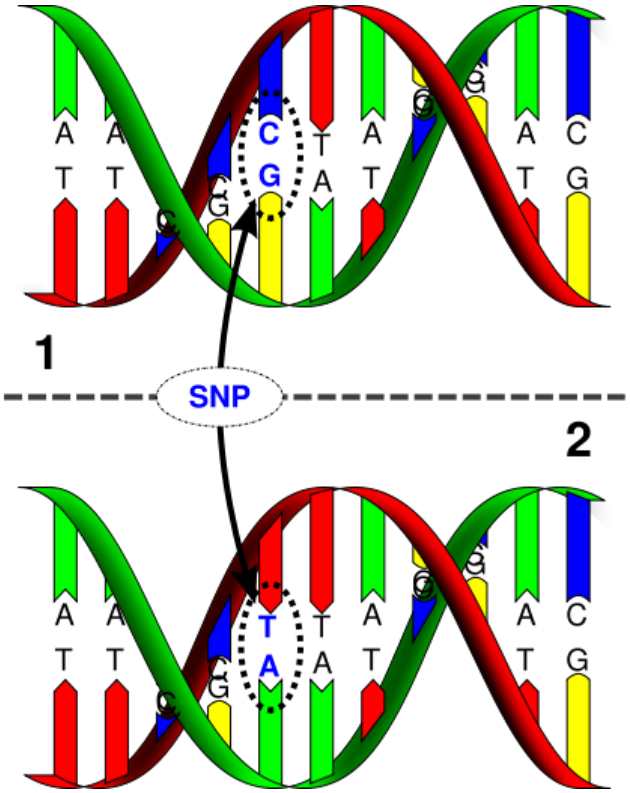
Mutations

- During DNA replication -> mutations occur
- Not all mutations lead to diseases
- Most mutations are harmless

- DNA repair

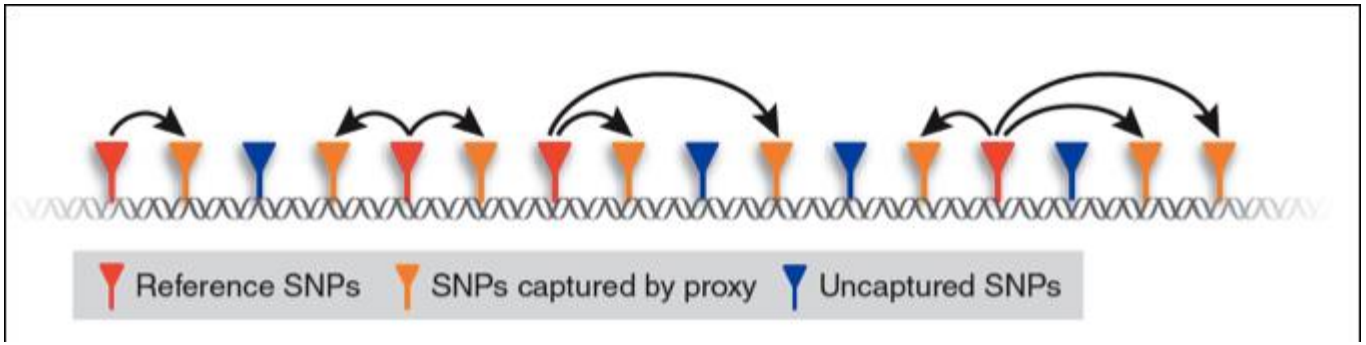
Single Nucleotide Polymorphism (SNP)

- Point mutation
- Common vs rare
- Hapmap Project:
  - To buillt genome-wide inventory of 3M human SNPs
- 1000 Genome project
  - Sequencing to identify nearly all variants



Linkage disequilibrium (LD)

