



Colonocyte telomere shortening is greater with dietary red meat than white meat and is attenuated by resistant starch

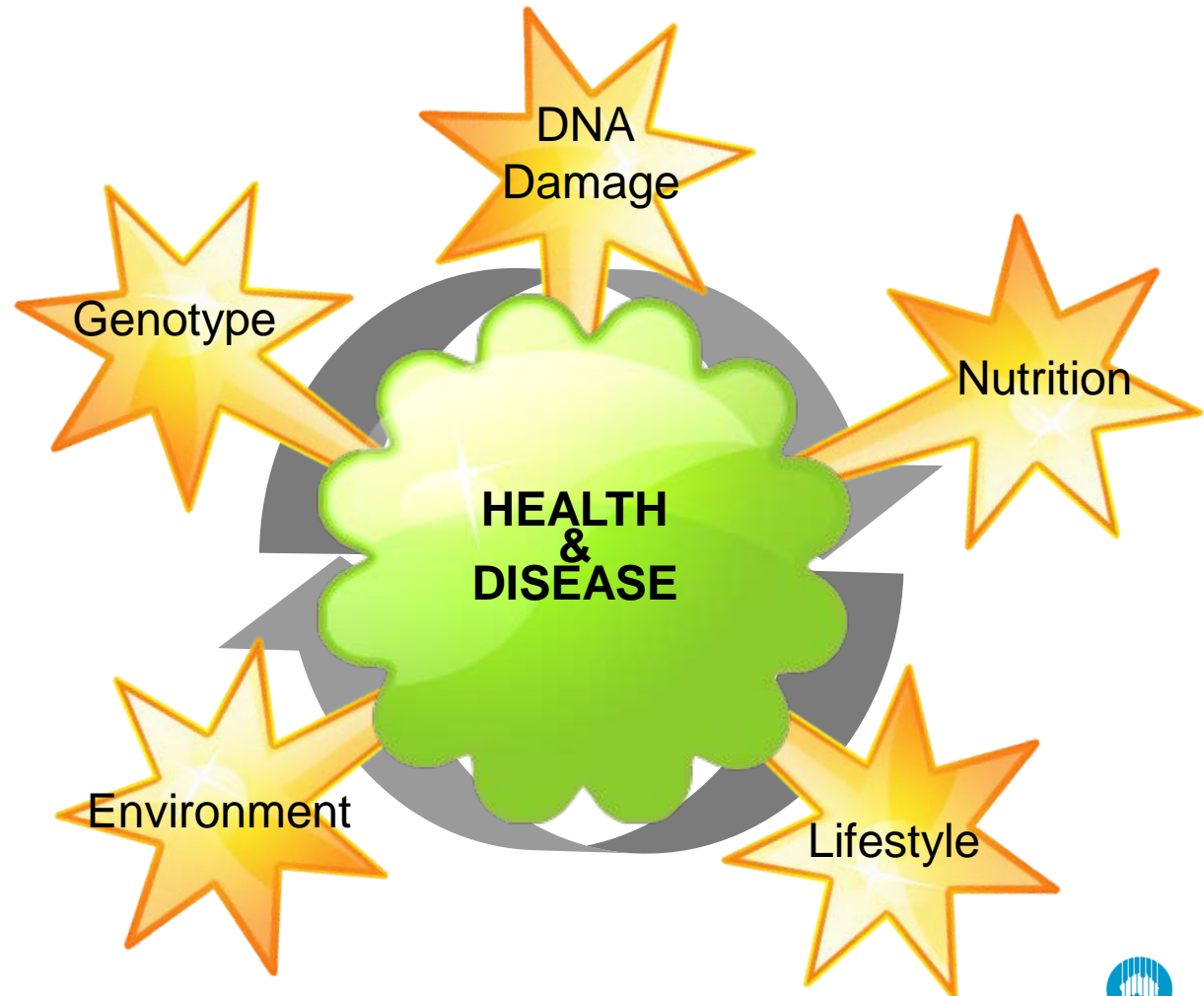
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**DNA Damage Research Group
and
CSIRO Food Futures National Research Flagship**

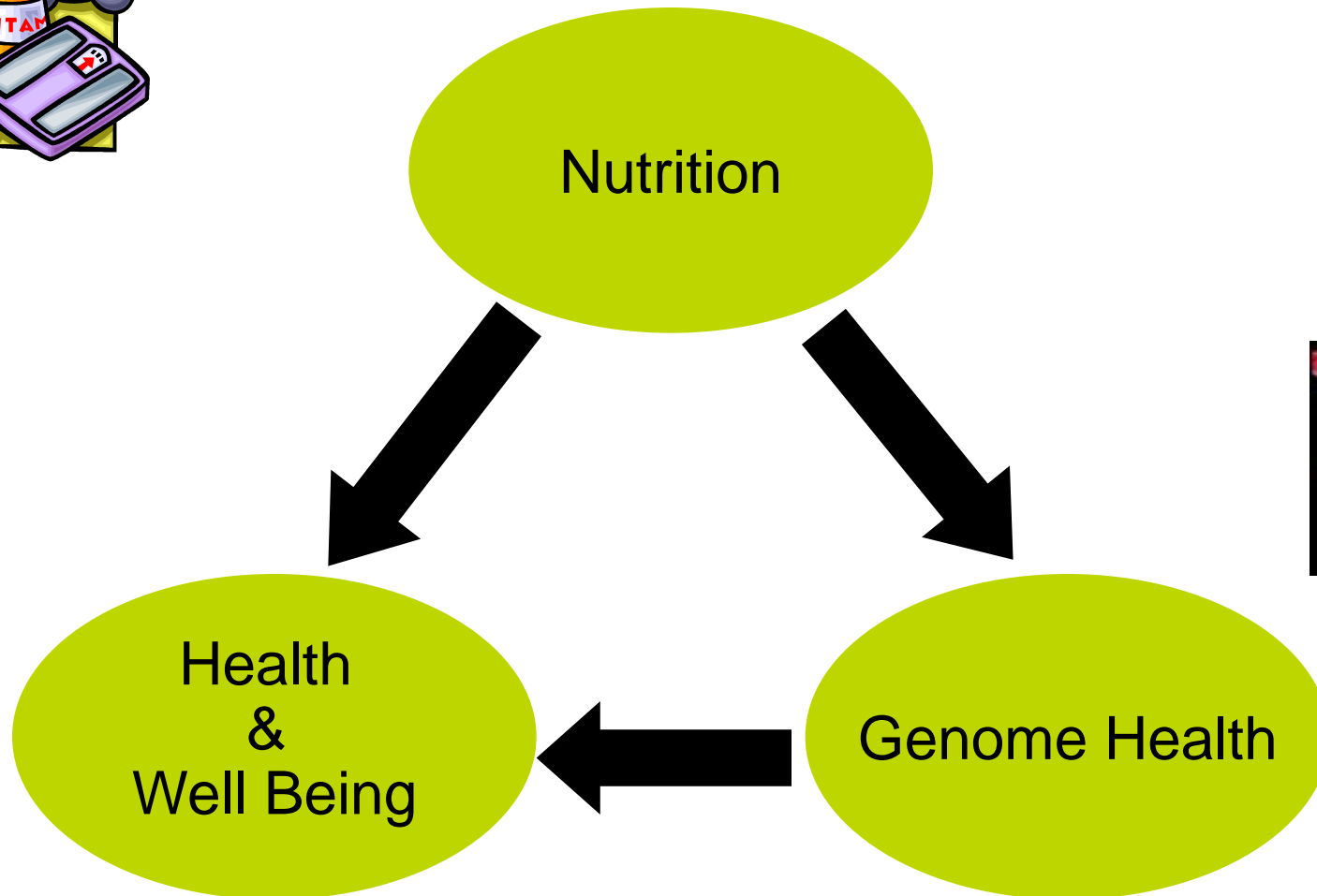
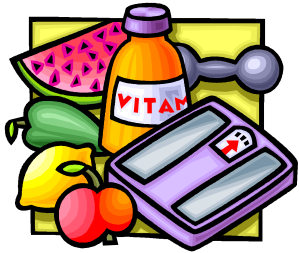


Overview

- Background
 - Telomeres
 - CRC risk
 - Fibre + Protein
- Animal study
 - Design
 - Results
- Conclusion

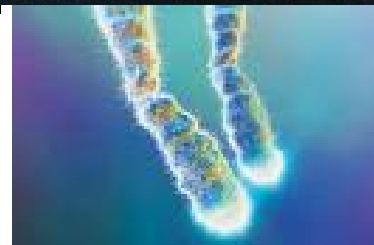
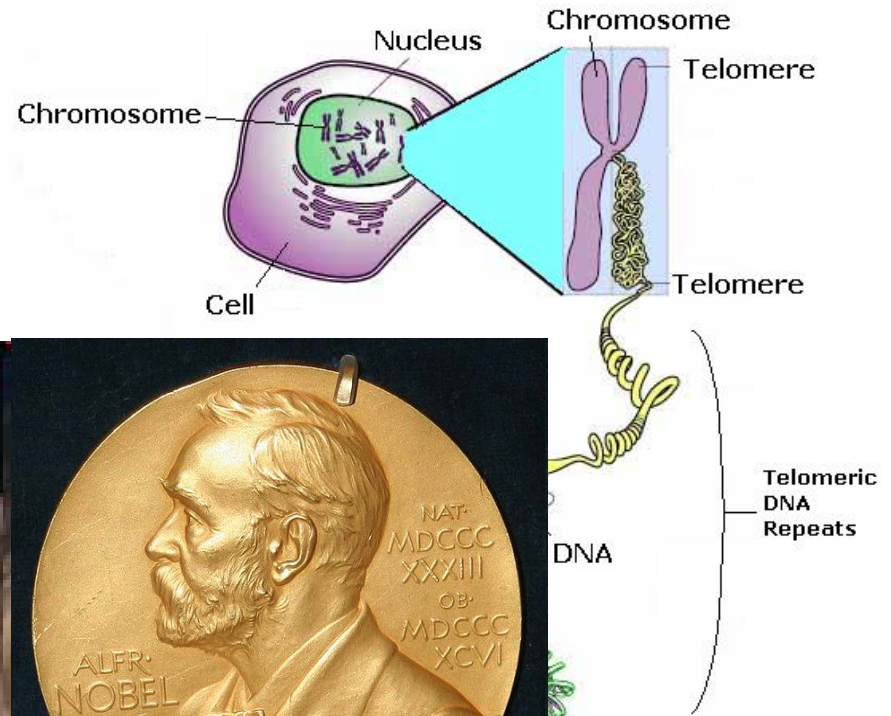


Nutrition, health and DNA

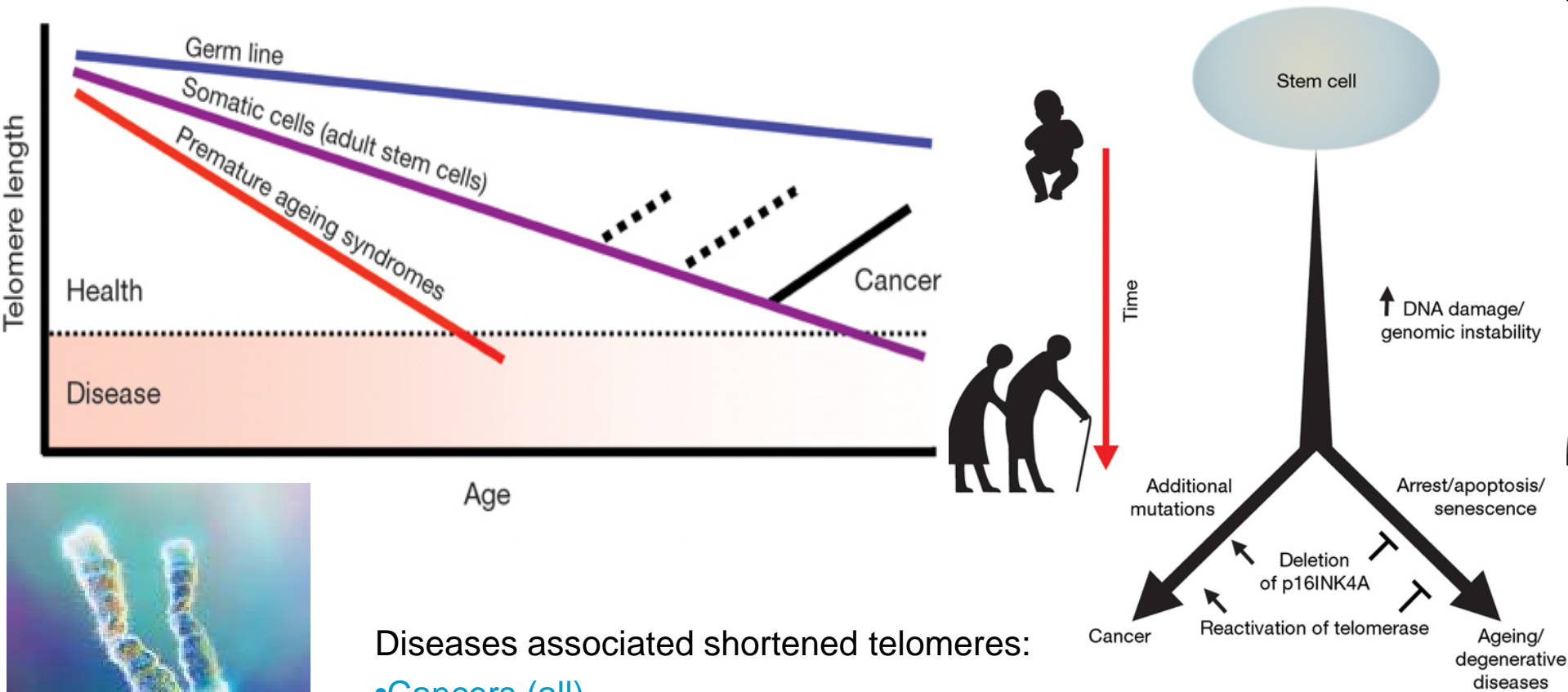


What are telomeres?