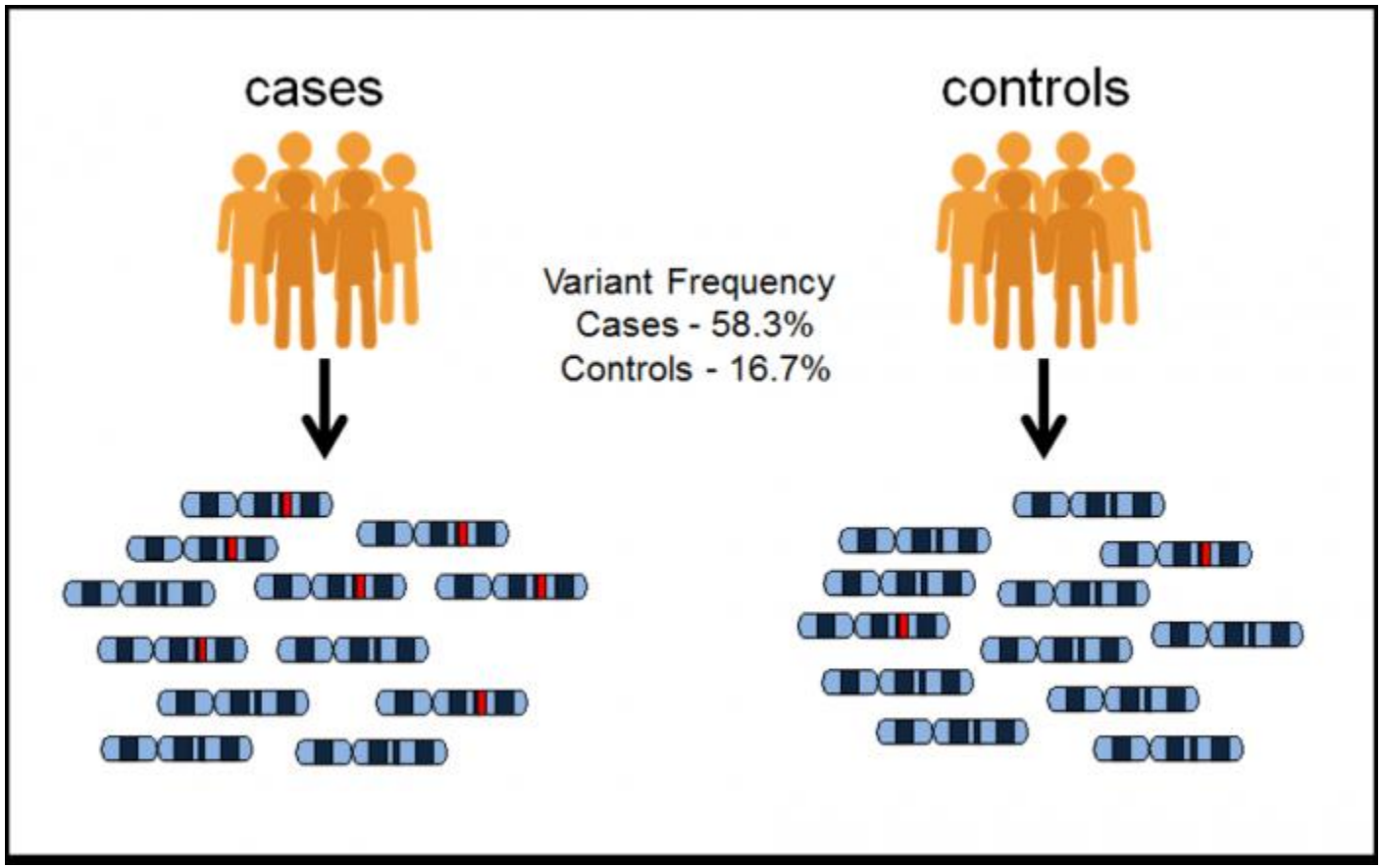
- Nearby variants on the chromosome are correlated



Why genetics?

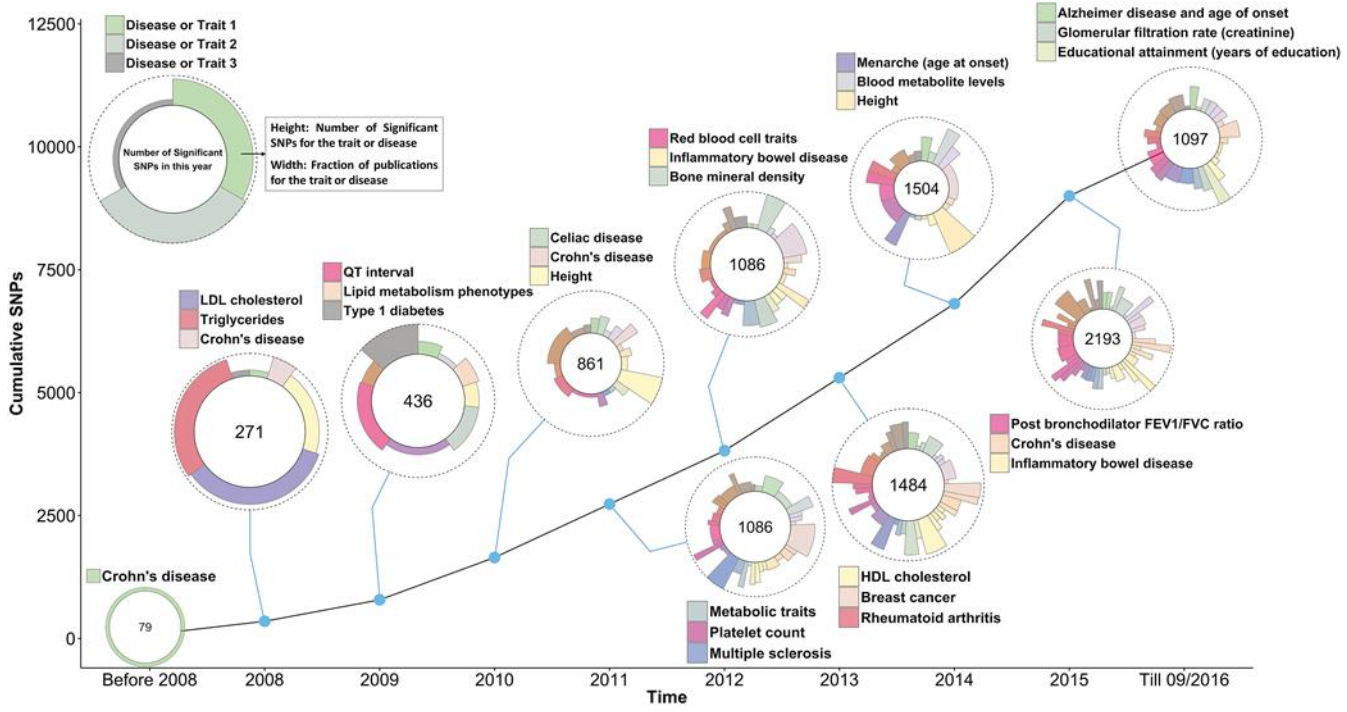
- Understanding the genetics of a disease may help understand mechanisms causing that disease
- May lead to new therapies