- protection, replication, and stabilisation of the chromosome ends
- all vertebrates appear to have the same simple sequence repeats
- (TTAGC)



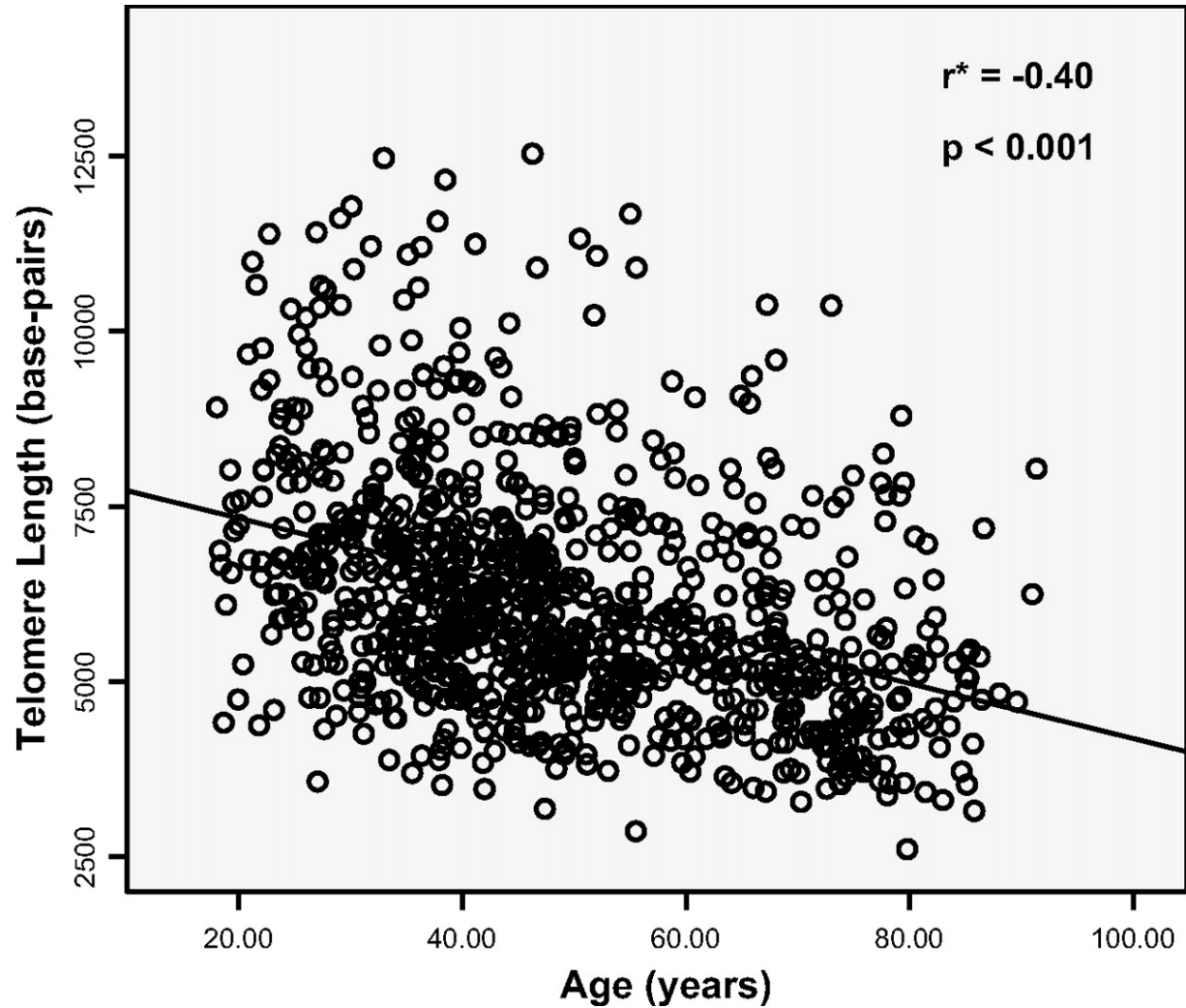
Telomeres, ageing and disease



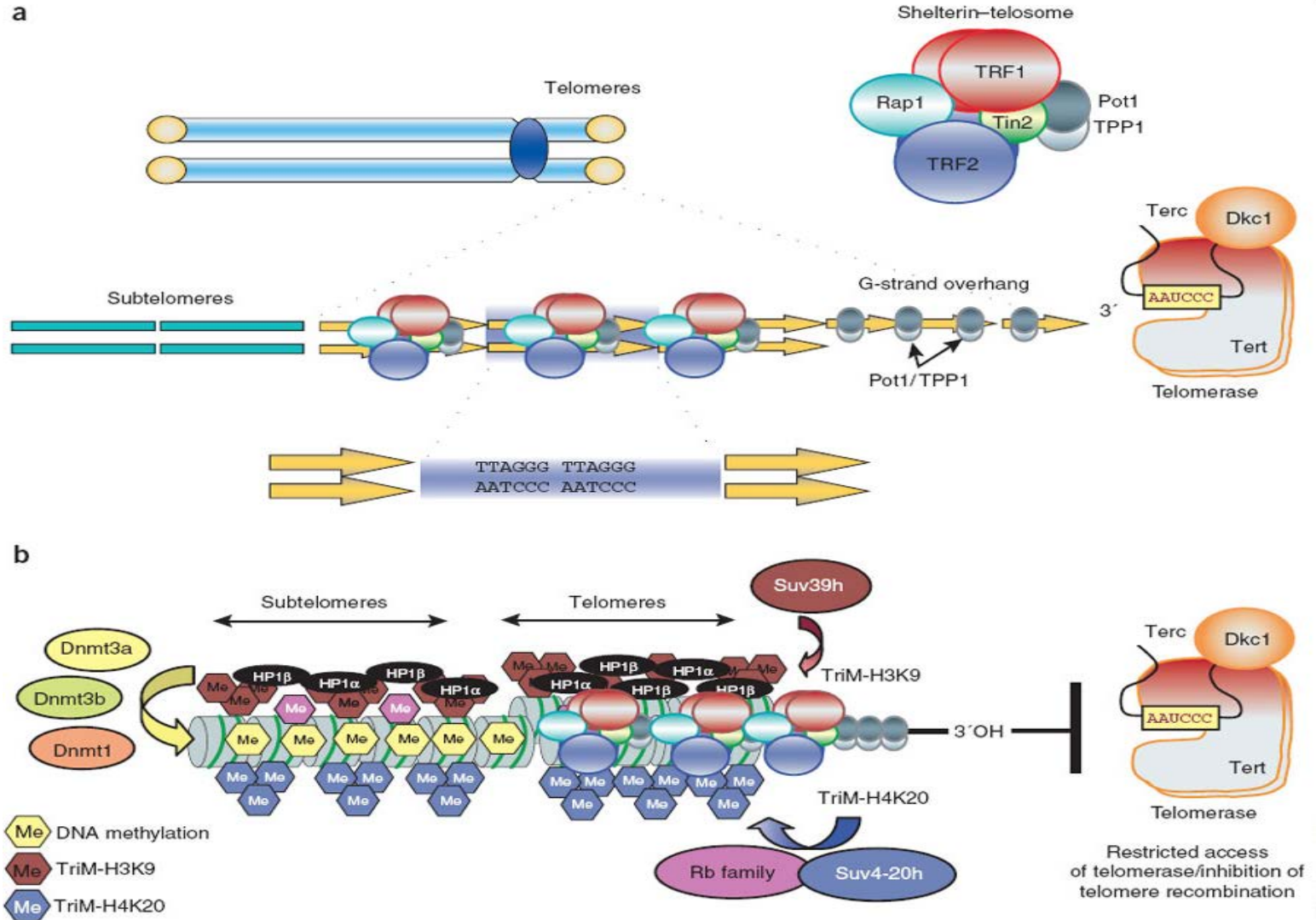
Diseases associated shortened telomeres:

- Cancers (all)
- Vascular: CVD, stroke
- Diabetes
- AD

Age and telomere length



Telomeres and the Telosome



Telomere length is modified by life-style factors

Telomere attrition accelerated by:

- Smoking
- Obesity and low physical activity
- Psychological stress
- Diet (inc. malnutrition)



Diet impacts on telomere length

Shorter telomeres are associated with:

low fruit & veg intake
Increased alcohol intake
Increased processed meat intake

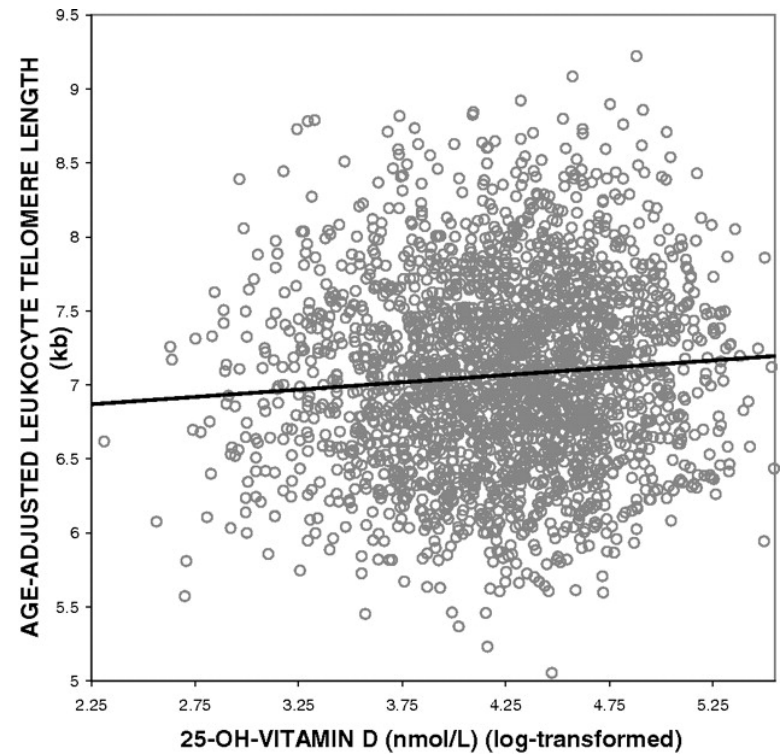
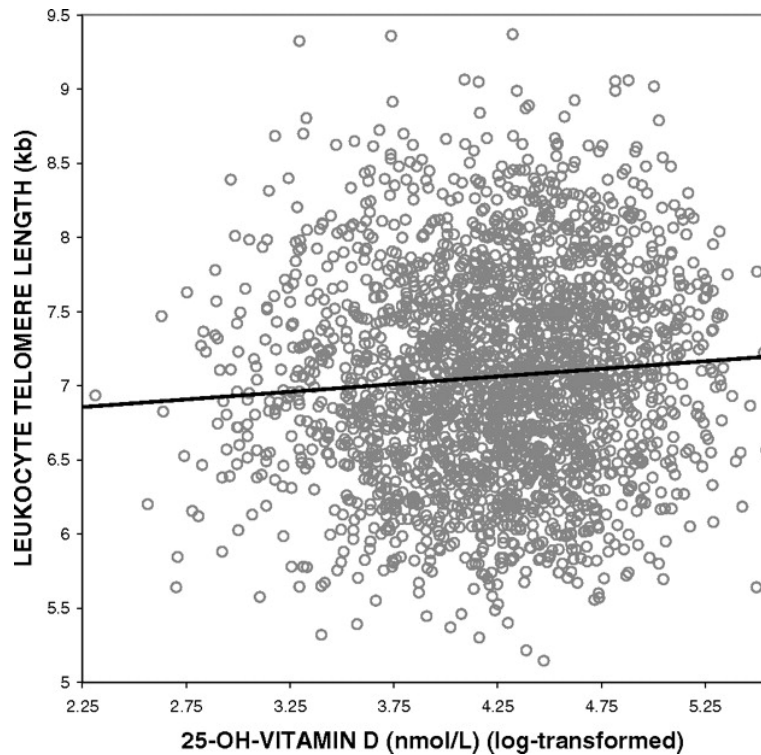


Telomere length is positively associated with:

plasma folate
Multi-vitamin use
Vitamin E
Fish intake
Dietary fibre (cereals)
Vitamin D



Vitamin D as an example



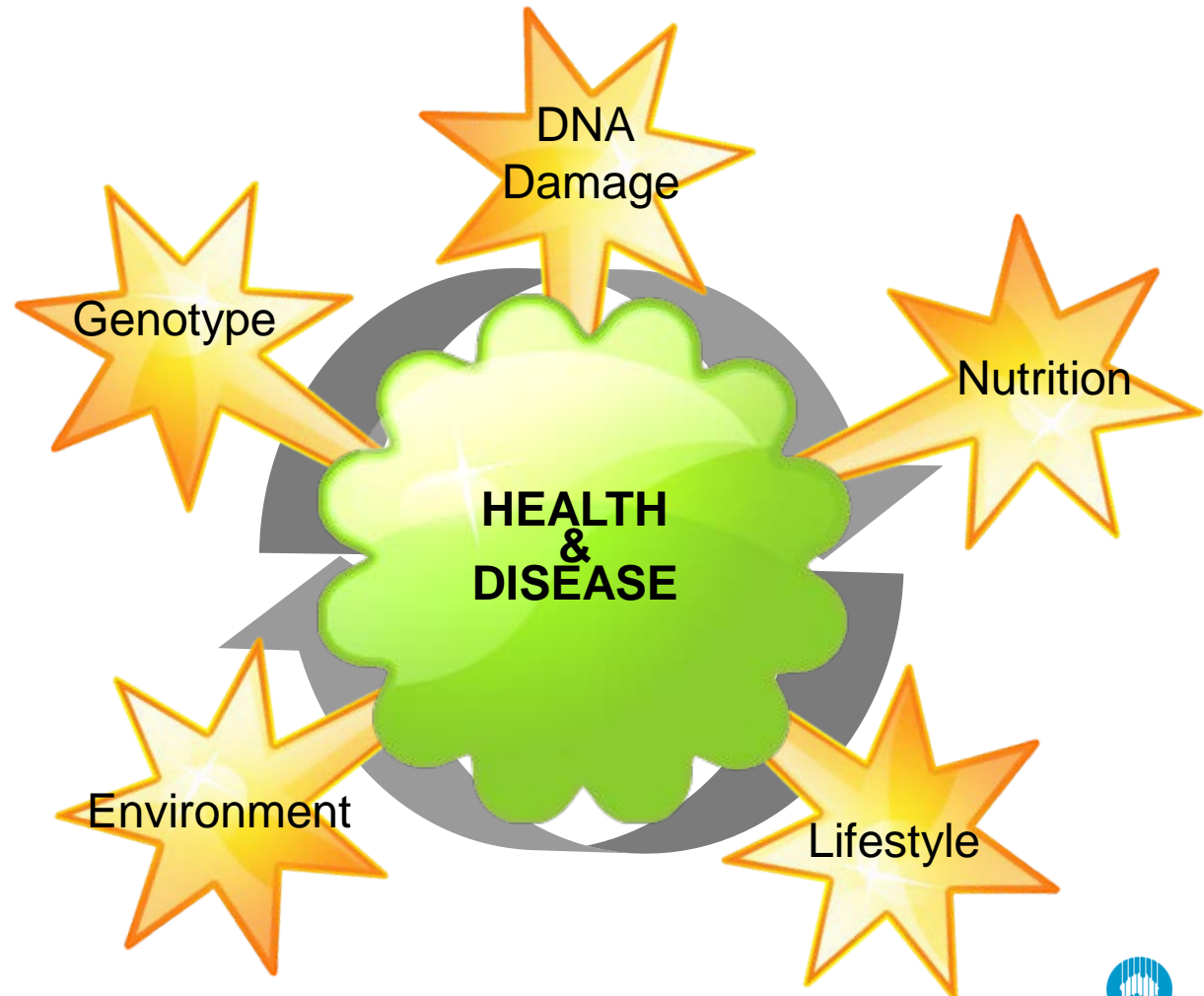
Richards, J B. et al. Am J Clin Nutr 2007;86:1420-1425

n = 2160, Pearson's correlation coefficient = 0.07, P = 0.0010
age-adjusted leukocyte telomere length

n = 2160, Pearson's correlation coefficient = 0.09, P < 0.0001

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Diet and Colorectal Cancer risk

- Most common internal malignancy in Australia
- Diet is an important factor in the aetiology of important non-infectious diseases, including colorectal cancer (CRC).

Epidemiology evidence - meat

- Based on recent human epidemiological studies red meat and processed meat intake is associated with colorectal cancer risk
- 500,000 people, followed over 4.8 years (EPIC)
Positive association between colorectal cancer incidents and red and processed meat (but not poultry) *(Norat et al. 2005)*
- 150,000 mature adults, followed over 20 years
Prolonged high intakes of red or processed meat were associated with elevated risks of colorectal cancer *(Chao et al. 2005)*
- 60,000 Swedish women, followed over 13.9 years
Positive association between red meat consumption and development of colon cancer *(Larsson et al. 2005)*

Epidemiological evidence - fibre

- Epidemiological studies show that fibre is inversely associated with colorectal cancer risk

Bingham et al. Lancet 2003

- Main fibre components identified:

- NSP (non-starch polysaccharides)
- RS (resistant starch)

- RS may have a greater role against colorectal cancer than NSP

Cassidy et al. B J Cancer 1994

- Potential Protective Mechanisms of RS

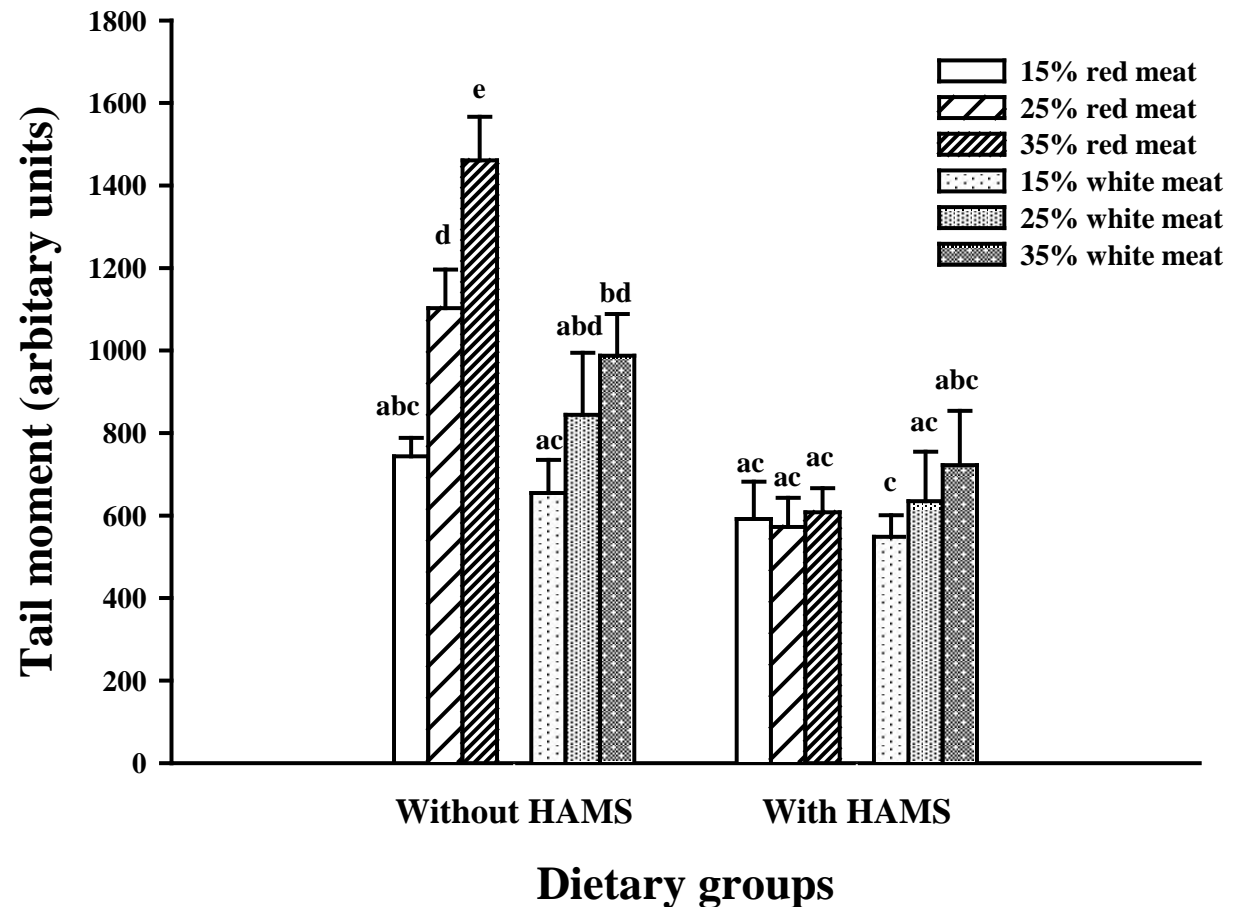
- Short chain fatty acids (SCFA)
- Increasing faecal bulking
- Reducing faecal pH (changing microbial environment)