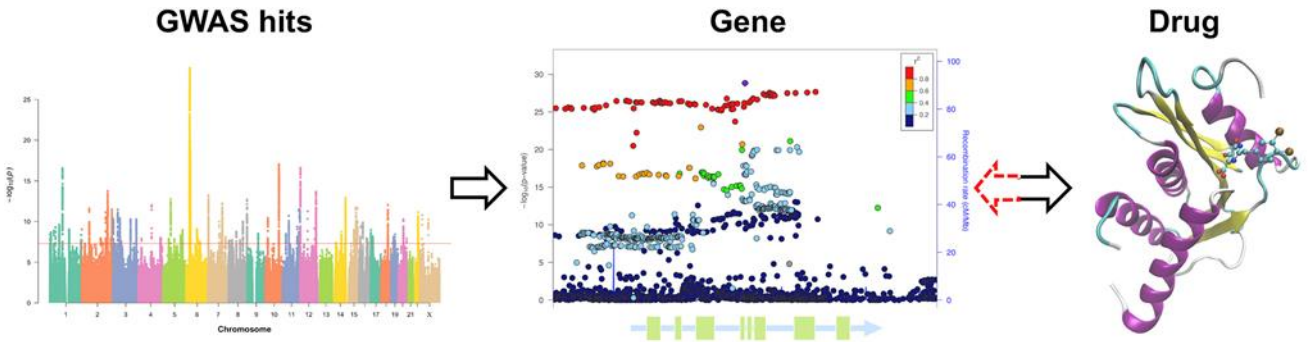
Genome-Wide association studies



GWAS

- To identify genetic variants associated with disease

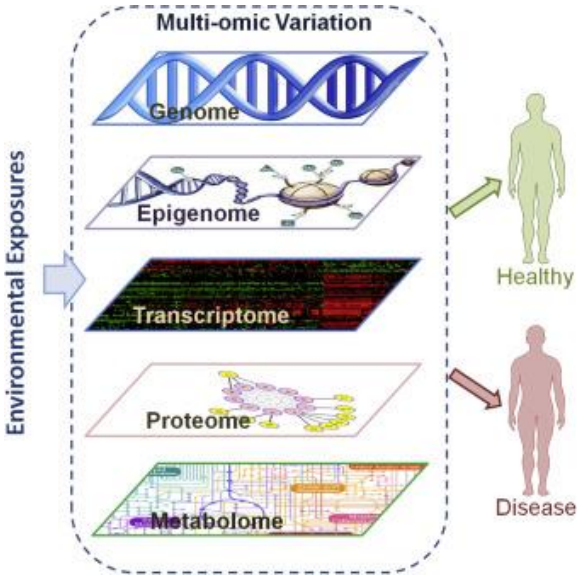


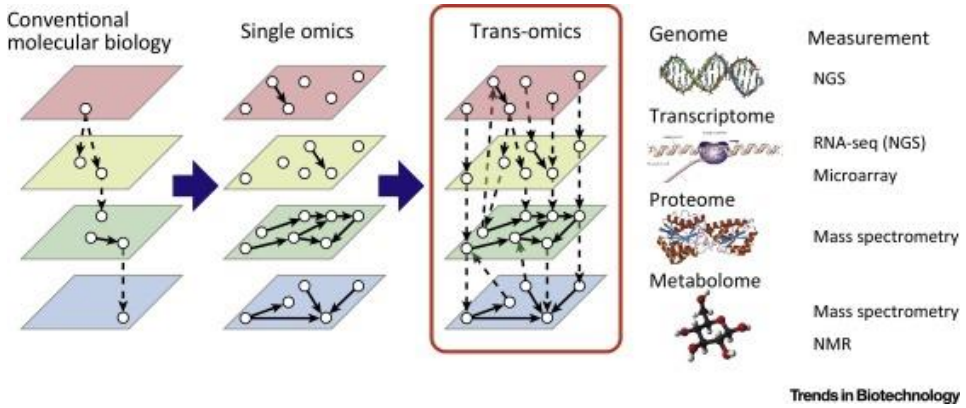


Trait	Gene with GWAS hits	Known or candidate drug
Type 2 Diabetes	*SLC30A8/KCNJ11*	ZnT-8 antagonists/Glyburide
Rheumatoid Arthritis	*PADI4/IL6R*	BB-Cl-amidine/Tocilizumab
Ankylosing Spondylitis(AS)	*TNFR1/PTGER4/TYK2*	TNF-inhibitors/NSAIDs/fostamatinib
Psoriasis(Ps)	*IL23A*	Risankizumab
Osteoporosis	*RANKL/ESR1*	Denosumab/Raloxifene and HRT
Schizophrenia	*DRD2*	Anti-psychotics
LDL cholesterol	*HMGCR*	Pravastatin
AS, Ps, Psoriatic Arthritis	*IL12B*	Ustekinumab