RS mitigates colonic DNA damage

RS reduces protein-induced colonic DNA damage in a dose-dependent manner

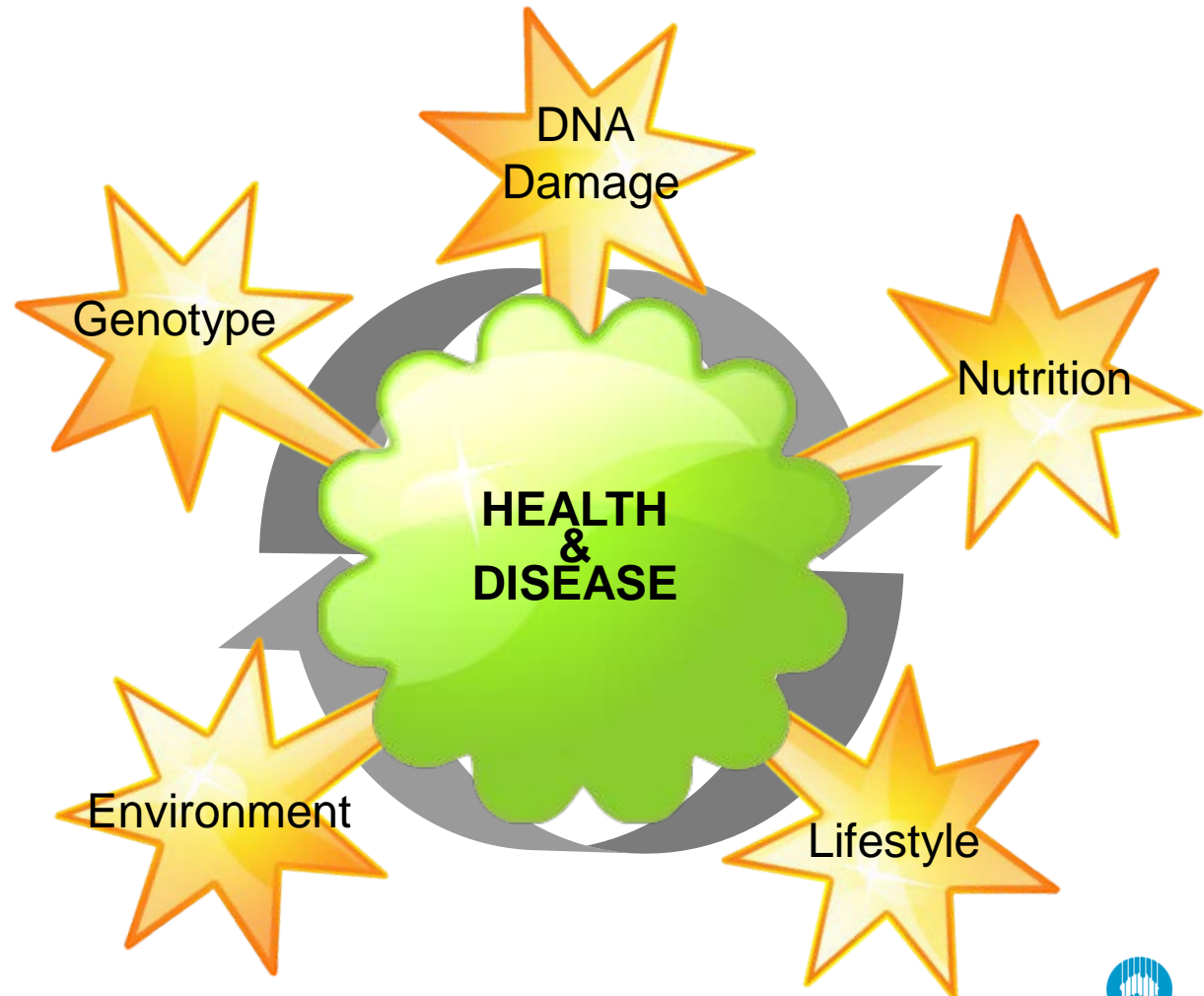
RS restored reduction of the mucus layer thickness induced by a high-protein diet

10% RS in the diet was able to attenuate the colonic DNA damage



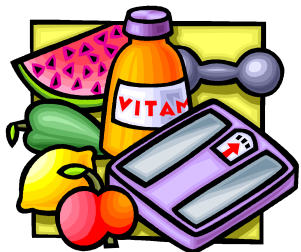
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Study Objectives

- Associative evidence on dietary factors that may affect telomere length,
 - specific impact that increased red meat intake and increased RS has on telomere length in colorectal mucosa is unknown.
- AIM
 - to determine whether telomeres are influenced by dietary red and white meat and whether these effects are modulated by RS within the colon.



Dietary Groups

4- week trial

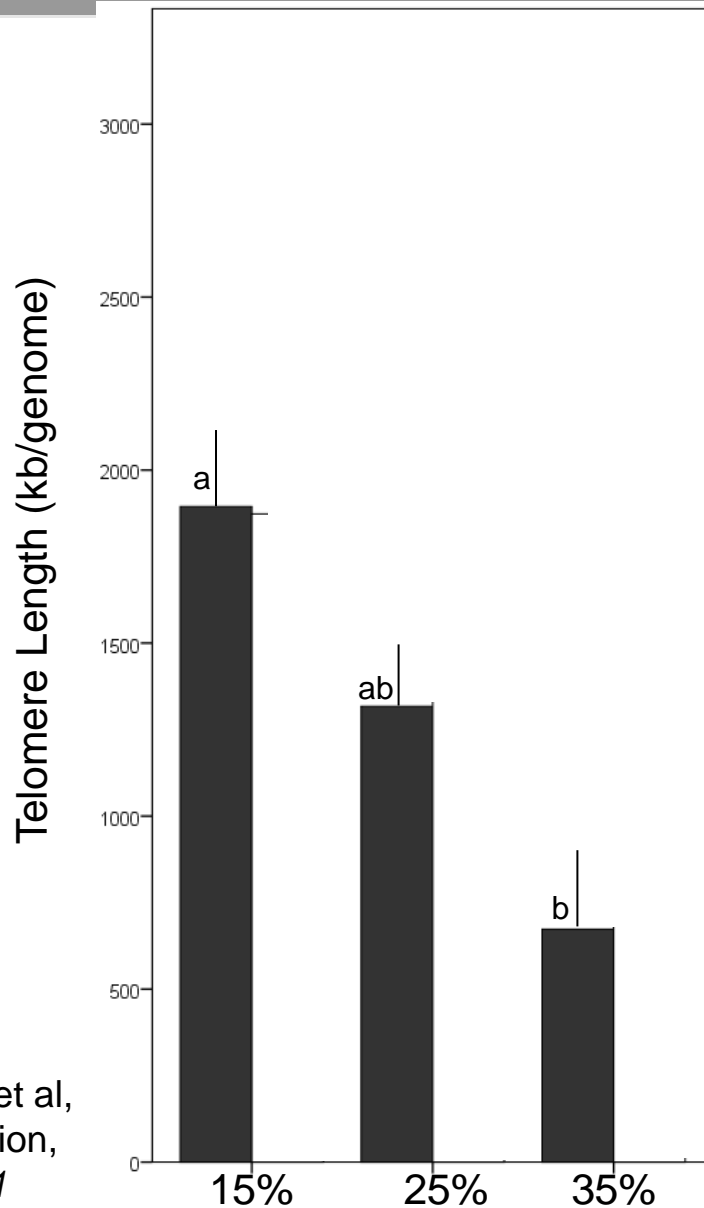
12 dietary groups

- 15, 25 & 35 % Red Meat
 - 15, 25 & 35 % White Meat
 - With or Without Dietary RS
-
- Male Sprague-Dawley rats
 - N=8 per group

 - Colonocytes collected
 - DNA isolated
 - Telomere length measure by qPCR



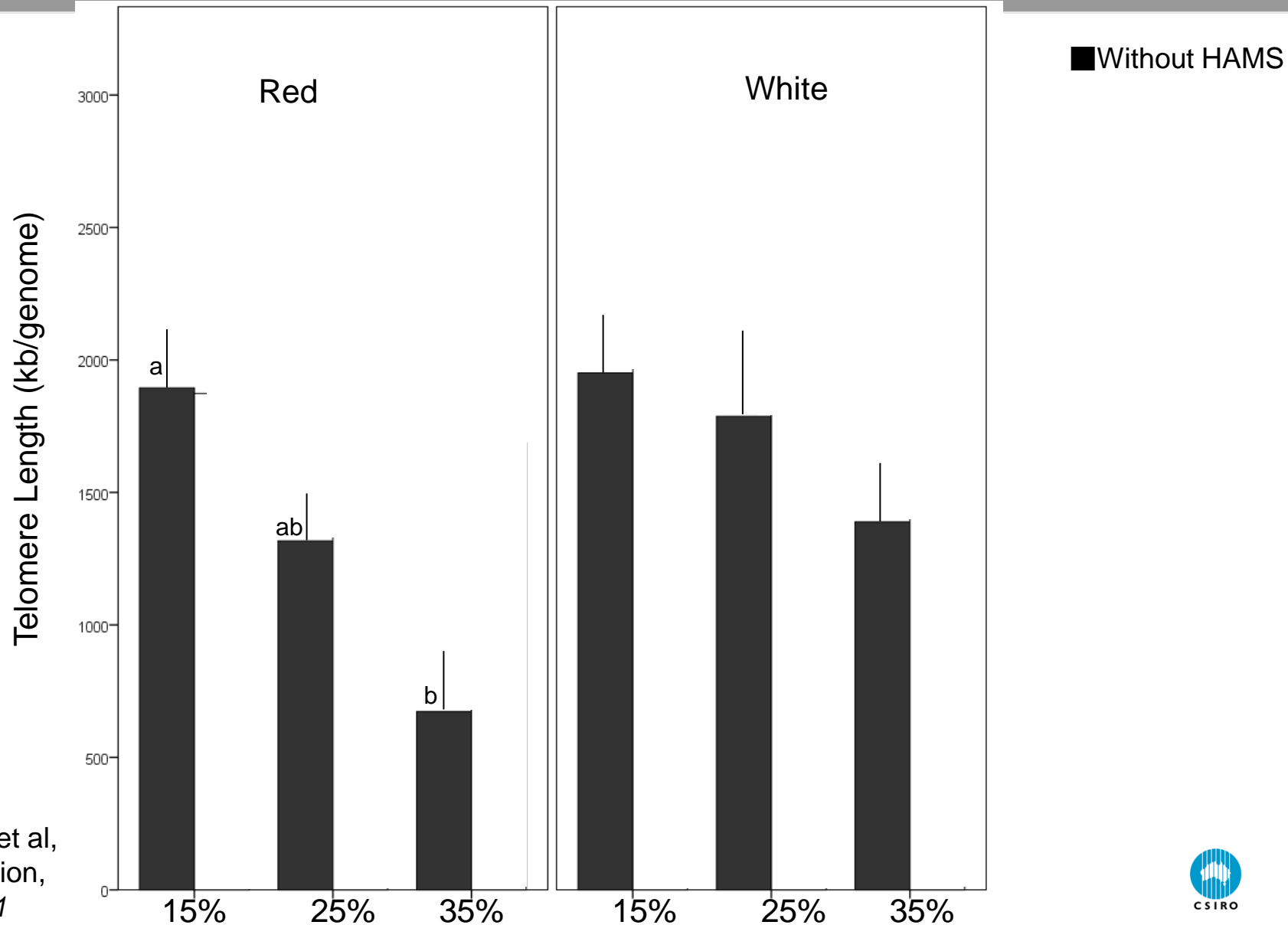
Telomere length shortening with increasing dietary red meat