Other sources of information

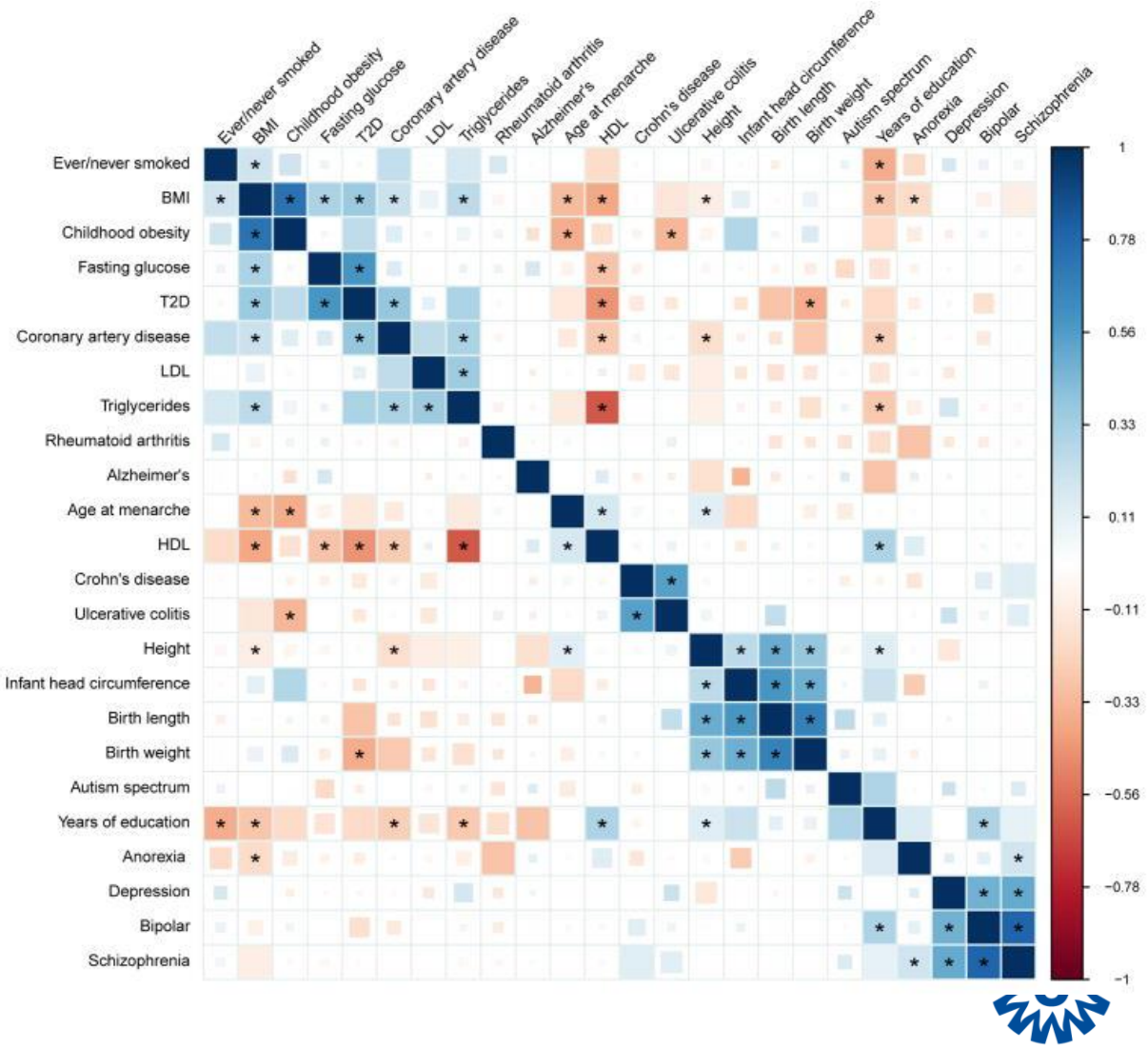
- SNPs are only one layer of variation in the genome



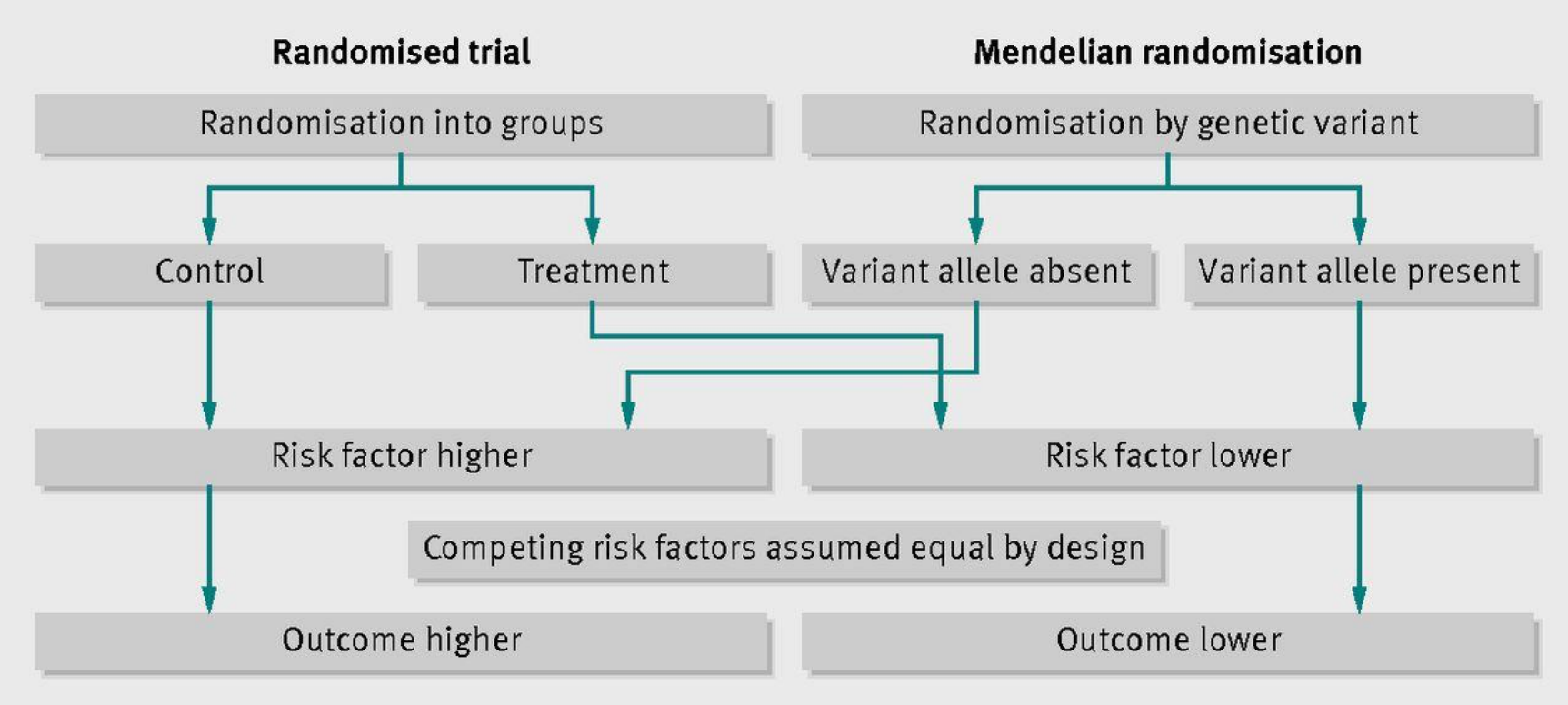


How can we use this information to understand mechanisms

- Genetic correlation between traits



Concept of Mendelian Randomization



http://www.mrbase.biocompute.org.uk/

Here you can perform your online MR study with summarized data

Burgess S, Br Med J 2012

Age at menopause

ARTICLES

nature genetics

Large-scale genomic analyses link reproductive aging to hypothalamic signaling, breast cancer susceptibility and BRCA1-mediated DNA repair

54 common SNPs and 2 rare variants associated

FR Day et al. *Nature Genetics* **volume 47**, 1294–1303 (2015)

GWAS

- GWAS menopause
  - Day FR et al. Nat Genet 2015; 47(11):1294-1303
  - 54 SNPs
- GWAS CHD
  - Nikpay M et al. Nat Genet 2015; 47(10):1121-1130
  - 46 SNPs
- GWAS T2D
  - Scott RA Diabetes 2017; DOI: 10.2337/db16-1253
  - 128 SNPs

Questions

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Assignment

- Combine different datasets to identify new mechanisms behind the association between menopause and cardiometabolic diseases

What to do?

- We do not have all data in one dataset
- A lot of data is publically available online
- Sources:
  - Genetic data: Reprogen, Diagram consortium, cardiogramplusc4d, dbgap (https://www.ncbi.nlm.nih.gov/gap)
  - Link between different sources of data: BIOS
    - https://www.bbmri.nl/omics/
  - DNA methylation (epigenetics, diabetes and obesity are there): http://202.97.205.78/diseasemeth/