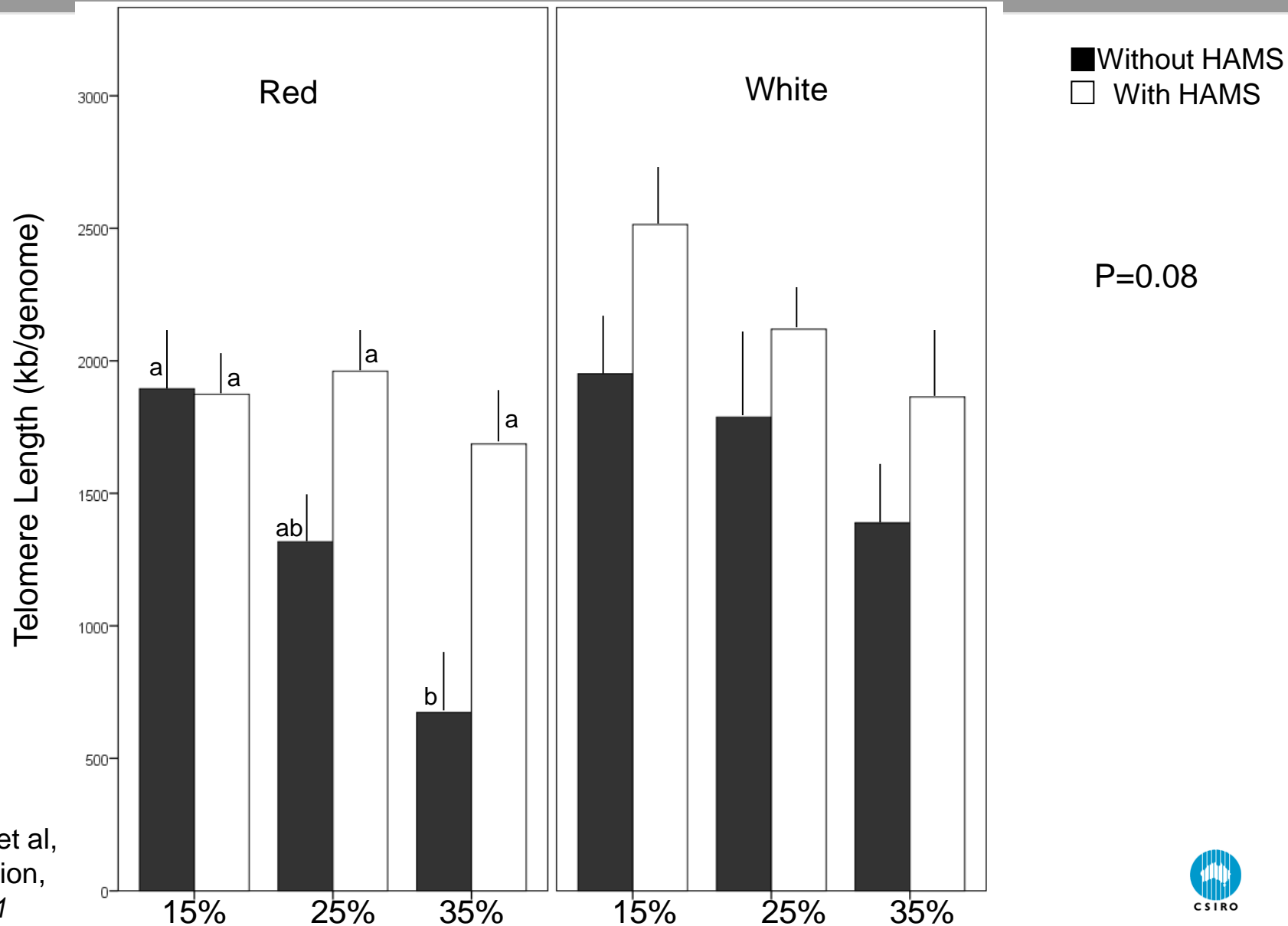
■ Without HAMS

P=0.08,
P-trend=0.03

Telomere length shortening with increasing dietary meat



Telomere length shortening with increasing dietary meat is attenuated by RS



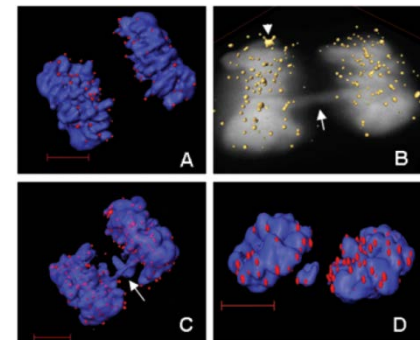
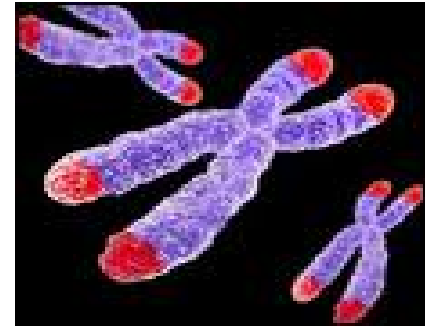
Telomere length was related to other indices of colonic health

Variable	Correlation (r)
COMET	
Single strand breaks	-0.36 *
Double strand breaks	-0.37**
Colonic Malondialdehyde	-0.28 *
Caecal SCFA Pools	
Acetate	0.31 *
Propionate	0.28 *
Butyrate	-0.04
Total caecal SCFA	0.31 *
Caecal phenol	-0.51
Caecal <i>p</i> -cresol	-0.11

*indicates P<0.05; **indicates P<0.01; n=96; SCFA = short chain fatty acid

Conclusions

- increased dietary red leads to greater telomere shortening in rat colonocytes.
- inclusion of RS in the diet attenuated telomere shortening
 - induced by feeding high levels of red meat.
- This study provides greater evidence for dietary components significantly influences genomic stability within the colon.
 - Can dietary intervention alter CRC risk?



Acknowledgements

- Food Futures Flagship

- Shusuke Toden
- Tony Bird
- David Topping
- Michael Conlon

National Research
FLAGSHIPS
Food Futures



- Michael Fenech

Diets

Table I. Composition of experimental diets (g/kg diet)

	Dietary treatment											
	0% HAMS						20% HAMS					
	Red meat			White meat			Red meat			White meat		
	15%	25%	35%	15%	25%	35%	15%	25%	35%	15%	25%	35%
Red meat	150	250	350	0	0	0	150	250	350	0	0	0
White meat	0	0	0	130	220	300	0	0	0	130	220	300
Cornstarch	580	500	418	585	503	430	380	300	218	385	303	230
HAMS	0	0	0	0	0	0	200	200	200	200	200	200
Sucrose	100	100	100	100	100	100	100	100	100	100	100	100
Sunflower oil	30	30	30	30	30	30	30	30	30	30	30	30
Tallow	40	20	1.5	55	47	40	40	20	1.5	55	47	40
Wheat bran	50	50	50	50	50	50	50	50	50	50	50	50
L-cystine	3	3	3	3	3	3	3	3	3	3	3	3
Choline bitartrate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Vitamins (AIN-93)	10	10	10	10	10	10	10	10	10	10	10	10
Minerals (AIN-93)	35	35	35	35	35	35	35	35	35	35	35	35

Total protein and fat of white meat groups were matched with corresponding red meat groups. Diets based on AIN-93 formulation.